Fibroblast Growth Factor 23–Mediated Bone Disease

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KEYWORDS

• *FGF23* • α-Klotho • Hypophosphatemia • Hyperphosphatemia • Rickets
• Osteomalacia

KEY POINTS

- Fibroblast growth factor (FGF) 23, one of the circulating FGFs, is produced by osteocytes and exerts its action on the kidney and parathyroid glands to maintain phosphate homeostasis and regulate vitamin D synthesis and metabolism.
- *FGF23* is regulated by systemic factors such as 1,25-dihydroxyvitamin D3 ($1,25(OH)_2D_3$), phosphate, calcium, parathyroid hormone, iron, and local factors expressed in bone, such as *PHEX* (phosphate-regulating gene with homologies to endopeptidases on the X chromosome), matrix extracellular phosphoglycoprotein (MEPE), dentin matrix protein 1 (*DMP1*), and ectonucleotide pyrophosphatase/phosphodiesterase 1 (*ENPP1*); *FGF23* requires the presence of α-Klotho for interaction with and activation of the FGF receptor (FGFR) 1c.
- *FGF23* excess results in hypophosphatemia secondary to reduced renal phosphate reabsorption and dysregulated vitamin D synthesis, which lead to bone demineralization and fractures.
- Causes of *FGF23* excess include ectopic production of *FGF23* (tumor-induced osteomalacia), *FGF23* missense mutations that prevent *FGF23* protein degradation (autosomal dominant hypophosphatemic rickets), and overproduction of *FGF23* in bone through either overgrowth of dysplastic bone (fibrous dysplasia, osteoglophonic dysplasia) or deficiency in local regulatory factors, such as *PHEX* (X-linked hypophosphatemic rickets), *DMP1* (autosomal recessive hypophosphatemic rickets [ARHR] 1), *ENPP1* (ARHR2).
- *FGF23* deficiency results in hyperphosphatemia secondary to renal phosphate retention and increased $1,25(OH)_2D_3$ level, which lead to ectopic calcification in various tissues known as tumoral calcinosis. Mechanisms of *FGF23* deficiency include inactivating mutations in the *FGF23* gene, defective *FGF23* glycosylation due to N-Acetylgalactosaminyl transferase-3 (*GALNT3*) mutations that render *FGF23* more susceptible to proteolytic cleavage and inactivation, and *FGF23* resistance due to mutations in α-Klotho, the *FGF23* co-receptor.

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INTRODUCTION

The fibroblast growth factors (FGFs) are a family of proteins with numerous important functions in both embryonic and adult tissues. Based on their mechanism of action, they have been classified into 2 main groups: the canonical FGFs, which exert their function by binding to and activating FGF receptors (FGFRs); and the noncanonical FGFs, which exert their actions intracellularly, independent of FGFRs. Although most FGFs are membrane-bound proteins exerting their effects in an autocrine or paracrine fashion, a subgroup of FGFs, including FGF19, FGF21, *FGF23*, circulate in the bloodstream to affect distant target organs in a true endocrine fashion.

The discovery and characterization of *FGF23* has significantly improved the understanding of phosphate and vitamin D homeostasis and many clinical disorders of phosphate homeostasis.

PATHOPHYSIOLOGY

Fibroblast Growth Factor 23 and Klotho

The *FGF23* gene is located on human chromosome 12p13 and consists of 3 coding exons. The full-length *FGF23* is a 32-kDa glycoprotein (251 amino acids) with an N-terminal hydrophobic region and a C-terminal domain. The N-terminus contains the FGFR binding domain and the C-terminus is important for interaction with its coreceptor, α-Klotho. Cleavage of *FGF23* occurs at the 176RXXR179/S180 motif, a subtilisin-like proprotein convertase proteolytic site, resulting in 2 inactive cleavage products (**Fig. 1**). Glycosylation at the S129 residue by UDP-N-acetyl-alpha-D-galactosamine: polypeptide N-acetylgalactosaminyl transferase-3 (*GALNT3*) results in resistance to proteolytic cleavage and inactivation.[1] For activation of the FGFR, *FGF23* requires the presence and direct interaction with its obligate coreceptor, α-Klotho. The equal importance of both molecules is suggested by the finding of a similar phenotype with increased serum phosphate levels in both Klotho[2] and *FGF23* knockout mice.[3]

Although FGFRs are ubiquitously distributed in the body, α-Klotho expression is limited to certain tissues, such as the proximal and distal renal tubules, parathyroid, pituitary, heart, and testis. Here, the membrane-bound α-Klotho interacts with several FGFRs, such as FGFR1c, FGFR3c, and FGFR4, therefore it determines tissue specificity for *FGF23*.[4] A soluble form of Klotho, produced by cleavage of the membrane-bound Klotho ectodomain, is released into the circulation and exerts both paracrine and endocrine functions independent of the *FGF23* signaling pathway.[5] Unlike the tissue-specific form, the soluble Klotho shows enzymatic activity with important implications in mineral homeostasis. By preventing endocytosis of tubular reabsorption of phosphate (TRP) V5, it enhances renal calcium reabsorption[6] and, through proteolysis

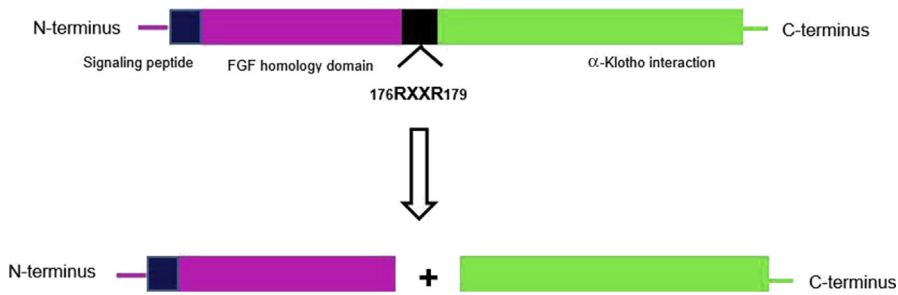

Fig. 1. Cleavage of the intact *FGF23* at the 176RXXR179 motif resulting in N-terminal and C-terminal inactive domains.