Inorganic phosphate (Pi) is an essential physiologic compound for several biologic functions, including intracellular signal transduction, energy exchange, production and function of cell membranes, and the composition of hydroxyapatite in bone and teeth (1, 2). Hyperphosphatemia contributes to vascular calcification in patients with chronic kidney disease and hemodialysis patients and is independently associated with cardiac mortality. Pi homeostasis is regulated by the coordinated function of renal and intestinal sodium-dependent phosphate (NaPi) transporters with dietary Pi, parathyroid hormone, 1,25-dihydroxyvitamin D₃, and fibroblast growth factor 23. The type II NaPi transporter/SLC34 family, with three members identified to date, is mainly responsible for Pi homeostasis in the body. SLC34A1 and SCL34A3 are predominantly expressed in the kidney, whereas SLC34A2 is expressed in the small intestine. The role of each SLC34 in the body was recently established by studies of gene-targeted mice. Mutation of SLC34A1 causes Fanconi syndrome and mutation of SLC34A3 causes autosomal recessive hereditary hypophosphatemic rickets with hypercalcuria. SLC34A2 is thought to be a major intestinal NaPi transporter and mutation of SLC34A2 causes pulmonary alveolar microlithiasis. A detailed understanding of Pi regulation in the body is important toward maintaining health.

Key Words phosphate, transporter, intestine, kidney

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3. Gene Knockout of NaPi Transporters

Renal Pi reabsorption is markedly reduced in NaPi-IIa knockout (KO) (Npt2a\(^{-/-}\)) mice, resulting in hyperphosphaturia. Serum 1,25-dihydroxyvitamin D\(_3\) concentrations and serum and urine Ca\(^{2+}\) concentrations are significantly increased in Npt2a\(^{-/-}\) mice \((1, 4)\). In mice, NaPi-IIa has a major role in Pi reabsorption.

Although Pi homeostasis remains normal in NaPi-IIc KO (Npt2c\(^{-/-}\)) mice hypercalciuria and higher levels of serum 1,25-dihydroxyvitamin D\(_3\) concentrations are observed. NaPi-IIc has a minor role in Pi reabsorption in mice \((1, 4, 6)\).

Neither Npt2a\(^{-/-}\) nor Npt2c\(^{-/-}\) mice exhibit bone abnormalities such as rickets/osteomalacia \((6, 7)\).

Homozygous NaPi-IIb KO mice display embryonic lethality. Based on several studies of heterozygous NaPi-IIb KO (Npt2b\(^{-/+}\)) mice and conditional KO mice \((3, 5, 8)\), NaPi-IIb is the most important transcellular NaPi transporter.

4. Phosphate Transporter and Related Disease

Mutation of human NaPi-IIa causes autosomal recessive Fanconi syndrome with hypophosphatemic rickets \((9)\). This mutation of NaPi-IIa is a homozygous in-frame duplication. Functional studies indicate a complete loss of function of mutant NaPi-IIa. Accumulation of mutant NaPi-IIa protein in the cells may have toxic effects leading to Fanconi syndrome.

Mutation of NaPi-IIc causes autosomal recessive disorder hereditary hypophosphatemic rickets with hypercalciuria (HHRH) \((4, 10)\). Clinical studies suggest that HHRH is a primary renal Pi wasting disorder, resulting in increased serum 1,25-dihydroxyvitamin D\(_3\) concentrations with associated intestinal Ca\(^{2+}\) hyperabsorption, hypercalciuria, and rickets/osteomalacia. Functional studies suggest that homozygous or compound heterozygous mutation of NaPi-IIc significantly decreases NaPi transport activity in Xenopus oocytes and opossum kidney cells \((11)\). A recent report suggested that mutations in NaPi-IIc are associated with kidney stones and nephrocalcinosis \((12)\). NaPi-IIc knockout (Npt2c KO) mice exhibit hypercalciuria and higher levels of serum 1,25-dihydroxyvitamin D\(_3\) concentrations, but not hypophosphatemia, rickets or nephrocalcinosis \((6)\). Furthermore, only NaPi-IIa/NaPi-IIc double-KO mice exhibit a physiology similar to that of patients with HHRH \((13)\).

NaPi-IIc has more important roles in Pi reabsorption in humans than in mice. Both NaPi-IIa and NaPi-IIc are important NaPi transporters in humans; however, there are several differences between humans and rodents. Further studies are needed to clarify their precise role in human kidney function.

Mutation of NaPi-IIb causes pulmonary alveolar microlithiasis (PAM) \((14)\). The deposition of Ca/Pi microliths throughout the lungs is observed in PAM patients. NaPi-IIb is specifically expressed in type II alveolar cells, and NaPi-IIb mutations abolish the normal gene function.

5. Future Studies

The review is summarized in Fig. 1 and Table 1. Control of Pi balance is tightly regulated in the body via Pi homeostasis-regulating factors and transporters. Several factors, such as the basolateral/excretion type of Pi transporter, remain unidentified. In addi-
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...tion, while intestinal Pi passive diffusion is thought to be mediated through a paracellular pathway, it has not yet been identified. Blood Pi control is highly important for patients with CKD and HD to avoid cardiovascular disease. Identification of the intestinal paracellular Pi transport mechanism may lead to therapy targets for hyperphosphatemia.

More detailed information regarding Pi homeostasis in the body will provide important clues to maintaining health.

REFERENCES


