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Review

Paracrine and endocrine functions of osteocytes

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Highlights

- Osteocytes embedded in bone matrix produce paracrine and endocrine factors.
- Osteocytes control bone mass through the secretion of sclerostin and RANKL.
- Osteocytes play a central role in phosphate metabolism by producing FGF23.

Abstract. Osteocytes are dendritic-shaped cells embedded in the bone matrix and are terminally differentiated from osteoblasts. Inaccessibility due to their location has hindered the understanding of the molecular functions of osteocytes. However, scientific advances in the past few decades have revealed that osteocytes play critical roles in bone and mineral metabolism through their paracrine and endocrine functions. Sclerostin produced by osteocytes regulates bone formation and resorption by inhibiting Wnt/β-catenin signaling in osteoblast-lineage cells. Receptor activator of nuclear factor κ B ligand (RANKL) derived from osteocytes is essential for osteoclastogenesis and osteoclast activation during postnatal life. Osteocytes also secrete fibroblast growth factor 23 (FGF23), an endocrine FGF that regulates phosphate metabolism mainly by increasing phosphate excretion and decreasing 1, 25-dihydroxyvitamin D production in the kidneys. The regulation of FGF23 production in osteocytes is complex and multifactorial, involving many local and systemic regulators. Antibodies against sclerostin, RANKL, and FGF23 have emerged as new strategies for the treatment of metabolic bone diseases. Improved undrstanding of the paracrine and endocrine functions of osteocytes will provide insight into future therapeutic options.

Key words: osteocytes, sclerostin, bone mass, fibroblast growth factor 23, phosphate metabolism

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Introduction

Osteocytes are dendritic-shaped cells with long processes embedded deeply in the mineralized bone matrix and terminally differentiated from bone-forming osteoblasts (1, 2). They are the most abundant cells among cells of adult bone, but their location and inaccessibility have hindered molecular analyses of their function. However, in the past few decades, evidence has accumulated indicating that osteocytes profoundly impact bone and mineral metabolism *via* their paracrine and endocrine functions, as summarized in **Fig. 1**. Osteocytes seem to control bone mass through the production of sclerostin, a potent inhibitor of bone formation, and receptor activator of nuclear factor κ B ligand (RANKL), an essential molecule for osteoclast formation and activation (3–5). Furthermore, osteocyte secrete fibroblast growth factor 23 (FGF23), an endocrine FGF that plays a central role in phosphate homeostasis (6, 7). Neutralizing antibodies against sclerostin, RANKL, and FGF23 have been developed for therapeutic use (8–10). Thus, osteocytes are drawing attention as cellular targets for research and drug discovery.

This review aims to provide an updated overview of osteocytes' paracrine and endocrine functions that regulate bone and mineral metabolism.

Osteoblast-to-Osteocyte Differentiation

Osteocytes have long lifespans and comprise 90–95% of all bone cells in the adult skeleton (1, 2). A subpopulation of osteoblasts on the bone surface becomes embedded in the matrix proteins they produce and terminally differentiate into dendritic-shaped osteocytes, while the remainder of osteoblasts become flattened bone lining cells or undergo apoptosis (2). Osteocytes reside in small cavities known as "lacunae" in the bone matrix, and are interconnected with each other and osteoblasts on the bone surface by their long processes extending through the tunnels called "canaliculi". The lacuna-canaliculi system is filled with extracellular fluids. According to Buenzli *et al*., the average human skeleton contains ~ 42 billion osteocytes with 23 trillion connections, and the total surface area of the lacuna-canaliculi network

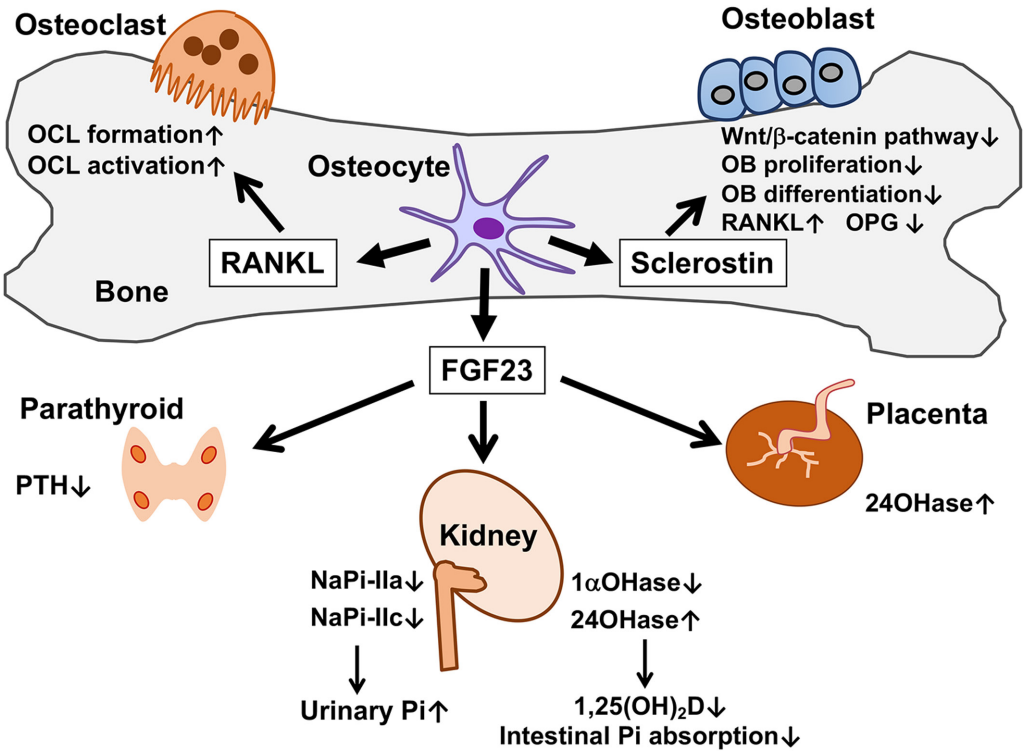

Fig. 1. Paracrine and endocrine functions of osteocytes. Osteocytes produce paracrine factors, sclerostin and receptor activator of NF-κB ligand (RANKL). Sclerostin produced by osteocytes inhibits Wnt/β-catenin signaling in osteoblasts (OB) in a paracrine manner, leading to the suppression of their proliferation and differentiation, the up-regulation of RANKL and the down-regulation of osteoprotegerin (OPG). Although RANKL is expressed in osteoblasts as well as osteocytes, RANKL derived from osteocytes plays a major role in the formation and activation of osteoclasts (OCL) in postnatal life. FGF23 secreted by osteocytes exerts its effects on distant targets in an endocrine manner. In the kidneys, FGF23 suppresses the expression of NaPi-IIa and NaPi-IIc to increase Pi excretion. Moreover, FGF23 reduces the expression of 25-hydroxyvitamin D-1α-hydroxylase (1αOHase) and induces that of 25-hydroxyvitamin D-24-hydroxylase (24OHase). The resultant decrease in serum $1,25(OH)_2D$ level leads to the reduction in the intestinal Pi absorption. Animal studies have suggested that FGF23 also suppresses the secretion of PTH in the parathyroid glands and induces the expression of 24OHase in the placenta.

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is 215 m^2. The complexity of the communication network of osteocytes is similar to that of neurons (11). The maturation of osteoblasts into osteocytes is associated with a decreased production of matrix proteins, marked changes in morphology, and the expression of genes characteristic of osteocytes, including those involved in bone homeostasis and mineral metabolism (1, 2).

Paracrine Regulation of Bone Formation by Osteocytes

Osteocytes embedded in the mineralized bone matrix sense mechanical forces and exert bone anabolic signals on other bone cells via their lacuna-canaliculi system in a paracrine manner. Genetic ablation of osteocytes in mice causes marked bone loss with the suppression of mechanically induced bone formation (12).

Osteocytes regulate bone formation mainly through the production of sclerostin, a secreted inhibitor of Wnt/β-catenin signaling. In bones, the activation of Wnt/β-catenin signaling promotes the commitment of mesenchymal progenitor cells into osteoblasts and accelerates the proliferation and differentiation of committed osteoblasts (13, 14). Wnt/β-catenin signaling also suppresses the relative expression of RANKL in osteoblast-lineage cells to reduce the formation and activation of osteoclasts, which are responsible for bone resorption (13, 14). Sclerostin inhibits Wnt/β-catenin signaling by binding to Wnt co-receptors low-density lipoprotein receptor-related protein 5 (LRP5), and LRP6 (15). The critical role of sclerostin in controlling the bone mass has been suggested by the discovery that inactivation or reduced expression of *SOST*, the gene for sclerostin, is responsible for rare bone-sclerosing genetic disorders such as sclerosteosis 1 (MIM #269500) and van Buchem disease (MIM #239100). Sclerosteosis 1 is an autosomal recessive disease characterized by sclerosing bones, progressive skeletal overgrowth, and syndactyly. It is frequent in the Afrikaner population in South Africa and is caused by the inactivation of variants in the *SOST* gene (16). Van Buchem disease is an autosomal recessive disease characterized by marked osteosclerosis in the skull, lower jaw, clavicles, ribs, and diaphysis of the long bones and short tubular bones, resulting in increased cortical bone density. In a large consanguineous Dutch family with van Buchem disease, a homozygous 52-kb deletion located downstream of the *SOST* gene has been identified as a responsible factor for the disease (17). This deletion results in suppressed gene expression. *Sost*-knockout mice also exhibit a high bone mass phenotype with increased bone formation and strength (18).

Sclerostin expression is regulated by mechanical forces. Animal experiments by Robling *et al.* demonstrated that *Sost* transcripts and sclerostin protein levels in osteocytes were dramatically reduced by mechanical loading, and this effect was both local and regional (3). Hence, osteocytes may coordinate local and regional bone formation by modulating sclerostin levels in response to mechanical forces. Recently, a mechano-sensor channel, Piezo1, was suggested to mediate mechanical force-induced suppression of *Sost* (19).

It is well established that intermittent administration of parathyroid hormone (PTH) exerts anabolic effects on the bone (20). Teriparatide, a recombinant human PTH[1–34], is the first approved anabolic agent that increases bone formation and is widely used to treat osteoporosis (21). PTH-induced bone formation is also mediated by downregulation of *Sost* in osteocytes (22, 23). A recent study suggested that PTH signaling leads to the phosphorylation of salt-inducible kinase 2 (SIK2), which causes nuclear translocation of histone deacetylase 4 (HDAC4) and HDAC5. In the nucleus, HDAC4/5 inhibits myocyte enhancer factor 2C (MEF2C)-mediated transactivation of *SOST* (24). The expression of *SOST* is also regulated by other factors, such as prostaglandin E2 (25), transforming growth factor (TGF) β (26), bone morphogenetic proteins (BMPs) (27), hypoxia (28), and gp130 signaling (29).

Because the sclerostin expression is virtually restricted to osteocytes, it has emerged as an attractive therapeutic target for treating skeletal diseases characterized by low bone mass. Anti-sclerostin-neutralizing antibodies stimulate bone formation and suppress bone resorption by inhibiting Wnt/β-catenin signaling in the bone. Clinical trials of the anti-sclerostin antibody romosozumab suggested that the risk of cardiovascular events might increase when compared with bisphosphonate alendronate (30); however, romosozumab was approved in January 2019 in Japan for the treatment of osteoporosis in patients at high fracture risk and was launched in March 2020, followed by approval in the United States, Canada, and Europe for treating the postmenopausal women at high fracture risk (31). A recent systematic review and meta-analysis have demonstrated the efficacy and safety of romosozumab in the treatment of postmenopausal osteoporosis (8).

Osteogenesis imperfecta (OI) is a heterogeneous genetic disorder characterized by low bone mass and increased bone fragility (32). The beneficial effects of anti-sclerostin antibodies on bone mass and strength have been demonstrated in some mouse models of OI, such as *Brtl/+* mice harboring a heterozygous glycine to cysteine substitution in *Col1a1* (33), *Crtap*$^{-/-}$ mice, a model of OI type VII (34), and *oim/oim* mice, a model for OI type III (35). In humans, in a randomized phase 2a trial, the anti-sclerostin antibody BPS804 stimulated bone formation, reduced bone resorption, and increased lumbar spine areal bone mineral density in adult patients with moderate OI (36). Antibody-mediated inhibition of sclerostin is a promising approach to tackle various conditions with low bone mass and bone fragility.

Paracrine Regulation of Bone Resorption by Osteocytes

Osteoclasts are multinucleated cells responsible for bone resorption and are formed from monocyte/

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macrophage-lineage cells. RANKL is a membrane-associated cytokine expressed in osteoblast-lineage cells, including osteocytes, that plays an essential role in osteoclastogenesis (37). RANKL binds to its cognate receptor, RANK, on the surface of osteoclast precursors to induce osteoclast differentiation. Mature osteoclasts also express RANK, which activates their bone-resorbing activity (37). Osteoprotegerin is a soluble decoy receptor for RANKL that inhibits osteoclast differentiation and activation by preventing RANKL-RANK binding (37). Denosumab is a humanized monoclonal antibody against RANKL (9) that is used to treat osteoporosis, rheumatoid arthritis, and bone disease associated with solid cancers and multiple myeloma. However, pediatric data on the use of denosumab is limited (38). The suppressive effects of denosumab on bone turnover rapidly disappear after its discontinuation, and rebound increases in bone turnover may cause severe hypercalcemia (38).

In 2011, two groups reported that osteocyte-specific deletion of RANKL in mice using *dentin matrix protein 1* (*Dmp1*)-Cre transgene caused postnatal progressive osteopetrosis despite normal skeletal development and bone mass at birth (4, 5). *Sost*-Cre-mediated deletion of RANKL from osteocytes results in a similar high bone mass phenotype (39). Using a series of Cre-deleter mouse strains, Xiong *et al.* demonstrated that hypertrophic chondrocyte-derived RANKL regulates the resorption of mineralized cartilage and that osteocyte-derived RANKL is essential for bone remodeling and controls unloading-induced bone loss. In contrast, RANKL derived from osteoblasts and bone-lining cells contribute less to bone remodeling (5, 39). It has also been suggested that osteocyte-derived RANKL is upregulated by senescence and is involved in age-related cortical bone loss (40). These findings indicated that osteocyte-derived RANKL is required for postnatal bone homeostasis. However, how RANKL on the surface of osteocytes located in the bone matrix reaches osteoclast precursors to induce their differentiation and activation remains to be elucidated.

Endocrine Regulation of Phosphate Metabolism by Osteocytes

Osteocytes also function as endocrine cells. Fibroblast growth factor 23 (FGF23), a central regulator of phosphate metabolism, is produced mainly by osteocytes in the bone and exerts its effects on distant organs such as the kidneys in an endocrine manner (1, 2, 6, 7, 41).

In mammals, phosphate homeostasis is maintained by the influx and efflux of inorganic phosphate (Pi) in the intestines, kidneys, bones, and soft tissues, and endocrine factors such as 1,25-dihydroxyvitamin D ($1,25(OH)_2D$), PTH, and FGF23 mediate interorgan communication to regulate the fluxes of Pi (42). $1,25(OH)_2D$, which is an active vitamin D metabolite, is predominantly produced in the kidneys and increases the intestinal absorption of Pi through the upregulation of the type IIb sodium/Pi (Na^+/Pi) co-transporter NaPi-IIb (43). PTH secreted from parathyroid cells decreases renal Pi reabsorption by reducing the amounts of type IIa and IIc Na^+/Pi co-transporters (NaPi-IIa and NaPi-IIc, respectively) on the brush border membrane of proximal tubules (44, 45).

The kidneys are the main target of FGF23, which increases Pi excretion by suppressing the expression of NaPi-IIa and NaPi-IIc. Furthermore, FGF23 decreases the level of $1,25(OH)_2D$ by suppressing the expression of 25-hydroxyvitamin D 1α-hydroxylase and inducing the expression of 25-hydroxyvitamin D 24-hydroxylase (46). The decreased level of $1,25(OH)_2D$ leads to the reduced Pi absorption in the intestines. Bioactive intact FGF23 is inactivated by cleavage between Arg^{179} and Ser^{180} by subtilisin-like proprotein convertase (47).

In contrast to canonical FGFs, which function as autocrine and/or paracrine factors, FGF23 acts as an endocrine factor in distant organs. It has been suggested that its low binding affinity to heparin/heparan sulfate enables FGF23 to enter the circulation while escaping capture by extracellular matrices (48). At physiological concentrations, FGF23 requires the single-pass transmembrane protein αKlotho as a cofactor to evoke its signal through FGF receptors (FGFRs) (49, 50). Hence, organs and tissues expressing both FGFR and αKlotho, such as the kidneys, parathyroid glands, and placenta, may be physiological targets for FGF23 (51–53).

The FGF23-mediated interaction between the bone and kidney plays a central role in Pi homeostasis, and the activity of this interaction appears to determine serum Pi levels. Our recent mouse studies have demonstrated that the production of FGF23 in osteocytes increases from youth to adulthood, which leads to growth-related enhancement of the FGF23-mediated bone-kidney axis and a decline in serum Pi levels (7).

The parathyroid glands express both FGFR and αKlotho, and animal studies have demonstrated that administration of recombinant FGF23 suppresses PTH gene expression and secretion *via* the mitogen-activated protein kinase (MAPK) signaling pathway (51). However, since FGF23-induced suppression of PTH secretion was still observed in mice with parathyroid-specific conditional deletion of αKlotho (54), FGF23 is likely to regulate PTH secretion in both α a Klotho-dependent and -independent manner.

The placenta can also be a target of FGF23. The placenta contains both maternal and fetal tissues, and FGFR1 and αKlotho are colocalized at the feto-maternal interface of the placenta in both mice and humans (52). Using pregnant mothers of hypophosphatemic *Hyp* mice, a murine model for X-linked hypophosphatemic rickets (XLH, MIM #307800), we have found that maternal FGF23 produced by osteocytes of pregnant mothers, not fetal FGF23, exerts its effects on the placenta and influences fetal vitamin D metabolism by increasing the placental expression of *Cyp24a1* encoding 25-hydrpxyvitamin D 24-hydroxylase. In contrast, maternal FGF23 did not affect the placental expression of Na^+/Pi co-transporters or fetal serum Pi levels (52).

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Thus, the role of FGF23 in mineral metabolism may differ between fetal and postnatal life. Our results in *Hyp* pregnancies have demonstrated that pathologically elevated maternal FGF23 regulate placental vitamin D metabolism; however, the physiological significance of this observation remains to be elucidated.

FGF23-Related Hyperphosphatemic and Hypophosphatemic Disorders

The bone-kidney axis mediated by FGF23/FGFR/αKlotho signaling is crucial for Pi homeostasis, its disruption or excess causes diseases with abnormal serum Pi levels. Inactivating variants of *FGF23* and *KLOTHO* have been identified as causative elements for hyperphosphatemic familial tumoral calcinosis-2 (HFTC2, MIM #617993) and HFTC3 (MIM #617994), respectively, both of which are associated with hyperphosphatemia, normal to elevated serum $1,25(OH)_2D$ levels, and ectopic calcification (55, 56). HFTC1 (MIM #211900) is caused by inactivation of variants in the *GALNT3* gene encoding the enzyme UDP-*N*-acetyl-α-D-galacosamine:polypeptide *N*-acetylgalactosaminyltransferase 3 (GalNAc-T3), which mediates the *O*-glycosylation of FGF23 on Thr^{178} (57, 58). O-glycosylation has been suggested to prevent cleavage-mediated inactivation of FGF23 (58).

Excessive expression of FGF23 leads to hypophosphatemic diseases characterized by urinary Pi wasting, hypophosphatemia, inappropriately normal to low levels of serum $1,25(OH)_2D$, and impaired skeletal mineralization, such as rickets and osteomalacia. These disorders are collectively called FGF23-related hypophosphatemic rickets/osteomalacia, which includes tumor-induced osteomalacia (TIO) caused by the overproduction of FGF23 by tumors and genetic disorders such as XLH, autosomal dominant hypophosphatemic rickets (ADHR, MIM #193100), autosomal recessive hypophosphatemic rickets 1 (ARHR1, MIM #241520), ARHR2 (MIM #613312), and Raine syndrome (RNS, MIM #259775) (59, 60).

Among hereditary FGF23-related hypophosphatemic rickets/osteomalacia, ADHR is caused by variants in FGF23 at Arg^{176} or Arg^{179}, which make the protein resistant to cleavage-mediated inactivation (61). However, the penetrance of ADHR is incomplete, and it has been suggested that iron deficiency triggers the accumulation of uncleaved bioactive FGF23 and leads to the onset of symptoms (62, 63).

XLH is the most common form of hereditary hypophosphatemic rickets and is caused by the inactivation of variants in the *phosphate-regulating gene homologous to endopeptidase on the X chromosome* (*PHEX*) (64, 65). PHEX is highly expressed in osteocytes, as is FGF23 (6, 7). Patients with XLH show increased levels of serum intact FGF23, which leads to renal Pi wasting, hypophosphatemia, and reduced levels of $1,25(OH)_2D$ (64). Although the mechanisms underlying FGF23 overproduction in XLH remain elusive, studies using *Phex*-deficient *Hyp* mice have suggested the involvement of enhanced FGFR signaling (6, 66, 67). We demonstrated that the osteocytic expression of canonical FGF ligands (*Fgf1* and *Fgf2*), FGF receptors (*Fgfr1–3*), and *early growth response 1,* a downstream target for FGFR activation, was markedly higher in *Hyp* mice than in wild-type mice (6). Furthermore, Xiao *et al.* reported that osteocyte-specific ablation of *Fgfr1* in *Hyp* mice partially restored the elevation of serum FGF23 levels, and ameliorated hypophosphatemia and rickets (66). Enhanced FGFR signaling in *Hyp* osteocytes is interesting since previous studies, including ours, have implicated that FGFR might play a role in the transduction of signals evoked by increased extracellular Pi and/or Pi sensing (42, 68–71).

ARHR1 is caused by inactivating variants of the *DMP*1 gene, which is highly expressed in osteocytes in bone and odontoblasts in dentin (72, 73). *DMP*1 encodes a matrix protein belonging to the small integrin-binding ligand N-linked glycoprotein (SIBLINGs) family. Deletion of *Dmp1* in mice resulted in increased FGF23 expression in osteocytes and impaired skeletal mineralization, similar to the clinical manifestations in patients with ARHR1. Overproduction of FGF23 in *Dmp1*-null mice has also been attributed to enhanced FGFR signaling in osteocytes (59).

ARHR2 is caused by inactivating variants of *ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1)*, which encodes an ectoenzyme that produces pyrophosphate (PPi) (74, 75). As PPi is a potent inhibitor of mineralization, inactivating variants in the *ENPP1* gene also cause disorders characterized by ectopic calcification, such as generalized arterial calcification of infancy 1 (CAGI1, MIM #208000) (76). The expression of *ENPP1* is broadly detected, with higher expression in vascular smooth muscle cells, chondrocytes, osteoblasts, and osteocytes. It was reported that *Enpp1*-deficient mice showed increased expression of *Fgf23* in the bone, and dosing these mice with ENPP1-Fc recombinant protein demonstrated a negative correlation between *Enpp1* and *Fgf23* transcription (77).

RNS is an autosomal recessive disorder caused by inactivating variants in the *family with sequence similarity 20, member C (FAM20C)* gene, and is characterized by osteosclerotic bone dysplasia and cranial malformation (78). The prognosis of RNS is usually poor, and patients who survive infancy may manifest elevated levels of serum FGF23, hypophosphatemia, and dental anomalies (79, 80). *FAM20C* encodes a secreted protein kinase (47, 81) that is highly expressed in osteocytes (82). *FAM20C* directly phosphorylates FGF23 at Ser^{180}, which may prevent its *O*-glycosylation at Thr^{178} and facilitate cleavage-mediated inactivation (47). Hence, inactivation of *FAM20C* in RNS leads to reduced phosphorylation at Ser^{180}, increased *O*-glycosylation at Thr^{178}, and impaired FGF23 inactivation.

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Regulators of FGF23

Since PHEX, DMP1, ENPP1, and FAM20C are expressed in osteocytes, and their inactivating variants cause overproduction of FGF23, these molecules are considered to function as local negative regulators of FGF23. However, as described above, analysis of *Hyp* mice and *Dmp1*-null mice has suggested that activation of FGFR signaling in osteocytes positively regulates FGF23 production (6, 59, 66). The regulation of FGF23 production by FGFR signaling is also supported by the fact that osteoglophonic dysplasia, a human disease caused by activating mutations in *FGFR1,* may be associated with FGF23-related hypophosphatemia (83). In addition to these local regulators, other systemic factors have been suggested to regulate FGF23 production in osteocytes. Systemic regulators of FGF23 include $1,25(OH)_2D$, Pi, PTH, iron, insulin, and circadian rhythms. Thus, the regulation of FGF23 is complex and contextual. Since excellent reviews on the regulators of FGF23 can be found elsewhere (84, 85), only some of them are described here. **Table 1** summarizes local and systemic regulators of FGF23 expression.

FGF23 transcription is stimulated by $1,25(OH)_2D$ in osteoblast lineage cells *via* the vitamin D receptor (86, 87). The importance of $1,25(OH)_2D$ in regulatingFGF23 is supported by the observation that patients with vitamin D deficiency have low serum FGF23 levels (88).

Pi also stimulates FGF23 production, hence, dietary phosphorus loading increases serum FGF23 levels (89, 90). Treatment with high Pi levels increased the production of FGF23 by primary murine osteocytic cells, which appeared to occur at the protein level rather than at the mRNA level (7). Elevated levels of Pi upregulated the expression of *Galnt3* in osteoblast lineage cells, leading to increased FGF23 production without increasing its mRNA expression (71).

PTH has also been shown to increase FGF23 production. Patients with Jansen-type metaphyseal chondrodysplasia (MIM #156400), a disease caused by activating variants of *PTH1R* encoding PTH receptor 1, may show elevated levels of serum FGF23 and hypophosphatemia (91). Furthermore, mice with constitutive activation of PTH1R in osteocytes exhibit increased expression of *Fgf23* (92).

Iron deficiency stimulates transactivation of the *Fgf23* promoter through the accumulation of hypoxia-inducible factor 1α (HIF1α) (63). In healthy human subjects, iron deficiency accelerates both the production and cleavage-mediated inactivation of FGF23 in a coupled manner, leading to normal levels of intact FGF23 in the serum and normophosphatemia. In contrast, in patients with ADHR, impaired cleavage leads to the elevation of bioactive FGF23 during iron deficiency, leading to hypophosphatemia (62).

Insulin signaling may also influence FGF23 production in osteocytes. Bar *et al.* reported a negative correlation between plasma FGF23 levels and increased plasma insulin levels following oral glucose load in women (93). The authors also demonstrated that insulin and insulin-like growth factor 1 (IGF-1) reduced the production of FGF23 in cultured osteoblastic cells (93). To further confirm that osteocytes respond to insulin to regulate FGF23 production, we generated mice with an osteocyte-specific deletion of phosphatase and tensin homolog deleted from chromosome 10 (PTEN), a molecule that antagonizes insulin/IGF-1-induced AKT activation. These mice exhibit decreased skeletal and serum levels of intact FGF23, reduced urinary Pi excretion, and elevated serum Pi levels (94). Our *in vitro* studies suggest the involvement of the AKT/mechanistic target of rapamycin complex 1 (mTORC1) in insulin/IGF-1-induced suppression of FGF23 (94).

The circadian clock regulates physiology and metabolism for the optimal adaptation of living organisms to environmental changes, including nutrient availability (95, 96). Our mouse studies demonstrated that skeletal expression of *Fgf23* was higher in the dark phase. The duration of food intake determines the circadian profile of skeletal *Fgf23* expression via sympathetic activation, which is regulated by a peripheral clock in the skeleton (97).

Table 1. Local and systemic regulators of FGF23 discussed in this article

Regulators	Effects on FGF23	References
Local regulators		
PHEX	↓	(6, 64, 66, 67)
DMP1	↓	(72, 73)
ENPP1	↓	(77)
FAM20C	↓	(47, 79, 80)
FGF receptor activation	↑	(6, 59, 66, 83)
Systemic regulators		
$1,25(OH)_2D$	↑	(86, 87)
Phosphate	↑	(7, 89, 90)
PTH	↑	(91, 92)
Iron deficiency	↑	(62, 63)
Insulin	↓	(93, 94)
Sympathetic activation	↑ (circadian rhythm dependent manner)	(97)

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Conclusion

Osteocytes deeply embedded in the bone matrix play an important role in controlling of bone mass and Pi homeostasis by secreting paracrine and endocrine factors. Sclerostin produced by osteocytes inhibits Wnt/β-catenin signaling in osteoblast-lineage cells, stimulating bone formation and suppressing bone resorption. RANKL, derived from osteocytes, plays a significant role in osteoclastogenesis and osteoclast activation during postnatal life. FGF23, the central regulator of Pi metabolism, is secreted by osteocytes and exerts its effects on distant organs such as the kidneys in an endocrine fashion. Osteocytes also express *PHEX*, *DMP1*, *ENPP1*, *and FAM20C*, the genes responsible for FGF23-related hypophosphatemic rickets/osteomalacia, indicating that these cells function as command centers for Pi homeostasis. Since many local and systemic factors are involved, the regulation of FGF23 in osteocytes is complex. Further clarification of the paracrine and endocrine functions of osteocytes will contribute to the development of new strategies for the diagnosis and treatment of bone and mineral metabolism disorders.

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