Fibroblast growth factor 23 (FGF-23) is a bone-derived hormone that inhibits phosphate reabsorption and 1,25-dihydroxyvitamin D3 (1,25(OH)2D) production by the kidney Figure 1. Physiologically, FGF-23 regulates systemic phosphate homeostasis and vitamin D metabolism through a bone-kidney axis. However, excess FGF-23 in genetic disorders leads to hypophosphatemic rickets as well as may play a pathogenic role in adverse outcomes in chronic kidney disease. Primary increases in FGF-23 have been reported in rare hereditary hypophosphatemic disorders in humans and their mouse homologues, including X-linked hypophosphatemic rickets (XLH)/Hyp mice, caused by inactivating mutations of Phex, autosomal recessive hypophosphatemic rickets 1 (ARHR1), caused by inactivating mutations of Dmp1, ARHR2, caused by inactivating mutations in ENPP1, and Raine Syndrome (RNS), caused by inactivation mutations in FAM20C. As well as tumor-induced osteomalacia (TIO). Secondary elevations of FGF-23 occurs in chronic kidney disease (CKD). Elevated FGF-23 is initially an adaptive response to altered mineral metabolism in chronic kidney disease (CKD), but chronic elevations of FGF-23 are maladaptive and linked to increased morbidity and mortality, cardiovascular disease, and inflammation in CKD. Therefore, control of FGF-23 levels as well as its upstream and downstream signaling pathways could serve as a potential target to improve outcomes in many disease conditions. Currently, fibroblast growth factor receptors (FGFR) tyrosine kinase inhibitor (NVP-BGJ398), CYP24A1 inhibitor, FGF-23 antibody (KRN23), and FGF-23 antagonist are being developed to treat disorders of excess FGF-23. This review will summarize recent advances in these areas.

**FGFR KINASE INHIBITOR**

There is compelling evidence to support pharmacological inhibition of FGFRs in excess FGF-23. First, FGF-23 signaling is transduced by members of the FGF receptor (FGFRs, 1, 3, 4) family in conjunction with the essential co-receptor Klotho, which confers tissue-specificity for endocrine FGF-23 signals owing to its...
predominant expression in kidney (Figure 1). Second, hereditary hypophosphatemic disorders such as XLH/Hyp and ARHR1 involve activation of FGF-23 signaling and FGF-23 expression in osteocytes and osteocyte-specific deletion of Fgfr1 in Hyp mice markedly suppresses FGF-23 production. Third, a gain-of-function mutation in Fgfr1 causes osteophagic dysplasia (OGD), which is also associated with hypophosphatemia and elevated FGF-23 levels. Theoretically, it is useful to develop FGFR inhibitors that control FGF-23 signaling and production in disorders of excess FGF-23. In this regard, FGFR tyrosine kinase inhibitor (NVP-BGJ398) has been developed to treat FGF-23-mediated hypophosphatemic diseases and has been shown to block both the production and end-organ effects of FGF-23.

However, NVP-BGJ398 is a small molecule with potent inhibitory activity of FGFRs 1, 3, and 4 and lacks selectivity for FGF-23/FGFR1/α-KL signaling, and their generalized ability to inhibit FGFRs in multiple tissues would have undesirable effects. In addition, a small molecule, SSR128129E (SSR), which binds to the extracellular part of FGFR, was reported to act as a FGFR antagonist. So far, SSR128129E are being developed as anti-tumor drugs since these compounds have limitations, including specificity and potential toxicities. At present, there are no small molecules that specifically modulate FGF-23 activation of FGFR/α-KL complexes. The discovery of such molecules would not only provide research tools to elucidate FGF-23 biological actions, but also would advance the discovery of new treatments based on this novel bone/kidney endocrine network.

FGF-23 Antibody

A FGF-23 specific antibody [Burosumab, KRN23, Ultragenix (USA) and Kirin (Japan)] has been developed as a therapy for XLH, and KN23 binds to and inhibits the biological activity of FGF-23. However, loss of FGF-23 function can have serious side effects, including hyperphosphatemia and soft-tissue calcifications. Indeed, preclinical studies in CKD models show that inhibiting FGF-23 with a high affinity blocking antibody increased mortality, leading to no current plans to test KRN23 in CKD. Lowering FGF-23 in CKD is controversial, since use of calcimimetics to suppress PTH leads to modest reductions in FGF-23 and improved survival in patients with end-stage renal disease (ESRD).

FGF-23 C-Terminal Peptides

Full-length FGF-23 is a 32-kDa protein that can be cleaved at 176RXXR179 site by a cellular endoprotease fur in, leading to the 22-kDa N-terminal and 16-kDa C-terminal fragments. Recent studies have shown that the C-terminal tail of FGF-23 (FGF-23C) can compete with length ligand for binding to the FGFR/α-KL complex, and hence can antagonize the phosphaturic activity of FGF-23 in vivo, both in healthy rats and in a mouse model of phosphate wasting disorders. In order to increase the half-life of the FGF-23C peptide, the investigators generated a FGF-23Fc fusion molecule and demonstrated that repeated injection of this molecule (twice a week, 10 mg/kg)selectively modulates the phosphate pathway via regulation of NPT2A expression in vivo by competitive antagonism of FGF-23 binding to the FGFR/α-KL co-receptor in Hympic mice, a preclinical model of XLH. The unique ability of FGF-23Fc molecule to preferentially modulate the FGFR1/α-KL phosphate pathway but not FGFR3&4/α-KL in the control of 1,25(OH)2D levels in kidney makes this molecule ideal for use as a new the rapeutic in the treatment of XLH, with the potential to significantly improve bone formation in XLH patients with limited safety concerns.

FGF-23 Impairs the production of renal 1,25(OH)2D through either inhibiting the expression of CYP27B1, the enzyme that converts 25-(OH)D to its active metabolite, or upregulating the expression of vitamin D 24-hydroxylase (CYP24A1), a mitochondrial enzyme responsible for inactivating vitamin D metabolites through the C-24 oxidation pathway. In the overexpressing mutant FGF23R176Q and Hyp mouse models, hypophosphatemic rickets with high levels of FGF-23 are also associated with increased renal CYP24A1 expression, suggesting that elevated CYP24A1 activity is pivotal to the pathophysiology of these disorders. Knockout of CYP24A1 in the Hyp and FGF23R176Q-transgenic mice in near-complete recovery of rachitic bony abnormalities, but serum levels of phosphorus and 1,25(OH)2D did not improve in these murine models of human disease. Interestingly, treatment of Hyp and FGF23R176Q-transgenic mice with the CYP24A1 inhibitor CTA102 also ameliorated their rachitic bones. Whether pharmacologic inhibition of CYP24A1 activity goes solo as a therapeutic target remains to be further investigated.
develop lead compound for preclinical screening and late clinical trials.

THE POTENTIAL SIDE EFFECTS OF THESE FGF-23 TARGETED THERAPIES

As shown in Table 1, all of current FGF-23 targeted therapies have their advantages and disadvantages. The FGFR inhibitors show a strong inhibition of FGFR tyrosine kinase activity; these compounds can block both the production and end-organ effects of FGF-23, but demonstrate no specificity and potential tissue and organ toxicity. In contrast, FGF-23 antibody plays a function blocking on FGF-23 and displays a high specificity of treatment. However, FGF-23 antibody needs parenteral delivery and high cost treatment. FGF-23 C-terminal peptides also have a high specificity of treatment, but the increased proteolytic instability during treatment would limit its use as a long-time therapeutic strategy. CYP24A1 inhibitor almost completely recover rachitic bone of hypophosphatemic disorder, but this compound has no effect on levels of phosphorus and 1,25(OH)2D. FGF-23 antagonist could be a promising therapeutic strategy because of its oral bioavailability, dose titratability, and cost-effective if the optimization overcomes the short half-time of the compound.

CONCLUSION

Fibroblast growth factor-23 is a circulating hormone that regulates phosphate and vitamin D metabolism. Excess actions of FGF-23 result in reductions in serum phosphate and 1,25(OH)2D levels and hypophosphatemic crickets. Therefore, it is necessary to develop therapeutic methods to suppress the activities of that hormone. In fact, patients with hypophosphatemic disorders by FGF-23 excess were reported to benefit from FGF-23 blocking antibodies or inhibitors of FGF-23 signaling. However, these therapies need careful monitoring dosing-use because deficient actions of FGF-23 result in hyperphosphatemic disease. Indeed, management of FGF-23 levels in patients with CKD seems to be debatable since modest reductions in FGF-23 with calcimimetics could improve survival in patients with ESRD, while inhibiting FGF-23 with a high affinity blocking antibody increased mortality in CKD, leading to questionable benefit from these novel therapies in CKD. However, use of either low affinity FGF-23 antibody or FGF-23 inhibitors to control FGF-23 excess actions remains a promising therapy for both hereditary and acquired hyperphosphatemic diseases.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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