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Fibroblast Growth Factor–Based Pharmacotherapies for the Treatment of Obesity-Related Metabolic Complications

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Abstract

The fibroblast growth factor (FGF) family, which comprises 22 structurally related proteins, plays diverse roles in cell proliferation, differentiation, development, and metabolism. Among them, two classical members (FGF1 and FGF4) and two endocrine members (FGF19 and FGF21) are important regulators of whole-body energy homeostasis, glucose/lipid metabolism, and insulin sensitivity. Preclinical studies have consistently demonstrated the therapeutic benefits of these FGFs for the treatment of obesity, diabetes, dyslipidemia, and nonalcoholic steatohepatitis (NASH). Several genetically engineered FGF19 and FGF21 analogs with improved pharmacodynamic and pharmacokinetic properties have been developed and progressed into various stages of clinical trials. These FGF analogs are effective in alleviating hepatic steatosis, steatohepatitis, and liver fibrosis in biopsy-confirmed NASH patients, whereas their antidiabetic and antiobesity effects are mild

and vary greatly in different clinical trials. This review summarizes recent advances in biopharmaceutical development of FGF-based therapies against obesity-related metabolic complications, highlights major challenges in clinical implementation, and discusses possible strategies to overcome these hurdles.

INTRODUCTION

The prevalence of overweight and obesity, caused by increased sedentary lifestyle and overnutrition, has reached epidemic proportions worldwide (1). Obesity is a major risk factor for a cluster of cardiometabolic diseases, including insulin resistance, type 2 diabetes (T2D), nonalcoholic fatty liver disease (NAFLD), cardiovascular and neurodegenerative disorders, sleep apnea, and certain types of cancer (2). However, pharmacological options for the treatment of obesity and its related medical complications remain limited. Most of the antiobesity medications were withdrawn from the market due to their severe adverse effects (3). None of the current antidiabetic drugs can cure diabetes, and diabetic patients need life-long medication (4). Furthermore, there is no approved pharmacotherapy for NAFLD, which often co-occurs with obesity and T2D (5). Therefore, there is an urgent need to develop effective long-term therapeutics for management of these obesity-related metabolic complications.

The fibroblast growth factor (FGF) family consists of 22 evolutionarily and structurally related proteins that regulate diverse biological processes, including cell growth and differentiation, embryonic development, angiogenesis, and wound repair (6). Based on differences in sequence homology and phylogeny, the human *FGF* gene family has been categorized into seven subfamilies (7). Most members of the FGF family are canonical FGFs (including FGF1–10, FGF16–18, FGF20, and FGF22), which act as autocrine and/or paracrine factors to bind and activate the single-pass transmembrane FGF receptors consisting of four highly conserved members (FGFR1–4) with tyrosine kinase activity (8). Aberrant activation of fibroblast growth factor receptors (FGFRs) and/or postreceptor signaling pathways is a well-known contributor to the pathogenesis of several types of cancers and inherited diseases (9). A number of chemical inhibitors, neutralizing antibodies, and silencing RNAs targeting the canonical FGF signaling pathways have been developed as potential pharmacotherapies for malignant diseases and are currently under different phases of clinical trials (10).

In contrast to canonical FGFs, the three members of the endocrine FGF subfamily, designated FGF19 (the mouse ortholog FGF15), FGF21, and FGF23, possess weak heparin-binding properties and can thereby be released from the extracellular matrix into the bloodstream to exert their pleiotropic effects in distal organs. These three endocrine FGFs require single-pass transmembrane glycoproteins, namely α-Klotho (for FGF23) and β-Klotho (for FGF19 and 21), as coreceptors to activate their cognate FGFRs (11). While most tissues express one or more FGFR isoforms, the expression of α-Klotho and β-Klotho is highly restricted in several organs, thus determining the target specificity of these endocrine FGFs (8). FGF23 plays a key role in maintaining phosphate and vitamin D homeostasis by stimulating FGFR/α-Klotho complexes in the kidney and parathyroid gland (12). Burosumab (Crysvita), an antibody drug targeting FGF23, has been approved by the US Food and Drug Administration for the treatment of X-linked hypophosphatemia (13). On the other hand, FGF19 and FGF21, both of which act through the FGFRs/β-Klotho complex, are the key regulators of bile acid (BA), glucose, and lipid metabolism in both rodents and humans (8). Due to their pleiotropic metabolic benefits and relatively safe pharmacological profiles, a growing number of FGF21 and FGF19 analogs and/or agonists have been developed as potential therapies for obesity and its related metabolic complications, such

as T2D and NAFLD (8, 14, 15). Furthermore, several members of the canonical FGFs, including FGF1 and FGF4, have recently emerged as important regulators of energy homeostasis and glucose/lipid metabolism beyond their classical function as growth factors (16–19).

In this review, we aim to (*a*) summarize recent preclinical and clinical findings on metabolic functions of FGF21, FGF19, FGF1, and FGF4; (*b*) highlight the latest advances in the biopharmaceutical development of these FGF analogs and agonists for treatment of obesity-related metabolic complications, including T2D, dyslipidemia, and NAFLD; and (*c*) discuss the current challenges in translating FGF-based pharmacotherapy from the bench to clinic and propose possible strategies to address these hurdles.

FGF19: A GUT-DERIVED HORMONE

FGF15/19 Biology and Pathophysiology

Human FGF19 and its mouse ortholog, FGF15, were the first members of the endocrine FGF subfamily identified in the 1990s (8). Given their sequence divergence, the mouse *Fgf15* and human *FGF19* genes were not initially considered to be orthologs. However, highly conserved synteny around their gene loci eventually led to the acceptance of *FGF19* as the human ortholog of mouse *Fgf15* (20). Although both FGF15 and FGF19 are predominantly expressed in the ileum (20), a certain degree of divergence in their tissue expression and biological activities has been reported (21). FGF15/19 is strongly induced by the nuclear receptor farnesoid X receptor (FXR) in small intestine in response to the postprandial reuptake of BA (22). Furthermore, several other nuclear receptors such as the vitamin D receptor (VDR), retinoid X receptor (RXR), and pregnane X receptor (PXR) also promote *Fgf15* expression in mice (23, 24). DIET1, a 236-kDa membrane protein consisting of tandem low-density lipoprotein (LDL) receptor and meprin-A5-protein tyrosine phosphatase mu domains, has been shown to modulate FGF15/19 secretion posttranscriptionally from enterocytes, possibly through its interaction with FGF15/19 (25).

FGF15/19 exerts its physiological actions by binding to its receptor complexes comprising FGFR4 and β-Klotho, both of which are highly enriched in the liver (22, 26). In hepatocytes, FGF15/19 suppresses BA biosynthesis by repressing the gene encoding cholesterol 7α-hydroxylase (*CYP7A1*) through a mechanism that is dependent on the orphan nuclear receptor small heterodimer partner (SHP) (22) (**Figure 1**). Mice lacking *Fgf15*, *Fgfr4*, or *β-Klotho* exhibit increased BA synthesis and serum BA levels (22, 27, 28). In contrast, hepatic overexpression of FGFR4 inhibits *CYP7A1* expression and in turn lowers the BA pool size (29). The ability of FGF15/19 to inhibit BA synthesis is therapeutically exploited to prevent BA-induced enterohepatic damage in cholestasis and nonalcoholic steatohepatitis (NASH) (30). Nonetheless, the intracellular signaling pathways that link the FGF15/19 receptor complex with *CYP7A1* expression remain poorly defined.

Apart from its regulation in BA homeostasis, FGF15/19 also participates in lipid and carbohydrate metabolism (31). *Fgf15* knockout mice are unable to maintain appropriate serum glucose concentrations and display diminished hepatic glycogen contents and glucose intolerance, whereas FGF19 administration reverses these metabolic damages (32). Mechanistically, FGF15/19 promotes hepatic glycogen synthesis through activation of extracellular-signal-regulated kinase (ERK) and subsequent phosphorylation and inactivation of the glycogen synthase kinase-3 (GSK3) independent of insulin actions (32). Furthermore, FGF15/19 blocks the expression of genes involved in hepatic gluconeogenesis by dephosphorylation and inactivation of the transcription factor cAMP regulatory element-binding protein (CREB), thereby blunting the expression of peroxisome proliferator–activated receptor γ coactivator-1α (*PGC-1α*) and other genes involved in hepatic metabolism (33). Transgenic overexpression of *Fgf19* or administration of recombinant

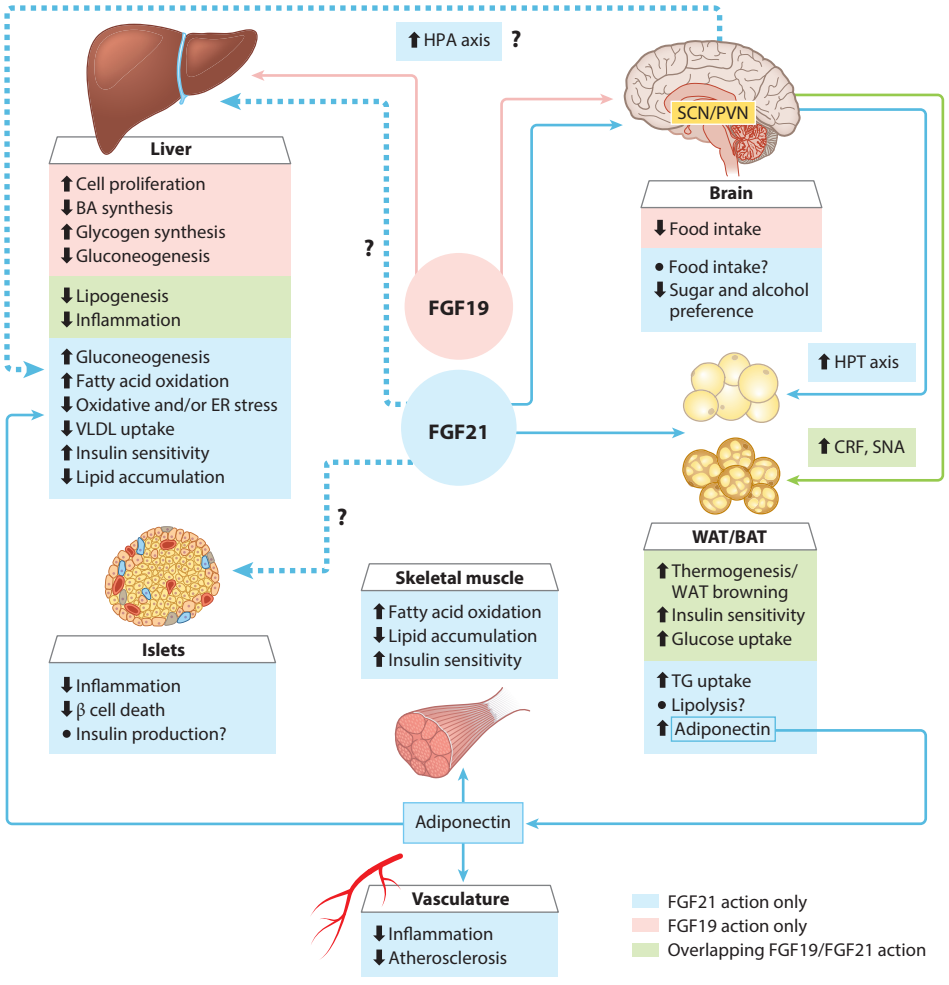

Figure 1

Overlapping and differential metabolic actions of FGF19 and FGF21 in major target tissues: Pharmacological effects of both FGF19 and FGF21 on weight loss, glucose-lowering, and insulin sensitization appear to be mediated by the FGFR1/β-Klotho receptor complex in adipose tissues and brain. However, due to the distinct binding affinity to different isoforms of FGFRs, differential effects of FGF19 and FGF21 have been observed. FGF19 can act directly on hepatocytes via FGFR4/β-Klotho to inhibit BA synthesis and gluconeogenesis, whereas various FGF21 actions in the liver and vasculature appear to be indirect, such as via induction of adiponectin. FGF21, but not FGF19, has been reported to prevent β cell death and regulate alcohol/sugar preference via central actions. Question marks and dashed arrows denote unclear pathways, uncertain effects, or obscure mechanisms of action. Abbreviations: BA, bile acid; BAT, brown adipose tissue; CRF, corticotropin-releasing factor; ER, endoplasmic reticulum; FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; HPA, hypothalamic-pituitary-adrenal; HPT, hypothalamic-pituitary-thyroid; SCN/PVN, suprachiasmatic nucleus/paraventricular nucleus; SNA, sympathetic nerve activation; TG, triglyceride; VLDL, very-low-density lipoprotein; WAT, white adipose tissue.

FGF19 increases energy expenditure and counteracts obesity, hepatic steatosis, and diabetes in both dietary and genetically inherited obese mice (34–36). Intracerebroventricular injections of FGF19 produce strong antidiabetic effects, possibly by activation of sympathetic neurons in diabetic rodent models, including improvement of glucose tolerance, decrease in food intake and

body weight, and increase in energy expenditure (34, 37–39). Additionally, FGF15/19 promotes browning and adaptive thermogenesis of white adipose tissues (WATs) (40), but such thermogenic effects of FGF15/19 on adipose tissues are not required for its antiobesity effects in mice (41). The therapeutic benefits of pharmacological doses of FGF19 on obesity and diabetes are mediated by the FGFR1/β-Klotho complex but not by FGFR4 (42).

In healthy individuals, circulating FGF19 levels display a diurnal fluctuation closely related to postprandial serum BA (43). Fasting FGF19 levels vary from 49 to 590 pg/mL but increase by 250% after administration with chenodeoxycholic acid, supporting the role of the postprandial BA in FGF19 induction via FXR, thereby transmitting signals from the intestine to liver for suppression of hepatic CYP7A1 (43). Decreased fasting plasma levels of FGF19 have been observed in patients with inflammatory bowel disease, concomitant primary BA malabsorption, obesity, T2D, and NAFLD, whereas higher FGF19 plasma levels have been detected in individuals undergoing chronic hemodialysis (44–48) or obese individuals after receiving bariatric surgery (49).

Biopharmaceutical Development of FGF19 Analogs for Metabolic Diseases

Despite potent pharmacological benefits of FGF19 administration against obesity, diabetes, and fatty liver disease, its mitogenic activity and involvement in tumorigenesis represent the major challenges in translating FGF19-based pharmacotherapy from the bench to clinic (50–54). In mice, ectopic expression of *Fgf19* promotes hepatocyte proliferation, hepatocellular dysplasia, and neoplasia, while upregulated FGF19 expression is associated with tumor progression and poor prognosis in patients with hepatocellular carcinoma (HCC) (52, 53). This tumorigenic activity has been ascribed to FGFR4, as *Fgfr4* deletion or the use of an FGFR4-neutralizing antibody is able to reduce increased tumor burden by ectopic *Fgf19* expression in mice (55, 56). Therefore, intensive efforts have been made to dissect the structural basis underpinning the metabolic and mitogenic activities of FGF19, aiming to develop FGF19 variants devoid of tumorigenic properties (**Figure 2**).

FGF15/19 interacts with its receptor complexes by the binding of its C-terminal domain to β-Klotho and its N-terminal immunoglobulin (Ig) domain-3 to FGFR4 (57). As its tumorigenic activity has been ascribed predominantly to FGFR4, several FGF19 variants that lack the FGFR4 binding properties, such as FGF19-4, FGF19-5, and FGF19-6 engineered by the combined mutagenesis of amino acids 38–42 in the N terminus and in one or both of the heparin-binding domains, have been shown to lose the ability of FGFR4-mediated mitogenic signaling in cells and tumorigenesis in mice (54). Remarkably, these FGF19 variants retain their ability to promote glucose uptake in myotubes and to lower glucose levels in diabetic mice, possibly through their engagement with the FGFR1c/β-Klotho receptor. FGF19v, another FGF19 analog made by conjugating amino acids 1–20 of FGF21 with amino acids 25–194 of FGF19, also exhibits abrogated mitogenic activity but intact metabolic functions (58). Likewise, several FGF19 variants with diminished ability to induce dimerization of FGFR4 have been reported to display dramatic loss in mitogenic activity, whereas their effects on glycemic controls and BA metabolism are indistinguishable from wild-type FGF19 (59). However, none of these nonmitogenic FGF19 analogs has progressed into clinical trials so far.

NGM282 (also named M70 and aldafermin), another nonmitogenic FGF19 variant engineered by substituting three amino acids (A30S, G31S, H33L) and deleting five amino acids in the N terminus (60), is one of several FGF19 analogs under extensive clinical trials for treatment of various metabolic and liver diseases. While wild-type FGF19 has been shown to promote tumor progression by activating signal transducer and activator transcription 3 (STAT3), NGM282 lacks such activities but retains its function in the activation of the ERK signaling pathway regulating CYP7A1

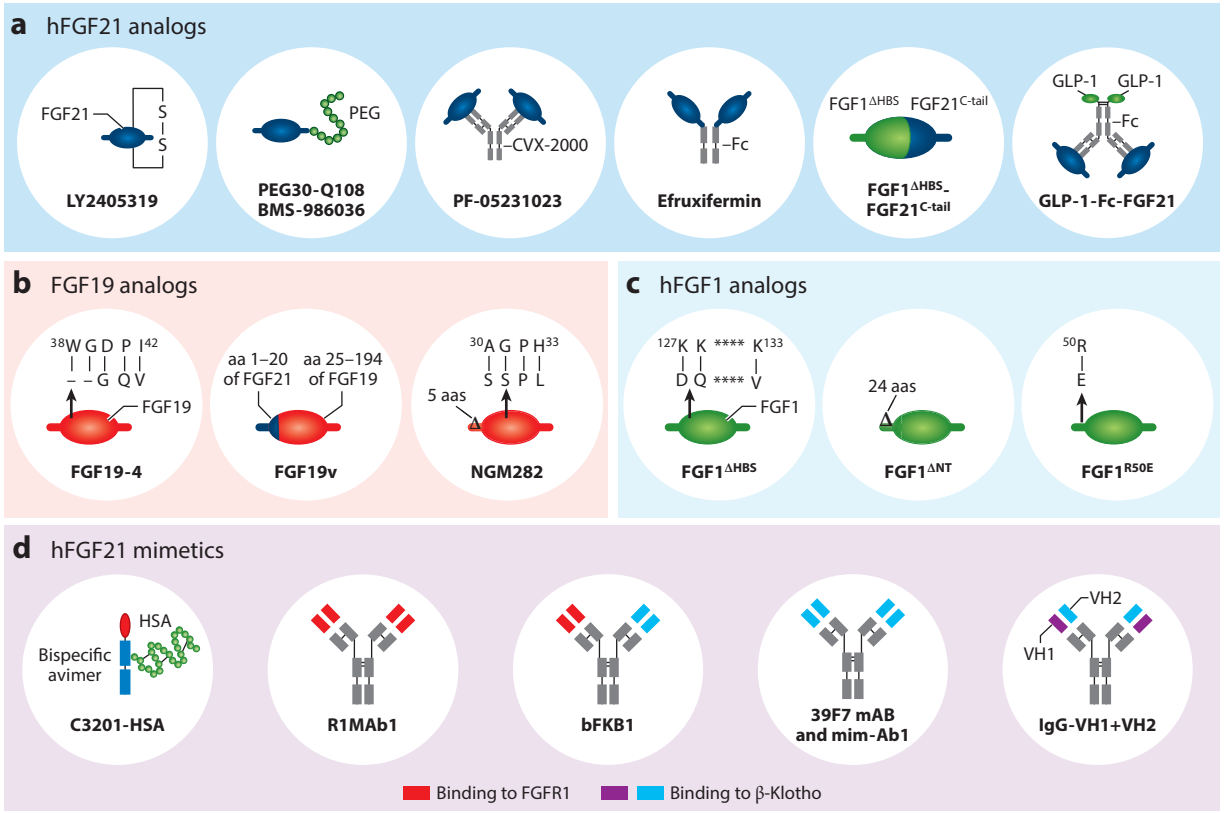

Figure 2

A summary of engineered FGF analogs and mimetics for the treatment of obesity-related metabolic complications. (*a*) Various hFGF21 analogs with improved biophysical properties and stability are made by introducing an additional disulfide bond (such as LY2405319). Analogs with improved pharmacokinetic profiles are made by PEGylation (such as PEG30-Q108 and BMS-986036) and by fusion to an antibody scaffold named CVX-2000 (such as PF-05231023) or the Fc of an antibody (such as efruxifermin). The chimeric $FGF1^{\Delta HBS}$-$FGF21^{C\text{-}tail}$ is made by linking an HBS-deficient amino terminus of FGF1 to the carboxy terminus of hFGF21. GLP-1-Fc-FGF21 D is a dual agonist made by conjugation of both GLP-1 and a hFGF21 mutant to IgG4 Fc, which has an enhanced binding property to β-Klotho. (*b*) Several FGF19 variants without the FGFR4-binding property are generated by combined mutagenesis of aa 38–42 in the NT and in one or both of the HBS (FGF19-4), by conjugating aa 1–20 of FGF21 with aa 25–194 of FGF19 (FGF19v), or by substituting three aas (A30S, G31S, H33L) and deletion of five aas in the NT (NGM282). (*c*) Several FGF1 variants with abrogated mitogenic activity are generated by mutations of three lysine residues (K127D, K128Q, and K133V) in the HBS ($FGF1^{\Delta HBS}$), by deletion of 24 aas at its N-terminal domain ($FGF1^{\Delta NT}$), or by mutagenesis of Arg50 to Glu in the integrin binding site ($FGF1^{R50E}$). (*d*) FGF21 receptor agonists are shown, including C3201-HSA (a bispecific avimer conjugated to human serum albumin), agonistic antibodies that bind to FGFR1 (R1MAb1), a bispecific mAb (bFKB1 and 39F7 mAb, mim-Ab1) that binds to both FGFR1 and FGFR1/β-Klotho, and a biparatopic agonist antibody for FGFR1/β-Klotho complex (IgG-VH1+VH2). Abbreviations: Δ, deletion; aa, amino acid; Fc, fragment crystallizable region; FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; GLP, glucagon-like peptide; HBS, heparan sulfate-binding site; hFGF, human fibroblast growth factor; IgG, immunoglobulin G; mAb, monoclonal antibody; NT, N terminus; PEG, polyethylene glycol; VH, heavy chain variable domain.

expression (60). Despite its highly potent antidiabetic effects in rodent models, NGM282 fails to reduce hyperglycemia in a randomized, double-blinded, placebo-controlled trial in 81 patients with T2D (61). A modest effect on reducing body weight and insulin resistance was observed only in patients who were administered with a high dose of NGM282 (10 mg). In contrast, NGM282 treatment led to a rapid, robust, and sustained reduction in liver fat content and liver injury

markers and an improvement in liver histology in patients with NASH. The potent therapeutic benefits of NGM282 in the reduction of liver fat content, NAFLD activity scores, and liver fibrosis have also been observed in another two Phase II clinical trials in biopsy-proven NASH patients (62, 63).

Furthermore, aldafermin effectively decreases serum levels of BAs, markers of liver injury [aspartate aminotransferase (AST), alanine aminotransferase (ALT)], and liver fibrosis [N-terminal propeptide of type III collagen (PRO-C3)] in patients with NASH (64) or with metabolic or cholestatic liver disease (65). However, a recent report showed that aldafermin failed to hit its primary end point in a Phase IIb ALPINE 2/3 trial for NASH with stage 2 or 3 liver fibrosis (66). The clinical outcomes from another ongoing Phase IIb clinical trial (NCT04210245) are expected to provide further insights on the therapeutic efficacy of long-term aldafermin treatment for NASH and NASH-associated fibrosis.

FGF21: A STRESS-RESPONSIVE METABOLIC MESSENGER

FGF21 Biology, Physiology, and Pharmacology

The metabolic activity of FGF21 was first identified in 2005 by Kharitonenkov et al. (67) in a cell-based, high-throughput screening study as a positive hit with glucose-lowering properties, owing to its ability to induce glucose uptake in adipocytes. Although liver is a major source of circulating FGF21, expression of FGF21 is also detectable in several other metabolic organs, including adipose tissue, pancreatic islets, and skeletal muscle (14, 68). Long-term fasting, ketogenic and high-carbohydrate diets, and free fatty acids are potent inducers of FGF21 (69–71). Fasting-mediated induction of FGF21 requires the nuclear receptor peroxisome proliferator–activated receptor α (PPARα) (71).

Similar to FGF19, FGF21 in itself is not sufficient to activate FGFRs and requires the recruitment of β-Klotho as a coreceptor (72, 73). In vitro assays in BaF3 cells or L6 myoblasts coexpressing FGFR splice variants and β-Klotho show that FGF21 only activates FGFR1c and FGFR3c, whereas FGF19 can activate FGFR1c, FGFR2c, FGFR3c, and FGFR4 (73–75). In mice, the biological functions of FGF21 are mediated predominantly by the FGFR1c/β-Klotho receptor complex. The binding of FGF21 to its receptor complex triggers several downstream signaling pathways, including ERK1/2, protein kinase B (Akt), adenosine monophosphate (AMP)-activated protein kinase (AMPK), and mammalian target of rapamycin complex 1 (mTORC1) (67, 68, 72, 73, 75, 76). Although phosphorylation of ERK1/2 and activation of its downstream targets have been widely used as indicators for FGF21 signaling transduction, ERK1/2 is unlikely to mediate all the metabolic functions of FGF21. The molecular events that link the FGF21 receptor complex with its distal effects remain poorly characterized.

Physiologically, FGF21 is an indispensable player in mediating metabolic adaptation to a variety of stressors, including starvation, nutrient excess, toxicity, mitochondrial stress, exercise, and cold exposure (77). Starvation-induced ketogenesis, fatty acid oxidation and gluconeogenesis, and cold exposure–induced adaptive thermogenesis are largely compromised in *Fgf21*-deficient mice (77). Pharmacological administration of FGF21 at supraphysiological doses decreases body weight and fat mass and alleviates insulin resistance, hyperglycemia, and dyslipidemia in both monkeys and rodents with obesity and diabetes (78, 79). Furthermore, treatment with FGF21 or its analogs ameliorates hepatic steatosis, NASH, vascular inflammation, atherosclerosis, and diabetic cardiomyopathy in mice (80). Unlike FGF19, pharmacological administration of FGF21 does not induce mitogenesis or carcinogenesis in animals. FGF21 transgenic mice are resistant to chemically induced tumorigenesis in liver (81).

FGF21 in Interorgan Cross Talk

FGF21 exerts its pleiotropic beneficial effects on adiposity, insulin sensitivity, glucose and lipid metabolism, and vascular homeostasis through its either direct or indirect actions in several major organs, especially adipose tissue, brain, and liver (82) (**Figure 1**).

FGF21 actions in adipose tissue. Both WAT and brown adipose tissue (BAT) express high levels of β-Klotho and FGFR1c and are therefore the direct targets of FGF21 (14). The pharmacological effects of FGF21 administration in decreasing hyperglycemia and insulin resistance are abrogated in lipodystrophic mice, whereas transplantation of WAT from wild-type mice into lipodystrophic mice largely restores the therapeutic benefits of FGF21 (83, 84). Likewise, the effects of FGF21 on the reduction of body weight, plasma glucose, insulin, and triglycerides (TGs) and on increases in insulin sensitivity and adiponectin are largely compromised in mice with adipocyte-selective ablation of *β-Klotho* or *Fgfr1* (85, 86). Notably, although the weight loss effects of both FGF19 and FGF21 are compromised in these knockout mice, the therapeutic benefits of FGF19 remain intact (86), suggesting the differential role of adipose tissues in mediating metabolic actions of FGF19 and FGF21. However, since the aP2-Cre transgene used in these studies is also expressed in the central nervous system, these findings cannot exclude the central actions of FGF21 and FGF19 in mediating its metabolic effects in peripheral organs.

In adipose tissues, FGF21 stimulates glucose uptake via insulin-independent glucose transporter 1 (Glut1), modulates lipogenesis and lipolysis, and promotes browning and thermogenesis (67, 72, 79). FGF21 also facilitates lipoprotein metabolism in both WAT and BAT, thereby lowering plasma TGs (87). Furthermore, treatment with FGF21 or its analogs increases both expression and secretion of adiponectin, an adipokine with insulin-sensitizing, anti-inflammatory, antiatherosclerotic, and hepatoprotective properties (83, 88, 89). A robust elevation in plasma adiponectin has also been consistently observed in monkeys (90, 91) and humans after treatment with FGF21 analogs in several clinical trials (91–96). The pharmacological benefits of FGF21 on alleviation of hyperglycemia, dyslipidemia, insulin resistance, NASH, atherosclerosis, and diabetic cardiomyopathy are abolished in *Adiponectin*-null mice (88, 89, 97–99), suggesting an obligatory role of adiponectin as a downstream effector in mediating the pleiotropic effects of FGF21 in multiple organs where β-Klotho is not expressed. In contrast, another mouse study showed that adiponectin is dispensable for the chronic effects of FGF21 on energy expenditure and insulin sensitivity (100).

Chronic FGF21 administration enhances adaptive thermogenesis in both subcutaneous WAT and interscapular BAT, thereby increasing whole-body energy expenditure (79). However, *Fgf21*-deficient mice only display impairments in cold exposure–induced beiging of WAT without obvious changes in the activation of classical BAT (101). FGF21 mediates cold-induced biogenesis of beige adipocytes in subcutaneous WAT by induction of PGC-1α and the C-C motif chemokine ligand 11 (CCL11), the latter of which in turn initiates type 2 immune responses (101, 102). By contrast, FGF21-induced thermogenic activation of BAT is attributed to its central actions for the activation of the sympathetic nervous system (103). Despite the potent effect of FGF21 in the induction of uncoupling protein 1 (UCP1; a hallmark of brown/beige adipocytes), it remains debatable whether increased UCP1 contributes to the metabolic benefits of FGF21. While one study supported a critical role of UCP1 in postprandial glucose disposal by FGF21, another two studies found no obvious difference in FGF21-mediated decreases in body weight, hyperglycemia, and dyslipidemia between *Ucp1*-deficient mice and their wild-type littermates (104, 105). These discrepant findings can be possibly explained by compensatory upregulations of several UCP1-independent thermogenic pathways, including creatine substrate and Ca^{2+} cycling (106). Indeed,

the FGF21 agonistic antibody has been shown to stimulate thermogenesis in BAT independent of UCP1 (107).

FGF21 actions on the central nervous system. A growing body of evidence supports the idea that the brain is an important target organ conferring both physiological and pharmacological effects of FGF21 (14). While all four FGFRs are broadly expressed throughout the brain, expression of β-Klotho is restricted to the suprachiasmatic nucleus/paraventricular nucleus in the hypothalamus and dorsal vagal complex of the hindbrain, which regulates circadian rhythm, ovulation, nutrient preference, and starvation-associated metabolic adaptation (108–110). FGF21 can cross the blood-brain barrier (111) and is present in human cerebrospinal fluid (112) and in the hypothalamus of fasted mice (108), where it induces ERK1/2 phosphorylation (113). Intracerebroventricular injection of FGF21 increases energy expenditure and insulin sensitivity in dietary obese rats (114), and central administration of FGF21 is sufficient to promote hepatic gluconeogenesis in lean mice (108). β-Klotho expression in the central nervous system is required for several chronic actions of FGF21, including its effects on ketogenesis, growth, circadian behavior, and female reproduction (109, 115). Likewise, the beneficial metabolic effects of FGF21 or its agonistic antibody on the stimulation of energy expenditure, reduction of fat mass, and insulin resistance are abolished in obese mice lacking hypothalamic *β-Klotho* (103). FGF21 acts centrally to stimulate sympathetic nerve outflow to BAT, where it induces fatty acid oxidation and thermogenesis. Furthermore, FGF21-induced sympathetic outflow into WAT is also implicated in the browning of WAT and the lipolysis required for hepatic ketogenesis (103, 109).

FGF21 actions on liver. The liver is a major organ for both the production and actions of FGF21 (14). Hepatocyte-secreted FGF21 plays an indispensable role in mediating metabolic adaptation of the liver to fasting/starvation, including ketogenesis, gluconeogenesis, fatty acid oxidation, and growth hormone (GH) resistance (116). The pharmacological benefits of FGF21 on the amelioration of obesity-induced glucose dysregulation, dyslipidemia, NASH, and other comorbidities are attributed in part to its actions in hepatocytes, including alleviation of hepatic insulin resistance by suppression of mTORC1 (117), reduction of liver fat accumulation by promoting PGC-1α-induced fatty acid oxidation (118), inhibition of lipogenesis via repression of sterol regulatory element binding protein 1c (SREBPB1c) (119), and decrease of hepatic uptake of TG-enriched very-low-density lipoprotein (VLDL) via downregulation of VLDL receptor expression (120). Furthermore, therapeutic administration of FGF21 prevents hepatotoxic drug–induced oxidative and endoplasmic reticulum stresses via upregulation of antioxidant genes and protects against endotoxin-induced liver inflammation and injury as well as dimethylnitrosamine-induced liver fibrosis by blocking nuclear factor κB (NF-κB) in mice (121, 122). However, since FGFR4 is the predominant isoform of FGFRs in hepatocytes, whereas FGFR1c is hardly detectable, whether FGF21 exerts its direct effects in hepatocytes remains a matter of debate (72). Unlike FGF19, FGF21 cannot activate the FGFR4/β-Klotho receptor complex (72). Instead, while administration of FGF21 induces hepatic expression of PGC-1α and gluconeogenesis in mice, it has no such effects in either isolated mouse liver or primary cultures of rat or mouse hepatocytes (118, 121). Hepatocyte-selective ablation of *β-Klotho* does not compromise the effects of FGF21 in decreasing liver fat contents, blood glucose, insulin, and body weight (42). Instead, transgenic expression of *Fgf21* has been shown to antagonize the effect of FGF15/19 on hepatic FGFR4/β-Klotho complex, thereby increasing the BA pool by induction of CYP7A1 (123). The therapeutic benefits of FGF21 on alleviating obesity-induced NAFLD and insulin resistance are largely diminished in *Adiponectin*-deficient mice (88, 89). Given that hepatocytes are the well-known direct target of adiponectin and have an abundant expression of adiponectin receptors (adipoR1, adipoR2, and

T-cadherin) (124, 125), it is highly possible that the hepatic effects of FGF21 administration are mediated in part by induction of adiponectin in adipose tissue or through a brain-liver axis (42, 80).

FGF21 actions in pancreatic β cells. Both acute and chronic treatments with FGF21 decrease plasma levels of insulin (88), possibly secondary to increased systemic insulin sensitivity. Conflicting data have been reported with respect to the roles of FGF21 in regulating insulin secretion in pancreatic β cells. Wente et al. (68) found that islets and INS-1E β cells treated with FGF21 are partially protected from glucolipotoxicity and cytokine-induced apoptosis. Treatment with FGF21 increases insulin content and glucose-stimulated insulin secretion (GSIS) in islets isolated from diabetic rats but not in islets from healthy lean rats (68). In contrast, Singhal et al. (126) demonstrated that *Fgf21* knockout mice develop significant islet hyperplasia and periductal lymphocytic inflammation when fed with an obesogenic diet, without obvious changes in GSIS and plasma insulin levels. This study also found that acinar cells of the exocrine pancreas are the predominant action site of FGF21, whereas the β cell itself is not an FGF21 target, as evidenced by co-staining analysis showing that FGF21-induced signaling (determined by ERK1/2 phosphorylation) occurred mainly in half of acinar cells as well as glucagon-synthesizing α cells and somatostatin-synthesizing δ cells but not in insulin-secreting β cells (126). Instead, we found that β-Klotho regulates GSIS via modulation of glycolysis, independent of FGF21 and FGF15/19 (127).

FGF21 Analogs/Mimetics in Preclinical and Clinical Development

Despite its multiple therapeutic benefits for metabolic diseases, native human FGF21 (hFGF21) is not druggable due to its poor pharmacokinetic profile, a short acting half-life (0.5–1.5 h), undesirable biopharmaceutical properties such as its propensity for aggregation in soluble formulations, and proteolytic instability (14, 78, 128–130). Therefore, various biopharmaceutical engineering approaches have been adopted to develop hFGF21 analogs and receptor agonists with improved biophysical properties and pharmacokinetic and pharmacodynamic profiles that are suitable for future clinical applications (14) (**Figure 2**).

Genetically engineered hFGF21 analogs. Efforts to optimize production and stability led to the development of several hFGF21 analogs using different genetic engineering approaches. LY2405319, developed by Eli Lilly and Company, is the first hFGF21 analog tested in humans. This hFGF21 analog is designed to reduce aggregation in solution by introduction of an additional disulfide bond through Leu118Cys and Ala134Cys mutations. LY2405319 exhibits substantial improvements in its biopharmaceutical properties, with biological activities that are identical to native hFGF21 (90, 131). Nevertheless, LY2405319 is still a short-acting hFGF21 analog owing to its low molecular weight and therefore requires once-daily administration (90, 92, 131). In a randomized, placebo-controlled, double-blind study, three ascending doses of LY2405319 (3, 10, or 20 mg) were administered by daily subcutaneous injection for 28 days in patients with obesity and T2D (92). Disappointingly, in contrast to the robust glucose-lowering activity of LY2405319 in mice and monkeys (90, 131), the much-anticipated primary outcome of glycemic control did not reach statistical significance in this clinical study. Instead, the most pronounced effect of LY2405319 treatment was alleviation of dyslipidemia, including decreases in LDL cholesterol and TGs and increases in high-density lipoprotein (HDL) cholesterol, which could be observed as early as 2 days after the first injection. Notably, LY2405319 treatment led to an obvious reduction in fasting insulin levels and a marked elevation in plasma levels of adiponectin and the proportion of its

high-molecular-weight complex, indicative of increased insulin sensitivity. A modest but statistically significant reduction in body weight relative to baseline was observed only in the high-dose groups at the completion of the 28-day treatment regimen.

PF-05231023 is a long-acting hFGF21 analog made by conjugating two molecules of modified hFGF21 (ΔHis1, Ala129Cys) to the fragment antigen-binding region (Fab) of a scaffold antibody (CVX-2000) via the mutated Cys129 residue of hFGF21, resulting in an approximately 188-kDa bivalent molecule (130). The half-life of PF-05231023 is 70-fold longer than that of the native hFGF21, and the therapeutic activities are fully preserved in both mice and monkeys (130, 132, 133). In a Phase Ib clinical trial, intravenous injection of PF-05231023 twice a week improved circulating lipid profiles, increased plasma adiponectin levels, and decreased body weight, but it had no effect on glycemic control or plasma insulin concentrations in individuals with overweight/obesity and T2D (91). However, once weekly intravenous injection with PF-05231023 did not induce significant body weight loss in another clinical study in individuals with obesity, with or without T2D (94).

Efruxifermin [formerly known as AKR-001, Fc-FGF21(RGE), AMG 876] is another long-acting human IgG1 fragment crystallizable region (Fc)-FGF21 fusion protein with a C-terminal region that has been modified with two amino acid substitutions (P171G and A180E) (134). These targeted mutations substantially reduce proteolytic degradation and increase the binding affinity to β-Klotho, thereby enhancing FGFR-mediated signaling activity, functional potency, and duration of action of efruxifermin, with a half-life of 3–3.5 days in humans (96, 134, 135). A Phase I multiple ascending study in patients with T2D showed the significant effects of this hFGF21 analog in improvements of lipoprotein profiles and markers of insulin sensitivity (96). In a recent randomized, placebo-controlled Phase IIa trial in biopsy-confirmed NASH patients with F1–F3 fibrosis (NCT03976401), weekly subcutaneous administration of efruxifermin for 16 weeks significantly reduced liver fat by 63–72% and improved glycemic control and lipid profile (with reductions in TGs of 39% to 48%, compared to a 6% increase for placebo) (136). Likewise, once-monthly injection of LLF580 (now called BOS-580), another Fc-hFGF21 fusion protein with an additional disulfide bond at an unspecified location, led to an over 50% reduction in liver fat content and serum TG and marked elevations of HDL and adiponectin but had no effect on body weight and hyperglycemia (137, 138). However, the dose of LLF580 (300 mg) is very high, and further studies are needed to evaluate whether the superior duration of action of LLF580 can also be achieved in patients at a substantially lower, and thus more cost-effective, dose.

Two PEGylated forms of hFGF21, PEG30-Q108 and pegbelfermin (BMS-986036), were developed by conjugation of hFGF21 to a 30-kDa polyethylene glycol (PEG) in order to extend the half-life. Administration of PEG30-Q108 in obese mice (four times over 2 weeks) effectively normalized insulin-stimulated whole-body glucose utilization (139). Pegbelfermin, designed for once-weekly injection, has superior pharmacokinetic and safety profiles in humans (93, 95). In a clinical study in patients with obesity and T2D, treatment with ascending doses of pegbelfermin for 12 weeks had no significant effects on hemoglobin A1c (HbA1c) but increased adiponectin, alleviated dyslipidemia, and decreased plasma levels of PRO-C3, a biomarker of hepatic fibrosis that reflects the severity of and fibrosis stage in NASH (95). Therefore, a multicenter, randomized, double-blind, and placebo-controlled Phase IIa study was conducted in biopsy-confirmed NASH patients with stage 1–3 fibrosis (93). A total of 75 eligible patients were randomized to three groups: placebo or subcutaneous administration of pegbelfermin either 10 mg daily or 20 mg weekly for 16 weeks. Both pegbelfermin-treated groups exhibited significant reductions in hepatic fat fraction and liver stiffness, as well as marked decreases in PRO-C3 and liver injury (ALT and AST), and obvious elevation of adiponectin compared with placebo controls (93). Two parallel Phase IIb studies are currently underway to evaluate the safety and efficacy of weekly

administration of pegbelfermin in patients with NASH with stage 3 fibrosis or compensated cirrhosis (NCT03486899 and NCT03486912) (140).

There are several other forms of FGF21 analogs with promising pharmacological properties in preclinical studies. $FGF1^{\Delta HBS}$-$FGF21^{C\text{-}tail}$, an engineered chimera made by substituting the thermally labile and low-receptor-affinity core of FGF21 with an HS binding–deficient endocrinized core of FGF1 ($FGF1^{\Delta HBS}$), shows a fivefold increase in half-life compared to that of native FGF21 and is much more effective in correcting hyperglycemia and ameliorating insulin resistance in diabetic mice and monkeys (129). GLP-1-Fc-FGF21 D1, in which both GLP-1 and a hFGF21 mutant with enhanced binding property to β-Klotho are conjugated to IgG4 Fc, is substantially more potent than FGF21 or GLP-1 alone in reducing body weight and hyperglycemia and in alleviating NASH in mice (141), supporting the synergism between these two hormones in combating obesity-related metabolic diseases.

FGF21 mimetics. The identification of FGFR1 and β-Klotho as key components of the FGF21 receptor complex has led to the development of several FGF21 receptor agonists (FGF21RAs). C3201, the first FGF21RA engineered by fusion of an 18-kDa bispecific avimer polypeptide that binds both FGFR1 and β-Klotho with high affinity and specificity, is more potent than FGF21 in improving glucose and lipid profiles in both rodents and monkeys with obesity (142). A number of monoclonal antibodies (mAbs) that bind and activate either FGFR1 or the FGFR1/β-Klotho complex have also been shown to mimic the metabolic benefits of FGF21 with excellent pharmacokinetic profiles in both rodents and monkeys, including R1MAb1 (anti-FGFR1 mAb) (143), mimAb1, and 39F7 mAb (anti-FGFR1/β-Klotho mAb), which are generated by immunization of human FGFR1/KLB complex in XenoMouse (144, 145). bFKB1 (also known as BFKB8488A) is a bispecific agonistic mAb engineered by assembling one arm binding to β-Klotho and the other binding to FGFR1c (107, 146). In a randomized, placebo-controlled, single ascending-dose study in overweight/obese human participants, subcutaneous injection with BFKB8488A caused transient body weight reduction and sustained improvement in cardiometabolic parameters (decreased TG and LDL cholesterol and increased adiponectin) (147). Administration of BFKB8488A every other week significantly reduced liver fat, serum TGs, and PRO-C3 levels, accompanied by increased circulating adiponectin and HDL cholesterol (80). Likewise, MK-3655 (formerly NGM313), another bispecific antibody targeting β-Klotho and FGFR1c, has also been shown to improve glycemic control; reduce liver fat content, serum TG, and LDL cholesterol; and increase HDL cholesterol in obese, nondiabetic subjects after 36 days of treatment (80). Additionally, a biparatopic agonistic antibody for the FGFR1/β-Klotho complex, which was constructed by grafting two heavy chain variable domains (VHs) specific to different epitopes of β-Klotho onto the VH and light chain variable domain (VL) positions of an IgG scaffold, has also been shown to mimic FGF21 activity in vitro, whereas its therapeutic potential has not been evaluated in animals (148).

FGF21 analogs and mimetics being tested in clinical trials were generally well tolerated. However, pegbelfermin treatment reduced BAs in patients with NAFLD, which has previously been shown to have toxic effects on the liver (149). Additional studies to understand how pegbelfermin regulates BAs may provide additional information about its potential use as a treatment for NAFLD. PF-05231023 treatment caused elevations in blood pressure and heart rate as well as modest rises in plasma markers of bone formation and reabsorption (91), thus raising the safety concern that FGF21 induces bone loss, which has been reported in mice (150). Another adverse effect was the generation of anti-FGF21 antibodies, which was detected in more than 50% of pegbelfermin-treated patients as well as those receiving LY2405319 (92, 95).

Distinct and Overlapping Effects of FGF15/19 and FGF21

FGF21 and FGF15/19 exert many similar metabolic functions in rodents and humans (**Figure 1**). Mice with transgenic expression or therapeutic administration of FGF21 and FGF19 show overlapping metabolic changes such as increases in brown adipocyte activity and energy expenditure and decreases in body weight, fat mass, blood glucose, and fatty liver (34–36, 79, 103). In humans, treatment with both FGF19 and FGF21 analogs led to a robust reduction in liver fat content and alleviation of steatohepatitis and liver fibrosis (62–65, 93, 95, 136, 137). However, FGF21 and FGF15/19 are differentially regulated under various pathophysiological conditions and play distinct or even opposing roles with respect to mitogenesis and BA metabolism. In contrast to serum FGF19, circulating FGF21 levels are increased in patients with obesity or NAFLD, possibly due to compensatory responses or FGF21 resistance (151). Bariatric surgery leads to an increase in serum FGF19 but a decrease in serum FGF21 in obese individuals (152, 153). Furthermore, serum FGF19 and FGF21 display different circadian rhythms during the 24-h cycle (154).

While FGF15/19 is mitogenic and promotes hepatocyte proliferation (74), FGF21 transgenic mice are refractory to diethylnitrosamine-induced HCC (81). Vice versa, *Fgf21* knockout mice are more prone to developing obesogenic diet–induced HCC (155). FGF19 potently decreases BA biosynthesis by suppression of hepatic CYP7A1 (156), but FGF21 has little or even the opposite effect (157). In contrast to FGF21 and its analogs that robustly improve lipid profiles, FGF19 and its analogs increase cholesterol and TG, possibly secondary to the inhibition of BA biosynthesis. Additionally, FGF19 has been shown to decrease hepatic gluconeogenesis and induce glycogen synthesis (32, 33), whereas FGF21 appears to induce hepatic gluconeogenesis through its central actions (108). These differential effects of FGF19 and FGF21 are attributed to their distinct binding affinity to FGFRs (FGFR4 ≥ FGFR1c ≥ FGFR2c ≥ FGFR3c for FGF19, versus FGFR1 ≥ FGFR3c ≥ FGFR2c ≥ FGFR4 for FGF21). While FGF19-specific actions in promoting hepatocyte proliferation and suppressing BA synthesis are dependent on the FGFR4/β-Klotho receptor complex in liver, the overlapping metabolic benefits are mediated by the FGFR1/β-Klotho complex in brain and adipose tissues (154). Although both FGF19 and FGF21 act centrally, FGF19 crosses the blood-brain barrier less efficiently than does FGF21 (151). Further studies are needed to determine whether such a difference in brain permeability contributes to the differential physiologic or pharmacologic effects of FGF19 and FGF21.

FGF1 AND FGF4: NEW WEAPONS AGAINST OBESITY AND DIABETES?

Antidiabetic Effects of FGF1

FGF1 is a well-established autocrine/paracrine regulator whose binding to heparan sulfate proteoglycans effectively precludes its secretion into the bloodstream (6). Although FGF1 is considered to be a mitogenic factor critically involved in embryonic development, wound healing, neurogenesis, and angiogenesis, *Fgf1* knockout mice display no obvious change in any of these processes (158) but develop severe hyperglycemia and insulin resistance when challenged with a high-fat diet (HFD) (159). FGF1 expression in adipose tissue is controlled by PPARγ and is robustly induced by feeding and HFD challenge. Such a PPARγ-FGF1 axis is crucial for maintaining adipose homeostasis and systemic insulin sensitivity (159, 160). Remarkably, parenteral delivery of a single dose of recombinant FGF1 (rFGF1) protein can normalize blood glucose levels without inducing hypoglycemia in *ob/ob*, *db/db*, and dietary obese mice (16). Furthermore, chronic treatment with rFGF1 protein causes sustained glucose lowering by promoting insulin-dependent glucose uptake in skeletal muscle and suppressing hepatic glucose production (HGP), thereby achieving whole-body insulin sensitization (16). The glucose-lowering and insulin-sensitizing effects of rFGF1

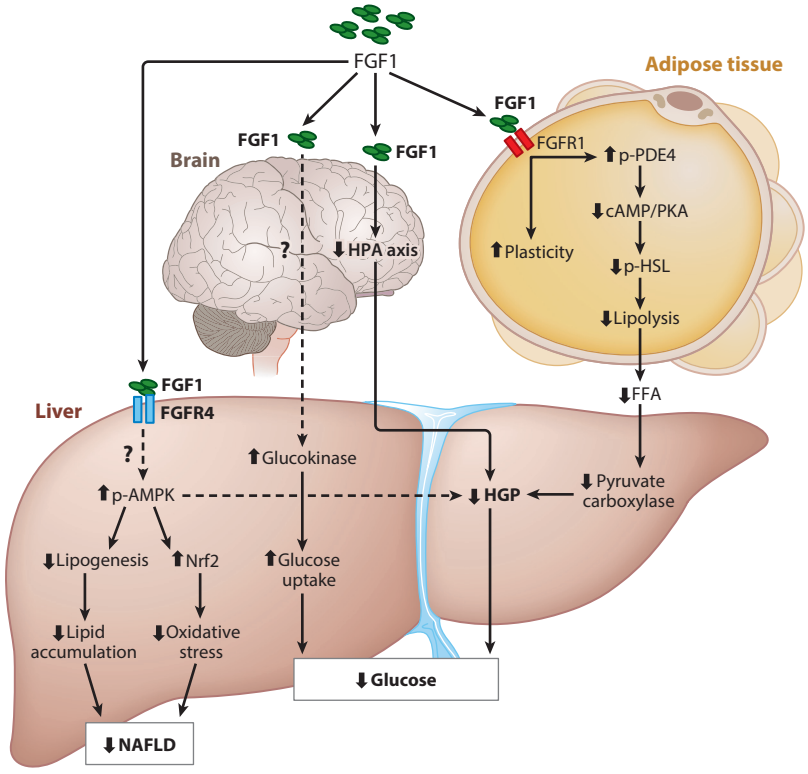

Figure 3

FGF1 exerts its metabolic effects through both its central and peripheral actions. FGF1 acts directly on adipose tissue via FGFR1, where it increases adipose plasticity and suppresses lipolysis via activation of PDE4 and subsequent inhibition of the cAMP-PKA-HSL axis, leading to a reduced supply of FFA and pyruvate carboxylase activity and, consequently, decreased hepatic gluconeogenesis. FGF1 also lowers glucose levels through its central actions to increase hepatic glucose uptake via induction of hepatic glucokinase via an unknown brain-liver axis and to reduce hepatic gluconeogenesis by limiting the activity of the HPA axis. Additionally, FGF1 alleviates obesity-induced fatty liver by activation of AMPK in the liver. Abbreviations: AMPK, AMP-activated protein kinase; cAMP, cyclic adenosine monophosphate; FFA, free fatty acid; FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; HGP, hepatic glucose production; HPA, hypothalamic-pituitary-adrenal; HSL, hormone-sensitive lipase; NAFLD, nonalcoholic fatty liver disease; Nrf2, nuclear factor erythroid 2–related factor 2; PDE4, phosphodiesterase 4; PKA, protein kinase A.

were abolished in mice with aP2-Cre-driven ablation of *Fgfr1*, suggesting that the antidiabetic effect of FGF1 is mediated in part by FGFR1 in adipose tissues (16). Mechanistically, FGF1 inhibits lipolysis in adipose tissue via activation of phosphodiesterase 4D and subsequent inhibition of the cAMP-PKA axis, thereby leading to acute suppression of HGP (17) (**Figure 3**). Systemic administration of a nonmitogenic FGF1 variant has been shown to alleviate obesity-induced NAFLD by activation of AMPK in liver (161).

In addition to its peripheral effects, a growing body of evidence suggests that the antidiabetic activity of FGF1 is also attributed to its central actions. FGF1 can cross the blood-brain barrier (162) and has been linked to the central regulation of feeding suppression (163). A single intracerebroventricular injection of rFGF1 protein at a dose one-tenth of that for peripheral administration leads to sustained remission of hyperglycemia for weeks in *ob/ob* and *db/db* mice as well as in leptin receptor–deficient Zucker diabetic fatty rats (164). The central effect of FGF1 in lowering

hyperglycemia is attributed to its ability to induce hepatic glucokinase, thereby increasing hepatic glucose uptake independent of insulin (165). Furthermore, intracerebroventricular injection of FGF1 and FGF19 has been shown to reverse diabetes in streptozotocin-induced type 1 diabetic rats by suppression of the hypothalamic-pituitary-adrenal axis, leading to decreased HGP, hepatic acetyl CoA levels, and lipolysis (166). However, the precise types of neurons and specific brain regions conferring the central actions of FGF1 to counteract hyperglycemia remain elusive.

Despite its potent glucose-lowering and insulin-sensitizing effects, the tumorigenic risk of chronic FGF1 administration dampens the enthusiasm to develop FGF1-based pharmacotherapy for diabetes. Nevertheless, the mitogenic and antidiabetic activities of FGF1 appear to be separable: While FGF1 induces cell proliferation mainly through FGFR3 and FGFR4, its metabolic activity is mediated predominantly by FGFR1 (8, 16, 143). A number of engineered FGF1 variants have been developed to diminish its mitogenic property while preserving its metabolic activity by mutations to abolish its heparan sulfate–assisted FGFR dimerization and activation [$FGF1^{\Delta HBS}$ (167)] or by deletion of 24 amino acids at its N-terminal domain [$FGF1^{\Delta NT}$ (16)] (**Figure 2**). An integrin-binding defective FGF1 mutant (Arg-50 to Glu, $FGF1^{R50E}$) acts in a dominant-negative manner to suppress tumorigenesis (168). However, whether this FGF1 variant remains metabolically active has not been tested.

Metabolic Functions of FGF4

FGF4 is another autocrine/paracrine factor critical for embryonic development, including implantation, morphogenesis, and organogenesis. In adults, it is expressed at a low level in the duodenum, ileum, and colon, where it maintains intestinal stem cells (6). FGF4 shows the highest binding preference to FGFR1c, followed by FGFR2c, FGFR3c, and FGFR4 (6). Notably, a recent study identified FGF4 as a potent antihyperglycemic factor that does not affect food intake (18). Acute administration of FGF4 to *db/db* mice improves insulin resistance and suppresses adipose macrophage infiltration and inflammation. FGF4 exerts its direct action on macrophages, where it blocks the inflammatory responses in liver, muscle, and adipose tissue, and triggers AMPK activation to subsequently upregulate GLUT4 expression and translocation to the cell membrane in skeletal muscle (18).

In addition to its glucose-lowering effect, FGF4 is protective against dietary obesity–induced NAFLD and other stress-induced liver damage (19). Expression of hepatic FGF4 is inversely associated with pathological grades of NAFLD in both human patients and mouse models (19). Hepatic steatosis, inflammation, markers of liver injury, and fibrosis are aggravated by ablation of hepatic *Fgf4* but are diminished by pharmacological administration of recombinant FGF4 (19). However, the tumorigenic risk of long-term FGF4 administration remains a major challenge.

CONCLUDING REMARKS AND FUTURE PERSPECTIVES

It has become evident that four members of the FGF family (FGF1, FGF4, FGF19, and FGF21) are important regulators of energy homeostasis, glucose, and lipid metabolism, with potent pharmacological effects on the alleviation of hyperglycemia, dyslipidemia, and other metabolic comorbidities. A growing number of long-acting hFGF21 analogs, antibody-based FGF21RAs, and nonmitogenic hFGF19 variants have been developed for clinical evaluation. However, in contrast to their robust glucose-lowering activities in rodents, most clinical trials show a rather modest or no effect on glycemic control in T2D patients, highlighting the interspecies differences in FGF19/FGF21 regulation of glucose metabolism between rodents and humans. Such differences may be due to the distinct expression patterns of FGFRs and β-Klotho, the latter of which determines the target specificity of both FGF19 and FGF21 (72). In particular, while β-Klotho is

abundantly expressed in several discrete regions of the brain in mice, it is hardly detectable in human brain samples (169). Given that hypothalamic β-Klotho has been linked to the glucose-lowering effects of both FGF19 and FGF21, further studies are required to investigate whether the lack of central actions explains the inability of FGF19 and FGF21 to decrease hyperglycemia in humans. Additionally, it is also plausible that the loss of antidiabetic and antiobesity effects of FGF21 and FGF19 is attributable to altered β-Klotho expression in different tissues of obese subjects with T2D (62, 63, 92), which may alter the selectivity of FGF21 and FGF19 target tissues.

Despite the disappointing outcomes in glycemic control and weight loss, the potent therapeutic benefits of hFGF21 analogs and mimetics on the amelioration of dyslipidemia and NAFLD have been reproducibly observed in different clinical trials. In light of the fact that there are currently no approved effective drugs available for NAFLD, which often co-occurs with T2D in obese individuals, combination of hFGF21 or nonmitogenic hFGF19 analogs with the existing antidiabetic agents might represent a promising pharmacotherapeutic strategy for the treatment of a cluster of obesity-related metabolic comorbidities. Future clinical investigations are warranted to evaluate the therapeutic efficacy of this combined treatment. Furthermore, given the remarkable effects of hFGF21analogs/mimetics on the improvement of lipid profiles and induction of adiponectin, whether these favorable changes can lead to reduced cardiovascular events is worthy of future clinical trials with long-term treatments.

Although the sustained effects of FGF1 and FGF4 on diabetes remission have been replicated in a number of studies in rodents, their safety and therapeutic efficacy remain to be evaluated in large animals and humans. The concerns regarding tumorigenesis limit further development of these two mitogenic FGFs into metabolic drugs, which often require lifelong medication. Further in-depth studies to precisely define the target tissues, subtype of FGFRs, and intracellular signaling pathways conferring the metabolic benefits of these FGFs may help to develop FGF-based pharmacotherapies with improved specificity, safety, and efficacy for the management of obesity-related cardiometabolic complications.

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The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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