

Endocrine FGFs and Klothos: emerging concepts

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Endocrine fibroblast growth factors (FGFs) control a variety of physiological processes including suppression of bile acid synthesis in hepatocytes, promotion of lipolysis in adipocytes, and inhibition of phosphate reabsorption and vitamin D biosynthesis in renal tubular cells. Endocrine FGFs require the Klotho gene family of transmembrane proteins as co-receptors to bind cognate FGF receptors. Importantly, expression of endocrine FGFs is regulated by nuclear receptors whose lipophilic ligands are generated under the control of these hormones in their target organs. Thus, novel endocrine axes have emerged that regulate diverse metabolic processes through feedback loops composed of the FGF, Klotho, and nuclear receptor gene families. This review covers roles of Klotho family proteins in the regulation of activity and expression of endocrine FGFs.

Introduction

Fibroblast growth factors (FGFs) signal through the FGF receptor (FGFR) tyrosine kinases and primarily regulate developmental and morphogenic processes in a variety of tissues in a paracrine and/or autocrine fashion [1–3]. The mammalian FGF and FGFR families are composed, respectively, of 22 (FGF1–23, FGF15 is the mouse ortholog of human FGF19) and 4 (FGFR1–FGFR4) members. In addition, alternative splicing events in FGFR1, FGFR2, and FGFR3 generate ‘b’ and ‘c’ isoforms that have different FGF-binding specificities, further increasing the complexity of the FGF-FGFR signaling system (Box 1) [4,5].

Phylogenetic and sequence analyses have segregated FGF15 (the mouse ortholog of human FGF19), FGF19, FGF21, and FGF23 from the other FGF family members, and these comprise the FGF19 subfamily [5]. The FGF19 subfamily members are different from the other FGF family members in many aspects (Box 2). The most salient feature of the FGF19 subfamily members is that they function as endocrine factors or hormones. Recent studies have unveiled not only their metabolic activities but also the molecular and structural basis behind the endocrine mode of action, resulting in identification of novel endocrine axes. Briefly, FGF15/19 is secreted from intestine upon feeding and acts on liver to suppress bile acid synthesis. FGF21 is secreted from liver upon fasting and acts on adipose tissue to promote lipolysis. FGF23 is secreted from bone and acts on kidney to suppress renal phosphate reabsorption and vitamin D synthesis. This review focuses

on recent progress in understanding of (1) the unique molecular mechanism by which these endocrine FGFs find their target organs and (2) the significant similarity in the molecular design of feedback mechanisms shared by these novel endocrine systems.

FGF23

The FGF23 gene was isolated based on sequence similarity to the other FGF family members. Function of FGF23 was unclear until it was identified as a gene mutated in a rare hereditary bone disorder called autosomal dominant hypophosphatemic rickets (ADHR) [6]. Patients with ADHR develop impaired bone mineralization due to excessive phosphate wasting into urine. FGF23 is expressed primarily in osteocytes in the bone [7]. FGF23 induces renal phosphate excretion and lowers serum phosphate levels when injected into rodents [8,9]. Elevated blood phosphate levels are associated with high FGF23 expression and high blood FGF23 levels in mice and humans [10,11]. Thus, FGF23 has been considered as a bone-derived phosphaturic hormone that induces negative phosphate balance in the regulation of phosphate homeostasis. ADHR patients carry missense mutations in the FGF23 gene that confer resistance to proteolytic inactivation of FGF23 protein, resulting in increased blood FGF23 levels and increased renal phosphate excretion [6,12]. Another hereditary bone disorder called X-linked hypophosphatemic rickets (XLH) is also associated with elevated serum FGF23 levels. XLH is caused by mutations in the *PHEX* gene (phosphate-regulating gene with homologies to endopeptidases on the X chromosome), which is involved in the process of proteolytic inactivation of FGF23 [13]. Although FGF23 was shown to bind to multiple FGFRs *in vitro*, the binding affinity ($K_D = 200\text{--}750\text{ nM}$) was too low to explain its potent activity *in vivo* (normal blood FGF23 levels are $\sim 1\text{ pM}$ in humans) [14], suggesting the existence of a co-factor(s) that selectively increases affinity of FGF23 to FGFRs only in its target organ(s).

Klotho

The *klotho* gene was originally identified as a gene mutated in the *klotho* mouse [15]. The *klotho* mouse displays complex phenotypes resembling human premature aging syndromes including shortened life span, poor growth, hypogonadism, skin atrophy, muscle atrophy, premature thymic involution, osteopenia, pulmonary emphysema, vascular calcification, and soft tissue calcification among others, in an autosomal recessive manner [15]. The *klotho*

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Box 1. Complexity of the FGF-FGFR system

Twenty-two members of the mammalian FGF gene family can be divided into three subfamilies: the intracellular FGFs (FGF11/12/13/14), the endocrine FGFs (FGF15/19/21/23), and the canonical or paracrine FGFs (the others) [5]. Some investigators exclude the intracellular FGFs from the FGF family because these FGFs function in an FGFR-independent manner. The difference between the endocrine and the canonical FGFs is described in Box 2.

The FGFR1, FGFR2, and FGFR3 genes are composed of 19 exons (Figure 1) [60]. Major splice events occur in exons 8 and 9, which alternatively encode the C-terminal half of the third immunoglobulin-like domain (Ig3). Exclusion of exon 9 or exon 8 results in mRNA for 'b' isoforms or 'c' isoforms, respectively. Other splice events occur in exons 3 and 4. Exon 3 encodes the first immunoglobulin-like domain (Ig1) in the extracellular domain, and exon 4 encodes the acid box and heparin-binding domain. Inclusion of both exons 3 and 4 encodes mRNA for the 'longest' isoforms. Exclusion of exon 3 encodes mRNA for shorter isoforms of FGFR1, FGFR2, and FGFR3. Exclusion of both exons 3 and 4 mRNA encodes the 'shortest' isoform of FGFR2. The FGFR4 gene is composed of 18 exons and no splice variant has been described [61]. These FGFR isoforms show distinct FGF-binding specificities and tissue distributions, further increasing the complexity of the FGF-FGFR signaling system.

gene was isolated by positional cloning and was found to encode a novel single-pass transmembrane protein that is expressed predominantly in the kidney. Expression of the *klotho* gene in the *klotho* mouse was undetectable by northern blot analysis, indicating that Klotho deficiency is responsible for the syndrome resembling aging [15]. By contrast, transgenic mice that overexpress Klotho exhibited increased resistance to oxidative stress [16] and significant extension of life span [17]. These observations suggest that the *klotho* gene might function as an aging suppressor gene.

Recent studies have revealed multiple functions of Klotho protein. Most notably, Klotho protein forms a complex with several FGFR isoforms and significantly

Box 2. Characteristics of the FGF19 subfamily members

Unlike the other FGF family members, the FGF19 subfamily of ligands (the endocrine FGFs; FGF15/19, FGF21, and FGF23) are released into systemic circulation and function as hormones. Molecular mechanisms behind the endocrine mode of action might lie in the fact that they have a low affinity to heparin [59,62,63]. The majority of FGFs have a conserved heparin-binding domain and exhibit a high affinity to heparin and heparan sulfate. The high-affinity interaction between heparan sulfate and FGFs could help tether them to extracellular matrices and allow them to function in a paracrine and/or autocrine fashion. By contrast, structural analysis of FGF19 and FGF23 proteins showed that their heparin-binding region diverges from that of the other paracrine-acting FGFs; the altered topologies of heparin-binding region preclude direct interaction between heparin/heparan sulfate and backbone atoms of FGF19 and FGF23, providing structural basis for the low affinity to heparin. The weak heparin-binding activity of the FGF19 family members might enable them to be released from extracellular matrices and function as endocrine factors. However, this weak heparin-binding activity can also reduce their ability to interact with FGFRs, because heparin and heparan sulfate promote the receptor-ligand interaction [4,64]. This could be a reason that the FGF19 subfamily of ligands requires co-factors (Klothos), in addition to heparin or heparan sulfate, to increase their binding affinity to FGFRs, specifically in target tissues (Table I).

Table I. Characteristics of endocrine versus canonical FGF family members

	FGF19 subfamily	Canonical FGFs
Mode of action	Endocrine	Paracrine/Autocrine
Affinity to heparin	Low	High
Primary function	Regulation of metabolism in adults	Regulation of development and morphogenesis
Co-receptor requirement	Klotho βKlotho	None

enhances their affinity for FGF23 [18]. This discovery was prompted by the fact that FGF23-deficient mice and Klotho-deficient mice display almost identical phenotypes; not only multiple aging-like phenotypes, but also metabolic

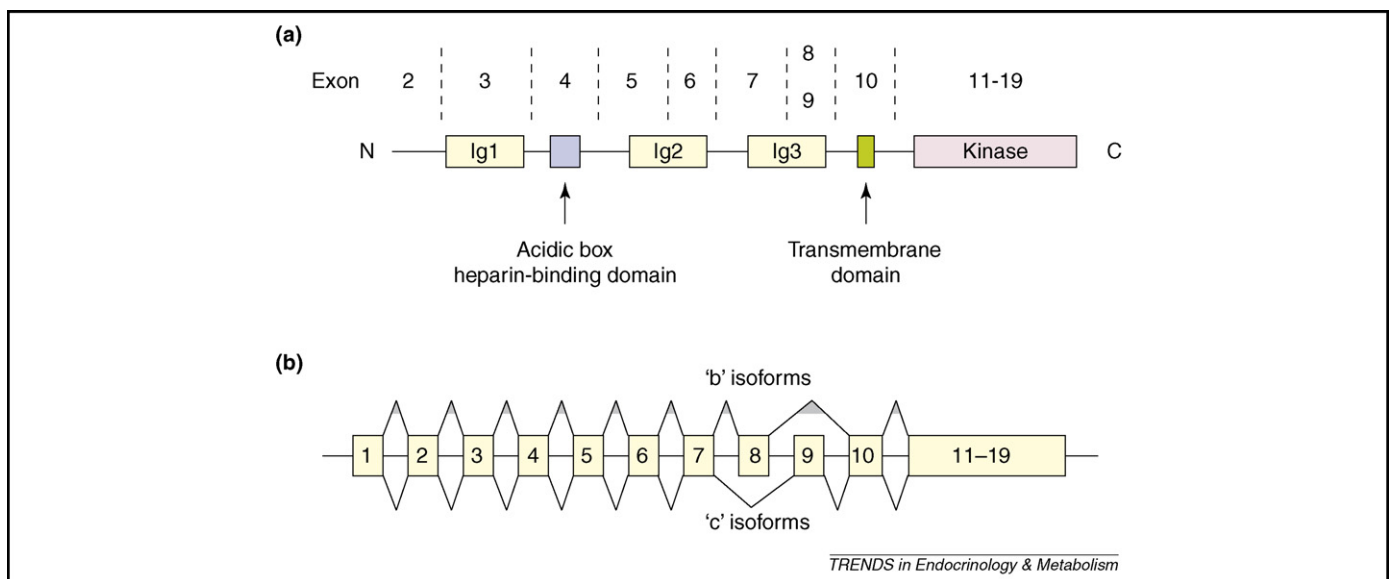


Figure 1. Structural basis of multiple FGFR isoforms. (a) General structure of FGFRs. The immunoglobulin-like (Ig) domains are involved in ligand interaction. The kinase domain is involved in tyrosine phosphorylation of FGFRs and FGF receptor substrates (FRS). (b) General structure of the FGFR1–3 genes. The shaded boxes indicate exons. Multiple isoforms of the FGFR with distinct ligand affinities are generated by alternative RNA splicing events at exons 3, 4, 8, and 9 in the FGFR1, 2, and 3 genes [18]. The major splicing occurs at exons 8 and 9 to generate 'b' and 'c' isoforms, which are preferentially expressed in epithelial lineage cells and mesenchymal lineage cells, respectively [59]. Klotho and βKlotho form complexes with 'c' isoforms.

abnormalities characterized by low blood glucose, high blood phosphate, and high active vitamin D levels in the blood [19–21]. These findings suggested that Klotho and FGF23 work in a common molecular pathway. Co-immunoprecipitation experiments indicated that Klotho binds to FGFR1c, 3c, and 4 with higher affinity than to the other FGFR isoforms. Binding of Klotho to these FGFRs significantly increases their affinity for FGF23 and facilitates activation of FGF signaling by FGF23, resulting in phosphorylation of FRS2 α (FGF receptor substrate 2 α) and ERK (extracellular signal-regulated kinase) [18,22]. These results were confirmed later in an independent study [10], which also demonstrated that Klotho-deficient mice had >1,000-fold higher serum FGF23 levels than wild-type mice. This finding further supports the notion that FGF23 requires Klotho as a co-receptor for its biological activity that induces renal phosphate excretion and suppresses biosynthesis of active vitamin D (1,25-dihydroxyvitamin D₃), which promotes absorption of calcium and phosphate from intestine. Thus, activation of the FGF23-Klotho system induces negative phosphate balance not only by increasing renal phosphate excretion but also by decreasing intestinal phosphate absorption.

Recently, a patient carrying a loss-of-function mutation in the *KLOTHO* gene was reported to exhibit hyperphosphatemia and severe vascular calcification [23]. The Klotho-FGFR complex likely serves as the functional FGF23 receptor under physiological conditions in mice and humans. This explains why Klotho-deficient mice and FGF23-deficient mice develop identical phenotypes. Kidney-specific expression of Klotho also explains why FGF23 recognizes kidney as its target organ among many other organs that express multiple FGFR isoforms. Importantly, lowering blood phosphate levels by restricting dietary phosphate intake or by ablating vitamin D biosynthesis or vitamin D receptor in Klotho-deficient mice and FGF23-deficient mice rescues not only hyperphosphatemia but also many aging-like phenotypes [20,24–26]. These observations indicate that phosphate retention is toxic and primarily responsible for the aging-like phenotypes in these mutant mice. The Klotho-FGF23 system could have evolved to eliminate excess phosphate from the body and prevent phosphate toxicity.

Klotho is also expressed in the parathyroid gland [27], suggesting that the parathyroid is another target organ of FGF23. The parathyroid gland secretes parathyroid hormone (PTH) in response to low blood calcium levels. Parathyroid cells monitor blood calcium levels using a G-protein coupled receptor (calcium-sensing receptor; CaR) on the cell surface, which is activated by high extracellular calcium concentration. Activation of CaR leads to suppression of PTH expression and secretion [28]. PTH acts on kidney to suppress calcium excretion and stimulate synthesis of active vitamin D (1,25-dihydroxyvitamin D₃) that promotes absorption of calcium and phosphate from intestine [29]. However, PTH can increase blood calcium levels without concomitant increase in blood phosphate levels, because PTH also has an activity that induces renal phosphate excretion [30]. FGF23 suppresses PTH expression and secretion by activating FGFR1 and/or FGFR3 and its downstream ERK in a Klotho-dependent manner [31],

although the precise molecular mechanisms behind this remain to be determined. These observations have identified another novel endocrine axis mediated by FGF23 and Klotho between bone and parathyroid that regulates calcium-phosphate homeostasis.

FGF15/19

FGF19 (the human ortholog of mouse FGF15) is secreted from intestinal epithelial cells in response to bile acid released into the intestinal lumen upon feeding [32]. FGF15/19 reaches the liver most likely through portal circulation and suppresses expression of the *cyp7a1* gene that encodes the rate-limiting enzyme for bile acid synthesis in the liver [32]. In addition, FGF15/19 acts on the gallbladder to induce bile acid filling, thereby limiting bile acid release into intestine [33]. Thus, FGF15/19 is an essential component of a postprandial negative feedback loop that regulates bile acid synthesis and release. Mouse genetic studies have demonstrated that both FGF15-deficient mice [32] and FGFR4-deficient mice [34] displayed increased expression of the *cyp7a1* gene and bile acid synthesis. These observations suggested that FGF15 might signal through FGFR4 in the liver.

β Klotho

β Klotho was identified based on its sequence similarity to Klotho [35]. Tissue distribution of β Klotho differs from that of Klotho; β Klotho is expressed predominantly in the liver and white adipose tissue, whereas Klotho is expressed mainly in the kidney. Mice defective in β Klotho expression displayed increased bile acid synthesis [36], which was similar to FGF15- and FGFR4-deficient mice. From the analogy of the Klotho-FGF23 story, it was speculated that β Klotho might form a complex with FGFR4 and increase the affinity of FGFR4 for FGF15/19 in the liver. Three groups independently demonstrated that β Klotho forms a complex with FGFR4 and is required for FGF19 to bind FGFR4 with high affinity and exert its biological activity [37–39]. This explains why defects in FGF15, FGFR4, or β Klotho result in identical phenotypic consequences (increased bile acid synthesis in the liver). In addition, these observations have raised the possibility that the Klotho gene family might have evolved in the regulation of tissue-specific activity of the FGF19 family of ligands.

FGF21

FGF21 was identified as a liver-derived endocrine factor that stimulates glucose uptake in adipocytes [40]. FGF21 increases glucose uptake through increasing expression of glucose transporter-1 and therefore requires several hours to exert this activity. It should be noted that FGF21-induced glucose uptake is independent of insulin-induced glucose uptake; insulin induces translocation of intracellular vesicles containing glucose transporter-4 to plasma membrane and therefore increases adipose tissue glucose uptake within minutes [41]. In addition to increasing glucose uptake, FGF21 mediates many metabolic changes associated with fasting, including promotion of lipolysis in white adipose tissue and ketogenesis in the liver [42]. Furthermore, FGF21 can induce torpor in mice, a

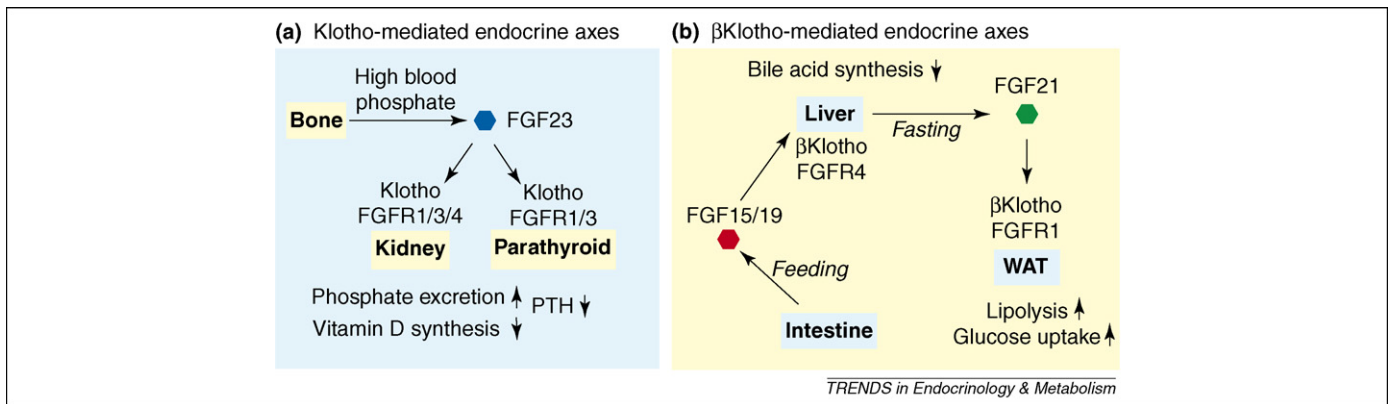


Figure 2. Endocrine axes mediated by the FGF and Klotho families. (a) Endocrine axes mediated by Klotho. FGF23 is secreted from bone in response to high blood phosphate levels and acts on kidney and parathyroid gland where Klotho and FGFR1c/3c/4 are expressed. FGF23 suppresses phosphate resorption and vitamin D biosynthesis in the kidney to prevent phosphate retention. (b) Endocrine axes mediated by β Klotho. FGF15/19 is secreted from intestine upon feeding and acts on liver where β Klotho and FGFR4 are expressed. FGF15/19 suppresses bile acid synthesis in the liver. FGF21 is secreted from liver upon fasting and acts on white adipose tissue (WAT) where β Klotho and FGFR1c are expressed. FGF21 promotes lipolysis and glucose uptake in WAT.

short-term hibernation state in which animals can save energy by reducing physical activity and body temperature [42].

It was reported that, like FGF19, FGF21 requires β Klotho for high affinity binding to FGFRs [43]. In fact, β Klotho forms a complex with FGFR1c and FGFR4 to increase their affinity for FGF21. These results were confirmed later by two independent studies [44,45]. Although both FGF19 and FGF21 require β Klotho for high-affinity binding to FGFR1c and FGFR4, they differ in the ability to activate FGFR4; FGF19 can signal through both β Klotho-FGFR1c and β Klotho-FGFR4 complexes, whereas FGF21 can signal only through the β Klotho-FGFR1c complex and not through the β Klotho-FGFR4 complex [37]. Because liver predominantly expresses FGFR4, FGF21 cannot activate FGF signaling in the liver, even though FGF21 indeed binds to the β Klotho-FGFR4 complex [37]. This could prevent FGF21 from acting as an autocrine factor in the liver. By contrast, FGF21 can act specifically on white adipose tissue where FGFR1 and β Klotho are expressed [37]. These observations have raised the possibility that the primary activity of FGF21 might be to promote lipolysis in adipocytes; FGF21-induced increase in ketogenesis in the liver could be a result of increased fatty acid input into the liver due to increased lipolysis in white adipose tissue. This notion remains to be determined.

These studies have established a novel concept that tissue-specific expression of the Klotho gene family members determines target organs of the FGF19-subfamily of ligands (Figure 2). This could represent a new mechanism for regulating ligand-receptor interaction in target organs.

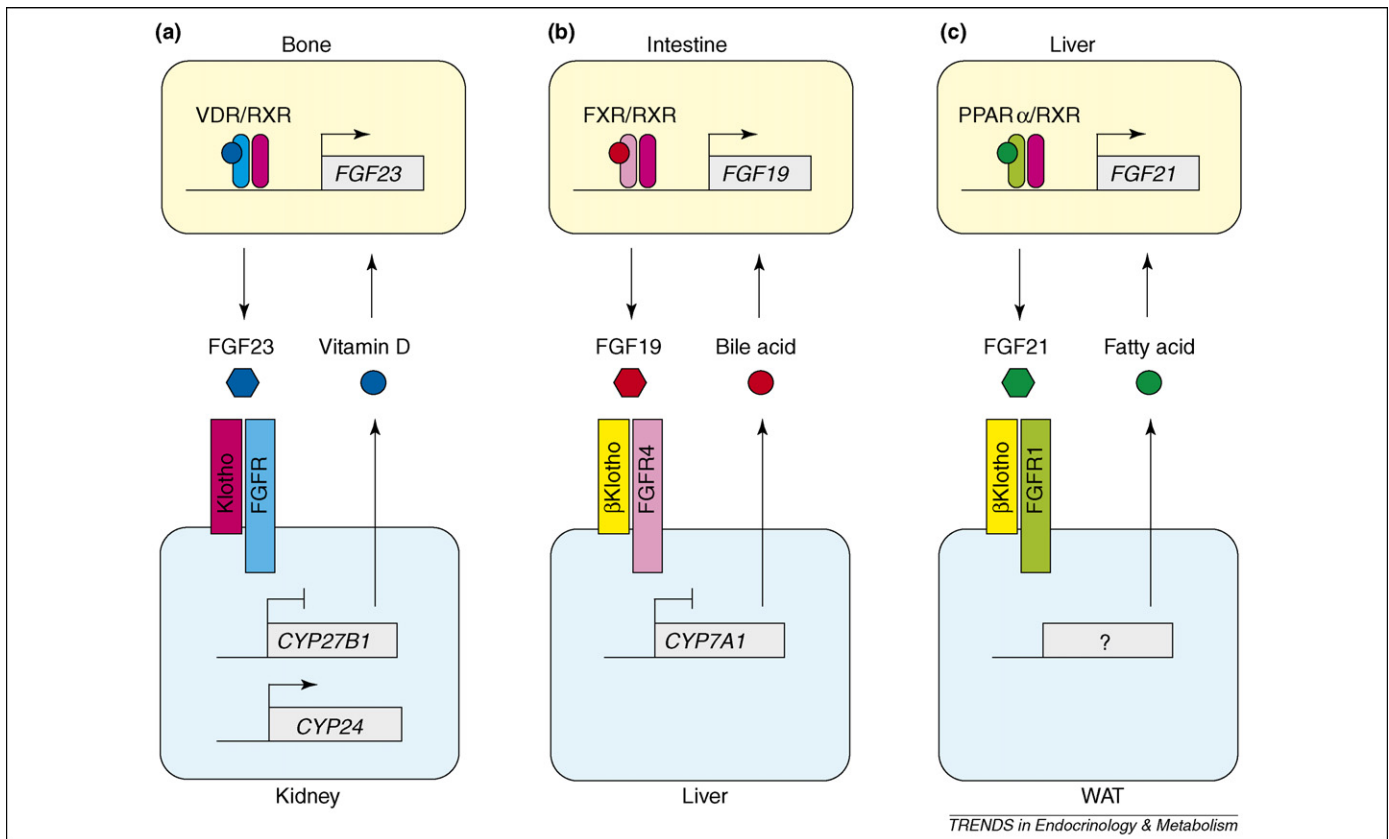
Nuclear receptor regulation of the FGF19 family FGF23

Expression of the FGF19 subfamily of ligands is regulated by nuclear receptor systems (Figure 3). Administration of active vitamin D (1,25-dihydroxyvitamin D₃) induces expression of FGF23 mRNA in the bone through activating vitamin D receptor (VDR) and increases serum levels of FGF23 protein in mice [9]. The ability of 1,25-dihydrox-

vitamin D₃ to increase FGF23 expression appears independent of its ability to increase blood phosphate levels through promoting intestinal absorption of phosphate, because 1,25-dihydroxyvitamin D₃ increases serum FGF23 levels before it increases serum phosphate levels [9,46]. The increased FGF23 then acts on kidney to suppress expression of the *cyp27b1* (1 α -hydroxylase) gene and induce expression of the *cyp24* (24-hydroxylase) gene [8,9,47]. 1 α -hydroxylase is the enzyme that synthesizes active vitamin D by converting 25-hydroxyvitamin D₃ to 1,25-dihydroxyvitamin D₃. By contrast, 24-hydroxylase is the enzyme that inactivates 1,25-dihydroxyvitamin D₃ by catalyzing it to calcitriolic acid [29]. Therefore, suppression of 1 α -hydroxylase and induction of 24-hydroxylase by FGF23 lead to reduction of 1,25-dihydroxyvitamin D₃ levels, which in turn suppresses FGF23 expression in the bone, forming a negative feedback loop in the regulation of vitamin D homeostasis [48]. This also explains why FGF23- and Klotho-deficient mice have paradoxically high levels of 1,25-dihydroxyvitamin D₃ despite the fact that their blood phosphate levels are elevated.

FGF15/19

Expression of FGF15/19 is regulated by bile acid and its nuclear receptor FXR (farnesoid X receptor) in the small intestine [49–51]. Bile acid released into intestinal lumen upon feeding enters intestinal epithelial cells in the process of enterohepatic circulation and binds to FXR. The ligand-bound FXR forms a heterodimer with retinoid X receptors (RXRs) and functions as a transcription factor that increases expression of FGF15/19. The increased FGF15/19 then acts on the liver through the β Klotho-FGFR4 complex to suppress expression of the *cyp7a1* gene [32,37], which encodes the rate-limiting enzyme in the cascade of bile acid synthesis from cholesterol. Again, this indicates the existence of a negative feedback loop in the regulation of bile acid homeostasis mediated by members of the FGF19, Klotho, and cytochrome P450 gene families. It is likely that FGF15/19 might be indirectly involved in cholesterol metabolism through regulating bile acid homeostasis [52].



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Figure 3. Feedback regulation of activity and expression of endocrine FGFs. Feedback loops mediated by the FGF and Klotho families share a common molecular design composed of the FGF, FGFR, Klotho, nuclear receptor, and cytochrome p450 (CYP) gene family members and lipophilic ligands. **(a)** The bone-kidney endocrine axis. Active form of vitamin D (1,25-dihydroxyvitamin D₃) binds to vitamin D receptor (VDR). The ligand-bound VDR forms a heterodimer with retinoid X receptor (RXR) and functions as a transcription factor that increases expression of FGF23 in osteocytes. Secreted FGF23 activates FGFR1c, 3c and/or 4 bound by Klotho in renal tubular cells and suppresses expression of the *CYP27B1* gene, which encodes an enzyme that synthesizes 1,25-dihydroxyvitamin D₃. In addition, FGF23 increases expression of the *CYP24* gene, which encodes an enzyme that hydrolyzes and inactivates 1,25-dihydroxyvitamin D₃. Thus, FGF23 reduces 1,25-dihydroxyvitamin D₃ levels. **(b)** The intestine-liver endocrine axis. Feeding increases release of bile acid that binds to farnesoid X receptor (FXR). The ligand-bound FXR forms a heterodimer with RXR and functions as a transcription factor that increases expression of FGF19 in intestinal epithelial cells. Secreted FGF19 activates FGFR4 bound by β Klotho in hepatocytes and suppresses expression of the *CYP7A1* gene, which encodes the rate-limiting enzyme for bile acid synthesis. Thus, FGF19 reduces bile acid synthesis in the liver. **(c)** The liver-WAT (white adipose tissue) endocrine axis. Fasting increases release of fatty acids that bind to peroxisome proliferator-activated receptor α (PPAR α). The ligand-bound PPAR α forms a heterodimer with RXR and functions as a transcription factor that increases expression of FGF21 in hepatocytes. Secreted FGF21 activates FGFR1c bound by β Klotho in adipocytes and promotes lipolysis. A CYP gene(s) regulated by the FGF21- β Klotho system in adipocytes remains to be identified.

FGF21

Expression of FGF21 in the liver is regulated by peroxisome proliferator-activated receptor α (PPAR α) [42,53]. PPAR α forms a heterodimer with RXR and binds to PPAR α -response elements in the promoter region of the *FGF21* gene to increase FGF21 expression. Consistent with the fact that PPAR α is activated upon fasting, expression of *FGF21* mRNA in the liver and serum levels of FGF21 are increased upon fasting. PPAR α is required for metabolic adaptation induction in the liver and other tissues in response to fasting, including stimulation of gluconeogenesis, ketogenesis, and fatty acid oxidation [54–56]. The ability of PPAR α to induce these fasting responses is largely mediated by FGF21, because knock-down of FGF21 in the liver results in impaired ketogenesis and fatty acid oxidation in mice [53]. It is interesting that hormones mediating fasting signals (FGF21) and fed signals (FGF15/19) share the same receptors (β Klotho-FGFR1c and β Klotho-FGFR4) [37], although the physiological significance of this remains to be determined.

Summary

Identification of the Klotho gene family of transmembrane proteins as co-receptors for the FGF19 subfamily of ligands has unveiled novel endocrine axes that regulate various metabolic processes through feedback regulatory loops that share a common molecular design composed of the FGF, FGFR, Klotho, nuclear receptor, and cytochrome p450 (CYP) gene family members and lipophilic ligands [57]. Specifically, 1) the bone-kidney endocrine axis mediated by the FGF23-Klotho system. FGF23 is secreted primarily from osteocytes in the bone and acts on the kidney where Klotho is expressed, resulting in prevention of phosphate retention through suppressing phosphate resorption and vitamin D biosynthesis. Vitamin D increases FGF23 expression in the bone through activating a nuclear receptor VDR. 2) The bone-parathyroid endocrine axis mediated by the FGF23-Klotho system. Bone-derived FGF23 acts on the parathyroid gland where Klotho is expressed and inhibits production and secretion of PTH that promotes vitamin D biosynthesis. 3) The intestine-liver-gallbladder endocrine axis mediated by the FGF15/

19- β Klotho system. Upon feeding, FGF15/19 is secreted from intestine in response to bile acid released into the intestinal lumen. FGF15/19 then acts on the liver and gallbladder where β Klotho is expressed, and suppresses bile acid synthesis and induces gallbladder filling. Bile acid increases FGF15/19 expression in intestine through activating a nuclear receptor FXR. 4) The liver-fat endocrine axis mediated by the FGF21- β Klotho system. FGF21 is secreted from the liver upon fasting and acts on white adipose tissue where β Klotho is expressed to promote glucose uptake and lipolysis. Fasting induces FGF21 expression in the liver through activating a nuclear receptor PPAR α .

Because most tissues express one or more FGFR isoforms, tissue-specific expression of Klotho or β Klotho virtually determines target organs of endocrine FGFs. Thus, tissues that express Klotho or β Klotho are potential targets of endocrine FGFs. Indeed, the parathyroid gland was identified as one of the target organs of FGF23 because it expressed Klotho [31]. The fact that Klotho is expressed in several other endocrine organs including the pituitary gland, testis, ovary, placenta, and prostate [58] suggests the existence of novel endocrine axes between the bone and these endocrine organs mediated by the FGF23-Klotho system. Analysis of tissue distribution of Klotho and β Klotho might lead to identification of novel endocrine axes mediated by endocrine FGFs that regulate a variety of metabolic processes.

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