The Skeleton: Endocrine Regulator of Phosphate Homeostasis

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Phosphorus is an essential element in skeletal development, bone mineralization, membrane composition, nucleotide structure, and cellular signaling. Phosphate, the principal form in which phosphorus is found in the body, is regulated by the complex interplay of the hormones parathyroid hormone (PTH), calcitriol ($1,25[OH]_2$ vitamin D_3), and fibroblast growth factor 23 (FGF23). These collectively govern bone mineralization, absorption of phosphorus by the intestine, and renal tubular reabsorption of phosphate. The skeleton is the major storage pool for phosphate and the principal production site for FGF23, a major phosphate regulatory hormone. Recent advances in understanding the molecular basis of disorders of phosphate metabolism have revealed new phosphate-regulatory hormones and provided insight into how these regulators may interface with previously known phosphate-regulatory pathways. Here we outline the current knowledge about the regulation of normal phosphate homeostasis and present a review of the molecular basis of disorders of phosphate homeostasis.

Introduction

Phosphorus is a critical element in skeletal development, bone mineralization, membrane composition, nucleotide structure, and cellular signaling. The predominant form of phosphorus as it exists in the body is the phosphate ion $(PO_4)^{3-}$. About 85% of phosphate is found in bone and teeth, where it is a component of the crystal hydroxyapatite $Ca_{10}(PO_4)_6(OH)_2$. It is laid down in the organic matrix of bone during the mineralization process, giving bone its strength. Therefore, the principal reservoir of phosphorus is the bone, while the kidney and the intestine are the most important organs for excretion and phosphate absorption, respectively. These organs, together with the parathyroid gland, act in a concerted humoral loop to regulate absorption, excretion, and skeletal deposition of phosphate (Fig. 1).

Physiologic Regulation of Phosphate Homeostasis: An Updated Model

The serum phosphate level is maintained within the normal range through a complex interplay involving intestinal absorption, exchange with intracellular and skeletal storage pools, and renal tubular reabsorption. This regulation is achieved through integration of the well-characterized calcitriol–parathyroid hormone (PTH) axis, the emerging fibroblast growth factor 23 (FGF23):α-Klotho axis, and sodium-phosphate cotransporters in the kidney and gut.

The most well-characterized pathway of phosphate regulation is that of calcitriol ($1,25[OH]_2$ vitamin D_3) and PTH. Both are primarily involved in maintaining serum calcium levels, but secondarily affect phosphate balance. PTH release is stimulated in response to low calcium levels, increasing the calcitriol production as well as increasing distal tubule calcium reabsorption. Calcitriol is synthesized in the kidney from 25(OH) vitamin D_3 by the enzyme 25- hydroxyvitamin D-1-α-hydroxylase (also referred to as CYP27B1 and 1-α-OHase).

Hypophosphatemia is also a potent stimulator of calcitriol synthesis. Calcitriol then facilitates the absorption of calcium and phosphate in the intestine, as well as calcium and phosphate mobilization from bone stores. The rise in serum calcium and calcitriol inhibit the release of PTH from the parathyroid gland. As PTH levels fall, renal calcium reabsorption is inhibited and phosphate reabsorption is enhanced in the proximal tubule. The net result is normalization of serum calcium and phosphate levels. The maintenance of normal PTH and calcium levels in the face of profoundly abnormal phosphate homeostasis such as observed in varying forms of hypophosphatemic rickets was indicative of the existence of a potent humoral regulator for phosphate. Through careful study of these rare hypophosphatemic syndromes, FGF23 was discovered to be that regulator.

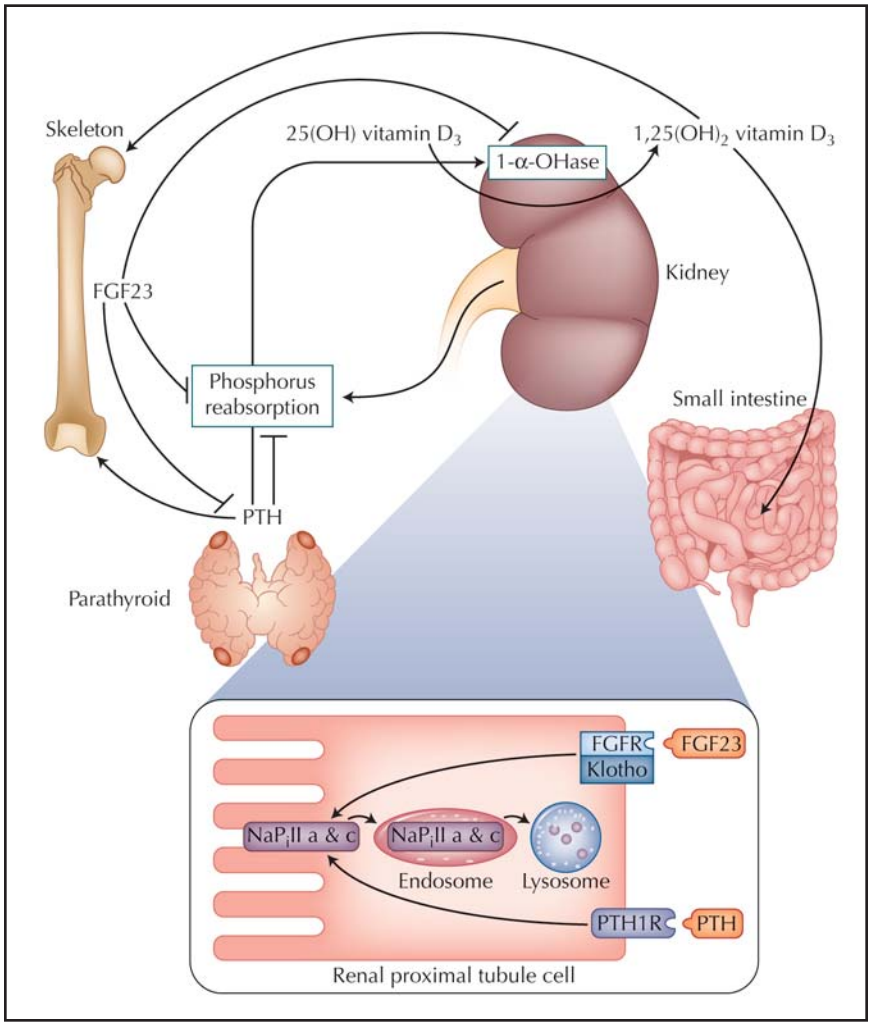

Figure 1. Working model of phosphate homeostasis. Phosphate homeostasis is maintained through a complex interplay between fibroblast growth factor 23 (FGF23) produced in the bone, parathyroid hormone (PTH) produced in the parathyroids, and calcitriol (1,25$[OH]_2$ vitamin D_3) produced in the kidney. FGF23 is secreted by osteocytes and osteoblasts in response to high serum phosphate levels and after the administration of the vitamin D metabolite, 1,25$(OH)_2$ vitamin D_3. FGF23, in turn, increases renal phosphorus excretion and thus serum phosphorus by reducing brush border membrane expression of NaP_iIIa and NaP_iIIc. In addition, FGF23 reduces calcitriol synthesis with resultant diminished intestinal calcium and phosphorus absorption. Moreover, FGF23 decreases serum PTH further reducing renal phosphorus excretion, calcitriol synthesis, and osteoclast-mediated liberation of calcium and phosphorus from bone. The net result is normalization of serum phosphorus without increase in serum calcium. The physiological action of FGF23 is accomplished through FGF23 binding to the cognate fibroblast growth factor receptors (FGFRs) and the cofactor Klotho in the kidney and the parathyroids. Stimulation is indicated by an *arrow* and inhibition is indicated by a *straight line*. PTH1R—parathyroid hormone receptor type 1.

FGF23 is a circulating fibroblast growth factor produced by osteocytes and osteoblasts [1,2]. FGF23 is processed in the Golgi apparatus by *O*-glycosylation at the subtilisin-like proprotein convertase recognition sequence ($RHTR^{179}$) between Arg^{179} and Ser^{180}, thus preventing its degradation by furin proteases and facilitating its secretion [3••]. FGF23 binds to a receptor complex comprised of the FGF receptor (most likely fibroblast growth factor receptor 1 [FGFR1] [IIIc]), and α-Klotho in the renal tubules and parathyroid glands [4••]. A deficiency in functional α-Klotho [5] in the mouse results in aberrant mineral metabolism and calcitriol synthesis, almost identical to that of the FGF23 null state [6]. Moreover, α-Klotho–deficient mice exhibit a 2000-fold increase in serum FGF23 concentrations, suggesting FGF23 resistance.

Mammalian α-Klotho exists as two isoforms: a full-length, membrane-bound form consisting of two external repeats (KL1 and KL2) with a similar homology to β-glucuronidases [7]; and a shorter, secreted form, due to a splice variant with an in-frame stop codon between KL1 and KL2 [8]. While both forms of α-Klotho can activate FGF23 signaling in vitro, the expression or the actual active form that is important in FGF23 signaling in vivo is not known. α-Klotho is expressed in the two known target organs of FGF23, namely the kidney and the parathyroids. Paradoxically, expression of α-Klotho in the kidney is thought to be limited to the distal tubule [5], whereas FGF23 acts on phosphate reabsorption in the proximal tubule—implying that in this case, the shorter form may be active.

Like PTH, FGF23 is a potent inhibitor of renal phosphate transport by regulating internalization of the major type IIa and IIc sodium-phosphate cotransporter (NaP_iIIa, NaP_iIIc) expressed in the renal proximal convoluted tubules (PCTs) [9,10]. Yet in contrast to PTH, FGF23 reduces expression of the key renal vitamin D metabolizing enzyme 25-hydroxyvitamin D-1-α-hydroxylase [11,12] also found predominantly in the PCTs. Conversely, administration of calcitriol results in an increase in circulating FGF23 [13,14], which suggests a negative feedback loop. Recent in vivo experiments in rats in which FGF23 was applied directly to the exposed parathyroid glands suggests an additional action of FGF23 is to reduce *PTH* gene expression and PTH secretion from the parathyroid glands [15••]. PTH reduction was also accompanied by an increase in α-Klotho expression, reinforcing PTH's role

as an essential cofactor conferring specificity to the action of FGF23 on its target organs. While great progress in identifying new phosphate-regulatory hormones and their individual actions has been achieved, elucidating integration of PTH and FGF23 signaling in the tissues that control phosphate homeostasis is virtually unexplored, but a critical question in understanding the physiological regulation of mineral metabolism.

Phosphate Homeostasis: Lessons from Metabolic Bone Diseases

Hypophosphatemic disorders

Hypophosphatemia secondary to renal phosphate wasting has a wide differential diagnosis. These disorders (Table 1) can result from primary renal defects (eg, Fanconi syndrome), PTH excess (eg, in hyperparathyroidism), overproduction of FGF23 from normal or dysplastic bone, ectopic production of FGF23 from tumors, or mutations in the sodium-phosphate transporters.

Syndromes of FGF23 excess

Tumor-induced osteomalacia: FGF23 excess is central to the pathophysiology of tumor-nduced osteomalacia (TIO) and three genetic disorders of renal phosphate wasting: X-linked hypophosphatemic rickets (XLH), autosomal-dominant hypophosphatemic rickets (ADHR), and autosomal-recessive hypophosphatemic rickets (ARHR).

TIO, or oncogenic osteomalacia, is an acquired, paraneoplastic syndrome of renal phosphate wasting. First described in 1947, TIO was shown in clinical and experimental studies to implicate the humoral factor(s) that tumors produce in the profound biochemical and skeletal alterations that characterize TIO. Although most TIO patients are adults, this syndrome may present at any age. These patients report longstanding, progressive muscle and bone pain. The occult nature of TIO delays its recognition and, even once the syndrome is recognized, an average of 5 years elapses from the time of diagnosis to identification of the underlying tumor.

The biochemical hallmarks of TIO are low serum concentrations of phosphate; phosphaturia, secondary to reduced proximal renal tubular phosphate reabsorption; and frankly low or inappropriately normal levels of serum calcitriol that are expected to be elevated in the face of hypophosphatemia. Calcium and PTH levels are typically normal. Bone histomorphometry reveals severe osteomalacia with clear evidence of a mineralization defect with increased mineralization lag time and excessive osteoid. The dual defect of renal phosphate wasting in concert with impaired calcitriol synthesis results in poor bone mineralization and fractures.

The mesenchymal tumors that are associated with TIO are characteristically slow growing, polymorphous neoplasms with the preponderance being phosphaturic mesenchymal tumor, mixed connective tissue type. These mesenchymal tumors ectopically express and secrete FGF23 and other phosphaturic proteins. That FGF23 excess is a powerful mediator of TIO, and perhaps the predominant one, is supported by abundant evidence. When injected into mice, FGF23 reduces serum phosphate and increases fractional excretion of phosphate [11]. Mice chronically exposed to FGF23–transfected Chinese hamster ovary (CHO) cell xenografts become hypophosphatemic with increased renal phosphate clearance, show reduced bone mineralization, and have reduced expression of renal 25-hydroxyvitamin D-1-α-hydroxylase with decreased circulating levels of calcitriol [16]. The biochemical and skeletal abnormalities of transgenic mice that overexpress FGF23 mimic human TIO [17]. This suggests that FGF23 is an upstream regulator of phosphate homeostasis, able to control both renal and calcitriol activity to decrease phosphate levels. In humans, FGF23 is highly expressed in many tumors associated with TIO by both mRNA and immunohistochemical evaluation [16,18–20]. FGF23 is measurable in serum and is elevated in most patients with TIO [21]. Furthermore, circulating FGF23 plummets after successful surgical removal of the causative tumor.

Other secreted proteins such as MEPE (matrix extracellular phosphoglycoprotein), FGF7, and sFRP4 (secreted frizzled-related protein 4) are highly expressed in mesenchymal tumors associated with TIO but the role of each of these "phosphatonins" in the disease process remains obscure [22•].

Autosomal-dominant hypophosphatemic rickets: ADHR is a rare form of hypophosphatemic rickets with clinical and biochemical characteristic similar to XLH (Table 1). Multiple early reports documented an inheritance pattern that included male-to-male transmission. A subset of patients with ADHR has a delayed onset of symptoms and there is incomplete disease penetrance within affected families. Positional mapping, cloning and sequence analysis have established that FGF23 was mutated in ADHR [23]. In ADHR, mutations at arginine residues 176 or 179 that reside in a subtilisin-like proprotein convertase recognition site render FGF23 resistant to cleavage and degradation, thus prolonging its biological activity [24–26].

X-linked hypophosphatemic rickets: XLH is an X-linked dominant disorder that manifests in children with progressive lower extremity bowing, dental manifestations, including abscessed noncarious teeth, enamel defects, enlarged pulp chambers, and taurodontism. In adults, bone and joint pain from osteomalacia, pseudofractures and enthesopathy are prominent features. Patients with XLH exhibit the same renal phosphate wasting and abnormal vitamin D metabolism as those with TIO and ADHR. Yet, the genetic defect is not in FGF23 but is due to loss-of-function mutations in a metalloprotease, PHEX [27]. The *PHEX* gene codes for a protein of unknown function that is a member of the M13 family of membrane-bound metalloproteases. Subsequent studies have shown that PHEX is present in osteoblasts,

Table 1. Hypophosphatemic disorders: biochemistry and pathogenesis of phosphate wasting disorders

Disease*	Defect	Biochemical features	Pathogenesis
TIO	Mesenchymal tumor	**Renal phosphate wasting:** low serum phosphate, decreased urinary phosphate reabsorption	Ectopic, unregulated production of FGF23 and other phosphatonins sFRP-4, MEPE, FGF7
		Inappropriately low 1,25(OH)$_2$ vitamin D$_3$: low or low normal	
		Absence of hypercalcemia or hyperparathyroidism: normal serum calcium, PTH, normal urinary calcium	
XLH (#307800)	*PHEX* gene, loss of function	As above	Increased FGF23 synthesis from bone
ADHR (#193100)	*FGF23* gene, gain of function	As above	Increased circulating intact FGF23 due to mutations that render it resistant to cleavage
ARHR (#241520)	*DMP1* gene, loss of function	As above	Loss of DMP1 causes impaired osteocyte differentiation and increased production of FGF23
Fibrous dysplasia (#174800)	*GNAS* gene, gain of function	As above	Increased FGF23 production from fibrous dysplastic bone; correlated with extent of bone disease
OGD (#166250)	*FGFR1* gene, gain of function	As above	Increased production of FGF23 by dysplastic bone
HR and HPT (#612089)	α-*Klotho* translocation, gain of function	**Renal phosphate wasting** **Inappropriately normal 1,25 (OH)$_2$ vitamin D$_3$** **HPT**	Increased α-Klotho, FGF23, and downstream FGF23 signaling
HHRH (#241530)	*SLC34A3* gene (NaP$_i$IIc), loss of function	**Renal phosphate wasting:** low serum phosphate, decreased urinary phosphate reabsorption	Loss-of-function mutations in NaP$_i$IIc results in renal phosphate wasting without defect in 1,25(OH)$_2$ vitamin D$_3$ synthesis
		Appropriately elevated 1,25(OH)$_2$ vitamin D$_3$	
		PTH is normal or suppressed	
		Variable hypercalcemia	
		Increased urinary calcium	
NPHLOP1 mutations (#182309)	*SLC34A1, NPT2*, NaP$_i$IIa, gene mutations, dominant negative	Similar to HHRH	Dominant negative mutations in NaP$_i$IIa result in renal phosphate wasting without defect in 1,25(OH)$_2$ vitamin D$_3$ synthesis
NPHLOP2 mutations (#612287)	*SLC9A3R1, NHERF1* gene, gain of function	**Renal phosphate wasting:** low serum phosphate, decreased urinary phosphate reabsorption	Mutations in *NHERF1* result in increased generation of cyclic AMP by PTH and inhibited phosphate transport
		Elevated 1,25(OH)$_2$ vitamin D$_3$	
		Absence of hypercalcemia or HPT: normal serum calcium, PTH, urinary calcium unknown	

* # = Online Mendelian Inheritance in Man.
ADHR—autosomal-dominant hypophosphatemic rickets; AMP—adenosine 5'triphosphate; ARHR—autosomal-recessive hypophosphatemic rickets; FGF23—fibroblast growth factor 23; HHRH—hereditary hypophosphatemic rickets with hypercalciuria; HPT—hyperparathyroidism; HR—hypophosphatemic rickets; NaP$_i$IIa—sodium-phosphate cotransporter 2a; NaP$_i$IIc—sodium-phosphate cotransporter 2c; NPHLOP—nephrolithiasis/osteoporosis, hypophosphatemic; OGD—osteoglophonic dysplasia; PTH—parathyroid hormone; TIO—tumor-induced osteomalacia; XLH—X-linked hypophosphatemic rickets.

osteocytes and odontoblasts but not in kidney tubules. While PHEX does not appear to cleave FGF23 directly [28,29], serum FGF23 levels are elevated in many XLH patients [21]. FGF23 expression also is increased in the bones of *hyp* mice, a mouse model of XLH [28]. These observations suggest that PHEX is involved in downregulation and control of FGF23; however, the precise interplay between FGF23 and PHEX is not currently understood.

Autosomal-recessive hypophosphatemic rickets: The genetic defect in the third form of hypophosphatemic rickets, ARHR, was identified as loss-of-function mutations in dentin matrix protein 1 (DMP-1), a matrix protein related to MEPE and a member of the small integrin binding ligand *N*-linked glycoprotein family [30••]. Interestingly, this protein appears to have two functions: it translocates into the nucleus to regulate gene transcription early in osteocyte proliferation and then, likely in response to calcium fluxes, becomes phosphorylated and is exported to the extracellular matrix to facilitate mineralization by hydroxyapatite in a process that requires appropriate cleavage of the full-length protein [31]. Loss of DMP-1 function in ARHR leads to modestly and variably increased serum FGF23, dramatically increased expression of FGF23 in bone, defects in osteocyte maturation, and impaired skeletal mineralization [30••,32]. It appears that the immature osteocytes overproduce FGF23, which then circulates and acts on the kidney to produce phosphaturia and aberrant vitamin D synthesis. The mechanism by which DMP-1 regulates FGF23 production remains obscure and is an area of active investigation.

Fibrous dysplasia and osteoglophonic dysplasia: FGF23 excess results in renal phosphate wasting in several disorders associated with dysplastic bone and fibrous cells. In patients with fibrous dysplasia, FGF23 levels correlate with the degree of phosphate wasting, and the response of the dysplasia to bisphosphonate therapy was correlated with a reduction in the FGF23 levels [33]. In a study of osteoglophonic dysplasia (OGD), where the underlying defect is an activating mutation of the FGFR1, one patient had normal phosphate homeostasis, normal FGF23 levels, and a low burden of cystic bone lesions. In contrast, another patient with OGD and a large burden of nonossifying bone lesions exhibited phosphate wasting and an elevated FGF23 serum level [34]. Thus, overproduction of FGF23 by dysplastic bone or fibrous cells appears to be a critical step in a common pathway for many of the acquired forms of renal phosphate wasting.

Klotho excess

Hypophosphatemic rickets with hyperparathyroidism: Brownstein et al. [35] reported on a patient with hypophosphatemic rickets, renal phosphate wasting, inappropriately normal calcitriol, and hyperparathyroidism secondary to a genetic translocation resulting in increased levels of α-Klotho, the cofactor necessary for FGF23 to bind and activate its receptor. Interestingly and somewhat unexpectedly, FGF23 serum levels are also markedly elevated in this disorder. These findings implicate α-Klotho in the regulation of serum phosphate, of FGF23 expression, and of parathyroid function.

Mutations in sodium-phosphate cotransporters and interacting proteins

Hereditary hypophosphatemic rickets with hypercalciuria: HHRH is a rare genetic form of hypophosphatemic rickets characterized by hypophosphatemia, renal phosphate wasting, and preserved responsiveness of calcitriol to hypophosphatemia [36]. This appropriate increase in calcitriol leads to increased calcium absorption from the gastrointestinal tract and thus to hypercalciuria and nephrolithiasis. The genetic defect in HHRH is loss of function mutations in the gene that encodes NaP_iIIc [37,38••,39]. Prominent features of HHRH, clinically similar to TIO, are bone pain, osteomalacia, and muscle weakness, yet the distinction is easily made with biochemical testing. In contrast to FGF23-mediated renal phosphate wasting syndromes, patients with HHRH exhibit elevated levels of calcitriol and hypercalciuria. The profound renal phosphate wasting observed in HHRH underscores the importance of NaP_iIIc in regulation of phosphate homeostasis in humans.

Renal type IIa sodium-phosphate cotransporter mutations: Mutations in the renal NaP_iIIa gene (*NPT-2*) were found to be heterozygous and dominant-negative in two patients with hypophosphatemia secondary to renal phosphate wasting and osteopenia or nephrolithiasis. Bone pain and myopathy are absent in those with *NPT-2* mutations. Furthermore, the presence of hypercalciuria and elevated calcitriol makes these patients easily distinguishable from those with FGF23-mediated phosphate-wasting syndromes [40].

***NHERF1* mutations:** Recently, three distinct heterozygous mutations in the sodium-hydrogen exchanger regulatory factor 1 (NHERF1)—a protein that interacts with NaP_iIIa and NaP_iIIc—were observed in seven patients with bone demineralization or nephrolithiasis [41]. These patients exhibit mild hyperphosphatemia, reduced renal phosphate reabsorption, and appropriately elevated calcitriol, with normal PTH and calcium. In vitro studies support the notion that *NHERF1* mutations potentiate PTH-induced cyclic AMP generation, consequently the inhibition of phosphate transport.

Therefore, either through mutations of the sodium-phosphate transporters themselves (as in HHRH) or interacting proteins (as in *NHERF1* mutations), damage to the proximal renal tubule (Fanconi syndrome), or through aberrant regulation via FGF23, it is likely that decreased expression or function of the renal sodium-phosphate cotransporters represent the common pathway in renal phosphate wasting observed in these syndromes [42].

Hyperphosphatemic disorders

Familial tumoral calcinosis: FGF23 deficiency

Genetic disorders that cause FGF23 deficiency present with an opposite phenotype to the syndromes of FGF23

Table 2. Hyperphosphatemic disorders: biochemistry and pathogenesis of hyperphosphatemic disorders

Disease*	Defect	Biochemical features	Pathogenesis
HFTC (#211900)	*GALNT3* gene mutations, loss of function	**Renal phosphate retention:** high serum phosphate, increased urinary phosphate reabsorption **Inappropriately normal 1,25 $(OH)_2$ vitamin D_3 levels** **Variable serum calcium levels:** high to slightly elevated	Dysfunctional GalNAc transferase 3 required for *O*-glycosylation of FGF23—a process essential for secretion of intact FGF23 and resistance to degradation. High C-terminal FGF23 levels but low intact levels
	FGF23 gene mutations, loss of function	As above	High C-terminal FGF23 levels but low intact levels
	α-Klotho homozygous missense mutation (H193R), loss of function	As above with the addition of hyperparathyroidism and frank hypercalcemia	FGF23 resistance. High FGF23 levels, both C-terminal and intact
HHS	*GALNT3* gene mutations, loss of function	As in HFTC above	An allelic disorder to HFTC arising from *GALNT3* mutations with the addition of the phenotypic feature of hyperostosis

* # = Online Mendelian Inheritance in Man.
FGF23—fibroblast growth factor 23; HFTC—hyperphosphatemic familial tumoral calcinosis; HHS—hyperostosis hyperphosphatemia syndrome.

excess discussed previously (Table 2). Mice lacking *Ffg23* develop hyperphosphatemia and elevated calcitriol [6] and appear similar to humans with familial tumoral calcinosis. Hyperphosphatemic familial tumoral calcinosis (HFTC) is a human disorder associated with hyperphosphatemia, elevated calcitriol, hypercalcemia, and ectopic calcification. Initially, loss-of-function mutations in the gene that encodes GALNT3, a protein involved in *O*-linked glycosylation, were identified in several families with tumoral calcinosis [43,44••]. This was puzzling as inactivating mutations in *FGF23* were hypothesized to be the molecular defect in HFTC. Subsequently, families with loss-of-function mutations in *FGF23* itself were recognized [45,46••,47]. Further investigation revealed that GALNT3 glycosylates threonine 178 in FGF23. This residue resides in the region that is cleaved to inactivate FGF23 (and the site of activating mutations in ADHR). Glycosylation protects FGF23 from degradation, and defective or absent glycosylation renders FGF23 vulnerable to cleavage and inactivation [3••]. Hyperostosis hyperphosphatemia syndrome (HHS) is a rare disease exhibiting similar biochemical features to HFTC but with the additional presentation of localized hyperostosis. Mutations in *GALNT3* have similarly been identified in families with HHS. Thus, HHS is likely not a distinct disorder from HFTC, but represents a phenotypic variation in the spectrum of HFTC [48].

FGF23 resistance

Similarly, a mutation in the gene encoding α-Klotho, a matrix molecule that acts as a cofactor/coreceptor for FGF23 and enhances binding to FGFR1c [4••,49•], was recently identified in a patient with hyperphosphatemic tumoral calcinosis [50••]. While FGF23 levels were markedly elevated, the biochemical and physical manifestations of tumoral calcinosis were more suggestive of FGF23 deficiency. This is an example of FGF23 resistance due to an impaired FGF23-klotho-FGFR signaling complex.

Loss of function of FGF23, either directly through loss-of-function mutations in FGF23, aberrant glycosylation of FGF23, or loss of its signaling cofactor, Klotho, results in tumoral calcinosis with its disordered phosphate and vitamin D homeostasis.

Conclusions

The study of hypo- and hyperphosphatemic disorders has led to a new understanding of the hormonal regulators of phosphate homeostasis. The centrality of FGF23 in these disorders make a compelling argument for FGF23 as an important physiological regulator of phosphate and vitamin D. Mutations in FGF23 or dysregulation of its expression provide a unifying explanation for these syndromes at a molecular level. However, intriguing questions remain to be dissected in both the regulation of FGF23 in the skeleton and its action in the kidney and the parathyroid. At the molecular level little is known of the signaling pathways activated by FGF23 and which ones specifically regulate the NaP_iII transporters and/or expression of 1-α-OHase. A more complete understanding of these questions will enhance our ability to integrate the traditional and emerging pathways that regulate phosphate homeostasis.

Disclosures

Suzanne M. Jan de Beur is a member of the Data Safety Review Committee for Kirin Pharma, USA. No other potential conflicts of interest relevant to this article were reported.

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