Kidney and Phosphate Metabolism

Nak-Won Choi, M.D.

Department of Internal Medicine, Konyang University College of Medicine, Daejeon, Korea

The serum phosphorus level is maintained through a complex interplay between intestinal absorption, exchange intracellular and bone storage pools, and renal tubular reabsorption. The kidney plays a major role in regulation of phosphorus homeostasis by renal tubular reabsorption. Type IIa and type IIc Na\(^+\)/P\(_i\) transporters are important renal Na\(^+\)-dependent inorganic phosphate (P\(_i\)) transporters, which are expressed in the brush border membrane of proximal tubular cells. Both are regulated by dietary P\(_i\) intake, vitamin D, fibroblast growth factor 23 (FGF23) and parathyroid hormone. The expression of type IIa Na\(^+\)/P\(_i\) transporter result from hypophosphatemia quickly. However, type IIc appears to act more slowly. Physiological and pathophysiological alteration in renal P\(_i\) reabsorption are related to altered brush-border membrane expression/content of the type II Na\(^+\)/P\(_i\) cotransporter. Many studies of genetic and acquired renal phosphate wasting disorders have led to the identification of novel genes. Two novel P\(_i\) regulating genes, PHEX and FGF23, play a role in the pathophysiology of genetic and acquired renal phosphate wasting disorders and studies are underway to define their mechanism on renal P\(_i\) regulation. In recent studies, sodium–hydrogen exchanger regulatory factor 1 (NHERF1) is reported as another new regulator for P\(_i\) reabsorption mechanism.

Key Words: phosphorus; sodium phosphate cotransporter proteins; PHEX; fibroblast growth factor 23; sodium–hydrogen exchanger regulatory factor 1

Introduction

Inorganic phosphate (P\(_i\)) is essential for various cellular metabolism and skeletal mineralization. It is an essential part of nucleic acids and the cell membrane, serves as an important mediator of intracellular signaling, and regulates protein activity. About 600 g (500-700 g) of phosphorus is present in normal adults, of which 80% to 85% is present in bone mineral. In serum, most of the phosphorus is present as P\(_i\) in normal concentration of 0.75 to 1.45 mmol/L (2.5 to 4.5 mg/dL). More than 85% of P\(_i\) in serum is present as the free ion and less than 15% is protein-bound. Free HPO\(_4\)^{-2} and NaHPO\(_4\) predominantly account for ~75% of the total phosphorus and free H\(_2\)PO\(_4\) accounts for ~10%. Major determinants of serum phosphorus concentration are dietary intake and gastrointestinal absorption of phosphorus, mainly via upper small intestine, urinary excretion of phosphorus, and shifts between the intracellular and extracellular spaces. Abnormalities in any of these steps can result either in hypophosphatemia or hyperphosphatemia\(^1,2\). Lower than age-appropriate levels of serum phosphorus are associated with severe skeletal defects and growth failure, unless appropriately treated\(^3,4\). The kidney is a major regulator of P\(_i\) homeostasis by reabsorptive capacity. Renal P\(_i\) excretion is the balance between free glomerular filtration and regulated tubular reabsorption. Under normal physiological conditions, 80-90% of filtered phosphorus is reabsorbed and the rest is excreted in the urine. Renal tubular reabsorption occurs primarily in proximal tubules by way of a transmembrane Na\(^+\) gradient-dependent process (Na\(^+\)/P\(_i\) cotransport) located on the apical brush border membrane\(^5\). Most of the hormonal and metabolic factors

Received October 27, 2008. Accepted November 14, 2008.
Corresponding author: Nak Won Choi, M.D.
Department of Internal Medicine, Konyang University Hospital, 685 Gosoowoondong, Seogu, Daejeon, Korea
Tel: +82-42-600-9060, Fax: +82-42-600-9092
E-mail: cnw7799@hanmail.net
that regulate renal tubular Pi reabsorption, including alterations in dietary phosphate content and parathyroid hormone, have been shown to modulate the proximal tubular membrane expression of the type II Na\(^+\)/Pi cotransporter protein\(^1\). Molecular and biochemical features of clinical disorders associated with abnormal Pi handling led to the identification of several genes and proteins involved in the maintenance of the Pi homeostasis.

Renal tubular phosphate reabsorption

1. Cellular mechanism

Renal Pi reabsorption occurs in the proximal tubule and involves the transport of Pi from the tubular lumen across the apical brush-border membrane (BBM). And then Pi absorbed by BBM Na\(^+\)/Pi cotransporters leaves the cell via the basolateral transport pathway. Na\(^+\)-dependent and Na\(^+\)-gradient (outside->inside) mechanism is maintained by the Na\(^+\),K\(^+\)-ATPase pump on the basolateral membrane.

2. Phosphate transport molecules

Three types of Na\(^+\)/Pi cotransporters (types I-III; solute carrier series SLC17, SLC34, and SLC20, respectively, in the human gene nomenclature database) have been identified in the proximal tubules of the rat kidney\(^3,4\). The type I Na\(^+\)/Pi transporter is expressed in the liver and kidney\(^5\). Its expression and activity are not regulated by the dietary phosphate or PTH status. Recent studies suggest that expression of the type I gene (Npt1) is transcriptionally regulated\(^7\) and that Npt1 may function as a modulator of intrinsic cellular Pi transport rather than a Na\(^+\)/Pi cotransporter\(^5\), but its role in the regulation of Pi homeostasis remains unclear\(^9\). By contrast, the type II Na\(^+\)/Pi cotransporter (NPT2, NaPi2, NaPi3) is the major molecule in the renal proximal tubule and is regulated by PTH, parathyroid hormone, fibroblast growth factor 23 (FGF23) (except Type IIb), and by 1,25-dihydroxyvitamin D (1,25(OH)\(_2\)D) and it is responsible for most of Pi reabsorption in the kidney and intestine\(^5,10,11\). Recently, three highly homologous isoforms of NPT2 have been identified. NPT2a (Type IIa) is mainly expressed in the kidney. The type IIa Na\(^+\)/Pi transporter (SLC34A1) is a key mediator of Pi reabsorption in the renal proximal tubules and is affected by various hormones. The type IIa and type IIc Na\(^+\)/Pi transporter is located in the apical membranes of renal proximal tubular cells\(^3\). Beck et al.\(^12\) demonstrated that disruption of the Npt2a gene in mice (Npt2a\(^−\)/ mice) leads to increased urinary Pi excretion and to a 70-80% reduction in luminal BBM Na\(^+\)-dependent Pi transport, which then results in hypophosphatemia. Type IIb Na\(^+\)/Pi cotransporter, which exhibits wide tissue distribution and is not expressed in the kidney, is likely responsible for intestinal absorption of Pi\(^13\). Type IIc Na\(^+\)/Pi cotransporter is identified as the growth-related Pi transporter expressed in the kidney\(^14\). Recent studies have led to the identification of homozygous or compound heterozygous mutations in SLC34A3, the gene encoding the Na\(^+\)/Pi cotransporter NPT2c, in patients affected by HHRH (hereditary hypophosphatemic rickets with hypercalciuria)\(^15-17\). These findings indicate that NPT2c has a more important role in phosphate homeostasis than previously thought. Regulation of the type IIc Na\(^+\)/Pi transporter by PTH and dietary phosphorus resembles that of the type IIa Na\(^+\)/Pi transporter. Increases in the expression of type IIa Na\(^+\)/Pi transporter results from hypophosphatemia quickly however, type IIc appears to act more slowly. Type III Na\(^+\)/Pi transporters have been identified and show a low homology with other Na\(^+\)/Pi cotransporters\(^18,19\). These proteins have been known as receptors for gibbon ape leukemia virus (Glvr) and murine amphotropic retrovirus (Ram-1)\(^19\). In contrast to type I and type II Na\(^+\)/Pi cotransporters, type III Na\(^+\)/Pi cotransporters (PiT1 and PiT2) are ubiquitously expressed in most species and particularly abundant in the kidney, liver, lung, muscle, heart, and brain\(^19\). Furthermore, PiT1 and PiT2 function as Na\(^-\)dependent Pi transporters\(^19\). PiT is involved in the regulation of bone mineralization. In the kidney, type III Na\(^+\)/Pi cotransporters are responsible for basolateral Pi influx in all tubular cells. Furthermore, studies suggest that elevated Pi stimulates smooth muscle cell phenotypic transition and mineralization via the activity of the type III Na\(^+\)/Pi cotransporters\(^18\). Thus, the type III transporters are likely to serve as a housekeeping function and act as important me-
diators of cell-mediated matrix mineralization.

3. physiological regulation

Physiological regulation of $P_i$ reabsorption involves, at the molecular level, an altered expression of a brush-border $Na^+/P_i$ cotransporter protein (type IIa $Na^+/P_i$ cotransporter)\(^1\). PTH, vitamin D, and dietary $P_i$ intake have long been known as major regulators of serum phosphorus\(^5\). In the proximal tubules, PTH inhibits reabsorption of phosphorus via effects on NPT2a and NPT2c\(^{11, 20, 21}\). In the proximal tubule, PTH also acts as an inducer of mRNA encoding $1,25(OH)_2D$. Proximal tubular biosynthesis of $1,25(OH)_2D$ is also induced by low serum phosphorus. Circulating $1,25(OH)_2D$ enhances the intestinal absorption of calcium and, to a lesser extent, phosphorus. It also suppresses the biosynthesis and secretion of PTH and stimulates FGF23 synthesis. Vitamin D is suggested to increase/stimulate proximal tubular $P_i$ reabsorption. $1,25(OH)_2D$ treatment of rats was found to stimulate BBM $Na^+/P_i$ cotransport\(^22\). In recent studies, not only Npt2a but also Npt2c are concerned in $P_i$ regulation. PTH and high $P_i$ intake inhibit $Na^+/P_i$ cotransport across the BBM by altered expression of Npt2a and Npt2c proteins from the BBM to the subapical compartment. On the other hand, low dietary $P_i$ intake and removal of PTH (parathyroidectomy) lead to an increase in BBM $Na^+/P_i$ cotransport\(^1\). FGF23, a novel regulator of renal $P_i$ handling, inhibits both types IIa- and IIc-mediated $Na^+/P_i$ cotransport\(^20\). Various hormonal and non-hormonal factors control proximal tubular $P_i$ reabsorption by stimulation or inhibition of BBM $Na^+/P_i$ cotransport\(^1\).

**Novel factors regulating $P_i$ homeostasis**

1. PHEX

PHEX (Phosphate regulating gene with homologies to Endopeptidase, on the X chromosome) is profusely expressed on the surface of bone and teeth. The bone expression is localized to osteoblast, osteocyte, and odontoblasts. PHEX gene expression occurs *in vitro* and *in vivo* during osteoblast differentiation, and loss of PHEX function results in defective mineralization\(^22\). PHEX also plays a major role in renal phosphate handling but is not expressed in the kidney, suggesting the secondary involvement of a circulating systemic factor. Recent studies confirm that, under normal conditions, PHEX gene expression degrades and inactivates hormone-like substances. The "circulating factor" called phosphatonininds promotes phosphate excretion and impairs bone mineralization. Therefore PHEX may also play a key role in phosphate homeostasis and mineralization\(^23\). PHEX gene mutations lead to under-expression of the $Na^+/P_i$ cotransporter in the kidney\(^24\). In patients with X-linked hypophosphatemia (XLH), inactivating mutations of PHEX probably result in a failure to inactivate the phosphatonininds.

2. FGF23

FGF23 is a recently identified member of the fibroblast growth factor family. FGF23 is thought to be one of the key molecules involved in the regulation of phosphate homeostasis and skeletogenesis\(^25\). FGF23 is required for normal phosphate balance and acts by suppressing both the reabsorption of phosphate in the renal tubule and the biosynthesis of $1,25(OH)_2D$. In human studies, and particularly in rodents, changes in serum phosphorus levels have been found to regulate serum FGF23\(^{26-28}\). FGF23 causes hypophosphatemia when injected into mice, and mice with ablation of the FGF23 gene have hyperphosphatemia and high levels of $1,25(OH)_2D$\(^29\). Furthermore, injection of FGF23 in mice decreases NPT2a levels and suppression of $1\alpha$-hydroxylase\(^30\). Excess circulating FGF23 concentration leads to marked depression in proximal renal tubular reabsorption of $P_i$. Recent studies have showed regulatory feedback mechanisms that involve the old and new regulators of phosphate homeostasis. It has been shown that $1,25(OH)_2D$ acts as a positive regulator of FGF23 expression in bone, as demonstrated by both *in vivo* and *in vitro* studies\(^31\). FGF23 expression in bone is normally suppressed by PHEX. So deficiency of PHEX results in increased serum FGF23 and renal phosphate wasting (as seen in patients with XLH). FGF23 also inhibits PTH synthesis in the parathyroid\(^32\). Recent studies suggest that FGF23 acts via known GFR receptor (FGFR). In cultured opossum
kidney cells, a cell line with a proximal tubular phenotype. FGF23 binds to the FGFR type 3c. Klotho, a membrane bound protein with β-glucuronidase activity, is also required as a co-receptor for FGF23 action. Klotho can bind FGF23, and its co-expression in cells converts FGFR1(IIIc) into a functional FGF23 receptor. The Klotho null animals show markedly elevated serum levels of FGF23. Fig. 1 shows the possible mode of action of FGF23/klotho in producing hypophosphatemia. First, FGF23 is bound to the membrane klotho/FGFR complex in the distal tubular cells or to the soluble klotho/FGFR complex in the proximal tubular cells of the kidney. Such interaction activates extracellular signal-regulated kinase (ERK) and its signaling to suppress the expression of type IIa/IIc Na+/Pi transporters in the BBM of proximal tubular cells. Alternatively, FGF23 could reduce the serum 1,25(OH)₂D₃ levels by suppression of 1α-hydroxylase. Reduction of the 1,25(OH)₂D₃ levels would result from a decrease in intestinal type IIb Na⁺/Pi transporter and also in a decrease in intestinal Pi absorption. The FGF23/klotho/FGFR signaling could cause hypophosphatemia by suppressing both intestinal Pi absorption and renal Pi reabsorption.

3. Other phosphaturic factors

A number of recent studies suggest that secreted frizzle-related protein 4 (SFRP4) and matrix extracellular phosphoglycoprotein (MEPE) may increase urinary phosphate excretion. Genetic studies of tumors inducing osteomalacia showed a high level of expression of the RNA for SFRP4 and MEPE. SFRP4 on opossum kidney epithelial cells have a reduction effect in phosphate reabsorption independent from PTH. The MEPE expression was reduced by 1,25(OH)₂D₃ in HYP mice, a model of XLH characterized by a high level of MEPE expression.

4. Sodium–hydrogen exchanger regulatory factor 1: New renal Pi-transporter regulatory protein

A recent study reported by Karim et al. presented another potential new mechanism of renal phosphate wasting: mutations in the sodium–hydrogen exchanger regulatory factor 1 (NHERF1). In the NHERF1 protein, two structural domains, named PDZ1 and PDZ2, were reported to be interacting proteins. PDZ1-domain protein interacts with the C-terminal tail of NPT2a and also NPT2c and plays an important role in renal Pi reabsorption by

---

Fig. 1. Fibroblast growth factor 23 (FGF23)/klotho action. FGFR; FGF receptor; Type IIa/IIb/IIc Na/Pi, Type IIa/IIb/IIc Na/Pi cotransporter; 24-OHase, 25-hydroxyvitamin D-24-hydroxylase; 1α-OHase, 25-hydroxyvitamin D-1α-hydroxylase.
Fig. 2. Phosphate Transport inhibition by parathyroid hormone (PTH) through sodium–hydrogen exchanger regulatory factor 1 (NHERF1) phosphorylation. PKA, protein kinase A; PKC, protein kinase C; NPT2, type II Na+/Pᵢ cotransporter; PDZK1, PDZ domain containing 1 protein; PTH1R, PTH type 1 receptor.

NPT2α⁴¹. Fig. 2 shows mechanisms of phosphorylation of NHERF1 by PTH signaling through the PTH type 1 receptor (PTH1R). Phosphorylation of NHERF1 leads to dissociation of NHERF1-NPT2α complexes, endocytosis of apical NPT2α protein, and inhibition of phosphate transport. The mechanisms of interactions between the PTH and PDZ domain containing 1 protein (PDZK1) and of PTH-induced NPT2c endocytosis remain unknown.

**Inherited and acquired renal phosphate wasting disorders**

1. **X-linked hypophosphatemia**

The most common inherited phosphate-wasting disorder, XLH, frequently becomes manifest during late infancy. The patient demonstrates skeletal deformities that include bowing of the long bones and widening of the metaphyseal region. These deformities are accompanied by diminished growth velocity, often resulting in short stature. In the adult stage, the patients can show osteomalacia, enthesopathy, degenerative joint disease, and continued dental disease. Hypophosphatemia in XLH patients is associated with inability of the renal proximal tubule to reabsorb phosphate. Despite the low serum phosphorus, serum 1,25(OH)₂D is not elevated. Serum calcium and PTH are typically normal, although some elevation of serum PTH is observed. Genetic linkage analysis of XLH homologies and following genomic studies have demonstrated inactivating mutations in PHEX, a gene located on Xp22.1⁴²,⁴³, since inactivating mutations lead to phosphate wasting by proteolytic cleavage failure of phosphatonin (PTN). However, PHEX-dependent proteolytic cleavage of FGF23 could not yet be demonstrated in vivo. Also, FGF23 cleavage in vitro was shown only in a single study and this could not be confirmed in others⁴⁴. At present, the physiological basis of PHEX remains unknown. Under normal conditions, the osteoblast produces PHEX and PTN. The PHEX protein degrades a large amount of the active phosphatonin (PTNa) to an inactive metabolite (PTNi). The remaining circulating active hormone interacts with a renal tubule cell receptor that, by unknown mechanisms and to a small degree, down-regulates the NPT2, thereby minimally compromising the transport of phosphate. In XLH, defective PHEX fails to inactivate the majority of PTNa. Thus, excessive PTNa interacts with the renal receptor and markedly decreases NPT2 mRNA and protein content (Fig. 3)⁴⁵.
2. Tumor-induced osteomalacia

Severe hypophosphatemia with osteomalacia and, if growth plates are still open, rickets, can occur as an acquired disorder in association with a tumor. Tumor extracts inhibit phosphate transport in renal epithelial cells and reduced both phosphate and calcitriol production in experimental animals. The tumor extract affects only phosphate transport, in contrast to PTH, it has no effect on calcium metabolism. Three potential phosphaturic hormones have been concerned in Tumor-induced osteomalacia (TIO): FGF23, MEPE, and SFRP4\textsuperscript{35, 36, 46, 47}. Serum FGF23 was elevated in patients with TIO and fell after surgery for removal. Clinical features are similar to XLH. Plasma calcitriol level is reduced, even though elevated levels are to be expected in the presence of hypophosphatemia. Thus, the underlying tubular defect that impairs phosphate re-absorption also appears to affect calcitriol synthesis. TIO tumor cells produce PTNa in excess. The increased PTN production, through a feedback mechanism, enhances PHEX production. However, the overproduction of PTNa exceeds the capability of PHEX to degrade sufficient amounts of the product to PTNi. Hence, in spite of enhanced PHEX, with an overabundance of PTNa, interaction with the receptor decreases the NPT2 mRNA and protein production (Fig. 4)\textsuperscript{45}.

3. Type IIa Na\textsuperscript{+}/P\textsuperscript{i} cotransporter deficiency

The homozygous ablation of Npt2a gene in mice
(Npt2a<sup>-/-</sup>) results from increased urinary phosphate excretion leading to hypophosphatemia<sup>12</sup>. Npt2c protein abundance is significantly increased in Npt2a<sup>-/-</sup> mice<sup>48</sup>, although up-regulation of Npt2c is not sufficient to compensate for loss of Npt2a function. Due to the hypophosphatemia, Npt2a-ablated mice show an appropriate elevation in the serum levels of 1,25(OH)<sub>2</sub>D leading to hypercalcemia, hypercalciuria, and decreased serum PTH levels. A study reported by Prie D et al.<sup>49</sup> showed that heterozygous mutations in the NPT2a gene may be responsible for hypophosphatemia and urinary phosphate loss in patients with urolithiasis or bone demineralization.

4. NHERF1 mutations

Recent studies from animal models suggest that NHERF1 controls renal phosphate transport. The study reported by Karim et al.<sup>38</sup> identifies NHERF1 mutations as a cause of renal phosphate loss that may increase the risk of renal stone formation or bone demineralization together with normal serum PTH concentrations. This study was carried out for the NHERF1 gene in 158 patients, 94 of whom had either nephrolithiasis or bone demineralization and identified three distinct mutations in seven patients with a low value of tubular maximal reabsorption of phosphate corrected for glomerular filtration rate (TmP/GFR). This study also showed increased PTH-induced cyclic adenosine monophosphate (cAMP) generation and then the inhibition of phosphate transport. Urinary cAMP excretion was significantly higher in the patients with NHERF1 mutations than patients without NHERF1 mutations<sup>38</sup>. PTH induced a significant decrease of phosphate uptake in all cell groups<sup>38</sup>. However, both PTH-induced cAMP generation and PTH-induced inhibition of phosphate uptake were increased in mutant NHERF1 complementary DNA (cDNA) as compared with human wild-type NHERF1 cDNA<sup>38</sup>.

5. Autosomal dominant hypophosphatemic rickets/osteomalacia

Autosomal dominant hypophosphatemic rickets (ADHR) is a rare isolated renal phosphate wasting disease with rickets or osteomalacia that is transmitted as an autosomal dominant trait. ADHR results from heterozygous mutations in FGF23 gene on chromosome 12p13<sup>50</sup>. In ADHR circulating FGF23 increased because PHEX cannot inactivate the mutated form of FGF23. Clinical manifestations are similar to X-linked disease but exhibits severe natured manifestations. Inappropriately low or normal 1,25(OH)<sub>2</sub>D levels are observed in patients with ADHR.

6. Hereditary hypophosphatemic rickets with hypercalciuria

HHRH is autosomal recessive genetic disorder caused by mutations of the renal type IIc Na<sup>+</sup>/P<sub>i</sub> cotransporter, which contains the gene SLC34A3 in chromosome 9q34<sup>15-17</sup>. Hypophosphatemic rickets and/or osteomalacia is the clinical manifestation in most patients. Nephrolithiasis associated with hypercalciuria frequently occurs, probably due to elevated serum 1,25(OH)<sub>2</sub>D that leads to increased intestinal absorption of calcium and phosphorus. Serum FGF23 is low to low-normal in HHRH<sup>15</sup>. Long-term phosphate supplementation is the only therapy in HHRH.

Conclusion

PTH and 1,25(OH)<sub>2</sub>D have been investigated as the most important regulators of phosphate homeostasis. FGF23 and PHEX are novel renal Pi regulator proteins, which are mutated in ADHR and XLH respectively. PHEX is an important negative regulator of FGF23. PTH and FGF23 both inhibit proximal tubular phosphate reabsorption. However, whereas PTH stimulates the synthesis of 1,25(OH)<sub>2</sub>D, FGF23 inhibits this. FGF23 appears to act via known FGFRs, but Klotho protein, as a co-receptor, is required for the action of FGF23. Mutations in the genes encoding two renal Na<sup>+</sup>/P<sub>i</sub> transporters, NPT2a and NPT2c, have been identified in patients with acquired and genetic Pi wasting disorders. In recent studies, NHERF1 was reported as another new regulator for the Pi reabsorption mechanism. NHERF1 phosphorylation by PTH has been shown to be important in the endocytosis of NPT2a. In humans, NHERF1 mutations play a causative role in patients with unexplained hypophosphatemia. Investigations for various phosphaturic hormones FGF23, SFRP4, MEPE, etc and re-
nal phosphate transporter genes are under way to define their mechanism on renal P_{i} regulation.

References

1) Berndt TJ, Knox FG: Renal regulation of phosphate excretion. In: The Kidney: Physiology and Pathophysiology, 2nd ed., edited by Seldin DW, Giebisch GH, Raven, 1992, p2511-2532

2) Dennis VW: Phosphate homeostasis. In: Renal physiology edited by Windgatter EE, New York American Physiological Society by Oxford University Press, 1992, p1785-1815

3) Miller WL, Portale AA: Genetic causes of rickets. Curr Opin Pediatr 11:333-339, 1999

4) Demay MB, Sabbagh Y, Carpenter TO: Calcium and vitamin D: what is known about the effects on growing bone. Pediatrics 119 Suppl 2:S141-144, 2007

5) Murer H, Hernando N, Forster I, Biber J: Characterization of a murine type II sodium-phosphate cotransporter. Endocrinology 141:2159-2165, 2000

6) Kempson SA: Peptide hormone action on renal phosphate handling. Kidney Int 49:1005-1009, 1996

7) Soumounou Y, Gauthier C, Tenenhouse HS: Murine and human type I Na-phosphate cotransporter genes: structure and promoter activity. Am J Physiol Renal Physiol 281: F1082-F1091, 2001

8) Broer S, Schuster A, Wagner CA, Broer A, Forster I, Biber J, et al.: Chloride conductance and Pi transport are separate functions induced by the expression of NaPi-1 in Xenopus oocytes. J Membr Biol 164:71-77, 1998

9) Zhao N, Tenenhouse HS: Npt2 gene disruption confers resistance to the inhibitory action of parathyroid hormone on renal sodium-phosphate cotransport. Endocrinology 141:2159-2165, 2000

10) Murer H, Forster I, Biber J: The sodium phosphate cotransporter family SLC34. Pflugers Arch 447:763-767, 2004

11) Tenenhouse HS: Phosphate transport: molecular basis, regulation and pathophysiology. J Steroid Biochem Mol Biol 103:572-577, 2007

12) Beck L, Karaplis AC, Amizuka N, Hewson AS, Ozawa H, Tenenhouse HS: Targeted inactivation of Npt2 in mice leads to severe renal phosphate wasting, hypercalciuria, and skeletal abnormalities. Proc Natl Acad Sci U S A 95:5372-5377, 1998

13) Hilfiker H, Hattenhauer O, Traebert M, Forster I, Murer H, Biber J: Characterization of a murine type II sodium-phosphate cotransporter expressed in mammalian small intestine. Proc Natl Acad Sci U S A 95:14564-14569, 1998

14) Lotscher M, Scarpetta Y, Levi M, Halaileh N, Wang H, Zajicek HK, et al.: Rapid downregulation of rat renal Na(P)i cotransporter in response to parathyroid hormone involves microtubule rearrangement. J Clin Invest 104:483-494, 1999

15) Lorenz-Depiereux B, Benet-Pages A, Eckstein G, Tenenbaum-Rakover Y, Wagenstaller J, Tiosano D, et al.: Hereditary hypophosphatemic rickets with hypercalciuria is caused by mutations in the sodium-phosphate cotransporter gene SLC34A3. Am J Hum Genet 78:193-201, 2006

16) Bergwitz C, Roslin NM, Tieder M, Loredo-Osti JC, Bastepe M, Abu-Zahra H, et al.: SLC34A3 mutations in patients with hereditary hypophosphatemic rickets with hypercalciuria predict a key role for the sodium-phosphate cotransporter NaPi-1c in maintaining phosphate homeostasis. Am J Hum Genet 78:179-192, 2006

17) Ichikawa S, Sorenson AH, Imel EA, Friedman NE, Gertner JM, Econs MJ: Intronic deletions in the SLC34A3 gene cause hereditary hypophosphatemic rickets with hypercalciuria. J Clin Endocrinol Metab 91:4022-4027, 2006

18) Collins JF, Bai L, Ghishan FK: The SLC20 family of proteins: dual functions as sodium-phosphate cotransporters and viral receptors. Pflugers Arch 447:647-652, 2004

19) Kavanaugh MP, Miller DG, Zhang W, Law W, Kozak SL, Kabat D, et al.: Cell-surface receptors for gibbon ape leukemia virus and amphotropic murine retrovirus are inducible sodium-dependent phosphate symporters. Proc Natl Acad Sci U S A 91:7071-7075, 1994

20) Berndt TJ, Schiavi S, Kumar R: "Phosphatonin" and the regulation of phosphorus homeostasis. Am J Physiol Renal Physiol 289:F1170-1182, 2005

21) Miyamoto K, Ito M, Tatsumi S, Kuwahata M, Segawa H: New aspect of renal phosphate reabsorption: the type Ic sodium-dependent phosphate transporter. Am J Nephrol 27:503-515, 2007

22) Thompson DL, Sabbagh Y, Tenenhouse HS, Roche PC, Drezner MK, Salisbury JL, et al.: Ontogeny of Phex/PHEX protein expression in mouse embryo and subcellular localization in osteoblasts. J Bone Miner Res 17:311-320, 2002

23) Brewer AJ, Canaff L, Hendy GN, Tenenhouse HS: Differential regulation of PHEX expression in bone and parathyroid gland by chronic renal insufficiency and 1,25-dihydroxyvitamin D. Am J Physiol Renal Physiol 286:F739-748, 2004

24) Hruska KA, Rifas L, Cheng SL, Gupta A, Halstead L, Aviol L: X-linked hypophosphatemic rickets and the murine Hyp homologue. Am J Physiol 268:F357-362, 1995

25) Schiavi SC, Kumar R: The phosphatonin pathway: new insights in phosphate homeostasis. Kidney Int 65:1-14, 2004

26) Perwad F, Azam N, Zhang MY, Yamashita T, Tenenhouse HS, Portale AA: Dietary and serum phosphorus regulate fibroblast growthfactor 23 expression and 1,25-dihydroxyvitamin D metabolism in mice. Endocrinology 146:5358-5364, 2005

27) Perwad F, Zhang MY, Tenenhouse HS, Portale AA: Fibroblast growth factor 23 impairs phosphorus and vitamin D metabolism in vivo and suppresses 25-hydroxyvitamin D-1alpha-hydroxylase expression in vitro. Am J Physiol Renal Physiol 293:F1577-1583, 2007
28) Burnett SM, Gunawardene SC, Brinthurst FR, Juppner H, Lee H, Finkelstein JS: Regulation of CHterminal and intact FGF23 by dietary phosphate in men and women. J Bone Miner Res 21:1187-1196, 2006

29) Shimada T, Kakitani M, Yamazaki Y, Hasegawa H, Takeuchi Y, Fujita T, et al.: Targeted ablation of Fgf23 demonstrates an essential physiological role of FGF23 in phosphate and vitamin D metabolism. J Clin Invest 113: 561-568, 2004

30) Shimada T, Hasegawa H, Yamazaki Y, Muto T, Hino R, Takeuchi Y, et al.: FGF23 is a potent regulator of vitamin D metabolism and phosphate homeostasis. J Bone Miner Res 19:429-435, 2004

31) Kolek OI, Hines ER, Jones MD, LeSueur LK, Lipko MA, Kiela PR, et al.: 1alpha,25HDihydroxyvitamin D3 upregulates FGF23 gene expression in bone: the final link in a renal-gastrointestinal-skeletal axis that controls phosphate transport. Am J Physiol Gastrointest Liver Physiol 289: G1036-1042, 2005

32) Ben-Hov IZ, Galitzer H, Lavi-HMoshayoff V, Goetz R, Kuro-Ho M, Mohammadi M, et al.: The parathyroid is a target organ for FGF23 in rats. J Clin Invest 117:4003-4008, 2007

33) Yamashita T, Konishi M, Miyake A, Inui K, Itoh N: Fibroblast growth factor (FGF)-23 inhibits renal phosphate reabsorption by activation of the mitogen-activated protein kinase pathway. J Biol Chem 277:28265-28270, 2002

34) Urakawa I, Yamazaki Y, Shimada T, Iijima K, Hasegawa H, Okawa K, et al.: Klotho converts canonical FGF receptor into a specific receptor for FGF23. Nature 444:770-774, 2006

35) Ben-Dov IZ, Galitzer H, Lavi-Moshayoff V, Goetz R, Kuro-o M, Mohammadi M, et al.: The parathyroid is a target organ for FGF23 in rats. J Clin Invest 117:4003-4008, 2007

36) Rowe PS, de Zoysa PA, Dong R, Wang HR, White KE, Econs MJ, et al.: MEPE, a new gene expressed in bone marrow and tumors causing osteomalacia. Genomics 67:54-68, 2000

37) Argiro L, Desbarats M, Glorieux FH, Ecarot B: Mepe, the gene encoding a tumor-secreted protein in oncogenic hypophosphatemic osteomalacia, is expressed in bone. Genomics 74:342-351, 2001

38) Karim Z, Gerard B, Bakouh N, Alili R, Leroy C, Beck L, et al.: NHERF1 mutations and responsiveness of renal parathyroid hormone. N Engl J Med 359:1128-1135, 2008

39) Hernando N, Gisler SM, Pribanic S, Deliot N, Capuano P, Wagner CA, et al.: NaPi-IIa and interacting partners. J Physiol 567:21-26, 2005

40) Villa-Bellosa R, Barac-Nieto M, Buresejem SY, Barry NP, Levi M, Sorribas V: Interactions of the growth-related, type IIc renal sodium/phosphate cotransporter with PDZ proteins. Kidney Int 73:456-464, 2008

41) Khundmiri SJ, Ahmad A, Bennett RE, Weinman EJ, Stepleck D, Cole J, et al.: Novel regulatory function for NHERF-1 in Npt2α transcription. Am J Physiol Renal Physiol 294:F840-849, 2008

42) Francis F, Henning S, Korn B, Reinhardt R, de Jong P, Pouska A, et al.: A gene (PEX) with homologies to endopeptidases is mutated in patients with X-linked hypophosphatemic rickets. The HYP Consortium. Nat Genet 11:130-136, 1995

43) Holm IA, Huang X, Kunkel LM: Mutational analysis of the PEX gene in patients with X-linked hypophosphatemic rickets. Am J Hum Genet 60:790-797, 1997

44) Benet-Pages A, Lorenz-Depiereux B, Zischka H, White KE, Econs MJ, Strom TM: FGF23 is processed by proprotein convertases but not by PHEX. Bone 35:455-462, 2004

45) Drezner MK: PHEX gene and hypophosphatemia. Kidney Int 57:9-18, 2000

46) Shimada T, Mizutani S, Muto T, Yoneya T, Hino R, Takeda S, et al.: Cloning and characterization of FGF23 as a causative factor of tumor-induced osteomalacia. Proc Natl Acad Sci U S A 98:6500-6505, 2001

47) Jonsson KB, Zahradnik R, Larsson T, White KE, Sugimoto T, Imanishi Y, et al.: Fibroblast growth factor 23 in oncogenic osteomalacia. Proc Natl Acad Sci U S A 98:6500-6505, 2001

48) Tenenhouse HS, Martel J, Gauthier C, Segawa H, Miyamoto K: Differential effects of Npt2a gene ablation and X-linked Hyp mutation on renal expression of Npt2c. Am J Physiol Renal Physiol 285:F1271-1278, 2003

49) Prie D, Huard V, Bakouh N, Planello G, Dells O, Gerard B, et al.: Nephrolithiasis and osteoporosis associated with hypophosphatemia caused by mutations in the type 2a sodium-phosphate cotransporter. N Engl J Med 347:983-991, 2002

50) White KE, Evans WE, ORiordan JL, Speer MC, Econs MJ, Lorenz-Depiereux B, et al.: Autosomal dominant hypophosphataemic rickets is associated with mutations in FGF23. Nat Genet 26:345-348, 2000