Regulation of renal phosphate transport by FGF23 is mediated by FGFR1 and FGFR4

Jyothsna Gattineni,1 Priyatharshini Alphonse,1 Qiuyu Zhang,1 Nisha Mathews,1 Carlton M. Bates,2 and Michel Baum1,3

1Department of Pediatrics, University of Texas Southwestern Medical Center at Dallas, Dallas, Texas; 2Department of Internal Medicine, University of Texas Southwestern Medical Center at Dallas, Dallas, Texas; and 3Department of Pediatrics, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

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FGF23, a bone-derived hormone with an important role in phosphate and vitamin D homeostasis, has been shown to induce left ventricular hypertrophy (9). The regulation of renal phosphate transport by FGF23 is mediated by FGFR1 and FGFR4. Fibroblast growth factor family members are known to bind to four known fibroblast growth factor receptors (FGFRs) and initiate intracellular signaling (8, 33). The four FGFRs are numbered 1–4 and are coded by four genes. Alternative splicing of FGFR1, 2, and 3 results in a total of seven isoforms, and these seven FGFRs have ligand binding specificity (32, 34). FGFR2 does not bind to FGF23 and is not present in the proximal tubule (12, 28). Previous data from our laboratory suggested that deletion of a single FGFR was not responsible for the phosphaturic actions of FGF23 (12). However, kidney conditional Fgfr1−/− mice and global Fgfr4−/− mice had an ∼1.4-fold increase in FGF23 levels at baseline compared with wild-type mice and had comparable serum phosphorus levels to wild-type mice. In response to exogenously administered pharmacological doses of FGF23, kidney conditional Fgfr1−/− mice did not become hypophosphatemic and Fgfr4−/− mice had an attenuated hypophosphatemic response compared with wild-type mice (12). To determine whether FGFR1 and FGFR4 together were the joint renal receptors for FGF23, we examined phosphate homeostasis in Fgfr1−/−/Fgfr4−/− mice.

METHODS

Generation of Fgfr1−/−/Fgfr4−/− mice (Pax3creTg+/−;Fgfr1Lox/Lox; Fgfr4Lox/Lox mice). We have previously studied individual kidney conditional Fgfr1−/− mice and Fgfr4−/− mice (12). As previously described, Fgfr4−/− mice are from a mixed 129/Black Swiss background. Conditional Fgfr1−/− mice were generated using the lox-p/cre recombinase technique as global Fgfr1−/− mice are embryonically lethal and are from mixed 129/Sv and C57BL/6J backgrounds as previously described (7, 12, 17, 26, 38). Pax3 cre recombinase is expressed in the metanephric mesenchyme and not in the ureteric bud (7). Mice expressing Pax3 cre when mated with mice that have the Fgfr1 gene flanked by lox-p sites will generate mice that have Fgfr1 deleted from the metanephric mesenchyme. Metanephric mesenchyme gives rise to nephron segments from the proximal tubule, the primary site of phosphate reabsorption (2), to the distal convoluted tubule (30). Fgfr4−/− mice were mated with mice that had the critical regions of Fgfr1 gene flanked by lox-p sites (Fgfr1Lox/Lox) (17) to generate mice...
that are both null for Fgfr4 and also have lox-p sites for Fgfr1 (Fgfr1lox/lox/Fgfr4−/−). Next, Fgfr1lox/lox/Fgfr4−/− mice were mated with mice transgenic for Pax3 cre (26) to finally generate Pax3cre/Fgfr1lox/lox/Fgfr4−/− mice (Fgfr1−/−/Fgfr4−/− mice). Wild-type littersmates that did not express the Pax3 cre (Fgfr1lox/lox/Fgfr4−/− or Fgfr1lox/−/Fgfr4−/−) and Fgfr4−/− mice that did not express the Pax3 cre (Fgfr1lox/lox/Fgfr4−/− or Fgfr1lox/−/Fgfr4−/−) were studied for comparison. We also studied Fgfr1−/+ mice and Fgfr4−/+ mice, and the data were similar to the data obtained from the wild-type littersmates described above (not shown). The mice were genotyped before the study and were studied at 2.5–4 mo of age. The mice were cared for at the animal facility at the University of Texas Southwestern Medical Center where the mice were on a 12:12-h day-night cycle. The mice were fed on a Teklad Global 16% protein standard rodent diet (TD 2016), and they were given free access to food and water. To study the effects of dietary phosphate depletion on the regulation of FGF23, mice were placed on a phosphate-depleted diet (TD 2016). The Institutional Animal Care and Use Committee at the University of Texas Southwestern Medical Center approved these studies.

Recombinant FGF23 administration. Recombinant mouse FGF23 (R&D Systems, Minneapolis, MN), at 200 ng/g body wt, was injected intraperitoneally into wild-type and (R&D Systems, Minneapolis, MN), at 200 ng/g body wt, was injected (1:1,000, Sigma, St. Louis, MO), and 100 mM mannitol titrated to pH 7.4 in isolation buffer containing 5 mM EGTA, 16 mM HEPES, 300 mM NaCl, and 0.05% TX). Serum 1,25(OH)2D3 levels were measured using the ELISA solution (Millipore, Billerica, MA). The uptake measurements were analyzed by 10.2±0.32±0.247 on July 5, 2017 http://ajprenal.physiology.org/ Downloaded from
FGF23 regulating phosphorus transport. Serum 1,25(OH)2Vitamin D3 phosphorus despite an increase in FGF23. In Fig. 1, we show and FGF23. Thus we examined whether deletion of both Fgfr1 and Fgfr4 in the kidney would result in hyperphosphatemia, demonstrating resistance to FGF23. In Table 1, we compare the serum phosphorus, FGF23, 1,25(OH)2Vitamin D₃, and PTH levels in wild-type, Fgfr1⁻/⁻/Fgfr4⁻/⁻, and Fgfr4⁻/⁻ mice. Compared with Fgfr4⁻/⁻ and wild-type mice, Fgfr1⁻/⁻/Fgfr4⁻/⁻ mice had 20- to 50-fold higher FGF23 levels and yet had higher serum phosphorus levels, consistent with FGFR1 and FGFR4 being the proximal tubule receptors regulating phosphorus transport. Serum 1,25(OH)2Vitamin D₃ levels were also elevated in Fgfr1⁻/⁻/Fgfr4⁻/⁻ mice compared with wild-type and Fgfr4⁻/⁻ mice. In Table 1, we also show that serum PTH levels were suppressed in Fgfr1⁻/⁻/Fgfr4⁻/⁻ mice compared with wild-type and Fgfr4⁻/⁻ mice. Elevated serum phosphorus levels normally increase PTH levels, but in Fgfr1⁻/⁻/Fgfr4⁻/⁻ mice the effect of serum phosphorus is likely mitigated by the elevated levels of 1,25(OH)2Vitamin D₃ and FGF23.

We next examined the cause for the increase in serum phosphorus despite an increase in FGF23. In Fig. 1, we show that BBMV phosphate transport was increased in Fgfr1⁻/⁻/Fgfr4⁻/⁻ mice compared with wild-type and Fgfr4⁻/⁻ mice. We next compared BBMV NaPi-2a and NaPi-2c protein abundance to determine whether either of the proximal tubule brush border transporters had increased protein expression. NaPi-2c protein expression relative to β-actin was increased in Fgfr1⁻/⁻/Fgfr4⁻/⁻ mice compared with both wild-type and Fgfr4⁻/⁻ mice (Fig. 2), while NaPi-2a protein expression was comparable in wild-type, Fgfr1⁻/⁻/Fgfr4⁻/⁻, and Fgfr4⁻/⁻ mice (Fig. 3). The relative mRNA expression of NaPi-2a/28s and NaPi-2c/28s was comparable in wild-type and Fgfr1⁻/⁻/Fgfr4⁻/⁻ mice (Fig. 4, A and B). Additionally, we examined whether gastrointestinal absorption of phosphorus played a role in the elevated serum phosphorus seen in Fgfr1⁻/⁻/Fgfr4⁻/⁻ mice. Twenty-four-hour stool phosphorus and phosphorus intake were measured. Gastrointestinal phosphorus absorption was comparable in wild-type, Fgfr1⁻/⁻/Fgfr4⁻/⁻, and Fgfr4⁻/⁻ mice (Table 1).

We examined the relative expression of Fgfr23 mRNA in calvarial bone to determine whether the elevated level of FGF23 in Fgfr1⁻/⁻/Fgfr4⁻/⁻ mice was due to increased production. In Fig. 5, we show that Fgfr23 mRNA expression is significantly higher in Fgfr1⁻/⁻/Fgfr4⁻/⁻ mice compared with wild-type mice. We did not find Fgfr23 mRNA expression in the kidneys of Fgfr1⁻/⁻/Fgfr4⁻/⁻ mice (data not shown). These data indicate that bone is the source of increased FGF23 levels in Fgfr1⁻/⁻/Fgfr4⁻/⁻ mice.

Fibroblast Growth Factor 23 Receptors

Table 1. Baseline serum characteristics of wild-type, Fgfr1⁻/⁻/Fgfr4⁻/⁻, and Fgfr4⁻/⁻ mice

<table>
<thead>
<tr>
<th></th>
<th>Wild-Type</th>
<th>Fgfr1⁻/⁻/Fgfr4⁻/⁻</th>
<th>Fgfr4⁻/⁻</th>
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<tbody>
<tr>
<td>Serum phosphorus, mg/dl</td>
<td>7.1 ± 0.2 (n = 25)</td>
<td>9.2 ± 0.3* (n = 16)</td>
<td>7.5 ± 0.3 (n = 8)</td>
</tr>
<tr>
<td>Serum FGF23, pg/ml</td>
<td>108.1 ± 7.3 (n = 10)</td>
<td>4,953.6 ± 675.9* (n = 10)</td>
<td>265 ± 30.9 (n = 10)</td>
</tr>
<tr>
<td>Serum 1,25(OH)2D₃, pmol/l</td>
<td>115.7 ± 8.2 (n = 27)</td>
<td>182.5 ± 22.4* (n = 17)</td>
<td>80.5 ± 12.1 (n = 10)</td>
</tr>
<tr>
<td>Serum PTH, pg/ml</td>
<td>143.0 ± 26.7 (n = 16)</td>
<td>66.4 ± 20.7* (n = 17)</td>
<td>181.6 ± 23.1 (n = 12)</td>
</tr>
<tr>
<td>24-h Gastrointestinal phosphorus absorption, mg/g body wt</td>
<td>0.6 ± 0.1 (n = 6)</td>
<td>0.8 ± 0.2 (n = 6)</td>
<td>0.7 ± 0.1 (n = 6)</td>
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Values are means ± SE. Using an unpaired t-test, FGF23 levels are significantly higher in Fgfr4⁻/⁻ mice compared with wild-type mice but not using ANOVA comparing all 3 groups. *P < 0.001, Fgfr1⁻/⁻/Fgfr4⁻/⁻ vs. wild-type and Fgfr4⁻/⁻ mice.

Fig. 1. Baseline brush border membrane vesicle (BBMV) phosphate transport in wild-type, Fgfr1⁻/⁻/Fgfr4⁻/⁻, and Fgfr4⁻/⁻ mice. Fgfr1⁻/⁻/Fgfr4⁻/⁻ mice had increased BBMV phosphate uptake compared with wild-type mice. Values are means ± SE.

Fig. 2. Baseline BBMV Na-Pi cotransporter NaPi-2c protein expression in wild-type, Fgfr1⁻/⁻/Fgfr4⁻/⁻, and Fgfr4⁻/⁻ mice. Baseline NaPi-2c protein expression relative to β-actin on BBMVs from the renal cortex was increased in Fgfr1⁻/⁻/Fgfr4⁻/⁻ compared with wild-type and Fgfr4⁻/⁻ mice. Twenty-five micrograms of BBMV were fractionated on 8% SDS gels.
We first examined baseline phosphorylation of MAPK (pMAPK) in wild-type and Fgf1−/−/Fgfr4−/− mice to study the activation of the MAPK signaling pathway. The baseline protein abundance of pMAPK in total kidney lysate was comparable between wild-type and Fgf1−/−/Fgfr4−/− mice as shown in Fig. 6. We next examined the effects of exogenous administration of mouse recombinant FGF23 on intracellular signaling of FGF23. As shown in Fig. 7, wild-type mice demonstrated increased pMAPK protein abundance 1 h after receiving recombinant FGF23, while Fgf1−/−/Fgfr4−/− mice did not demonstrate increased pMAPK protein abundance (Fig. 7).

Since Klotho is a cofactor for the interaction of FGF23 and its receptor, and Klotho−/− mice have elevated FGF23 levels, we measured Klotho protein and mRNA expression in the kidney. Both relative Klotho mRNA expression (Fig. 8A) and Klotho protein expression from whole kidney lysate were not different in wild-type and Fgf1−/−/Fgfr4−/− mice (Fig. 8B).

We studied the role of a phosphate-depleted diet on serum FGF23 levels in wild-type and Fgf1−/−/Fgfr4−/− mice. After 5 days on a phosphate-depleted diet, serum phosphorus in the animals was comparable in wild-type and Fgf1−/−/Fgfr4−/− mice (Fig. 9A), but serum FGF23 levels remained elevated in Fgf1−/−/Fgfr4−/− mice (Fig. 9B).

In summary, Fgf1−/−/Fgfr4−/− mice have elevated serum FGF23 levels compared with wild-type mice, and the elevated levels are likely due to increased synthesis of FGF23 from bone. Despite the elevated FGF23 levels, serum phosphorus levels are increased in Fgf1−/−/Fgfr4−/− mice compared with wild-type mice, demonstrating resistance to phosphaturic ac-
To assess the baseline MAPK signaling, 50 μg of whole kidney lysate from wild-type and Fgfr1−/−/Fgfr4−/− mice were fractionated on 8% SDS gels. Baseline phosphorylation of MAPK (pMPAK) was comparable in wild-type and Fgfr1−/−/Fgfr4−/− mice.

DISCUSSION

This study examined whether FGFR1 and FGFR4 together are the receptors that regulate the effects of FGF23 on renal phosphate transport. FGF23 levels were ~50-fold higher in Fgfr1−/−/Fgfr4−/− mice compared with wild-type mice. Despite the elevated FGF23 levels in Fgfr1−/−/Fgfr4−/− mice, these mice have elevated serum phosphorus levels and increased brush border membrane phosphate transport compared with their wild-type and Fgfr4−/− counterparts, indicating that the phosphaturic action of FGF23 is abrogated in Fgfr1−/−/Fgfr4−/− mice. In keeping with increased brush border membrane phosphate transport, brush border membrane NaPi-2c protein expression was increased in Fgfr1−/−/Fgfr4−/− mice in the absence of a change in mRNA expression. This indicates that there is posttranscriptional regulation of NaPi-2c in Fgfr1−/−/Fgfr4−/− mice. In response to exogenous recombinant FGF23 administration, phosphorylation of MAPK, a marker of intracellular signaling of FGF23, is also abrogated, demonstrating that FGFR1 and FGFR4 are critical receptors for FGF23 in the kidney. Gastrointestinal phosphate absorption was comparable in wild-type and Fgfr1−/−/Fgfr4−/− mice, indicating that the elevated phosphorus is primarily due to resistance to the phosphaturic actions of FGF23. Decreasing dietary phosphate content decreased serum phosphate in both wild-type and Fgfr1−/−/Fgfr4−/− mice to comparable levels, but serum FGF23 levels remained elevated in Fgfr1−/−/Fgfr4−/− mice compared with wild-type mice. While there are other possibilities of elevated FGF23 levels in Fgfr1−/−/Fgfr4−/− mice including decreased clearance of FGF23, we demonstrate that in Fgfr1−/−/Fgfr4−/− mice the likely source of elevated FGF23 levels is increased production from bone. The expression of Klotho, an important cofactor for the interaction of FGF23 with its receptors, was comparable in wild-type and Fgfr1−/−/Fgfr4−/− mice. These data together demonstrate that FGFR1 and FGFR4 are critical receptors for the renal phosphaturic effects of FGF23.

Identification of the FGFRs responsible for the various actions of FGF23 has been a topic of significant interest (12, 15, 25, 28, 48). Results from in vitro studies employing cell
had no decrease and Fgfr4<sup>-/-</sup> mice had an attenuated decrease in serum phosphorus levels compared with wild-type mice. We concluded that FGFR1 was the predominant receptor responsible for the hypophosphatemic actions of FGF23 with FGFR4 playing a minor role (12). Liu et al. (28) also demonstrated that deletion of Fgfr3 or Fgfr4 in Hyp mice (mouse model of X-linked hypophosphatemic rickets) did not reverse the hypophosphatemic phenotype of the Hyp mice, consistent with the importance of FGFR1 in mediating the actions of FGF23 on phosphate homeostasis.

Li et al. (25) and our laboratory (15) had previously concluded that FGF3 and FGF4 were the predominant receptors in the regulation of 1,25(OH)<sub>2</sub>Vitamin D<sub>3</sub>. We demonstrated that Fgfr<sup>-/-</sup>/Fgfr4<sup>-/-</sup> mice had ~2.6-fold higher 1,25(OH)<sub>2</sub>Vitamin D<sub>3</sub> levels at baseline compared with wild-type mice and 1,25(OH)<sub>2</sub>Vitamin D<sub>3</sub> levels did not decrease in response to pharmacological doses of exogenously administered FGF23 (15). In Fgfr1<sup>-/-</sup>/Fgfr4<sup>-/-</sup> mice, despite the higher serum phosphorus, lower PTH, and markedly elevated FGF23 levels, 1,25(OH)<sub>2</sub>Vitamin D<sub>3</sub> levels were higher (1.4-fold) than in wild-type mice. The present study suggests that

lines to identify the receptors for FGF23 have been controversial, with one study demonstrating the binding of FGF23 to only FGFR1 in the presence of Klotho (46) while another study demonstrated that FGF23 binds to FGFR1c, 3c, and 4 in the presence of Klotho (23). By studying individual Fgfr1<sup>-/-</sup> (kidney conditional), Fgfr3<sup>-/-</sup>, and Fgfr4<sup>-/-</sup> mice, we have previously shown that FGF23 levels were modestly elevated in Fgfr1<sup>-/-</sup> (1.5-fold) and Fgfr4<sup>-/-</sup> (1.3-fold) mice while the serum phosphorus levels remained comparable to their wild-type counterparts, suggesting the presence of compensatory mechanisms for the absence of one receptor at baseline (12). In response to pharmacological doses of FGF23, Fgfr1<sup>-/-</sup> mice

Fig. 8: A: baseline relative kidney Klotho mRNA expression in wild-type and Fgfr1<sup>-/-</sup>/Fgfr4<sup>-/-</sup> mice. Relative Klotho mRNA expression in whole kidney samples was not different between wild-type and Fgfr1<sup>-/-</sup>/Fgfr4<sup>-/-</sup> mice. Values are means ± SE. B: baseline kidney Klotho protein expression in wild-type and Fgfr1<sup>-/-</sup>/Fgfr4<sup>-/-</sup> mice. Baseline whole kidney lysate Klotho protein expression relative to β-actin was comparable in wild-type and Fgfr1<sup>-/-</sup>/Fgfr4<sup>-/-</sup> mice. Twenty-five micrograms of whole kidney lysate was fractionated on 8% SDS gels. Values are means ± SE.

Fig. 9: A: serum phosphorus levels in wild-type and Fgfr1<sup>-/-</sup>/Fgfr4<sup>-/-</sup> mice on a phosphate-depleted diet. Mice were placed on a phosphate-depleted diet for 5 days, and serum phosphorus was measured. Serum phosphorus was comparable in both wild-type and Fgfr1<sup>-/-</sup>/Fgfr4<sup>-/-</sup> mice. Values are means ± SE. B: serum FGF23 levels in wild-type and Fgfr1<sup>-/-</sup>/Fgfr4<sup>-/-</sup> mice on a phosphate-depleted diet. A phosphate-depleted diet resulted in a decrease in serum FGF23 levels in both wild-type and Fgfr1<sup>-/-</sup>/Fgfr4<sup>-/-</sup> mice; however, FGF23 levels were still ~60-fold higher in Fgfr1<sup>-/-</sup>/Fgfr4<sup>-/-</sup> mice compared with wild-type mice.
FGFR1 in conjunction with FGFR4 also appears to play a role in 1,25(OH)₂Vitamin D₃ homeostasis.

There are several known regulators of FGF23, including 1,25(OH)₂Vitamin D₃, PTH, and serum phosphorus (22, 27, 36, 40). While 1,25(OH)₂Vitamin D₃ increases FGF23 levels, it is unlikely that a 1.4-fold increase in 1,25(OH)₂Vitamin D₃ levels in Fgrf1⁻/⁻/Fgrf4⁻/⁻ mice can explain the ~50-fold increase in FGF23 levels seen in Fgrf1⁻/⁻/Fgrf4⁻/⁻ mice compared with wild-type mice. Administration of pharmacological doses of 1,25(OH)₂Vitamin D₃ (calcitriol) increased FGF23 in mice but by an order of magnitude less than what we find in Fgrf1⁻/⁻/Fgrf4⁻/⁻ mice (27). PTH has been shown to increase FGF23 levels, as seen in a mouse model of hyperparathyroidism (22) and in patients with Jansen’s metaphyseal chondrodysplasia due to activating mutations of the PTH/PTH-related peptide receptor (41). In addition, parathyroidectomy in mice with early chronic kidney disease decreased FGF23 levels (24). In our study, serum PTH levels were lower in Fgrf1⁻/⁻/Fgrf4⁻/⁻ mice than wild-type mice and thus are not contributing to the elevated FGF23 levels in Fgrf1⁻/⁻/Fgrf4⁻/⁻ mice.

Previous studies have examined the role of changes in dietary phosphorus in the regulation of FGF23. Changing the dietary phosphate content of mice from 0.02 to 1.6% resulted in a change in serum phosphorus from 3.7 to 9.3 mg/dl while the FGF23 levels increased from 9.3 to 65 pg/ml. Thus a 2.5-fold change in serum phosphorus resulted in a 7-fold increase in FGF23 levels (36). Of note, the total body phosphate content and changes in serum phosphorus could have differing roles in their regulation of serum FGF23 level. In Fgrf1⁻/⁻/Fgrf4⁻/⁻ mice, FGF23 levels are ~50-fold higher compared with wild-type mice in the face of a 30% increase in serum phosphorus levels in Fgrf1⁻/⁻/Fgrf4⁻/⁻ mice. In response to a phosphate-depleted diet, serum phosphorus levels decrease in wild-type and Fgrf1⁻/⁻/Fgrf4⁻/⁻ mice compared to comparable levels. In animals on a phosphate-depleted diet, serum FGF23 levels also decrease in WT and Fgrf1⁻/⁻/Fgrf4⁻/⁻ mice, but serum FGF23 levels still remained elevated in Fgrf1⁻/⁻/Fgrf4⁻/⁻ mice compared with wild-type mice. Thus the serum phosphorus level in Fgrf1⁻/⁻/Fgrf4⁻/⁻ mice is not the sole factor contributing to the elevated FGF23 levels in Fgrf1⁻/⁻/Fgrf4⁻/⁻ mice. As in early chronic kidney disease, the factors regulating the elevated FGF23 levels in Fgrf1⁻/⁻/Fgrf4⁻/⁻ mice are unclear at this time. There are several hypotheses that have been put forth for elevated FGF23 levels in early chronic kidney disease, including Klotho deficiency and an increase in total body phosphorus that is not reflected by an increase in serum phosphorus levels. However, these are speculative, and further work is needed to identify the regulatory factors for elevated FGF23.

It is intriguing that Fgrf1⁻/⁻/Fgrf4⁻/⁻ mice have significantly elevated serum FGF23 levels, and it appears that the well-known regulators of FGF23 alone do not appear to be the culprits. From our data, it is also apparent that FGF23 is synthesized in bone, and there is likely kidney-to-bone cross talk, as the kidney is the only organ in this mouse model with deletion of both Fgrf1 and Fgrf4. Recently, the use of FGFR1 blockers in bone marrow stem cells in H yp mice has been shown to decrease Fgfl mRNA expression, indicating that FGFR1 plays a role in regulating FGF23 expression (31). It is possible that FGFR1 present in the bones of Fgrf1⁻/⁻/Fgrf4⁻/⁻ mice plays an important role in the regulation of FGF23 production, but the signal from kidney to bone needs to be investigated further. Our data are consistent with FGFR1 and FGFR4 being primary renal receptors for the phosphaturic actions of FGF23. However, they are likely not the sole receptors. While Fgrf1⁻/⁻/Fgrf4⁻/⁻ mice have significantly elevated FGF23 levels compared with their wild-type counterparts and individual Fgrf1⁻/⁻ and Fgrf4⁻/⁻ mice, their serum phosphorus levels and serum 1,25(OH)₂Vitamin D₃ levels are not as elevated as the levels seen in Fgfl⁻/⁻/Fgrf4⁻/⁻ mice (43, 44). Thus FGF23 is still having some action to suppress serum 1,25(OH)₂Vitamin D₃ levels and regulate phosphate transport in Fgrf1⁻/⁻/Fgrf4⁻/⁻ mice. This suggests that there is still redundancy of FGFRs and compensatory mechanisms exist even in these Fgrf1⁻/⁻/Fgrf4⁻/⁻ mice.

GRANTS

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

Author contributions: J.G. provided conception and design of research; J.G., P.A., Q.Z., and N.M. analyzed data; J.G. and M.B. interpreted results of experiments; J.G. prepared figures; J.G. drafted manuscript; J.G., C.M.B., and M.B. edited and revised manuscript; J.G. and M.B. approved final version of manuscript.

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