The Role and Regulatory Mechanism of Fibroblast Growth Factor 23 in Bone Mineral Metabolism (Postprint)

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Date: 2017-11-08T00:00:00+00:00

Abstract

The bone-derived hormone fibroblast growth factor 23 (FGF23) mediates a negative feedback loop composed of the parathyroid gland, kidney, bone, and vitamin D, establishing a "bone-kidney-parathyroid" endocrine axis and playing an important role in bone mineral metabolism. Calcium, phosphorus, iron, vitamin D, parathyroid hormone (PTH), fibroblast growth factor receptor (FGFR)/FGF, and post-translational protein modifications regulate the secretion, activity, and intracellular processes of FGF23. As research progresses, novel therapies targeting FGF23 for the treatment of bone mineral metabolism disorders have been explored. This article reviews the research progress on the role of FGF23 in bone mineral metabolism and its regulatory mechanisms, aiming to provide a reference basis for related research.

Full Text

Fibroblast Growth Factor-23: Functions in Bone Mineral Metabolism and Regulatory Mechanisms

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Abstract

Fibroblast growth factor-23 (FGF23), a bone-derived hormone, plays a crucial role in bone mineral metabolism by mediating negative feedback loops involv-

ing the parathyroid gland, kidney, bone, and vitamin D, thereby establishing a "bone-kidney-parathyroid" endocrine axis. The secretion, activity, and intracellular processing of FGF23 are regulated by calcium, phosphorus, iron, vitamin D, parathyroid hormone (PTH), fibroblast growth factor receptors (FGFR)/FGF signaling, and post-translational protein modifications. As research on FGF23 has advanced, novel therapeutic strategies targeting FGF23 have been developed for treating bone mineral metabolism disorders. This review summarizes current research progress on the functions and regulatory mechanisms of FGF23 in bone mineral metabolism to provide a reference basis for related studies.

Keywords: fibroblast growth factor-23; bone mineral metabolism; calcium; phosphorus; iron

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Calcium and phosphorus are essential mineral elements for animal growth, skeletal development, and physiological function maintenance, forming the basic components of bone as hydroxyapatite crystals. Calcium and phosphorus metabolism constitutes a critical aspect of bone mineral metabolism and significantly influences bone turnover. Hypophosphatemia leads to rickets in young animals and osteoporosis in adult livestock and laying poultry, while hyperphosphatemia not only delays bone mineralization but also causes ectopic vascular calcification through calcium-phosphate crystal precipitation, subsequently activating calcium-regulating hormones and indirectly affecting bone formation. Iron, another important mineral involved in bone metabolism, hydroxylates proteins and regulates renal vitamin D secretion, playing a vital role in bone collagen synthesis; both excess and deficiency can directly or indirectly impact bone growth. FGF23, a hormone discovered in recent years, interacts with PTH and vitamin D to maintain calcium and phosphorus homeostasis. Furthermore, in certain hypophosphatemic bone diseases, FGF23 and iron mutually regulate each other to maintain bone mineral balance. The regulation of FGF23 is a complex, multi-layered process involving calcium, phosphorus, iron, PTH, vitamin D, FGFR/FGF signaling, and post-translational modifications. Abnormalities in FGF23 secretion, activity, or intracellular processing can cause bone mineral metabolism disorders and various bone diseases. In clinical practice, several FGF23-targeted therapies have been explored. This review examines recent advances in understanding FGF23' s role in bone mineral metabolism and its regulatory mechanisms.

1. Biological Characteristics of FGF23

FGF23 belongs to the fibroblast growth factor (FGF) family of polypeptide hormones and is synthesized and secreted by osteoblasts and osteocytes, with slight interspecies variations. In humans, the FGF23 gene is located on chromosome 12p13 and encodes a protein of 251 amino acids with a relative molecular mass of 32 kDa. Two forms exist in circulation: the active full-length mature FGF23, which contains FGFR binding sites at its N-terminus and α-Klotho (αKL) bind-

ing sites at its C-terminus; and inactive cleaved fragments, including N-terminal FGF23 and C-terminal FGF23 (cFGF23). FGFR exhibits very low binding affinity for FGF23 and requires αKL as a co-receptor to achieve high-affinity binding. FGF23 primarily acts on the kidney and parathyroid gland through the mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) signaling pathway, interacting with minerals (calcium, phosphorus, iron), vitamin D, and hormones such as PTH to indirectly regulate bone metabolism.

2.1. FGF23 and Vitamin D, PTH, Calcium, and Phosphorus

FGF23 reduces vitamin D activity through dual mechanisms: downregulating renal 1α-hydroxylase (Cyp27b1) expression to inhibit active vitamin D synthesis, while upregulating vitamin D-24-hydroxylase (Cyp24a1) expression to convert active vitamin D into less active metabolites. Conversely, vitamin D is an important regulator of FGF23 that directly promotes FGF23 secretion and enhances its activity. Studies have shown that vitamin D administration significantly increases circulating FGF23 levels in mice, and in cultured osteoblasts, vitamin D induces FGF23 expression and dose-dependently enhances its promoter activity [3].

FGF23 inhibits PTH synthesis and secretion through multiple pathways: acting on vitamin D receptors and calcium-sensing receptors in the parathyroid gland to suppress parathyroid cell proliferation, reducing PTH mRNA synthesis, and upregulating parathyroid 1α-hydroxylase (Cyp27b1) expression to promote active vitamin D synthesis, which in turn inhibits PTH. The parathyroid gland secretes PTH and expresses αKL, and FGF23 requires binding to αKL to exert its inhibitory effects, thereby establishing a potential negative feedback loop between the parathyroid gland and bone. Research has demonstrated that PTH and its downstream orphan nuclear receptor Nurr1 promote FGF23 mRNA synthesis in osteosarcoma cell lines [4]. In mice with diet-induced renal failure exhibiting significantly elevated circulating FGF23, parathyroidectomy reduces blood FGF23 levels [5].

Calcium homeostasis is maintained through integrated mechanisms: decreased blood calcium stimulates PTH secretion, which acts on the distal renal tubule to promote calcium reabsorption [6] while increasing renal 1α-hydroxylase (Cyp27b1) expression to enhance active vitamin D synthesis and raise blood calcium levels. Elevated blood calcium promotes intestinal absorption of calcium and phosphorus, which through negative feedback inhibits parathyroid PTH secretion, thereby reducing blood calcium levels.

Phosphorus metabolism is systemically regulated by an endocrine feedback loop involving the intestine, kidney, and bone, with the kidney serving as the primary organ for short-term blood phosphorus regulation. FGF23 controls blood phosphorus levels through several mechanisms: high blood phosphorus stimulates bone secretion of FGF23 [7], which acts on the kidney to directly downregulate

sodium-phosphate cotransporters NaPi-2a and NaPi-2c in proximal tubular epithelial cells, thereby reducing phosphorus reabsorption. FGF23 also inhibits PTH synthesis and secretion, indirectly affecting NaPi activity to decrease urinary phosphorus reabsorption and increase urinary phosphorus excretion. Additionally, FGF23 suppresses active vitamin D synthesis, and since intestinal phosphorus absorption depends on active vitamin D, this results in reduced intestinal phosphorus uptake [8], ultimately lowering blood phosphorus levels.

FGF23 interacts with vitamin D and PTH to regulate calcium and phosphorus metabolism, reducing blood calcium and phosphorus concentrations. Conversely, high calcium and phosphorus promote FGF23 secretion. Exogenous calcium supplementation slightly enhances FGF23 activity, while calcium channel blockers inhibit FGF23 activity [9]. In vitro cell culture experiments with low calcium combined with vitamin D or phosphorus (which normally upregulate FGF23 expression) fail to increase FGF23 expression [10].

2.2. FGF23 and Iron

Clinical and translational studies demonstrate that iron inhibits bone secretion of FGF23, while iron deficiency stimulates FGF23 transcription and increases circulating FGF23 levels. Pregnant women and adolescents are more prone to iron deficiency than the general population and have higher susceptibility to autosomal dominant hypophosphatemic rickets (ADHR) [11], with elevated blood FGF23 and cFGF23 levels that negatively correlate with blood iron concentration [12]. In patients with X-linked hypophosphatemia (XLH), blood FGF23 and cFGF23 levels are even higher, with cFGF23 showing significant negative correlation with blood iron [13]. These findings indicate that despite different pathogenic mechanisms in ADHR and XLH, both conditions exhibit increased blood cFGF23 levels that negatively correlate with blood iron concentration.

2.3. FGF23 and FGFR/FGF

FGF23 activity and expression are regulated by FGFR signaling. Studies show that FGFR1 agonists enhance FGF23 promoter activity, while dominant-negative FGFR1 constructs and inhibitors of phospholipase C and MAPK suppress promoter activity [14]. Treatment of wild-type mice with a monoclonal activating antibody against FGFR1 (R1Mab) increases blood FGF23 levels and induces mild hypophosphatemia, while stimulating FGF23 mRNA expression and secretion in mouse osteoblasts. FGFR1 knockout suppresses FGF23 activity [15].

Fibroblast growth factor 2 (FGF2) regulates bone secretion of FGF23 in concert with FGFR through distinct mechanisms: high molecular weight FGF2 (HMW-FGF2) activates FGFR1 signaling, while low molecular weight FGF2 activates cell surface FGFR. Bone-specific overexpression of HMW-FGF2 promotes FGF23 secretion and causes hypophosphatemic rickets. Bone marrow stromal cells from HMW-FGF2 transgenic mice exhibit high FGF23 levels and

intrinsic mineralization defects that can be ameliorated by FGF23-neutralizing antibodies, MAPK inhibitors, and FGFR tyrosine kinase inhibitors [16]. In HMW-FGF2 knockout mice, FGF23 mRNA expression is reduced, blood phosphorus and PTH levels are normal, bone mineral density is increased, and osteoblast activity is enhanced [17].

2.4. FGF23 and Post-Translational Modifications

The cellular regulatory system for FGF23 influences not only mRNA expression but also modulates protein levels through stepwise post-translational modifications according to real-time physiological status. Furin, a subtilisin-like proprotein convertase, cleaves FGF23 between arginine 179 (Arg179) and serine 180 (Ser180). In contrast, polypeptide N-acetylgalactosaminyltransferase 3 (GalNAcT3) specifically recognizes threonine 178 (Thr178) of FGF23 and catalyzes O-glycosylation at this site, preventing proteolytic cleavage and maintaining FGF23 stability and activity [18-19]. Family with sequence similarity 20, member C (FAM20C) phosphorylates FGF23 at Ser180, which inhibits GalNAcT3-mediated O-glycosylation and renders FGF23 susceptible to intracellular proteolytic cleavage [20]. Family with sequence similarity 20, member A (FAM20A) is a pseudokinase that forms a functional complex with FAM20C to enhance FAM20C activity [21], and their interplay can augment or diminish FGF23 activity.

3. Novel Therapies Targeting FGF23 for Bone Mineral Metabolism Disorders

Abnormalities in FGF23 secretion, activity, or intracellular processing can cause bone mineral metabolism disorders, leading to various genetic and acquired bone diseases. With deeper understanding of FGF23, several innovative therapies have emerged. These include inhibiting FGF23 activity to treat tumor-induced osteomalacia, an acquired hypophosphatemic disorder associated with FGF23 [22]; FGF23-neutralizing antibodies that nearly completely reverse the hypophosphatemic rickets phenotype in XLH mice [23]; and administration of the anti-FGF23 monoclonal antibody KRN23 to XLH patients, which improves biochemical parameters without causing hyperphosphatemia despite sustained elevations in blood vitamin D for over 50 days, while maintaining normal blood and urinary calcium levels [24]. In ADHR patients with iron deficiency who exhibit high blood FGF23 levels, iron supplementation improves biochemical indices including blood iron, phosphorus, vitamin D, and tubular maximum phosphate reabsorption/glomerular filtration rate. Once blood iron levels stabilize, rickets medications and iron can be gradually reduced or discontinued, with blood FGF23 levels normalizing and hypophosphatemia improving [25].

4. Summary and Outlook

Calcium, phosphorus, and iron are crucial minerals involved in bone metabolism, and their metabolic disturbances can cause various bone diseases. FGF23 comprehensively regulates bone mineral metabolism, including calcium, phosphorus, and iron homeostasis, through the "bone-kidney-parathyroid"endocrine axis. Numerous factors collectively influence FGF23 secretion, activity, and intracellular processing, and novel FGF23-targeted therapies for bone mineral metabolism disorders have been developed through research. This has transformed our understanding of bone mineral metabolism, making FGF23 a current research hotspot.

Bone mineral metabolism disorders are common and cause significant economic losses in livestock and poultry. Identifying and eliminating their causes is highly meaningful, not only for reducing economic losses in conventional livestock but also for protecting valuable rare wildlife, pets, and specialty economic animals. Unfortunately, current FGF23 research primarily focuses on animal models and humans, with few reports on livestock and poultry. However, livestock diseases share similarities with human conditions, offering several research avenues for investigators in animal nutrition and disease: validating correlations between blood FGF23 levels and bone diseases to assess its potential as an independent predictive biomarker; conducting in-depth molecular studies on FGF23 receptors and mechanisms to provide theoretical foundations for accurately determining dietary mineral (calcium, phosphorus, iron) and vitamin D requirements; and developing treatments for bone mineral metabolism disorders.

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