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INVITED REVIEW

Regulation of renal phosphate handling: inter-organ communication in health and disease

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Abstract In this review, we focus on the interconnection of inorganic phosphate (Pi) homeostasis in the network of the bone–kidney, parathyroid–kidney, intestine–kidney, and liver–kidney axes. Such a network of organ communication is important for body Pi homeostasis. Normalization of serum Pi levels is a clinical target in patients with chronic kidney disease (CKD). Particularly, disorders of the fibroblast growth factor 23/klotho system are observed in early CKD. Identification of phosphaturic factors from the intestine and liver may enhance our understanding of body Pi homeostasis and Pi metabolism disturbances in CKD patients.

Keywords Inorganic phosphate · Inorganic phosphate transporters · Chronic kidney disease (CKD) · Kidney–organ axis

Introduction

Inorganic phosphate (Pi) is essential for several biologic functions, such as intracellular signal transduction, energy exchange, production and function of cell membranes, and the composition of hydroxyapatite in the bones and teeth [1, 2]. Serum Pi levels are maintained within the normal range by a number of regulatory hormones. These modulate the intestinal uptake of Pi, its mobilization from bone, and renal excretion. Maintaining serum Pi levels is critical for proper bone development and for skeletal integrity [3]. Hypophosphatemia leads to bone abnormalities such as rickets/osteomalacia, whereas hyperphosphatemia contributes to vascular calcification in patients with chronic kidney disease (CKD) and hemodialysis and is independently associated with cardiac mortality [1, 2, 4]. The kidney is the major regulator of Pi homeostasis. Physiological and pathophysiological regulation of renal epithelial transport of Pi occurs through alterations in the levels of type II sodium-dependent Pi (Na/Pi) cotransporters (SLC34 family). Recent studies demonstrated that Pi reabsorption is regulated through orchestration of the kidney–organ axis, including the bone, intestine, parathyroid, and liver. The factors that regulate renal Na/Pi transporters are dietary Pi, parathyroid hormone (PTH), calcitriol, or 1,25-dihydroxyvitamin D_3 (the active form of vitamin D, $1,25(OH)_2D_3$), fibroblast growth factor 23 (FGF23), and pyridine nucleotides [2, 5–8]. In this review, we focus on the regulation of renal NaPi-II transporters by inter-organ communication.

Renal Pi reabsorption

A major regulator of Pi homeostasis is the kidney, and its Pi re-absorptive capacity can be increased or decreased to accommodate the requirements for Pi. Na^+-dependent Pi (Na/Pi) transport systems in the brush-border membrane (BBM) mediate the rate-limiting step in the overall Pi re-absorptive process [1, 8]. Pi ions influx from the tubular lumen across the apical BBM and efflux at the basolateral membrane [1, 8]. Na^+-dependent transport maintained by basolateral membrane-associated Na^+, K^+-ATPase drives the Na^+-gradient process. Na/Pi cotransport across the BBM is the target for physiologic/pathophysiologic regulation [8].

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Three types of Na/Pi cotransporters (types I–III) are located in the apical membrane of renal proximal tubular cells [1, 8]. Type I Na/Pi (SLC17A1/NPT1/NaPi-I/OATv1) is expressed in the liver and the kidney [1]. NPT1 was identified in an expression cloning study using *Xenopus laevis* oocytes based on the Na/Pi transport, and it was also localized to the apical side of the proximal tubules [1]. Following in vitro studies indicated that this transporter is involved in the proximal tubule transport of organic anions rather than Pi. Recently, Iharada et al. demonstrated that NPT1 mediates urate export into urine [9]. The role of NPT1 in Pi reabsorption remains unclear [1].

The SLC34 family, SLC34A1 (NaPi-IIa), and SLC34A3 (NaPi-IIc), are major functional transporters in the proximal tubular cells [1, 8]. While the overall molecular structure is predicted to be very similar, there are important differences between the two Na/Pi cotransporters. NaPi-IIa is electrogenic, coupling Pi transport (at physiologic pH mainly $HPO4^{2-}$) with the transport of three Na^{+} ions. In contrast, NaPi-IIc is electroneutral, only transporting two Na^{+} ions for every Pi. In addition, type III transporters (the SLC20A20 family, PiT2) are localized at the BBM of the proximal tubule cells [10–12].

Little is known about the molecules involved in Pi translocation across the cell membrane and the efflux of Pi across the basolateral membrane. The Pi exporter, xenotropic and polytropic retrovirus receptor 1 (XPR1), was recently identified [13–16]. XPR1 is a highly conserved multi-pass transmembrane protein originally identified as a receptor for xenotropic and polytropic murine retroviruses [13, 14]. Recent studies indicate that XPR1 has a specific role as a Pi exporter in the differentiation of tissue macrophages [15, 16]. XPR1 mutants show impaired bone remodeling that is indicative of osteoclast defects [14]. We previously reported that osteoclasts have a unique Pi efflux system [17] that is involved in the continuous release of Pi at the basolateral membrane to prevent the accumulation of intracellular Pi [17]. Giovannini et al. demonstrated that XPR1 mediates Pi export in cultured mammalian cells [18].

XPR1 mutations are reported to cause primary familial brain calcification [19]. These mutations alter phosphate export, implicating XPR1 in primary familial brain calcification [19]. Thus, XPR1 might be involved in the export of Pi from mammalian cells, but the role of this exporter in renal epithelial cells remains unknown.

A role for type II Na/Pi transporters (NaPi-IIa and NaPi-IIc or Npt2a and Npt2c) on renal Pi reabsorption is reported in rodents and humans [1]. In rodents, NaPi-IIa is important for renal Pi cotransport activity and Npt2a (NaPi-IIa)-knockout ($Npt2a^{-/-}$) mice have hypophosphatemia and hyperphosphaturia [20]. Serum $1,25(OH)_2D$ concentrations and serum and urine Ca^{2+} concentrations are significantly increased in $Npt2a^{-/-}$ mice [1, 20, 21]. $Npt2a^{-/-}$ mice exhibit increased urinary Pi excretion, ~70 % decrease in renal BBM vesicle Na/Pi cotransport, and hypophosphatemia [20]. $Npt2a^{-/-}$ mice also over-express Npt2c, which may support the residual renal Pi reabsorption function. These observations indicate that Npt2a has a major role in Pi reabsorption in mice.

In humans, several NaPi-IIa mutations have been reported. Prie et al. reported two patients with NaPi-IIa mutations (A48F and V147M) exhibiting urolithiasis or bone demineralization and persistent idiopathic hypophosphatemia with lower maximal renal Pi reabsorption [22]. Virkki et al., however, demonstrated that reduced Pi transport activity by the NaPi-IIa mutations cannot fully explain the massive phosphaturia observed [23]. In addition, mutation of human NaPi-IIa causes autosomal recessive Fanconi syndrome with hypophosphatemic rickets [24]. This mutation of NaPi-IIa is a homozygous in-frame duplication. Functional studies indicate a complete loss-of-function of mutant NaPi-IIa [24]. Accumulation of mutant NaPi-IIa protein in the cells may have toxic effects leading to Fanconi syndrome. Genetic analysis detected a homozygous in-frame duplication, leading to the insertion of seven additional amino acids [24, 25]. Heterozygous carriers of the mutation are clinically normal, suggesting that the mutation does not have a dominant negative effect [24, 25]. Fanconi syndrome is detected in the human carriers of the mutation, but not in $Npt2a^{-/-}$ mice. Thus, the disruption of human NaPi-IIa impairs overall renal Pi reabsorption, providing evidence for the critical role of NaPi-IIa in human renal Pi handling. The precise role of the NaPi-IIa transporter in humans, however, remains unknown.

In contrast, NaPi-IIc (Npt2c) may be a major functional Na/Pi cotransporter in the human kidney because the NaPi-IIc mutation causes hereditary hypophosphatemic rickets with hypercalciuria (HHRH) [26–29]. Clinical studies suggest that HHRH is a primary renal Pi wasting disorder, resulting in increased serum $1,25(OH)_2D$ concentrations with associated intestinal Ca^{2+} hyperabsorption, hypercalciuria, and rickets/osteomalacia [1, 30]. Functional studies suggest that homozygous or compound heterozygous mutations of NaPi-IIc significantly decrease Na/Pi transport activity in *Xenopus* oocytes and OK cells [31]. In rodents, NaPi-IIc (Npt2c) is important for Pi reabsorption in weanling animals [32], but mediates a very small percentage of Pi reabsorption in adult animals [32]. Npt2c knockout mice ($Npt2c^{-/-}$) mice exhibit hypercalciuria and higher levels of serum $1,25(OH)_2D$ concentrations, but not hypophosphatemia, rickets, or nephrocalcinosis [33]. Furthermore, only Npt2a/Npt2c double-KO mice exhibit a physiology similar to that of patients with HHRH [34]. NaPi-IIc (Npt2c) has a minor role in Pi reabsorption in mice [1, 21, 33]. More recently, Myakala et al. showed that

renal-specific and inducible depletion of NaPi-IIc in mice does not affect Pi or Ca homeostasis [35]. Neither Npt2a$^{-/-}$ nor Npt2c$^{-/-}$ mice exhibit bone abnormalities such as rickets/osteomalacia [20, 33]. Based on these findings, we suggest that human NaPi-IIc is more important than mouse NaPi-IIc for Pi homeostasis.

Finally, the marked differences in the phenotypes of Npt2a$^{-/-}$ and Npt2c$^{-/-}$ mice may be due to differential dominance of the transporters for Pi homeostasis [1, 33]. The role of NaPi-IIa (Npt2a) and NaPi-IIc (Npt2c) in renal Pi reabsorption differs between rodents and human. It remains unclear, however, why regulation of NaPi-IIa does not compensate for the loss-of-function mutation of NaPi-IIc in HHRH as it does in the absence of NaPi-IIc, such as in null mice.

Intestinal Pi absorption

The mechanisms and regulation of intestinal Pi absorption remain poorly defined. Intestinal absorption of Pi is characterized in several mammalian and avian species [36–40]. In intestinal Pi absorption, both saturated and unsaturated systems have been described. Unsaturated systems depend on the paracellular route via tight junctions. Saturated components are Na^+-dependent and Na^+-independent Pi transport systems in the apical membrane of intestinal epithelial cells [41]. Marks et al. demonstrated that Pi concentrations in the intestinal lumen are typically in the low millimolar range, and under these conditions Na^+-independent transport is likely to be the predominant pathway for Pi absorption in vivo [42, 43]. Based on studies using BBM vesicles of the small intestine, both Na^+-dependent and Na^+-independent components are present, with similar characteristics and pH dependence [44]. Candeal et al. characterized Na^+-independent components in the human intestinal cell line Caco2BBE [45]. Na^+-independent components are dependent on de novo RNA and protein synthesis [45]. The molecules involved in Na^+-independent Pi transport, however, remain unknown.

Na/Pi absorption is mediated primarily via the type IIb sodium-phosphate transporter (NaPi-IIb, Npt2b) [41, 46–52]. Numerous studies revealed that the regional profile for intestinal phosphate absorption differs between rats and mice. In rats, the highest rates of transport occur in the duodenum and jejunum, while in mice maximal absorption occurs in the ileum. During fasting and low dietary phosphate intake, Pi absorption may be mediated by NaPi-IIb, but when Pi levels are elevated post-prandially, transport could also occur via a Na^+-independent transcellular or paracellular pathway. The type III Na/Pi cotransporter PiT-1 is expressed in the apical membrane of enterocytes. The role of PiT-1 in Na/Pi cotransport remains unknown.

Mutation of human NaPi-IIb causes pulmonary alveolar microlithiasis [53]. Deposition of Ca/Pi microliths throughout the lungs is observed in patients with pulmonary alveolar microlithiasis. NaPi-IIb is specifically expressed in type II alveolar cells, and NaPi-IIb mutations abolish normal gene function. Homozygous NaPi-IIb KO mice are embryonic lethal. Based on several studies of heterozygous NaPi-IIb KO (Npt2b$^{+/-}$) mice and conditional KO mice [1, 54–58], NaPi-IIb is the most important transcellular Na/Pi transporter. The roles Pi transporters in the small intestine, however, remain unknown. Particularly, Na^+-independent Pi transporters require further characterization. The role of intestinal NaPi-IIb in Pi homeostasis is clearly more important than previously realized in mice.

Regulation of renal NaPi-IIa and NaPi-IIc by inter-organ communication

Parathyroid glands secrete PTH into the blood. PTH induces phosphaturia by decreasing Pi reabsorption in the kidney [5, 59]. 1,25$(OH)_2D_3$, which is synthesized in the kidney, acts in the gut to increase the absorption of dietary Pi and calcium, and in the bone to promote mobilization of these ions. As a result, blood levels of both Pi and calcium tend to increase. In addition to PTH and 1,25$(OH)_2D_3$, recent studies identified a novel regulator of Pi levels: fibroblast growth factor (FGF23) [2, 6]. This bone-derived hormone is currently considered to be the principal regulator of phosphaturia. FGF23 induces Pi excretion and inhibits vitamin D synthesis in the kidney, thus maintaining systemic Pi homeostasis [2, 6]. The parathyroid–kidney and bone–kidney axis are involved in two known phosphaturic factors, PTH and FGF23. In addition, recent studies demonstrated that the intestine and liver also contribute to systemic Pi homeostasis [2, 6]. For example, the control of renal Pi excretion by dietary Pi may involve the intestine–kidney axis. Nicotinamide is controlled by systemic Pi homeostasis. The liver–kidney axis is involved in nicotinamide metabolism. Below we describe the kidney–organ axis in Pi homeostasis (Fig. 1).

Bone–kidney axis

FGF23 is a hormone that promotes renal Pi excretion by decreasing its reabsorption in the proximal tubules while concurrently reducing serum 1,25$(OH)_2D_3$ by decreasing its biosynthesis and increasing its metabolism [60]. FGF23 requires an additional cofactor, klotho, to bind with high affinity and signal efficiently through its cognate FGF receptor. Klotho and FGF receptor 1 (IIIc) form a heterodimeric receptor for FGF23 [61, 62]. We previously reported that administration of FGF23 containing the

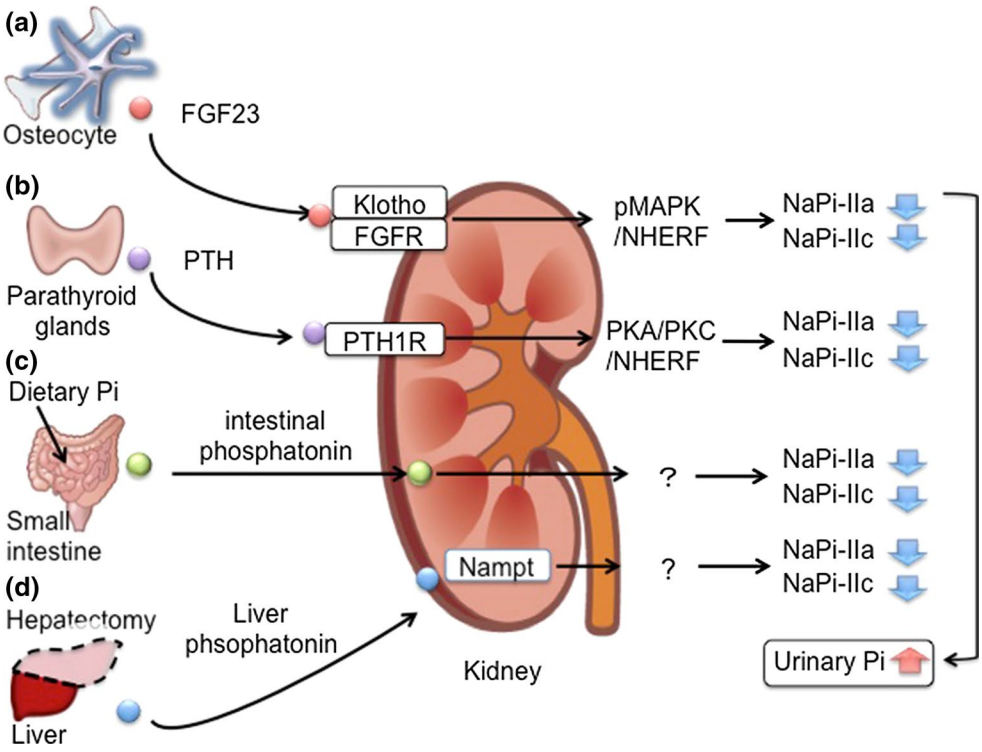

Fig. 1 Regulation of renal reabsorption by the inter-organ communication. **a** Bone–kidney axis: FGF23-dependent downregulation of NaPi-IIa is associated with MAPK-dependent NHERF1 phosphorylation and endocytosis into cellular compartments. **b** Parathyroid–kidney axis: PTH-dependent activation of either PKC or PKA in the renal proximal tubule cells inhibits Na^+-dependent Pi transport activity. **c** Intestine–kidney axis: Intestinal phosphatonin secretion induced by a high Pi diet may be involved in the downregulation of renal NaPi-IIa, NaPi-IIc transporters. **d** Liver–kidney axis: Liver phosphatonin secretion induced by hepatectomy activates renal Nampt function and downregulates NaPi-IIa, NaPi-IIc transporters

R179Q mutation (FGF23M) decreased the levels of Na/Pi transport activity and NaPi-IIa and NaPi-IIc expression [63, 64]. FGFR1 is the predominant receptor mediating the hypophosphatemic actions of FGF23 by decreasing BBM levels of NaPi-IIa and NaPi-IIc expression with FGFR4, which has an additional but relatively minor role [65]. FGF23 regulates proximal tubular $1,25(OH)_2D_3$ biosynthesis by a different receptor than that for the inhibition of Pi transport reuptake in the proximal tubule [66–68]. The mechanisms of FGF23 downregulation of NaPi-IIa are well studied include MAPK-dependent NHERF1 phosphorylation and endocytosis into cellular compartments [69–71].

The downregulation of NaPi-IIa by FGF23 is dependent on the presence of klotho, which is mainly expressed in the distal tubules. In the distal tubule-specific depletion of klotho–conditional KO mice, downregulation of NaPi-IIa is not observed after injection of FGF23. These findings suggest that complex FGF23/klotho/FGFR in the distal tubules is essential for the reduction of NaPi-IIa transporters [72].

We previously reported that administration of FGF23 containing the R179Q mutation (FGF23M) decreased the levels of Na/Pi transport activity and NaPi-IIc expression in $Npt2a^{-/-}$ [73]. We used $Npt2a^{-/-}$ mice and analyzed the localization and protein levels of Npt2c [73]. As described previously, the levels of Npt2c protein are increased in the proximal tubules in $Npt2a^{-/-}$ mice [73]. In $Npt2a^{-/-}$ mice, FGF23 treatment led to a reduction of renal BBM Na/Pi cotransport activities at 3 and 12 h after injection (H. Segawa et al., unpublished data). Urinary Pi excretion was significantly increased at 3 and 12 h. After FGF23 treatment, at 3 h, the amounts of NaPi-IIc protein were not changed when compared with non-injected controls. The effect of FGF23 on the rapid reduction of Na/Pi cotransport activity may be mediated by the phosphorylation-dependent inactivation of NaPi-IIc protein, but not NaPi-IIc protein levels. These data suggest that FGF23-dependent phosphaturic actions in $Npt2a^{-/-}$ mice are associated with NaPi-IIc inactivation in the apical membrane. Finally, the difference in the PTH regulation between NaPi-IIa and NaPi-IIc could affect the time scale of the downregulation by PTH. The downregulation of NaPi-IIa by PTH occurs within 1 h, while NaPi-IIc regulation takes up to four times longer (H. Segawa et al., unpublished data).

Parathyroid–kidney axis

PTH decreases the levels of NaPi-IIa and NaPi-IIc protein in the BBM [2, 6, 36, 74]. In response to PTH, NaPi-IIa undergoes clathrin-dependent endocytosis and is targeted to lysosomes [75]. Thus, PTH inhibits Pi transport by promoting Npt2a endocytosis and lysosomal degradation [5, 6, 74–76]. PTH receptors are expressed on both the apical and basolateral surfaces of the renal proximal tubular cells. The apical PTH1 receptor is signaled via a protein kinase C (PKC) pathway while the basolateral PTH1 receptor is signaled via a protein kinase A (PKA) pathway [77]. Previous studies suggest that PTH increases the phosphorylation of Na^+/H^+ exchanger regulatory factor-1 (NHERF-1)

[59, 78–80]. Weinman et al. demonstrated that biochemical modification of the serine77 of NHERF-1 decreases its binding affinity to NaPi-IIa, resulting in dissociation of the NaPi-IIa/NHERF-1 complex, and that this modification is required for PTH-dependent inhibition of Na/Pi transport [59, 79, 80]. They also indicated an important role for threonine 95 of the PDZ1 domain of NHERF-1 [80]. These data suggest that the phosphorylation of threonine 95 and the phosphorylation of serine 77 of NHERF-1 are essential for PTH-mediated inhibition of Pi transport [80]. In addition, NHERF1-KO mice exhibit PTH-resistant urinary Pi wasting, nephrocalcinosis, and osteopenia [81]. Thus, NHERF-1 is involved in the PTH regulation of NaPi-IIa endocytosis.

By contrast, in the regulation of PTH, NaPi-IIc is downregulated through a microtubule-dependent pathway that does not involve lysosomal degradation [74, 82]. After administration of PTH, the intensity of immunoreactive signals in apical and subapical type IIc transporters decrease in the renal proximal tubular cells in thyroparathyroidectomized rats [82]. Colchicine completely blocks the internalization of NaPi-IIc transporters [82]. In addition, leupeptin prevents PTH-mediated degradation of the NaPi-IIa transporter in lysosomes, but has no effect on PTH-mediated degradation of the lysosomal NaPi-IIc transporters [82]. The precise pathway for the decrease in the apical membrane expression of NaPi-IIc has not been determined, but recent evidence suggests that the protein is shifted to the base of the microvillar compartment where it undergoes in situ dissolution. Villa-Bellosta et al. reported that NaPi-IIc interacts with NHERF-3 in the apical membrane in OK cells and proximal tubules [83]. In NHERF-3-KO mice, NaPi-IIc translocation into the apical membrane is impaired after stimulation by a low Pi diet [84]. NaPi-IIc may bind indirectly to ezrin. The PDZ domain-containing protein NHERF-3, as an intermediate linking NaPi-IIc to ezrin, is necessary for many aspects of NaPi-IIc regulation. In addition, internalization of NaPi-IIc might be involved in Rab11-dependent recycling endosomes in the proximal tubular cells (H. Segawa et al., data not shown).

Intestine–kidney axis

Dietary Pi is the most important factor in body Pi homeostasis. Dietary Pi levels control active vitamin D synthesis, PTH secretion, and renal Pi reabsorption [36–40, 85]. Renal Pi reabsorption is a key determinant of serum Pi levels in the body [36]. A low-Pi diet can lead to almost 100 % renal reabsorption of filtered Pi, whereas a high-Pi diet leads to decreased proximal tubular Pi reabsorption. The factors controlling the dietary adaptive system are not known, but do not include PTH, vitamin D, growth hormone, thyroid hormone, calcitonin, or FGF23 [36, 85]. Several reports indicate that intestinal mucosal cells sense the dietary Pi content and secrete intestinal phosphatonin (a putative phosphaturic factor) [36]. Intestinal phosphaturic factors might be involved in the rapid regulation of renal type II transporters by the intestinal–kidney axis [86]. Burnts et al. showed that intraduodenal infusion of 1.2 M sodium phosphate, but not sodium chloride, increases Pi excretion within 20 min [86]. The response is not due to altered serum levels of Pi, PTH, FGF23, secreted frizzled-related protein 4; an increase in glomerular filtration rate; or the result of a neural reflex [86]. Burnts et al. concluded that an intestinal Pi sensor triggers the release of a phosphaturic factor from the duodenal mucosa [86]. Marks et al. demonstrated that matrix extracellular phosphoglycoprotein might be the intestinal phosphatonin proposed by Berndt et al. [87]. To date, however, there is no further published information on the mechanisms underlying this proposed entero-renal reflex or the identity of the putative phosphatonin [86, 88]. An intestinal Pi sensor may be involved in the secretion of FGF23 from the bone and also the regulation of the $1,25(OH)_2D_3$ levels.

We also characterized Pi homeostasis in $Npt2b^{+/-}$ mice. $Npt2b^{+/-}$ mice have significantly reduced intestinal Na/Pi cotransport activity in their BBMVs [56]. At 4 weeks of age, the $Npt2b^{+/-}$ mice showed hypophosphatemia and low urinary Pi excretion [56]. Serum FGF23 levels were significantly reduced and $1,25(OH)_2D_3$ levels were significantly increased in the $Npt2b^{+/-}$ mice compared with those in the $Npt2b^{+/+}$ mice, and their Npt2b mRNA levels were reduced to 50 % that in the $Npt2b^{+/+}$ mice [56]. In contrast, renal Npt2a and Npt2c transporter protein levels were significantly increased in the $Npt2b^{+/-}$ mice [56]. At 20 weeks of age, the $Npt2b^{+/-}$ mice showed hypophosphaturia and reduced Na/Pi cotransport activity in the distal intestine [56]. Recent reports revealed the importance of Npt2b in both acute and chronic adaptation of intestinal Pi transport, and FGF23 secretion [89]. It is possible that Npt2b is involved in the secretion of an intestinal phosphatonin mediated by dietary Pi. Further studies are needed to clarify the regulation of renal Pi excretion by the intestinal–kidney axis.

Liver–kidney axis

The number of patients receiving liver transplantation has steadily increased, and thus the incidence of partial hepatectomy (PH) has also increased [90]. Hypophosphatemia frequently occurs after liver resection [91–93]. Acute hypophosphatemia causes septicemia and is associated with a poor prognosis [93, 94]. The phenomenon is highly clinically relevant because numerous patients develop significant hypophosphatemia after hepatectomy requiring large doses of Pi replacement to maintain metabolic homeostasis

[91–93]. In many patients, urinary Pi excretion is markedly increased [95]. Post-hepatectomy hypophosphatemia is associated with hyperphosphaturia [96]. For a long time, the increased metabolic demands by the regenerating liver were viewed as the underlying pathologic mechanism of hypophosphatemia [93]. The magnitude of Pi uptake by the recovering liver, however, cannot explain the severity of hypophosphatemia. Post-hepatectomy hypophosphatemia is associated with increased FePi unrelated to intact FGF23, FGF7, or secreted frizzled-related protein 4 as phosphaturic factors [97]. Therefore, other factors must have a role in the pathogenesis of hypophosphatemia. These observations suggest that unknown factors are involved in the control of renal Pi in the liver–kidney axis.

Nicotinamide (an amide derivative of the water-soluble vitamin B3) is a potentially interesting alternative to phosphate binders. In vitro and in vivo data show that nicotinamide reduces hyperphosphatemia by inhibiting Na/Pi cotransport in the renal proximal tubules and the intestine [98–100]. Several recent clinical studies explored the potential value of nicotinamide in Pi control (as well as its effects on lipid) [101, 102]. How nicotinamide regulates systemic Pi homeostasis, however, remains unknown. We investigated the mechanisms for the reduction of NaPi-II (Npt2a, Npt2b, Npt2c) protein caused by abnormal cellular NAD metabolism. Nicotinamide phosphoribosyltransferase (Nampt) is a rate-limiting enzyme for NAD^+ synthesis from nicotinamide [103–105]. Elevation of Nampt protein is a candidate cause of hyperphosphaturia in PH animals [106]. Abnormal NAD metabolism is also a candidate cause of hyperphosphaturia with PH [106]. Nicotinamide inhibits intestinal and renal Na/Pi transport activity in normal rats [99]. Injections of pharmacologically relevant doses of nicotinamide increase NAD in inverse proportion to Na/Pi transport [98]. Indeed, we demonstrated that NaPi-IIa, IIb, and IIc protein levels in the kidney and small intestine are markedly decreased in PH animals, suggesting that the reduction of the transporters in PH animals is similar to that in nicotinamide-treated animals [106]. Thus, we demonstrated the possibility that hypophosphatemia and hyperphosphaturia are observed after 70 % hepatectomy due to abnormality of NAD/nicotinamide metabolism in the liver and kidney [106]. In addition, the Nampt inhibitor FK866 influences Pi metabolism in normal mice [106]. The expression of NaPi-IIa (Npt2a) and NaPi-IIc (Npt2c) is increased in the proximal tubules by FK866 treatment. Thus, the mechanism for the increase in Nampt following hepatectomy remains unknown, but nicotinamide may be metabolized in the liver–kidney axis and may be involved in the regulation of Nampt protein in the proximal tubules [106]. A putative phosphatonin in the liver may be involved in regulation of the renal Nampt activity and NAD metabolism in the mitochondria of proximal tubular cells (S. Tatsumi et al., data not shown).

CKD and inter-organ communication

Pi retention is a major harmful complication of CKD [107–109], leading to secondary hyperparathyroidism, uremic bone disease, and progression to end-stage renal disease. Hyperphosphatemia remains a risk factor for arterial calcification contributing to high cardiovascular mortality in patients with CKD [110, 111]. Tubular reabsorption of Pi decreases in proportion to the severity of CKD. As glomerular filtration rate diminishes, the degree of Pi excretion per nephron increases, and at a very low filtration rate levels tubular reabsorption of Pi is 10 to 20 %, or 80 to 90 % of the filtered load of Pi is excreted into the urine. In the early stages of CKD, the serum Pi concentration is maintained within the normal range by increases in the serum concentration of PTH and FGF23 [112–114], which serve to increase the urinary excretion of Pi, and decrease serum $1,25(OH)_2D_3$ concentrations, leading to decreased Pi absorption from the gastrointestinal tract. In more advanced stages of kidney disease, changes in the PTH, FGF23, and $1,25(OH)_2D_3$ levels are no longer sufficient to prevent hyperphosphatemia [115]. In CKD, increased PTH and FGF23 production enhances the excretion of Pi per nephron, thereby restoring normophosphatemia [116]. In CKD patients, however, FGF23 reduces $1,25(OH)_2D_3$ levels, contributing to an increase in PTH secretion, which occurs after FGF23 levels increase [116]. This process disrupts the bone–kidney–parathyroid endocrine axis and eventually fails to prevent the development of hyperphosphatemia as CKD progresses.

In addition, Nampt is a proinflammatory cytokine that has gained considerable attention in recent years with respect to induction of cardiovascular disease [117]. The Nampt pathway (liver–kidney axis) is also activated in CKD and diabetic nephropathy animals [96, 97]. These observations suggest that the bone–parathyroid–kidney and the liver–kidney axes may be activated to maintain Pi homeostasis in CKD. A new pathway of Pi metabolism in the liver–kidney axis may elucidate the abnormal Pi metabolism in CKD.

Compliance with ethical standards

Conflict of interest All authors have no conflicts of interest.

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