Precise regulation of FGF23 is required for bone health

Just the right amount of FGF23 is required to maintain healthy bone and mineral metabolism. FGF23 deficiency results in tumoral calcinosis, because loss of this factor impedes renal phosphate excretion and enables unopposed parathyroid hormone–dependent (PTH-dependent) stimulation of 1,25-dihydroxyvitamin D [1,25(OH)2D] production, which together culminate in hyperphosphatemia and metastatic calcification (1). In contrast, FGF23 overload results in hypophosphatemic rickets, which is characterized by inappropriately low circulating levels of 1,25(OH)2D and skeletal abnormalities. The precise mechanisms of how excess FGF23 leads to hypophosphatemic rickets are not clear. In this issue of the JCI, Bai and colleagues demonstrate that deletion or inhibition of CYP24A1, which initiates degradation of the active form of vitamin D, ameliorates skeletal abnormalities in two mouse models of hypophosphatemic rickets. While this work supports an important role for excess CYP24A1 activity in the pathogenesis of FGF23-mediated hypophosphatemic rickets, more work will need to be done before CYP24A1 inhibition can be integrated into the management of patients living with these diseases.

Targeting CYP24A1 ameliorates skeletal abnormalities

In this issue, Bai et al. shed important new light on this controversy (4). Specifically, the authors investigated the role of CYP24A1, the cytochromal enzyme that catalyzes the first step in vitamin D degradation, in the pathogenesis of two prototypical disorders of primary FGF23 excess: X-linked hypophosphatemic rickets (XLH), which is caused by mutations in PHEX that lead to elevated FGF23 through unknown mechanisms, and autosomal dominant hypophosphatemic rickets (ADHR), which results from activating mutations in FGF23 itself. Bai and colleagues crossed Hyp mice, which are the murine homolog of human XLH and FGF23 transgenic mice, which overexpress the cleavage-resistant form of FGF23 (FGF23R176Q) produced in human ADHR, with Cyp24a1-null mice. As a secondary approach to evaluate the involvement of CYP24A1 in these diseases, Hyp and ADHR mice were also treated with a pharmacological CYP24A1 inhibitor (4).

Using this experimental approach, Bai and colleagues demonstrated that either genetic deletion or pharmacological inhibition of CYP24A1 induces near-complete healing of rickets in Hyp and ADHR mice. Amelioration of the animals’ skeletal defects occurred in the absence of correcting severe hypophosphatemia or altering serum calcium levels. On the basis of these results, Bai et al. conclude that inactivation of CYP24A1 heals the skeleton by prolonging the local half-life of 1,25(OH)2D in bone, such that even low levels of circulating and locally produced 1,25(OH)2D have prolonged effects (4). The stable serum mineral levels observed in these models are especially noteworthy, because a large amount of calcium and phosphate must have been deposited in bone to achieve such substantial remineralization. Most likely, Cyp24a1 deletion induced a major increase in gastrointestinal absorption of calcium and phosphate due to prolonged effects of 1,25(OH)2D in enterocytes. Although Bai and colleagues did not directly explore this mechanism by performing metabolic balance studies, their results indirectly support this hypothesis, as circulating levels of PTH and 1,25(OH)2D were substantially decreased, and expression of vitamin D–dependent calcium transporters in the gut of the compound mutant mice was increased (4). Direct suppression of PTH by prolonged 1,25(OH)2D activity in the parathyroid glands is another possible mechanism to explain the low PTH and thus low systemic 1,25(OH)2D levels; however, this scenario is less likely, because primary suppression of PTH in the setting of massive bone calcium deposition would have resulted in severe hypocalcemia, unlike what Bai et al. report. Moreover, FGF23 levels were further increased in the compound Hyp Cyp24a1-null mice compared with levels...
Roles of circulating and local vitamin D metabolites

It should be noted that Bai et al. did not study the possible effects of other vitamin D metabolites. By catalyzing hydroxylation of 25-hydroxyvitamin D [25(OH)D] to 24,25-dihydroxyvitamin D [24,25(OH)2D], CYP24A1 reduces the amount of 25(OH)D that CYP27B1 can convert into the more potent 1,25(OH)2D (5, 6). CYP24A1 also reduces the half-life of previously synthesized 1,25(OH)2D by converting 1,25(OH)2D into 1,24,25(OH)3D, which is further metabolized into calcitroic acid (1-hydroxy-23-carboxyvitamin D) or 1α,25-(OH)2D3-26,23-lactone (7, 8). Consistently, previous reports have demonstrated a total absence of calcitroic acid and 1α,25-(OH)2D3-26,23-
deletion and administration of a systemically active pharmacological inhibitor of CYP24A1. Bone-specific Cyp24a1 deletion will be needed to definitively show that it is CYP24A1 in this organ that mediates the restoration of normal skeletal structure in their models. Regardless of the precise mechanism, by demonstrating that the skeletal abnormalities of hypophosphatemic rickets can be corrected without lowering elevated FGF23 or raising depressed serum phosphate levels, Bai and colleagues have provided important new evidence against these factors as direct mechanistic contributors to bone disease in XLH, ADHR, and other related conditions mediated by primary increases in FGF23 (4).

The totality of the data generally support the hypothesis that there is a direct and beneficial effect of suppressing bone CYP24A1 on the skeletal defects in hypophosphatemic rickets. However, an important limitation of the Bai et al. study is the inability to definitively implicate bone CYP24A1 as the cause of the phenotype as opposed to secondary effects conferred by global Cyp24a1 deletion and administration of a systemically active pharmacological inhibitor of CYP24A1. Bone-specific Cyp24a1 deletion will be needed to definitively show that it is CYP24A1 in this organ that mediates the restoration of normal skeletal structure in their models. Regardless of the precise mechanism, by demonstrating that the skeletal abnormalities of hypophosphatemic rickets can be corrected without lowering elevated FGF23 or raising depressed serum phosphate levels, Bai and colleagues have provided important new evidence against these factors as direct mechanistic contributors to bone disease in XLH, ADHR, and other related conditions mediated by primary increases in FGF23 (4).
lactone formation in Cyp24a1-KO mice (9). Since 1α,25-(OH)2D3-26,23-lactone can act as a vitamin D receptor antagonist and thus inhibit osteoclastogenesis and bone resorption (10), the extent to which rescue therapy inhibits osteoclastogenesis and bone act as a vitamin D receptor antagonist and thus inhibit osteoclastogenesis and bone resorption (10). The recent description of human mutations in CYP24A1 as the cause of previously idiopathic cases of hypercalcemia in newborns and adults has cast new light on the importance of the degradation pathway in health and disease that is elegantly emphasized by Bai et al. (14, 15).

Conclusions and future directions
The current standard of care for XLH and ADHR includes the administration of oral 1,25(OH)2D and phosphate supplements; however, these treatments, which address downstream consequences of the diseases rather than the root causes, are only partially effective and often poorly tolerated (16, 17). Novel strategies for these diseases are currently under development. For example, neutralizing antibodies against FGF23 directly target the underlying molecular mechanism of disease (18), and FGF receptor antagonists inhibit the end-organ effects of FGF23 (19). While the results of the current study by Bai and colleagues suggest that targeting CYP24A1 may be another viable therapeutic strategy, especially to correct the underlying skeletal defects, the inability to correct hypophosphatemia suggests that CYP24A1 antagonists may need to be reloaded to an adjunctive role. Furthermore, the finding that circulating 1,25(OH)2D levels increased significantly in Hyp mice that were treated with the CYP24A1 inhibitor raises the question as to whether exogenous calcitriol treatment, which was not tested by Bai et al., could have achieved similar skeletal success. More in-depth research will be needed to define a new and improved standard of care for XLH, ADHR, and related conditions.

Beyond those orphan diseases of primary FGF23 excess, could there be a role for CYP24A1 inhibition in diseases of secondary FGF23 excess, such as chronic kidney disease? If elevated FGF23 accelerates 1,25(OH)2D degradation by stimulating CYP24A1 in extra-renal tissues, as it appears to in bone, treating kidney disease patients with nutritional vitamin D supplementation or exogenous 25(OH)D may be only of marginal benefit, because excessive local CYP24A1 activity would degrade most of the 25(OH)D and 1,25(OH)2D that managed to make it to target cells. Likewise, exogenous 1,25(OH)2D that raises systemic 1,25(OH)2D levels might only serve to further upregulate CYP24A1 at the tissue level, resulting in minimal changes in end-organ effects of 1,25(OH)2D. It is into this gap that CYP24 inhibitors may ultimately prove to have a unique and potentially exciting profile to boost end-organ 1,25(OH)2D effects, without increasing serum phosphate or calcium levels. Stay tuned for more progress in a dynamic and rapidly evolving field.

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