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Review

Phosphate Homeostasis, Inflammation and the Regulation of FGF-23

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Key Words
$1,25(OH)_2D_3$ • Orai1 • iron deficiency • TNFα • TGFβ2

Abstract
Fibroblast growth factor 23 (FGF23) is released primarily from osteoblasts/osteocytes in bone. In cooperation with the transmembrane protein Klotho, FGF23 is a powerful inhibitor of 1α 25OH Vitamin D Hydroxylase (Cyp27b1) and thus of the formation of 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$). As $1,25(OH)_2D_3$ up-regulates intestinal calcium and phosphate absorption, the downregulation of $1,25(OH)_2D_3$ synthesis counteracts phosphate excess and tissue calcification. FGF23 also directly inhibits renal phosphate reabsorption. Other actions of FGF23 include triggering of cardiac hypertrophy. FGF23 formation and/or release are stimulated by $1,25(OH)_2D_3$, phosphate excess, Ca^{2+}, PTH, leptin, catecholamines, mineralocorticoids, volume depletion, lithium, high fat diet, iron deficiency, TNFα and TGFß2. The stimulating effect of $1,25(OH)_2D_3$ on FGF23 expression is dependent on RAC1/PAK1 induced actin-polymerisation. Intracellular signaling involved in the stimulation of FGF23 release also includes increases in the cytosolic Ca^{2+} concentration ($[Ca^{2+}]i$) following intracellular Ca^{2+} release and store-operated Ca^{2+} entry (SOCE). SOCE is accomplished by the Ca^{2+} release-activated calcium channel protein 1 (Orai1) and its stimulator stromal interaction molecule 1 (STIM1). Expression of Orai1, SOCE and FGF23-formation are up-regulated by the proinflammatory transcription factor NFκB. The present brief review describes the cellular mechanisms involved in FGF23 regulation and its sensitivity to both phosphate metabolism and inflammation. The case is made that up-regulation of FGF23 by inflammatory mediators and signaling may amplify inflammation by inhibiting formation of the anti-inflammatory $1,25(OH)_2D_3$.

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Introduction

Fibroblast growth factor 23 (FGF23) is primarily released from bone [1], to a lesser extent from the spleen and brain [1], and, under pathophysiological conditions, from other organs, including kidney [2]. FGF23 adjusts the regulation of calcium and phosphate metabolism to the mineralization of bone [1]. FGF23 down-regulates renal 1α 25OH vitamin D hydroxylase (Cyp27b1) and thus curtails the formation of 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$) [1]. Moreover, FGF23 accelerates $1,25(OH)_2D_3$ degradation by the up-regulation of 25-hydroxyvitamin D 24-hydroxylase (Cyp24) [1]. As $1,25(OH)_2D_3$ is a powerful stimulator of intestinal absorption and renal reabsorption of calcium and phosphate, the downregulation of $1,25(OH)_2D_3$ by FGF23 decreases plasma calcium and phosphate concentrations [1]. Furthermore, FGF23 directly inhibits the renal phosphate reabsorption and thus enhances renal phosphate excretion [1]. FGF23 thus limits intestinal phosphate uptake and increases renal phosphate elimination when bone mineralization is abundant [1]. FGF23 release is further stimulated by $1,25(OH)_2D_3$ or activation of the vitamin D receptor (VDR), a negative feedback loop contributing to the limitation of $1,25(OH)_2D_3$ formation [1].

The effect of FGF23 on renal $1,25(OH)_2D_3$ formation requires the cooperation with the co-receptor Klotho [1]. $1,25(OH)_2D_3$, calcium and phosphate plasma levels are excessive in mice deficient in either FGF23 or Klotho leading to severe tissue calcification [1, 3, 4], and a variety of disorders including deranged bone mineralization, growth deficit, cardiac hypertrophy, emphysema, hypogonadism, infertility, hearing loss, cognitive impairment, decreased physical performance, thymus atrophy, reduced fat tissue and sarcopenia [1, 2]. As a result, life span is dramatically decreased in FGF23- or Klotho-deficient animals [1]. The tissue calcification is not simply due to calcium phosphate super-saturation, but results from the triggering of osteogenic/chondrogenic trans-differentiation of affected cells [5]. In Klotho-deficient mice, the excessive formation of $1,25(OH)_2D_3$ is followed by dramatic increases in FGF23 release and plasma levels [1].

Parathyroid hormone (PTH) is another powerful stimulator of FGF23 synthesis and release. PTH acts in bone via the orphan nuclear receptor Nurr1 to enhance FGF23 transcription. Thereby, PTH enhances renal phosphate excretion directly and indirectly via FGF23. FGF23, in turn, suppresses PTH secretion in a Klotho-dependent manner, a mechanism defective in patients with chronic kidney disease with reduced levels of Klotho.

The present brief review discusses cellular mechanisms involved in the regulation of FGF23 formation/release and its involvement in inflammatory disease.

Stimulators of FGF23 release

In addition to excess of phosphate and $1,25(OH)_2D_3$, enhanced extracellular Ca^{2+} concentrations, parathyroid hormone (PTH), leptin, catecholamines, mineralocorticoids, volume depletion, lithium, inflammation, iron deficiency, high fat diet, TNFα and TGFß2 stimulate FGF23 release from bone [1, 6-13]. The increase of FGF23 plasma levels following high-fat diet is at least partially due to upregulation of TNFα [12].

In chronic kidney disease (CKD), FGF23 plasma levels are typically elevated prior to development of hyperphosphatemia and hyperparathyroidism [1, 14]. Common complications of CKD include inflammation and iron deficiency, both stimulators of FGF23 production in bone [11]. In contrast to Klotho-deficient mice, $1,25(OH)_2D_3$ plasma levels are decreased in CKD [2, 15]. Thus, $1,25(OH)_2D_3$ cannot account for the excessive FGF23 plasma levels in CKD. Treatment of uremic rats with neutralizing anti-FGF23 antibodies restores $1,25(OH)_2D_3$ plasma levels, but aggravates hyperphosphatemia and increases mortality [14]. FGF23 plasma concentrations are further enhanced in polycystic kidney disease [16], diabetic nephropathy [17], shiga toxin- induced hemolytic uremic syndrome [18] and nephrotic syndrome [19].

Cellular mechanisms regulating FGF23 release

FGF23 formation and release are inhibited by the phosphate-regulating gene with homology to endopeptidase (PHEX) and dentin matrix protein or cyclin D binding myb-like protein 1 (DMP-1) [1]. Loss of function mutations of PHEX or DMP-1 lead to dramatic increases in FGF23 release from bone with increased circulating levels of FGF23 [20, 21]) impaired $1,25(OH)_2D_3$ formation, renal phosphate wasting, hypophosphatemia, and impairment of bone mineralization [21-24], as amplified below.

The stimulating effect of $1,25(OH)_2D_3$ on FGF23 expression requires polymerized actin filaments which are regulated by the pro-inflammatory transcription factor nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB), ras-related C3 botulinum toxin substrate 1 (*Rac1*) and p21 protein-activated kinase 1 (*PAK1*) [25].

NFκB stimulates the expression of Orai1, a Ca^{2+} channel activated by the Ca^{2+} sensor STIM1 following Ca^{2+} depletion of intracellular Ca^{2+} stores [26]. Orai1/STIM1 thus affect store-operated Ca^{2+} entry (SOCE) [26]. Osteoblasts express Orai1, and SOCE in those cells is disrupted by pharmacological inhibition of either NFκB or Orai1 [26]. Stimulation of SOCE enhances FGF23 expression, an effect mimicked by the Ca^{2+} ionophore ionomycin [26]. Conversely, FGF23 expression is suppressed by pharmacologic or siRNA-mediated knockout of Orai1, as well as pharmacologic inhibition of NFκB [26]. Thus, FGF23 formation is up-regulated by Ca^{2+} entry through NFκB-dependent Orai1 [26]. As phosphate-induced osteogenic/chondrogenic transdifferentiation involves TGFß and NFκB [27, 28], it is tempting to speculate that TGFß, NFκB-activity, Orai1 expression and SOCE contribute to the phosphate-induced stimulation of FGF23 formation. However, further experiments are required to fully elucidate the role of this signaling pathway in the stimulation of FGF23 by phosphate.

NFκB-activity, Orai1 expression and SOCE are upregulated by aldosterone-inducible serum & glucocorticoid inducible kinase SGK1 [29]. Aldosterone up-regulates SOCE and FGF23 formation in osteoblasts. The effect of aldosterone on FGF23 expression is abrogated by blockage of the mineralocorticoid receptor and by pharmacological inhibition of SGK1, NFκB, and Orai1 [30]. FGF23 plasma concentration in mice increases following administration of the mineralocorticoid DOCA or by salt depletion [30]. Renal salt loss and extracellular volume depletion probably account for the enhanced FGF23 plasma levels in mice lacking functional thiazide-sensitive NaCl transporter NCC [10], mice which express the inactive Ste20-Related Proline/Alanine-Rich Kinase (SPAK) [31] or mice expressing the inactive oxidative stress-responsive kinase (OSR) [32]. It is unclear whether enhanced FGF23 levels in annexin 7- deficient mice [33] are due to volume depletion or inflammation.

NFκB-activity, Orai1 expression and SOCE are further up-regulated by treatment of osteoblasts with lithium [34]. Lithium-treatment enhances FGF23 plasma concentrations in both mice [35] and humans [36]. The effect of lithium on FGF23 in osteoblasts is disrupted by pharmacological inhibition of Orai1 und NFκB. Lithium thus stimulates FGF23 expression/release at least in part by stimulating NFκB with subsequent up-regulation of Orai1 and SOCE [34].

Orai1 expression and SOCE are downregulated by the energy sensing AMP-activated kinase (AMPK) [37, 38]. Accordingly, FGF23 gene transcription is enhanced in AMPKα1-knockout mice [39]. FGF23 gene transcription in UMR106 osteoblast-like cells is decreased by the AMPK activator, 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) and increased by the AMPK inhibitor, dorsomorphin dihydrochloride (compound C) [39].

The up-regulation of FGF23 by inflammation and iron-deficiency involves activation of hypoxia-inducible factor (HIF)-1α [40].

CO-releasing molecule (CORM-2) stimulates FGF23 release *in vivo* and *in vitro* [41] thus decreasing the formation of $1,25(OH)_2D_3$ [41].

FGF23 cleavage

FGF23 plasma levels are a function not only of FGF23 formation/release, but as well of FGF23 cleavage [13]. FGF23 cleavage is stimulated by iron deficiency [40] and the enhanced formation of FGF23 in iron deficiency is thus paralleled by enhanced FGF23 cleavage [40]. In autosomal dominant hypophosphatemic rickets (ADHR) gain-of-function mutations in FGF23 prevent the proteolytic FGF23 cleavage leading to phosphate wasting [13]. The extent depends on the rate of FGF23 formation which is enhanced by iron deficiency [13].

Clinical significance of FGF23 excess

The excessive increase of plasma FGF23 concentrations, compromized $1,25(OH)_2D_3$ formation and renal phosphate wasting in patients carrying loss of function mutations of PHEX [20, 22]) interferes with bone mineralization leading to several clinical disorders including limb deformity, short stature, arthritis, enthesopathy, hearing impairment, optic atrophy and nephrocalcinosis [21-24]. Loss of function mutations of DMP-1 lead to rickets/osteomalacia later during childhood or in adulthood [23].

The FGF23 excess in Klotho deficient mice is paralleled by pathological cardiac remodeling with left ventricular hypertrophy and myocardial fibrosis [42], activated cardiac Fgf23/Fgf receptor (Fgfr) 4/calcineurin/nuclear factor of activated T cell (NFAT) signaling, induction of pro-hypertrophic NFAT target genes including *Rcan1, bMHC*, brain natriuretic peptide (*BNP*), and atrial natriuretic peptide (*ANP*), activated cardiac ERK1/2 and enhanced expression of Tgf-β1, *collagen I*, and Mmp2 [42]. Those effects are not observed in other mice with excessive FGF23 and may require hyperphosphatemia and hypercalcemia [42].

FGF23 in the regulation of inflammation

The sensitivity of FGF23 formation to TGFß2, TNFα and the pro-inflammatory transcription factor NFκB links FGF23 release and $1,25(OH)_2D_3$-formation to inflammation (Fig. 1). As a matter of fact, the effects of $1,25(OH)_2D_3$ are not limited to regulation of mineral metabolism but affect a variety of functions including inhibition of inflammation [43-46]. It is tempting to speculate that the stimulation of FGF23 by inflammation functions as an amplifyer, as it suppresses the formation of the anti-inflammatory $1,25(OH)_2D_3$. Along those lines, the enhanced release of FGF23 during inflammation [47] and mineralocorticoid excess could explain the enigmatic association between enhanced FGF23 plasma levels and the unfavorable course of several diseases including CKD [2].

Clearly, additional investigations are warranted to elucidate the impact of the FGF23/$1,25(OH)_2D_3$ axis on inflammatory disease.

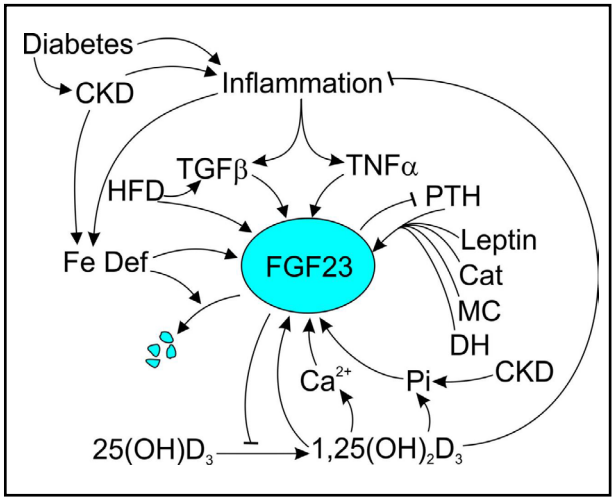

Fig. 1. Regulation of FGF23 and its impact on inflammation. Abbreviations: Cat = catecholamines, CKD = chronic kidney disease, DH = dehydration, Fe Def = iron deficiency, HFD = high fat diet, MC = mineralocorticoids, Pi = phosphate.

Conclusion

Stimulators of FGF23 formation and release include $1,25(OH)_2D_3$, phosphate excess, Ca^{2+}, PTH, leptin, catecholamines, mineralocorticoids, volume depletion, lithium, high fat diet, iron deficiency, TNFα and TGFß2. Signaling involved in the stimulation of FGF23 formation includes RAC1/PAK1 dependent actin-polymerisation and up-regulation of the transcription factor NFκB followed by increased expression of Ca^{2+} channel protein Orai1 and its stimulator STIM, which accomplish store operated Ca^{2+} entry (SOCE). The sensitivity of FGF23 formation to TNFα, TGFß2 and the proinflammatory transcription factor NFκB establishes a link between mineral metabolism and inflammation.

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Disclosure Statement

The authors declare they have no conflict of interest.

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