New Horizon of X-Linked Hypophosphatemia: Overview

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Abstract. The overview on X-linked hypophosphatemia (XLH) was presented by summarizing the current findings on the relationships between PHEX and FGF23 as well as on the homeostasis of extracellular phosphorus and vitamin D metabolism. There are urgent needs in the identification of phosphatonin. Concerning FGF23, its expression mechanisms, physiological roles, as well as the intracellular signaling pathway should be clarified.

Key words: autosomal dominant hypophosphatemic rickets (ADHR), FGF23, 1α,25-(OH)2-D3, PHEX, X-linked hypophosphatemia (XLH)

In this overview, I would like to summarize the current situation on the investigations of X-linked hypophosphatemic rickets (XLH). In these 10 yr, the causative gene of XLH and also the several molecules presumably related to the pathogenesis of XLH were identified one after another. There have remained, however, many unclear and confusing matters in the pathogenesis of XLH.

The regulation of extracellular phosphorus in the body is carried out by 4 systems. These are; intestinal absorption, entrance and exit between the bones, and also between the muscles and the soft tissues, and finally, excretion through the kidneys. In adults, about 6 g of phosphorus are filtrated daily by the kidney glomerulus but most of them are re-absorbed by the tubules. The parathyroid hormone (PTH) acts as an enhancer of phosphorus excretion by stimulating the tubules while active vitamin D, 1α,25-(OH)2-D3 (1,25D), enhances the re-absorption by also acting on the tubules. The intestinal absorption of phosphorus is also under the regulation of 1,25D (Fig. 1). Consequently, homeostasis in phosphorus is different from that of calcium; in that if the amount of phosphorus from the intestinal absorption is decreased over a certain level, phosphorus is no longer excreted through the kidneys. On the other hand, when the re-absorption of phosphorus by the tubules is disturbed and phosphorus loss occurs, the bone disorders such as rickets and osteomalacia are inevitably elicited. XLH is an archetypical disorder that occurs in such circumstances. Since massive phosphorus excretion associated with hypophosphatemia is seen in the patients with XLH; this disease was initially considered as one of the kidney diseases and the responsible gene was supposed to code phosphate transporter located in renal proximal tubular membrane. While renal phosphate transporting system had been identified as 3 types of sodium dependent phosphate co-transporter (Npt1, 2, 3) and the major mechanism of the massive phosphaturia seemed to be decreased expression of Npt2 on the luminal membrane of the renal proximal tubule, this gene does not
localize on X-chromosome. And about 10 yr ago, it was clarified that XLH is caused by the abnormality in the PHEX gene encoding the endopeptidase (1).

In fact, various types of mutations such as in splicing, insertion, deletion, nonsense and missense have been described by the PHEX gene. The first problem was that the PHEX that is not expressed in the kidneys affects the kidney; some kind of humoral factors that collaborate with abnormal PHEX are necessary. As to this conceivable factor, Dr. Drezner proposed a molecule that functions as a phosphaturic factor and the substrate for PHEX and named it phosphatonin (2). The idea was that the normal PHEX inactivated phosphatonin and only limited amounts of phosphatonin worked on the kidney and that when the PHEX lost its function by the mutation, a large amount of phosphatonin reached to the kidneys, causing massive phosphaturia. Such being the case, the introduction of the normal PHEX gene to the tissue other than kidney might rescue the disease phenotype. Significant amount of PHEX gene expression was identified in bone marrow cells, thus we tried the bone marrow transplantation from a normal mouse to the hyp mouse, which is a murine homologue of human XLH. And as the result, we confirmed that an increase in the Npt2, and also the serum phosphorus was elevated (3). After that, however, it was also reported that even with the over-expression of PHEX or with the promoter of osteocalcin, the phenotypes of the hyp mice could not be rescued (4, 5).

Thus, the physiological roles of PHEX in the hypophosphatemia remain unknown. Aside from these difficulties, however, the most pressing problem is to identify the aforementioned phosphatonin. The first candidate for the phosphatonin is the fibroblast growth factor 23 (FGF23). This factor was identified as a responsible factor for TIO (tumor induced osteomalacia), and for a similar disease, autosomal dominant hypophosphatemic rickets (ADHR) at almost the same time. The specific expression of FGF23 mRNA in the tumor of TIO was identified. The serum levels of FGF23 were abnormally high in TIO and it decreased soon after eradication of the causative tumor (6). Soon after that, a mutation was found in a specific region of the FGF23 molecule isolated from the patients with ADHR (7). It was considered that the increase in the levels of circulating FGF23 was caused by delayed degradation of the mutated FGF23 molecules.

There were still several problems that remained. For example, the serum levels of FGF23 in the patients with XLH are significantly high; however the values in XLH patients are markedly varied (91~2631 RU/ml) in comparison with the normal control (50.3 ± 19.0 RU/ml). And there is no relation between serum phosphorus level and FGF23. Other problems are the features on the levels of active vitamin D that are different between XLH and ADHR. In the patients with XLH, the levels of 1,25D are relatively low in conjunction with the degrees of hypophosphatemia; but in ADHR patients the stated 1,25D is absolutely low, regardless of the phosphate levels of each patient (Fig. 2). According to our study in which the
expression of 1α-hydroxylase (key enzyme of vitamin D activation in the kidneys) was examined by means of the competitive PCR, there were not any large differences in the expressions of 1α-hydroxylase between the hyp mouse and the normal mouse. On the other hand, Dr. Shimada (8) has reported that in the FGF23 deleted mouse, the serum levels of 1,25D were elevated; and they were extremely high. These evidences suggest that FGF23 has participated to some degree in the pathogenesis of XLH but the other unknown mechanisms can not be bypassed.

Currently, by summarizing all of these reports, the following scheme can be depicted (Fig. 3) (9). In normal situation, the PHEX degrades some oligopeptide substrates. Then, the substrates act on FGF23 enhancing its degradation into inactive fragments. In the case of mutated PHEX, which could not degrade oligopeptide substrates, full length active FGF23 directly bind to the renal receptors such as fibroblast growth factor receptors (FGFRs; Recent binding studies demonstrated that FGF23 binds to FGFR3C and FGFR2C). On the other hand, this substrate induces abnormality in the bones by affecting the MEPE (matrix extracellular phosphoglycoprotein). There was a recent report that MEPE is directly degraded by PHEX. Concerning FGF23, its expression mechanism and the physiological roles, as well as its intracellular signaling pathways are largely unknown; and phosphatonin has not yet been identified.
References


