CHAPTER 3

FGF23 AND SYNDROMES OF ABNORMAL RENAL PHOSPHATE HANDLING

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Abstract: Fibroblast growth factor 23 (FGF23) is part of a previously unrecognized hormonal bone-parathyroid-kidney axis, which is modulated by 1,25(OH)2-vitamin D (1,25(OH)2D), dietary and circulating phosphate and possibly PTH. FGF23 was discovered as the humoral factor in tumors that causes hypophosphatemia and osteomalacia and through the identification of a mutant form of FGF23 that leads to autosomal dominant hypophosphatemic rickets (ADHR), a rare genetic disorder. FGF23 appears to be mainly secreted by osteocytes where its expression is up-regulated by 1,25(OH)2D and probably by increased serum phosphate levels. Its synthesis and secretion is reduced through yet unknown mechanisms that involve the phosphate-regulating gene with homologies to endopeptidases on the X chromosome (PHEX), dentin matrix protein 1 (DMP1) and ecto-nucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1). Consequently, loss-of-function mutations in these genes underlie hypophosphatemic disorders that are either X-linked or autosomal recessive. Impaired O-glycosylation of FGF23 due to the lack of UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyl-transferase 3 (GALNT3) or due to certain homozygous FGF23 mutations results in reduced secretion of intact FGF23 and leads to familial hyperphosphatemic tumoral calcinosis. FGF23 acts through FGF-receptors and the coreceptor Klotho to reduce 1,25(OH)2D synthesis in the kidney and probably the synthesis of parathyroid hormone (PTH) by the parathyroid glands. It furthermore synergizes with PTH to increase renal phosphate excretion by reducing expression of the sodium-phosphate cotransporters NaPi-IIa and NaPi-IIc in the proximal tubules. Loss-of-function mutations in these two transporters lead to autosomal recessive Fanconi syndrome or to hereditary hypophosphatemic rickets with hypercalciuria, respectively.
INTRODUCTION

Identification of the genetic causes of rare familial disorders of renal phosphate handling has provided, over the past decade, important novel insights into the regulation of mammalian phosphate homeostasis. This chapter will provide an update on the current knowledge of the pathophysiology, the clinical presentation, diagnostic evaluation and therapy of FGF23-dependent and -independent disorders of phosphate homeostasis and tissue mineralization.

AUTOSOMAL DOMINANT HYPOPHOSPHATEMIC RICKETS
(ADHR, OMIM 193100)

Genetics of ADHR

In 1971 Bianchine et al described a small family, in which male-to-male transmission suggested an autosomal dominant form of hypophosphatemic rickets (ADHR, for a full list of abbreviations see Table 1). 1 Subsequently, Econs and McEnery identified a large family, in which numerous members are affected by ADHR. 2 The authors were able to map the disorder to a locus on chromosome 12p13, 3 which ultimately allowed identification of the genetic mutation leading to this rare inherited form of hypophosphatemia. 4 The incidence of ADHR is unknown; thus far, only a few families have been described in which hypophosphatemia follows an autosomal dominant trait. 4,6 ADHR thus appears to be much less frequent than X-linked hypophosphatemia (XLH), which affects approximately 1:20,000 births. 7 The ADHR patients described to date carry a heterozygous mutation in fibroblast growth factor 23 (FGF23, chromosome 12p13.3) at amino acid positions 176 or 179, a site for cleavage by subtilisin-like proprotein convertases (SPC) 4–6 (Fig. 1). Although the exact mechanism is unknown, it appears that ADHR mutations enhance resistance towards SPC leading to diminished intracellular cleavage of intact FGF23. The resulting secretion of inappropriate amounts of biologically active FGF23 suggests that the identified amino acid changes are “gain-of-function” mutations, which lead to renal phosphate wasting, possibly combined with an abnormal feed-back regulation of FGF23 synthesis, as discussed below.

The phosphaturic action of FGF23 requires the coreceptor alpha Klotho (KL, also see below). A genetic defect leading to a disorder resembling ADHR has recently been reported in a single sporadic case of hypophosphatemia. 8 The patient, a 13 month old girl, presented with rickets due to excessive renal phosphate excretion and hyperparathyroidism and cytogenetic studies revealed a de novo chromosomal translocation with the breakpoint being located adjacent to the gene encoding KL. As a result, plasma levels of soluble KL and KL-associated beta-glucuronidase activity were increased, along with increased levels of immunoreactive FGF23. It remains uncertain, however, whether the elevated levels of FGF23 and/or PTH are solely responsible for the increased urinary excretion of phosphate, or whether the elevated levels of soluble Klotho contribute to the abnormal renal handling of this mineral.

FGF23 Synthesis and Secretion

The main sources of FGF23 are osteocytes and osteoblasts in the skeleton, but low levels of uncertain biological significance can be detected in the ventrolateral thalamic nucleus,