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REVIEW

The FGF metabolic axis

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Abstract **Members of the fibroblast growth factor (FGF) family play pleiotropic roles in cellular and metabolic homeostasis. During evolution, the ancestor FGF expands into multiple members by acquiring divergent structural elements that enable functional divergence and specification. Heparan sulfate-binding FGFs, which play critical roles in embryonic development and adult tissue remodeling homeostasis, adapt to an autocrine/paracrine mode of action to promote cell proliferation and population growth. By contrast, FGF19, 21, and 23 coevolve through losing binding affinity for extracellular matrix heparan sulfate while acquiring affinity for transmembrane α-Klotho (KL) or β-KL as a coreceptor, thereby adapting to an endocrine mode of action to drive interorgan crosstalk that regulates a broad spectrum of metabolic homeostasis. FGF19 metabolic axis from the ileum to liver negatively controls diurnal bile acid biosynthesis. FGF21 metabolic axes play multifaceted roles in controlling the homeostasis of lipid, glucose, and energy metabolism. FGF23 axes from the bone to kidney and parathyroid regulate metabolic homeostasis of phosphate, calcium, vitamin D, and parathyroid hormone that are important for bone health and systemic mineral balance. The significant divergence in structural elements and multiple functional specifications of FGF19, 21, and 23 in cellular and organismal metabolism instead of cell proliferation and growth sufficiently necessitate a new unified and specific term for these three endocrine FGFs. Thus, the term "FGF Metabolic Axis," which distinguishes the unique pathways and functions of endocrine FGFs from other autocrine/paracrine mitogenic FGFs, is coined.**

Keywords FGF19; FGF21; FGF23; FGFR; metabolism; endocrine; Klotho

Introduction

Fibroblast growth factors (FGFs) are pleiotropic signal molecules for all types of cell and tissue systems in metazoans [1–3]. FGFs share a conserved core structure of β-trefoil fold consisting of 12-stranded β-sheets arranged in three similar lobes around a central axis, of which six strands form an antiparallel β-barrel [4,5]. Except for the four FGF-homologous intracrine factors that are functionally reminiscent of the ancestor FGF, the FGFs can be classified into mitogenic and metabolic FGFs, which overtly regulate cellular proliferation and substrate/energy metabolism, respectively, on the basis of their distinct functions and endpoint biological effects [6,7]. Both FGF classes signal through the same types of transmembrane receptor tyrosine kinases, that is, the FGF receptors (FGFRs) 1 to 4 with multiple splicing variants [8]. However, in physiology, these two types of regulatory activities driven by the two FGF classes appear to be spatially and temporally segregated. At a physiological level, mitogenic FGFs appear to be incapable of traveling far to other tissues, including metabolic tissues, to promote cellular metabolism because of local trapping after secretion that is mediated by high affinity binding to the extracellular matrix heparan sulfate (HS). On the other hand, metabolic FGFs circulate but are inactive for nonmetabolic tissues or cells that often undergo active tissue remodeling via the renewed cycles of cell proliferation and population growth because of the lack of critical transmembrane accessory coreceptors. This divergence necessitates a distinction of the metabolic axis that is a term as we call hereafter, which the metabolic FGFs drive, from the mitogenic axis that the mitogenic FGFs drive. The metabolic axis still shares the major aspects of structural coevolution [9,10] while gaining unique structural and functional divergence with the mitogenic axis within each subfamily (Table 1), as our recent structural studies have revealed [2,5,11]. From the evolutionary standpoint, although the two axes largely parallel and drive differential effects via divergent intracellular mechanisms, they aim for a common goal of promoting the survival and homeostasis

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of each cell/tissue system and the organism as a whole (Fig. 1), as we have summarized in a previous review [7].

The mitogenic FGF axis

The classic FGF family consists of 17 structurally related polypeptides, which are secreted and act as extracellular signaling molecules, in humans [1,3,7,12]. For the most part of FGF history beginning in the late 1970s [13,14], FGFs are known as short-range mitogens in a wide variety of cell types in the developing ectoderm, mesoderm, and endoderm. FGFs elicit a chemoattractant activity to promote cell migration and tissue remodeling and antiapoptotic effects to promote cell survival. FGF1 and 2 are the prototypes that are initially isolated based on potent mitogenic activity toward fibroblasts or fibroblast-like cells [13,14]. It was found early that the mitogenic FGFs bind tightly to the local extracellular matrix HS chains, do not circulate, and accordingly act in a paracrine or autocrine mode. This heparin/HS binding property renders their potent activity temporarily contained but timely released locally upon injury or demand of tissue remodeling [15]. These mitogenic FGFs include 14 members (Table 1), which strongly promote genomic DNA synthesis and subsequent cell division and population growth [12,16,17]. Therefore, mitogenic FGFs play critical roles in the development of multiple tissues/organs [18–20]. They initiate the mitogenic axis by binding to the Ig-like ectodomains of their cognate transmembrane FGFRs in complex with HS motifs on diverse target cells and tissues in the first step [1,21,22]. The subsequent activation of the intracellular kinase domains of FGFRs results in downstream signal relay primarily through the PI3K-AKT, RAS-MAPK, and PLCγ-PKC pathways [23–25], as we have summarized previously [3]. These HS and FGFR dependent activities driven by the mitogenic FGF axes contribute not only to the regulation of virtually all aspects of development and organogenesis but also to many natural processes of active post-developmental tissue repair, remodeling, and homeostasis [26].

Among mitogenic FGFs, FGF7, which is also known as keratinocyte growth factor (KGF), has the highest specificity for receptor isotypes [12,22,27]. FGF7 only activates the IIIb-type isoform of FGFR2. Given that FGF7 is produced in mesenchyme cells, while FGFR2IIIb resides on the epithelial or keratinocyte cells, FGF7 forms a unidirectional paracrine communication axis with FGFR2 from mesenchyme to epithelium compartment within a tissue or organ. On the other hand, epithelial cells secrete specific FGFs (e.g., FGF1 or 9), which then acts on mesenchymal cells that harbor FGFR1IIIc within two compartmental tissues. Therefore, these FGF1 and FGF7 driven mutual cell communication axes are poised to drive tissue remodeling and maintain tissue homeostasis [28]. The prolonged or abnormal activation of the FGFR-HS binary complexes by mitogenic FGF axes contributes to an array of cell/tissue-specific developmental diseases and multiple cancer types [3,29] (see a brief summary in Table 1). The proliferation- and survival-promoting

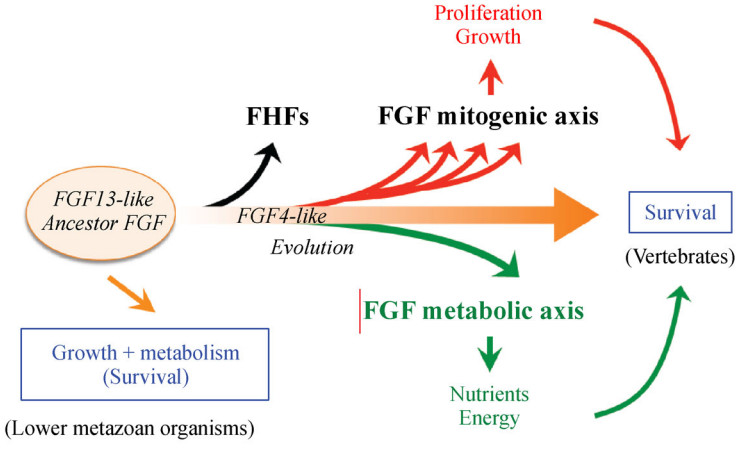

Fig. 1 Scheme of FGF metabolic axis evolution. The FGF family originates from a common FGF13-like ancestor molecule in early metazoans that bifurcates into the so-called intracrine FGF-homologous factor (FHF) subgroup (black arrow), including FGF11, 12, 13, and 14 (not shown), and FGF4-like molecule, which continues to bifurcate into two major functional subgroups with diverging structural and functional specifications. The so-called mitogenic FGF subgroups, including the FGF5, 8, 9, and 10 subfamilies (red arrows, Table 1), bind extracellular matrix heparan sulfate and drive autocrine/paracrine mitogenic signal axes to promote cell proliferation and population growth. By contrast, the endocrine FGF subgroup members (green arrow, Table 2), including FGF19, 21, and 23, drive metabolic signal axes that elicit broad-spectrum functions in regulating the metabolic homeostasis of bile acid, lipids, glucose, energy, and minerals without direct proliferation-promoting activity. However, both the FGF mitogenic and FGF metabolic axes are designed to promote cell and organismal survival in the vertebrates (orange arrows and blue-colored font).

activities of the diverse mitogenic FGF axes have been a major focus of utilities as regenerative and repair agents in a range of medical settings [30–34]. In the past, we demonstrated the benefits of the application of mitogenic FGFs to tissue damage complications of diabetes mellitus, including diabetic cardiomyopathy, nephropathy, and neuropathy [35–37], as well as to wound healing and spinal cord injury repair [38–40]. On the other hand, the mitogenic FGF mediated cell miscommunications have also been on the menu for developing inhibitors to be used in cancer therapy [29,41,42].

It should be pointed out that, although at a physiological level mitogenic FGFs are not evolutionarily designed to circulate and target distal tissues or organs for an endocrine effect, at pharmacological or supraphysiological levels, mitogenic FGFs exert certain regulatory activities beyond promoting cell proliferation and growth possibly due to their accumulation sufficiently to achieve an effect in distal metabolic tissues, where a cognate FGFR isotype is expressed. It was shown in the early 1990s that a bolus intravenous injection of FGF1 or 2 could target vascular endothelium to decrease arterial blood pressure [43]. FGF16 is expressed in classical brown fat depots during the later stages of embryonic development, and recombinant FGF16 is a mitogen for adipocytes [44]. Mice overexpressing FGF16 delivered by adeno-associated virus display dramatic weight loss and uncoupling protein-1 (UCP1) upregulation in inguinal white adipose tissue (WAT), which is a common site for emergent active brown adipose tissue (BAT). These effects are likely a combined result of reduced food and water intake and abnormal feces replete with lipid and bile acid due to the brain, liver, and intestinal actions of overexpressed FGF16 [45]. Mice deficient in FGF1 exhibit insignificant phenotypes under standard dietary conditions; however, under a chronic high-fat diet, these mice develop an aggressive diabetic phenotype coupled with aberrant adipose phenotypes, including multiple histopathologies in the adipose vasculature network, accentuated inflammatory response, aberrant adipocyte size distribution and expansion, and ectopic expression of pancreatic lipases [46]. In particular, we show by structure-based mutagenesis that FGF1 can be designed to have full metabolic activity of wild-type FGF1 but with reduced proliferative potential both *in vitro* and *in vivo* [47]. These studies underscore the important role of FGF1 in maintaining local adipose tissue homeostasis, which upon significant tissue perturbations impinges on the metabolic functions that subsequently affect the systemic metabolic state. Thus, the metabolic effects of several mitogenic FGF axes may be due to either a local function in maintaining cellular homeostasis that is closely associated with local metabolic state at a physiological concentration or an induced metabolic response to a supraphysiological concentration from circulation in the metabolic tissues or organs where FGFR resides. However, at pharmacological levels, few mitogenic FGFs may also be designed to elicit systemic metabolic effects.

The metabolic FGF axis

In contrast to mitogenic FGFs, the metabolic FGF subfamily contains only three members, namely, FGF19 (mouse FGF15), 21, and 23 [2,7,48–51]. However, the metabolic axes of these three FGFs regulate a wide range of metabolic pathways, resulting in tissue and organismal metabolic homeostasis of bile acids, lipid, glucose, energy, and minerals. Although the metabolic FGF axes do not overtly promote DNA synthesis, thereby leading to cell proliferation [12,52,53], both metabolic and mitogenic FGF axes appear to enhance cell survival and promote an optimal state of homeostasis in the target tissues and organisms [7].

Based on current knowledge, the metabolic FGFs appear to originate from a common FGF13-like ancestor molecule as mitogenic FGFs and then bifurcate in early evolution through an FGF4-like molecule from all other mitogenic members by acquiring unique structural and mechanistic properties [5,10,11,54], thereby leading to specific activities in modulating metabolic states in specific cell and tissue types [2]. Instead of acting locally, metabolic FGFs take a hormonal or endocrine route of action by traveling through circulation from the originating tissue to other peripheral tissues/organs. This endocrine action can be attributed to the loss of the structurally conserved HS-binding domain characteristic of the mitogenic FGFs [5]. Both the expression and target tissues of the metabolic FGFs are relatively limited to the metabolically active endocrine organs, such as liver, intestine, adipose tissue, pancreas, muscle, bone, kidney, heart, parathyroid, and specific neurons in specific regions of the central nervous system (CNS) [55,56]. In expression tissues, metabolic FGF genes are subject to direct transcriptional control by several major metabolite-responsive nuclear receptors, including farnesoid X receptor (FXR), peroxisome proliferator-activated receptor α (PPARA) and γ (PPARG), carbohydrate-response element-binding protein (ChREBP), sterol regulatory element-binding protein-1c (SREBP1c), retinoic acid-related orphan receptor α (RORA), liver X receptor β (LXRB), vitamin D receptor (VDR) [48–50,57–65], and stress-sensing transcription factors, such as ATF4 [66], depending on the location of specific nutrition/energy-sensing cells in specific tissues. In target tissues, the biological effects of the metabolic FGF axes are still mediated by FGFRs but in a different binary complex with a new transmembrane nonkinase accessory coreceptor, the α-Klotho (KL) or β-KL (KLB) [5,11,55,67] (Table 2), to which mitogenic FGFs do not bind.

Table 1 The mitogenic FGF axis

Subfamily	Ligand member	Physiological function (knockout phenotypes)	Known pathologies	Receptor specificity						
				1b	1c	2b	2c	3b	3c	4
FGF1	FGF1	Adipose tissue homeostasis	Amplification — ovarian cancer	✓	✓	✓	✓	✓	✓	✓
	FGF2	Wound healing and angiogenesis	Overexpression — several cancer types	✓	✓		✓		✓	✓
FGF4	FGF4	Limb bud and heart development	Amplification — breast cancer		✓		✓		✓	✓
	FGF5	Hair follicle growth and development	Overexpression — glioblastoma		✓		✓		✓	
	FGF6	Muscle development and regeneration	Overexpression — prostate cancer		✓		✓		✓	✓
FGF7	FGF3	Inner ear and skeleton development	1. Missense mutation — Michel aplasia, LAMM syndrome 2. Haploinsufficiency — otodental syndrome 3. Amplification — breast cancer	✓		✓				
	FGF7	Branching morphogenesis	1. Polymorphism — COPD 2. Overexpression — lung adenocarcinoma			✓				
	FGF10	1. Lung branching morphogenesis 2. Inner ear development 3. Hair follicle development 4. Fore and hind limb	1. Polymorphism — myopia 2. Nonsense mutation— LADD syndrome and ALSG 3. Overexpression — breast and prostate cancer	✓		✓				
	FGF22	Synaptogenesis	Undefined	✓		✓				
FGF8	FGF8	Brain, eye, ear, limb bud, kidney, and heart development	1. Missense mutation — cleft lip and palate, holoprosencephaly, craniofacial defects, and hypothalamo-pituitary dysfunction 2. Nonsense mutation — familial hypogonadotropic hypogonadism		✓		✓		✓	✓
	FGF17	Cerebellum and frontal cortex development	1. Missense mutation — familial hypogonadotropic hypogonadism 2. Overexpression — liver and prostate cancer		✓		✓		✓	✓
	FGF18	Lung alveolar and bone, CNS, skeletal, and palate development	1. Polymorphism — cleft lip and palate 2. Overexpression — liver cancer						✓	✓
FGF9	FGF9	Inner ear, gonad, and kidney development	1. Promoter mutation — sertoli cell-only syndrome 2. Missense mutation — multisynostosis syndrome 3. Mutations — colorectal and endometrial cancers 4. Overexpression — lung cancer		✓		✓	✓	✓	✓
	FGF16	Heart development	1. Nonsense mutation — 4-5 metacarpal fusion 2. Overexpression — ovarian cancer				✓	✓	✓	✓
	FGF20	Kidney, hair, teeth, cochlea, and central nervous development	1. Frame-shift mutation — bilateral renal agenesis 2. Polymorphism — risk of Parkinson's disease		✓	✓	✓	✓	✓	✓

Abbreviations: LAMM, labyrinthine aplasia, microtia, and microdontia; COPD, chronic obstructive pulmonary disease; LADD, lacrimo-auriculo-dento-digital syndrome; ALSG, aplasia of the lacrimal and salivary glands; and CNS, central nervous system.

Structurally, metabolic FGFs coevolve with coreceptor KL/KLB but also acquire new structural elements that direct specific contact interactions with KL/KLB and FGFRs, thereby leading to a tethered basic triad complex and subsequent activation of intracellular kinase domains of FGFRs [5,11]. The C-terminus of the metabolic FGFs mimics the interaction mode of a sugar chain that docks into the pseudo-glycolytic pocket of KL/KLB while interacting with FGFR ectodomains through the domains that are conserved across the FGF family [5,68]. Meanwhile, the interacting KL/KLB protrudes an "arm" from the membrane-proximal glycosidase domain griping onto the FGFR ectodomain.

Although the FGFRs, in particular FGFR1, are broadly expressed, the highly restricted expression of KL/KLB and metabolic FGFs, and the new structural elements and mutual interaction modes, set the tone for tissue-specific functions of the metabolic FGF axes (Table 2). The different intracellular molecular constituents in different cells types, which are tailored to perform specific biological functions, may be also an important limiting factor. For instance, the adult adipocytes are not poised in a normal context to increase population by direct proliferation due to the loss of several key proliferation-controlling pathways, thereby partly accounting for the inability of the activated FGFR1 by FGF21 to promote adipocyte proliferation. Overall, metabolic FGFs appear to be inducible stress factors in response to organismal metabolic perturbations [7,69] and signal distal peripheral tissues through the FGFR-KL/KLB complex to control due metabolic pathways. In this sense, the metabolic FGF acts as a key to ignite the FGF-FGFR-KLB/KLB triad complex, which functions similarly as an engine with an axis to drive effects in a tissue-specific manner, thereby leading to beneficial effects that offset the initial adverse metabolic changes and prevent metaflammation and tissue damage not only in the FGF-producing tissues but also systemically [2,7] (Table 2). Consequently, both the analogs of endocrine FGFs and the agonists of FGF-KL/KLB have been actively pursued clinically for the prevention and treatment of a wide range of metabolic diseases and comorbidities [2,70–75].

Table 2 The metabolic FGF axis.

Subfamily	Members of ligands	Physiological function (knockout phenotypes)	Known pathologies	Receptor specificity								
				1b	1c	2b	2c	3b	3c	4	KL	KLB
FGF19	FGF19	1. Bile acid metabolism 2. Gall bladder filling 3. Lipid and energy metabolism	1. Bile acid diarrhea, IBD 2. Cholestasis 3. Overexpression — liver cancer		✓		✓		✓	✓		✓
	FGF21	1. Lipid metabolism — lipolysis, fatty acid oxidation, lipogenesis 2. Energy metabolism — uncoupling thermogenesis 3. Macronutrient preference 4. Starvation response and associated physiology 5. Insulin sensitivity and glucose homeostasis	1. Obesity 2. Diabetes 3. NAFLD 4. Hyperlipidemia 5. Metabolic syndrome 6. Pancreatitis		✓				✓			✓
	FGF23	Phosphate, calcium, sodium, and vitamin D homeostasis	1. Activation mutation — autosomal dominant hypophosphatemic rickets and tumor-induced osteomalacia 2. Inactivation mutation — familial tumoral calcinosis 3. Increase — X-linked dominant hypophosphatemia, CKD 4. Decrease — GALNT3-related familial tumoral calcinosis		✓				✓	✓	✓		

Abbreviations: IBD, inflammatory bowel disease; NAFLD, nonalcoholic fatty liver disease; CKD, chronic kidney disease; and GALNT3, polypeptide N-acetylgalactosaminyltransferase 3.

FGF19 metabolic axis

FGF19 is the prime controller of diurnal bile acid flux, and the FGF19-driven metabolic axis is a temporal interorgan crosstalk from the ileum to the liver in response to the increase in the postprandial serum and transintestinal flux of bile acids [2,49] (Fig. 2). This axis serves to control the enterohepatic and systemic levels of bile acids negatively, which facilitate the uptake and absorption of dietary lipids after a meal but are toxic as biodetergent if the flux is prolonged at increased levels. The ileal initiation of the FGF19 signal is under the transcriptional control of FXR, which is stimulated by the reabsorbed enterocyte bile acids as a natural ligand that is originally released from gallbladder and mixed with food traveling down from the duodenum to jejunum and ileum. This enterocyte-derived FGF19 activates the remote FGFR4-KLB complex [67] residing across the membrane of hepatocytes in the liver, resulting in a major feedback termination of the transcription of the rate-limiting enzymes Cyp7A1 and Cyp8b1 in the bile acid biosynthesis pathways [49,76]. Therefore, the FGF19 axis triggers the shut-off of hepatic biosynthesis of new bile acids from cholesterol and the refilling of gallbladder approximately 2 h after the peak of serum bile acids is reached.

In experimental animals, FGF19 overexpression or administration elicits other metabolic effects [77,78]. Excessive FGF19 promotes lipolysis, metabolic rate, and energy expenditure and reduces body weight, serum glucose, and lipids. The FGFR1-KLB complex on adipose tissues, including WAT and BAT, was suggested in a large part to mediate these metabolic effects [79] (Fig. 2). However, the direct metabolic roles of bile acid fluctuation and bile acid-activated FXR and TGR5 cannot be excluded.

Although there is no evidence for any genetic mutation of FGF19 gene that may be involved in human metabolic diseases, its reduced synthesis and blood levels are suggestive of a causative factor of chronic bile acid diarrhea [80,81] and certain metabolic disorders, such as metabolic syndrome, nonalcoholic fatty liver disease (NAFLD), and insulin resistance. Experimentally, the

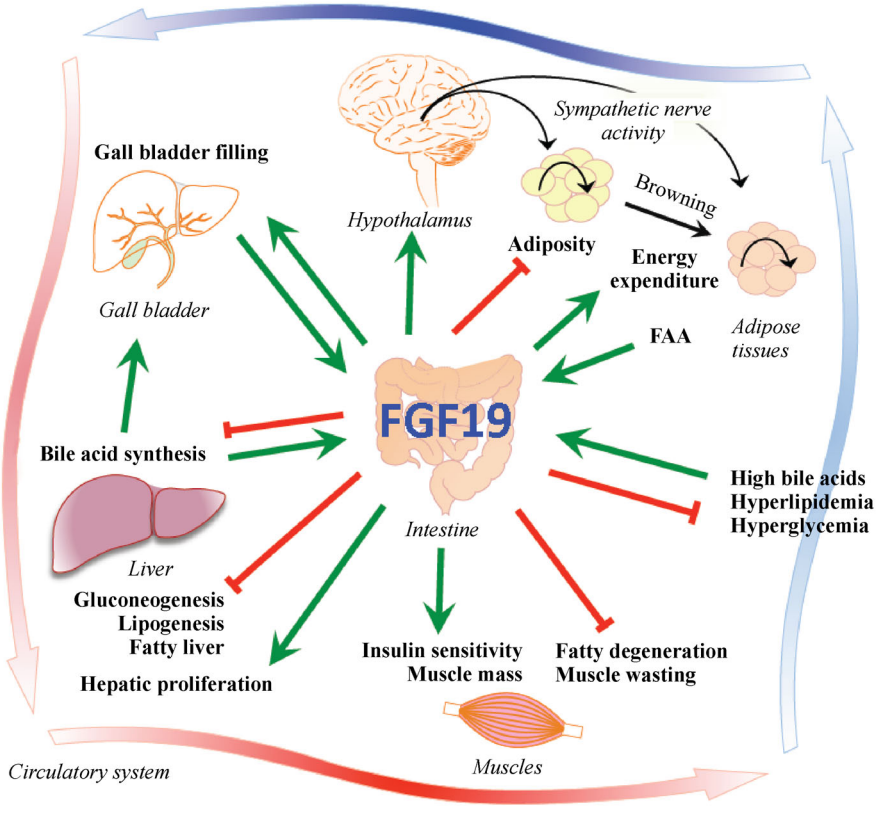

Fig. 2 FGF19 metabolic axis. The major FGF19 metabolic axis drives a temporal interorgan crosstalk from the ileum to the liver in response to the increase in postprandial serum and transintestinal flux of bile acids to discontinue the biosynthesis of new bile acids after sufficient food digestion, thereby preventing the prolonged exposure of tissues to potential bile acid toxicity. Pharmacological FGF19 may also initiate multiple signal axes to drive effects on multiple tissues/organs, such as promoting (green arrow) energy expenditure in white and brown adipose tissues, increasing muscle mass and insulin sensitivity, and preventing (red long-tailed "T" sign) systemic hyperglycemia and hyperlipidemia. FAA: free fatty acids.

neutralization of FGF19 by specific anti-FGF19 antibodies causes severe diarrhea in monkeys accompanied by the increases in bile acid synthesis, serum and fecal total bile acids, specific bile acid transporters, and liver toxicity [82]. In obese patients who undergo Roux-en-Y gastric bypass bariatric surgery, FGF19 increases to normal values, which at least partially underlie the benefits of this approach [83]. On the other hand, high FGF19 expression levels are found in the livers of patients with extrahepatic cholestasis [84,85], suggesting FGF19 as a therapeutic target for this disease.

Recently, the FGF19 axis was shown to elicit hypertrophic and protective effects on the skeletal muscle presumably through a KLB-FGFR4-dependent mechanism by increasing myofiber size in the soleus, muscle mass, and grip strength [86]. Pharmacological FGF19 ameliorates skeletal muscle atrophy and prevents muscle wasting in mice with glucocorticoid treatment, obesity, or sarcopenia. These results highlight a potential treatment strategy for muscle wasting induced by glucocorticoid treatment, obesity, aging, and cachexia. However, whether the same treatment will have a similar adverse effect on the liver still has to be determined because muscle-specific transgenic mice developed prominent hepatocellular carcinoma (HCC) [87].

Despite the tumorigenic concern, the FGF19 analog NGM282 was tested in patients with nonalcoholic steatohepatitis (NASH). It markedly reduced liver fat content but with significant side effects [70]. In a phase 2 trial in patients with type 2 diabetes and chronic idiopathic constipation, NGM282 significantly improved bowel function by accelerating gastric emptying and colonic transit [81]. Furthermore, NGM282 was further tested in mouse models and human patients with cholestasis and primary biliary cholangitis, showing efficacy in significantly reducing bile acid levels and improving hepatic inflammatory injury and fibrosis [84,88,89].

FGF21 metabolic axis

FGF21 is a prime lipid catabolic factor that regulates energy balance. However, the physiological roles and pharmacological effects of FGF21-driven metabolic axes are multifaceted [2,7,90] (Fig. 3). FGF21 was discovered as a driver of glucose uptake in adipocytes and a PPARα-dependent hepatic starvation hormone [48,50,51]. In mice, FGF21 levels are induced when calories are restricted or when glucose is low to allow fats to be burned for energy supply. The increasing levels of FGF21 drive diverse aspects of the adaptive starvation response, including stimulation of hepatic fatty acid oxidative for ketone body production during prolonged fasting and starvation. Whether this action of FGF21 is autocrine/paracrine in the liver or endocrine in adipose tissues through adipose lipolysis and fatty acid oxidation is a matter of debate. The liver is a major contributor to the circulating FGF21 levels, which is associated with hepatic fat content and adiposity but inversely associated with serum glucose levels [91–93]. The hepatic expression of FGF21 is responsive not only to starvation but also to a broad spectrum of cellular, metabolic, or pathological changes in the liver as well as systemic metabolic perturbations [7,69,94]. As FGF21 is incapable of activating FGFR4-KLB complex [67], which is predominant in the liver that expresses FGFR1-KLB with lower levels, hepatic FGF21 acts mainly as an endocrine factor to drive the metabolic pathways in peripheral tissues, including WAT, BAT, muscle, heart, kidney, and CNS that express high levels of FGFR1/2/3-KLB, leading to the correction of metabolic derangements and amelioration of metaflammation and stress damage (Fig. 3) [7,94].

Although the liver is unlikely a major direct target of FGF21, the effects of FGF21 on the liver are prominent. In addition to its role as a regulator of integrated hepatic metabolism in multiple aspects [48,50,95–98], including fatty acid oxidation, ketogenesis, gluconeogenesis, and macronutrient preference, FGF21 counteracts hepatic pathologies in response to a number of nutritional and chemical insults, including ketogenic diet, high fat diet, high fructose diet, methionine and choline deficient diet, ethanol-supplemented diet, and diethylnitrosamine [99–103]. Under a chronic obesogenic diet, FGF21-deficient mice developed a spectrum of progressive fatty liver disease, including simple hepatosteatosis to NASH, fibrosis, and HCC, which is the most lethal complication of this disorder. These findings highlight the role of FGF21 metabolic axis as a defensive barrier for the deleterious stress damage caused by metabolic disorders in the liver [104]. Current clinical trials with FGF21 analogs show promising efficacy against NAFLD, NASH, and fibrosis without noticeable adverse side effects [73].

Acting on WAT and BAT, the FGF21 axis drives an array of catabolic effects, including insulin-independent glucose uptake, lipid droplet expansion inhibition, lipolysis, fatty acid oxidation, white adipocyte beigeing, and thermogenic dissipation of energy [79,105,106]. This route of action has been proposed as a major endocrine axis of FGF21 for insulin sensitization; lowering of systemic glucose, triacylglycerol, and LDL; fighting against obesity, diabetes, fatty liver diseases, hyperlipidemia, and associated comorbidities; and achieving metabolic health [2,73, 74,107]. Some of these effects are likely mediated by adipokines, such as CCL11 and adiponectin, as shown in mice [108,109]. In cold-induced nonshivering thermogenesis or exercise stress condition, BAT also becomes a source of endocrine FGF21 in a β-adrenergic- and cAMP-dependent manner, which in turn facilitates mitochondrial genesis, oxidative capacity, uncoupling, and heat generation, leading to adaptation to cold conditions and core body temperature maintenance [110–112].

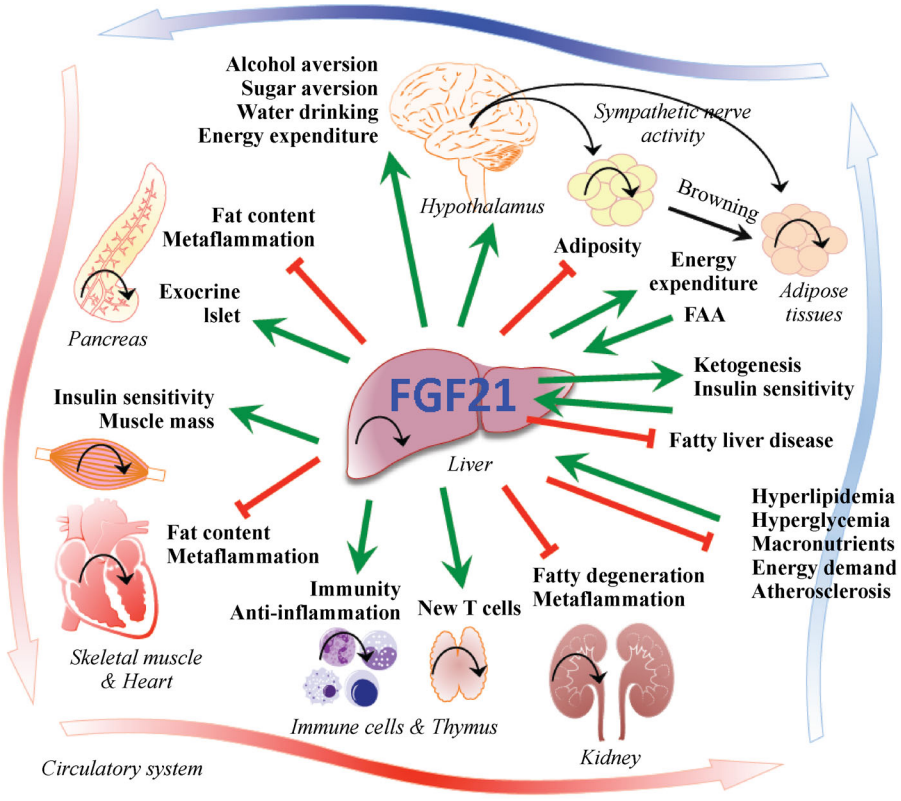

Fig. 3 FGF21 metabolic axis. The liver is the major organ of origin of endocrine FGF21 in response to a broad spectrum of stress conditions. The hepatic and pharmacological FGF21 drive multiple signal axes in multiple tissues/organs, resulting in multifaceted beneficiary metabolic effects, including promoting (green arrow) glucose, lipid, and energy homeostasis; offsetting metabolic derangements; and preventing (red long-tailed "T" sign) metaflammation, inflammatory tissue damage, and tissue-specific pathogenesis, including obesity, type 2 diabetes, fatty liver disease, metabolic syndrome, and associated comorbidities. FAA: free fatty acids. Black semicircular arrows indicate possibility of paracrine mode of FGF21 within local tissue environment.

In line with the beneficial effects of FGF21 on maintaining metabolic homeostasis during diverse adverse conditions, pharmacological FGF21 markedly extends the lifespan of mice by blunting the growth hormone/insulin-like growth factor-1 signaling pathway in the liver without reducing food intake or affecting longevity-associated markers of NAD^+ metabolism, AMP kinase, and mTOR signaling pathways [113]. The thymus functions in producing new T cells for the immune system, but with age, it becomes fatty and loses the ability to produce a sufficient amount of new T cells, which is an important cause of increased risks of infections, obesity, diabetes, and certain cancer types, leading to reduced lifespan in the elderly people. The FGF21 level in thymic epithelial cells is several folds higher than that in the liver. The high level of FGF21 is proposed to protect thymus from the age-related fatty degeneration and to increase the production of new T cells to bolster immune function, thereby lowering the incidence of diseases and promoting longevity [114].

The acinar cell compartment in the pancreas expresses the highest levels of FGF21 constitutively among tissues, but contributes little to the circulation [56,115]. Acinar cells appear to be both the dominant source and target (via FGFR1-KLB complex) of pancreatic FGF21. The high levels of FGF21 is proposed to act as an exocrine pancreas secretagogue to stimulate pancreatic digestive enzyme secretion and pancreatic juice flow to the intestine, thereby relieving potential self-digestion caused proteostasis stress and protecting pancreas from pancreatitis, including but not limited to those caused by high-fat diet, pancreatic toxins, and alcoholism [116]. Although islets express significantly lower amounts of FGF21, acinar cell derived or endocrine FGF21 helps protect against fatty pancreas, high-fat diet induced islet hyperplasia, and inflammatory damage [117–119]. Demyelination in the CNS can cause severe neurological deficits, such as multiple sclerosis and neurological dysfunction. Pancreatic FGF21 acts on oligodendrocyte precursor cells to promote the remyelination process, leading to better recovery of neurological functions in mice [120].

Exposure to alcohol or sugar induces hepatic FGF21 through ChREBP, which then acts on the hypothalamus reward pathway to suppress the desire for sugar and alcohol in favor of drinking water in mice depending on the β-adrenergic circuit [97,98,121,122]. This finding may represent a new hydration pathway that is independent of the classical renin-angiotensin-aldosterone thirsty pathway in the kidney in response to nutritional stress, suggesting a previously underappreciated association of water intake to metabolism through the FGF21 metabolic axis. A human rs838133 allele in FGF21 is associated with higher alcohol and sugar intake and higher blood pressure and waist-hip ratio, with lower total body-fat percentage [123]. Comparison of the genomes of more than 105 000 light and heavy social drinkers also identifies a variation in the rs11940694 locus of the *KLB* gene in association with the aversion for alcohol [124]. Neuronal cell stress reaction, such as those caused by disturbances in the mitochondria and endoplasmic reticulum (ER), is an important factor in the development of neurodegenerative diseases. Studies found that the integrated stress response induces neuronal FGF21, which presumably serves to attenuate stress and neural damage [125].

In addition to the liver, pancreas, and adipose tissues, cardiac muscle produces FGF21 in response to cardiac stress, cardio exercise, and endurance training [126,127], which then speeds up glucose uptake, lipid catabolism, and energy metabolism, and protects against cardiovascular stress damage, apoptosis, and heart dysfunctions, such as cardiac hypertrophy, myopathy, steatosis, ischemic infarction, and atherosclerosis [128–132]. Through a multiorgan crosstalk, hepatic FGF21 drives the expression of angiotensin-converting enzyme 2 in adipocytes and renal cells, which hydrolyzes angiotensin II to active vasodilator angiotensin-(1-7) in the renin-angiotensin system, thereby alleviating angiotensin II-associated hypertension and reversing vascular damage [133]. Skeletal muscle under the bouts of exercise or stress, such as mitochondrial myopathies, also induces FGF21 expression [134–136]. In turn, FGF21 acts on muscle and adipose tissue to reduce lipid load by increasing lipolysis, fatty acid utilization, energy expenditure, and insulin sensitivity, thereby preventing diet-induced obesity and insulin resistance [137–140].

Hepatic FGF21 acts on the paraventricular nucleus in the hypothalamus to drive the release of corticotropin-releasing factor, which then stimulates the involuntary sympathetic nerve activity. This leads to the activation of brown adipose tissue by upregulaing UCP1 and increases of glucose uptake, lipolysis, mitochondrial oxidation of fatty acids and glucose, body heat generation, and weight loss [141,142]. The increase in corticotropin-releasing factor levels may also stimulate the pituitary gland to release adrenocorticotrophic hormone and subsequent corticosterone production in adrenal cortex, leading to increased hepatic gluconeogenesis during prolonged fasting to prevent hypoglycemia [143]. Hepatic FGF21 acts on the suprachiasmatic nucleus (SCN) in the hypothalamus to suppress the vasopressin-kisspeptin and gonadotropin-releasing hormone signaling cascade, which then inhibit the proestrus surge in luteinizing hormone from anterior pituitary gland, thereby contributing to female infertility in response to nutritional challenge, such as prolonged starvation [144]. The SCN action of FGF21 may also alter circadian behavior [145]. By increasing neuropeptide Y levels and Y1 receptor activation, the hypothalamus action of FGF21 may decrease locomotive activity, metabolic rate, and body temperature, leading to torpor under nutrition limitation [146]. FGF21 may also act on the hippocampus to decrease reactive oxygen species and inflammatory damage, thus decreasing brain cell damage and improving cognition [147,148].

The endocrine FGF21 axes as well as the paracrine FGF21 axes within the local tissue compartments have been shown in many tissues and organs to counteract stress response and attenuate stress-ensued inflammation and inflammatory damage [7,104,117]. Therefore, FGF21 is not only a stress-responsive or -induced factor but also an anti-stress and anti-inflammatory factor. The stress-offsetting effects, in particular the anti-inflammatory activities, can be attributed to the metabolic effects of FGF21 axes that prevent fatty degeneration, gluco-lipotoxicity, oxidative and ER stress, and inflammatory and immune cell infiltration. These metabolic activities may be mediated in part through efficient and durable systemic and local glycemic and lipidemic control, improvement of insulin sensitivity, and promotion of lipid catabolism (lipolysis and fatty acid oxidation), adipose beigeing, and futile energy expenditure in adipose tissues, local adipocytes, and brain in both UCP1-dependent and adrenergic sympathetic nervous system-dependent mechanisms [79,105,106,141,149,150]. As a result, FGF21 effectively reverses hepatic steatosis in obese mice and clinical obese patients [73,105,151]. Furthermore, the pharmacological FGF21 analogs and FGFR1-KLB agonists have been shown to directly improve the spectrum of adverse components of metabolic syndrome, including central obesity, insulin resistance, fasting hyperglycemia, dyslipidemia, systemic hypertension, and fatty liver, which are the major risk factors for cardiovascular disease (CVD), type 2 diabetes mellitus, chronic kidney disease (CKD), and all-cause mortality [2,7,73,74,107]. The FGF21 axes suppress atherosclerotic plaque by reducing hypercholesterolemia, oxidative stress, and smooth muscle cell proliferation via adiponectin-dependent and adiponectin-independent mechanisms [129]. FGF21-deficient mice developed significant islet hyperplasia and periductal lymphocytic inflammation upon chronic challenge of an

obesogenic high-fat diet, indicating a protective role of FGF21 in compensatory islet hyperplasia and pancreatic inflammation associated with obesity [117,152]. FGF21 directly suppresses triglyceride levels and lipid accumulation in kidney tissues, thereby reducing lipotoxicity, oxidative stress, inflammation, glomerular abnormalities, fibrotic renal injury in diabetic nephropathy, while deficiency of FGF21 aggravates these conditions [153,154], indicating a defensive role of FGF21 against kidney pathogenesis associated with obesity and diabetes.

The anti-stress and anti-inflammatory effects of FGF21 may be also attributable to its direct action on non-metabolic cells and non-metabolic activities. FGF21 directly inhibits cardiomyocyte apoptosis, oxidative stress, myocardial injury, thereby reducing the risk of pathological cardiac remodeling and dysfunction, cardiac hypertrophy, myocardial ischemia, and heart failure in ischemic heart tissue and diabetic cardiomyopathy [130,155]. FGF21 protects the pancreas from caerulein- and L-arginine-induced pancreatitis, acinar cell injury, and fibrosis in mice [118,119,156]. FGF21 acts directly on renal mesangial cells to reduce glucose reabsorption and prevent hyperglycemia-induced fibrogenesis in *db/db* mice [157,158]. Interestingly, recent evidence supports that FGF21 can directly act on inflammatory and immune cells to attenuate inflammation and inflammatory damage. FGF21 activates THP-1-derived macrophages to promote cholesterol efflux, oxidized low-density lipoprotein (oxLDL) uptake, and foam cell formation and inhibits macrophage inflammatory capacity through the Nrf2 pathway [156,159,160]. Adipose tissue is an endocrine organ and plays an active role in the inflammation in obesity that can favor CVD and CKD progression by inducing a chronic and low-grade inflammation via secreted proinflammatory adipokines and cytokines. Studies in diet-induced obesity and pancreatitis models indicate that FGF21 promotes anti-inflammatory macrophage polarization in adipose depots and pancreas, WAT browning, and insulin sensitivity, thereby effectively preventing adipose tissues from adapting proinflammatory profiles and the pancreas from inflammatory fibrosis [109,156,159,161]. Interestingly, FGF21 was found highly expressed in neutrophils and monocytes among circulating leukocytes and stimulates phagocytosis, glucose uptake, and reactive oxygen species production in a NADPH oxidase-dependent manner in the neutrophil-like HL-60 and monocytic THP-1 cells [162–164]. In the type II collagen-induced arthritis mouse model, FGF21 acts on the spleen to reduce inflammatory IL-17, TNF-α, IL-1β, IL-6, IL-8, and MMP3 and the number of splenic TH17 cells, thereby alleviating arthritis severity [165]. These studies highlight the potential mediator role of FGF21 in innate immunity and inflammatory disorders. The direct impact of FGF21 on the function of inflammatory and immune cells and associated health consequences is yet to be validated.

FGF23 metabolic axis

FGF23 is a key hormonal regulator of phosphate, vitamin D, and calcium metabolism, and its metabolic axes drive a complex interorgan crosstalk network for bone health and systemic mineral balance (Fig. 4) [2,61,166–168]. Osteoblastic cells in osseous tissue are the major source of FGF23 in response to elevated calcitriol, increased phosphate and calcium burdens, increased parathyroid hormone, iron and magnesium loss, and active bone remodeling in a vitamin D receptor dependent mechanism. Acting on kidneys that express the FGFR1-KL complex, the FGF23 signal axis represses the expression of NPT2a and NPT2c, the sodium-phosphate cotransporters in the proximal tubule, thereby decreasing reabsorption and increasing secretion of phosphate in renal brush border membrane vesicles. Another important function of this bone to kidney FGF23 signal axis is suppressing the expression of 25-hydroxyvitamin D3-1-α-hydroxylase and stimulating the expression of 1,25-dihydroxyvitamin D(3) 24-hydroxylase, thereby inhibiting the production of active calcitriol in renal proximal tubules, which subsequently inhibits the expression of NPT2b and phosphate absorption in the apical brush border of small intestine. The bone FGF23 acts on the basolateral FGFR1-KL complex in the renal distal tubules to increase the intracellular transport of fully glycosylated TRPV5 from the Golgi apparatus to the plasma membrane, thereby stimulating calcium reabsorption in distal renal tubules and preventing calcium loss [169]. These FGF23-associated axes also directly increase the membrane abundance of the Na^+:Cl^- cotransporter NCC in distal renal tubules, and thus, increase sodium reabsorption, plasma volume, and blood pressure [170]. This change may be a new cause of high blood pressure and heart disease under the modern processed phosphate-rich foods.

Bone FGF23 also acts on the parathyroid gland to inhibit the production and secretion of parathyroid hormone (Fig. 4) [171], which then reduces serum calcium through its effects on the bone, kidney, and intestine. High serum FGF23 levels in patients with CKD decrease calcitriol, thereby contributing to the development of secondary hyperparathyroidism, which has a crucial role in increasing the levels of FGF23 because the parathyroid hormone stimulates FGF23 expression.

Recent studies revealed the potential roles of the FGF23 axis in suppressing erythropoiesis in bone marrow. Erythroid progenitor cells highly express FGF23 and FGFR-KL, suggesting that they are both a source and a target of FGF23. The loss of FGF23 or injection of an FGF23-blocking peptide in mice results in increased erythropoiesis, reduced erythroid cell apoptosis, and increased renal and bone marrow erythropoietin (EPO) expression with increased circulating EPO levels. On the other hand, the increased EPO or acute blood loss increases

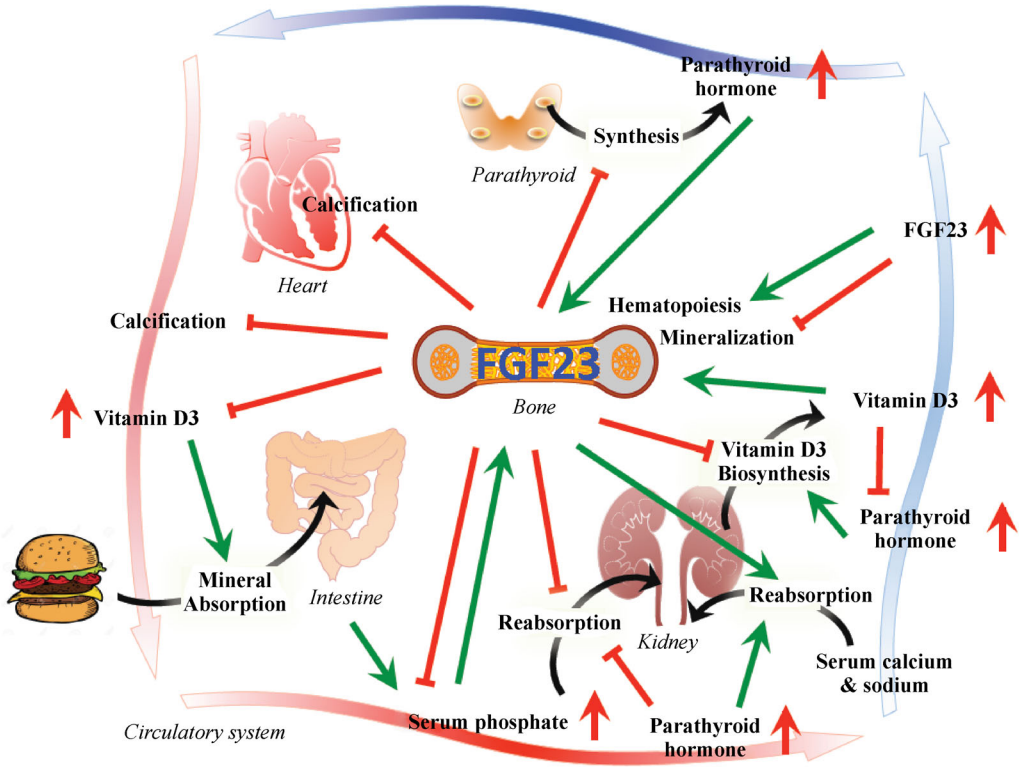

Fig. 4 FGF23 metabolic axis. The bone-derived FGF23 drives signal axes to promote (green arrows) the metabolic homeostasis of phosphate, vitamin D, and calcium through a complex interorgan crosstalk network for bone health and systemic mineral balance. The bone to the kidney axis of FGF23 is central to the metabolic roles of FGF23, which inhibits (red long-tailed "T" sign) the reabsorption of phosphate and the production of active calcitriol in renal proximal tubules while increasing the calcium and sodium reabsorption in renal distal tubules. The bone to parathyroid axis of FGF23 inhibits the production and secretion of parathyroid hormone that also plays critical roles in mineral and vitamin D balance.

FGF23 expression in the bone marrow with a concomitant increase in serum FGF23 [172,173]. A recent study suggests that FGF23 is involved in the association between functional iron deficiency, increased EPO levels, and death. The further elucidation of the role of the EPO-FGF23 signaling axis in hereditary anemia and chronic hemolytic diseases, CKD, and mineralization disorders will add to the understanding of the pathophysiology of these diseases and life expectancy and will inform new treatment strategies for the diseases.

Current evidence indicates that FGF23 is more structurally unique than FGF19 and 21 [5]. FGF23 contains a conserved furin-sensitive ^{176}RHTR^{179} cleavage site near the C-terminus, which inactivates the intact FGF23 upon cleavage, leading to signal attenuation. The biological importance of this activity control mechanism is demonstrated by point mutations (e.g., R176Q, R179Q, and R179W) of this site, which results in cleavage-resistant FGF23 and increased circulating levels of active FGF23, in autosomal dominant hypophosphatemic and vitamin D-deficient rickets characterized by renal phosphate wasting, hypophosphatemia, rickets, osteomalacia, leg deformities, short stature, bone pain, and dental abscesses [168,174, 175]. FGF23 levels are increased and may play important roles in other hereditable and acquired phosphate wasting disorders, including X-linked dominant hypophosphatemic rickets, autosomal recessive hypophosphatemic rickets, hypophosphatemic rickets associated with McCune-Albright syndrome/fibrous dysplasia of bone, and linear sebaceous nevus syndrome [176,177]. The increased FGF23 levels are also found in acquired phosphate wasting disorders in some tumor types, such as the benign mesenchymal neoplasm phosphaturic mesenchymal tumor, causing tumor-induced osteomalacia, a paraneoplastic syndrome [168].

During post-translational modification, FGF23 is glycosylated at Thr-178 in the cleavage site by GalNT3, which facilitates its secretion and protects the protein from being broken down, suggesting a novel posttranslational regulatory model of FGF23 involving competing O-glycosylation and proteolytic processing to determine the level of secreted active FGF23 [178]. The importance of this glycosylation modification is demonstrated by inactivating GalNT3 mutations that render FGF23 susceptible to

proteolysis [179,180], thereby reducing circulating intact hormone levels and leading to autosomal recessive familial tumoral calcinosis that manifests with hyperphosphatemic and massive calcium deposits in the skin and subcutaneous tissues throughout the body. Consistently, at least seven mutations in the conserved backbone of FGF23, such as S71G, M96T, S129F, and F157L, destabilize the tertiary structure and render it susceptible to degradation, thereby resulting in autosomal recessive familial tumoral calcinosis with hyperphosphatemia [2,5,181–184].

Patients with CKD have increased serum levels of phosphate as well as FGF23, which lead to increased uptake of calcium by the kidneys, resulting in vascular calcification. This explains the CVD complications, such as cardiac hypertrophy and congestive heart failure, in patients with CKD [185,186]. The inhibition of FGF23 or its axis could be a strategy to bring CVD and vascular calcification under control. The FGF23 level in patients with CKD can even indicate their life expectancy. The dysregulation of calcium levels can have an array of serious health consequences. Chronic hypocalcemia can potentially lead to heart failure, nervous system and muscle disorders, and encephalopathy, while hypercalcemia can increase the risk of kidney stones, cause muscle weakness, and worsen psychological issues, such as dementia and depression. This may explain some current observations that people with high serum FGF23 can be at risk of dementia, and that mice lacking FGF23 exhibit defective learning and memory problems similar to those seen in KL-deficient mice [187,188].

Conclusions and future perspectives

The three members of the metabolic FGFs, including FGF19, 21, and 23, share a conserved core structure of β-trefoil fold but diverge in functions from other mitogenic members of the FGF family during evolution (Fig. 1). These metabolic FGFs acquire specific structural elements that endow them with abilities to function via an endocrine mode and to bind new accessory receptors that have strict expression patterns in metabolic tissues. Although metabolic FGFs still signal through the transmembrane FGFR tyrosine kinases as the mitogenic FGFs, these new properties divert their functions to metabolic regulation. As such, FGF19, 21, and 23 drive a wide range of diverse metabolic axes that function in maintaining the homeostasis of bile acids, glucose, lipids, energy, and minerals; offsetting detrimental metabolic derangements; and achieving optimal metabolic health without an overt effect on cell proliferation and population growth. In this sense, each of the metabolic axes of FGF19, 21, and 23 stands alone as a driver of specific metabolic effects with important physiological functions and pathological consequences. Therefore, these axes together constitute the "FGF Metabolic Axis," which is a new term that we start to call hereafter, with broad-spectrum pathophysiological roles and consequences on the quality of survival (Fig. 1).

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Compliance with ethics guidelines

Xiaokun Li declares no conflict of interests. This manuscript is a review article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

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