Review Article

Molecular Bases of Diseases Characterized by Hypophosphatemia and Phosphaturia: New Understanding

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Abstract. Serum phosphate levels are regulated in both calcium-dependent and -independent fashions. Active vitamin D increases while PTH decreases serum phosphate levels in association with the elevation of serum calcium. On the other hand, a calcium-independent phosphaturic factor, historically called phosphatonin is believed to exert a physiological function based on findings in hereditary and tumor-induced diseases characterized by hypophosphatemia with normocalcemia. Among them, autosomal dominant hypophosphatemic rickets (ADHR) has contributed greatly to its elucidation because the gene responsible for ADHR encodes fibroblast growth factor 23 (FGF23) that has been found to have a phosphaturic effect. In addition, FGF23 has been proved to be involved in most cases of oncogenic osteomalacia and X-linked hypophosphatemic rickets that are also characterized by hypophosphatemia and normocalcemia. Moreover, familial tumoral calcinosis, which represents the metabolic mirror image of hypophosphatemic conditions, is caused by a loss-of-function mutation in the *FGF23* gene in some patients. Very recently, hereditary hypophosphatemic rickets with hypercalciuria has been found to be caused by mutations in the *SLC34A1* gene which encodes a type of sodium phosphate cotransporter. These findings may provide new strategies for treating patients with abnormal phosphate metabolism.

Key words: hypophosphatemia, phosphaturia, rickets, FGF23, phosphate

Introduction

The serum phosphate level is regulated by many factors within a narrow range (1, 2). Among them, active vitamin D and PTH are representative: the former increases and the latter decreases the level of serum phosphate. However, active vitamin D and PTH increase serum calcium levels at the same time, and their serum levels are in turn tightly regulated by

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serum calcium which forms a negative feedback. Therefore, the main target of active vitamin D and PTH is believed to be the serum calcium level, not the phosphate level. Actually, diseases associated with impaired vitamin D and PTH metabolism show abnormal levels of both phosphate and calcium, but hypocalcemia creates clinical problems such as tetany and convulsion more frequently.

On the other hand, hereditary and neoplastic diseases manifesting hypophosphatemia associated with normocalcemia are well known, and phosphaturia is the main cause of hypophosphatemia in these diseases (3, 4). Phosphaturia means reduced renal phosphate reabsorption which is diagnosed by low %TRP (tubular reabsorption of phosphate) and more accurately low Tmp/GFR (maximal tubular reabsorption of phosphate per glomerular filtration rate). These diseases involve X-linked and autosomal dominant hypophosphatemic rickets, hereditary hypophosphatemic rickets with hypercalciuria and oncogenic osteomalacia. They can be categorized as hypophosphatemic rickets because rickets or osteomalacia is commonly observed. Recently, the molecular pathophysiological bases of these diseases have been elucidated, leading to better understanding of the regulation of serum phosphate levels. In this review article, we briefly summarize the recent findings of phosphate level regulation and try to update the knowledge of readers in this field.

FGF23

FGF23 (fibroblast growth factor 23) has been proved to be a phosphaturic factor by analysis using molecular genetics and molecular biology as described below. However, this does not exclude any phosphaturic factors other than FGF23. *FGF23* is a member of the *FGF* family that consists of 22 kinds of *FGF* in human (5). The encoded whole human FGF23 product,

including a signal sequence and a mature or active form of human FGF23, consist of 251 and 227 amino acids, respectively. The cleavage site of mature FGF23 is between amino acid 179 and 180, and the cleavage leads to inactivation in terms of a phosphaturic effect. It is not fully understood which cells produce FGF23 physiologically, but bone, especially osteoblasts, is thought to be the main source of circulating FGF23 (6). In addition, FGF23 mRNA has been detected by RT-PCR or *in situ* hybridization in the heart, liver, thyroid and parathyroid, small intestine, thymus and brain (7, 8).

A receptor for FGF23 is so far not conclusive at the molecular level. Authentic FGF receptors consist of 4 members and their alternative splicing forms, and Yu *et al.* reported that c splice isoforms of FGF receptor types 1-3 and FGF receptor 4 are activated by FGF23 (9). However, their specificity and affinity as well as physiological relevance remain to be questioned. Thus, the molecular mechanism underlying FGF23 action is unclear, although FGF23 exerts a final effect on sodium-phosphate transporter in renal tubules (10). In addition, FGF23 decreases the production of 1,25-dihydroxyvitamin D [$1,25(\text{OH})_2\text{D}$] in renal tubules, and ablation of the *Fgf23* gene leads to the enhanced expression of 1 α -hydroxylase, the key enzyme of 1,25(OH) $_2$ D production (11, 12). Low or relatively low levels of 1,25(OH) $_2$ D are clinically known in patients with oncogenic osteomalacia and X-linked hypophosphatemia, although hypophosphatemia itself is a stimulatory factor of 1,25(OH) $_2$ D production. FGF23 is the missing link between hypophosphatemia and low levels of 1,25(OH) $_2$ D, whereas 1,25(OH) $_2$ D increases the expression of FGF23 (13–16). In addition, phosphate up-regulates the expression of FGF23 (17). In response to the increase in dietary phosphate intake, serum levels of FGF23 seem to elevate and probably function to increase the urinary wasting of phosphate to maintain serum phosphate levels (14, 18).

Autosomal Dominant Hypophosphatemic Rickets

Autosomal dominant hypophosphatemic rickets (ADHR, MIM 193100) is a rare disease characterized by low levels of serum phosphate, elevated levels of alkaline phosphatase (ALP) and phosphaturia, and is inherited in an autosomal dominant fashion. In 2000, genetic analysis of families with the disease successfully identified that the *FGF23* gene is responsible for the disease (19). Amino acids from 176 to 179 form a consensus sequence for proteolytic cleavage, RXXR, where X indicates any amino acid. Mutations of the *FGF23* gene in patients with the disease are located in the conserved amino acid in this consensus sequence (R176Q, R179W and R179 where Q and W mean Gln and Trp, respectively) (20). Thus, mutant FGF23 proteins are resistant to cleavage and remains as an active intact form, leading to exaggerated urinary excretion of phosphate (Fig. 1) (20). The *FGF23* gene is the first and only *FGF* in which mutations are associated with human disease. The discovery of FGF23 as a cause of ADHR has shed light on the humoral regulation of the reabsorption of phosphate in renal tubules.

Oncogenic Osteomalacia

Oncogenic osteomalacia (OOM), also called tumor-induced osteomalacia, is a paraneoplastic syndrome characterized by hypophosphatemia and osteomalacia, although it is very rare in childhood. Thus, it is an acquired form of hypophosphatemic osteomalacia. Tumors that cause OOM are usually benign, and are often mesenchymal tumors. When the tumor is excised, the patients recover from hypophosphatemia and osteomalacia. Thus, a phosphaturic factor secreted by the tumor is surmised. By analysis of the gene expression of the tumor, several factors including FGF23, MEPE (matrix extracellular phosphoglycoprotein), Frizzled-Related Protein-4 and FGF7 have been

Fig. 1 FGF23 is involved in hypophosphatemic rickets. FGF23 is a secreted protein which has phosphaturic effects and is cleaved to an inactive form. Thus, the amount of the intact form is limited in normal conditions. In contrast, the serum levels of the intact form of FGF23 are elevated in three diseases of hypophosphatemic rickets. The resistance to cleavage due to mutations in the FGF23 gene is the underlying mechanism of autosomal dominant phosphatemic rickets (ADHR). Overproduction in a tumor leads to hypophosphatemic rickets in oncogenic osteomalacia (OOM)/tumor-induced osteomalacia (TIO). The *PHEX* gene is responsible for X-linked hypophosphatemic rickets (XLH), although the role of the mutant *PHEX* protein in elevated levels of serum FGF23 in XLH remains unclear.

reported as causal factors of OOM (11, 21–23). However, in most cases, OOM is caused by the overproduction of FGF23 by tumors (Fig. 1) (24, 25). Indeed, ectopic overproduction of FGF23 mimics OOM, including the reduced expression of sodium phosphate cotransporter type IIa, which is a key molecule of phosphate reabsorption in the renal tubules, in mice (26).

X-linked Hypophosphatemic Rickets

X-linked hypophosphatemic rickets (XLH, MIM 307800) is the most familiar form of hypophosphatemic rickets to pediatricians. In

1995, the gene responsible for the disease was identified as *PHEX* (phosphate regulating gene with homologies to endopeptidases on the X chromosome) (27). Originally it was named *PEX*, but the name was changed to *PHEX* because *PEX* is the name of the gene involved in peroxisome. To date, nearly 200 mutations have been found in the *PHEX* gene and they are listed at <http://www.phexdb.mcgill.ca>. The *PHEX* gene encodes the proteolytic enzyme belonging to endopeptidases. *PHEX* is mainly expressed in osteoblasts and osteocytes (27). The substrate of *PHEX* remains unknown, although FGF23 is a good candidate because inactive *PHEX* leads to an increased amount of the active form of FGF23 (28). However, an increasing number of reports support the conclusion that *PHEX* does not cleave FGF23 (29). Nevertheless, patients with XLH show high concentrations of intact FGF23, although the levels vary from upper normal to 20 times higher. Some data suggest FGF23 overproduction in XLH, although the role of *PHEX* in overproduction remains unclear (30, 31). Thus, FGF23 is involved in hypophosphatemia and phosphaturia in XLH as well as ADHR and OOM (Fig. 1). Consistent with this conclusion, there is a report showing that the neutralizing antibody against FGF23 restores the phenotype of hyp, the murine counterpart of human XLH (Aono Y *et al.* 25th annual meeting of the American Society for Bone and Mineral Research, 2003).

Hereditary Hypophosphatemic Rickets with Hypercalciuria

Hereditary hypophosphatemic rickets with hypercalciuria (HHRH, MIM 241530) is a rare autosomal recessive disease characterized by hypophosphatemia and hypercalciuria. This disease was first described in a Bedouin tribe family. Hypercalciuria is sometimes associated with renal calcification and stone formation. Serum levels of 1,25(OH)₂D are elevated and the administration of phosphate ameliorates

Fig. 2 NaPi-IIa is involved in the reabsorption of phosphate in renal tubular cells. NaPi-IIa, a type of sodium-phosphate co-transporter, is located at the brush border membrane of renal tubular cells and participates in the reuptake of phosphate as well as sodium. FGF23 or PTH translocates NaPi-IIa from the membrane to the lysosome, where NaPi-IIa is degraded, by endocytosis. In addition, FGF23 or PTH suppresses the transcription of the NaPi-IIa gene. Both results lead to the increased urinary excretion of phosphate, known as phosphaturia.

hypophosphatemia and hypercalciuria, suggesting that loss of phosphate in urine is the primary cause of this disease.

Very recently, HHRH has been shown to be caused by the abnormal function of a sodium phosphate cotransporter, NaPi-IIc (32, 33). The first candidate was NaPi-IIa, which is the predominant cotransporter expressed in proximal renal tubules and is involved in phosphate reabsorption (Fig. 2) (34, 35). The effect of FGF23 and PTH on the reabsorption of phosphate is mediated, at least in part, by the reduced expression of NaPi-IIa. Indeed, mice with deleted NaPi-IIa show hypophosphatemia and phosphaturia (36, 37). In addition, patients with mutations in the NaPi-IIa gene exhibit the phenotype of osteoporosis and nephrolithiasis (38). However, patients with HHRH do not have an abnormal *NaPiIIa* gene (39). NaPi-IIc is encoded by *SLC34A1* (Solute Carrier Family 34,

Sodium Phosphate Cotransporter Member 1) and its expression is developmentally regulated in proximal renal tubules and is involved in the reabsorption of phosphate (40). FGF23 levels are low normal or reduced in patients with HHRH (41).

Familial Tumoral Calcinosis

Familial tumoral calcinosis (FTC, MIM 114120 or 211900) is characterized by ectopic and vascular calcification especially in the hip, elbow and shoulder, hyperphosphatemia with normocalcemia and elevated or normal levels of $1,25(\text{OH})_2\text{D}$. FTC is inherited both in an autosomal recessive and dominant mode. FTC seems to represent the metabolic mirror image of hypophosphatemic conditions, which are characterized by decreased serum phosphate levels, reduced tubular phosphate reabsorption and rickets. A loss-of-function type *GALNT3* gene or the *FGF23* gene is the cause of the disease. The *GALNT3* gene encodes UDP-N-acetyl- α -D-galactosamine:polypeptide N-acetylgalactosaminyltransferase 3 (ppGalNAc-T3) which suggests that the requirement of glycosylation for the activation of FGF23 (42, 43); however, the actual binding site of glycation is unclear. It is likely that mutated FGF23 found in the disease is structurally compromised and unstable, which could result in the overproduction of partially- or non-functional FGF23 protein. Secretion of the wild-type product of FGF23 is also impaired and this explains the dominant inheritance.

Other Diseases Related to FGF23

McCune-Albright syndrome (MAS, MIM 174800) is caused by the somatic gain-of-function mutation of the *GNAS* gene encoding a signal transducer, $\text{Gs}\alpha$ and is characterized by skin café-au-lait spots, polyostotic fibrous dysplasia and endocrine abnormalities. Endocrine abnormalities

include precocious puberty, hypersecretion of adrenal hormones (ex. Cushing syndrome) and pituitary hormones (ex. pituitary gigantism). Hypophosphatemia is sometimes observed in patients with McCune-Albright syndrome. We, as well as others, have reported elevated levels of FGF23 in patients with MAS and hypophosphatemia (41, 44). Cells of osteogenic lineage comprising osteoblasts, abnormal osteoblasts and osteocytes in dysplastic bone predominantly express FGF23 mRNA in patients with MAS and hypophosphatemia. On the other hand, serum levels of FGF23 are not significantly elevated in patients with MAS without hypophosphatemia.

Congenital microvillous atrophy is associated with chronic diarrhea and its rare complication is hypophosphatemic rickets due to the massive loss of phosphate in urine and watery stools (45). This disease is extremely rare, and the role of FGF23 in this disease remains to be elucidated.

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