FGF23 Ligand Trap: New Biologic for Treating Kidney Diseases

Innovative and efficacious treatments for chronic kidney disease and phosphate-wasting diseases.

Technology

Dr. Mohammadi's research group at New York University School of Medicine recently achieved a milestone by determining the atomic structure of a 1:1:1 ternary complex consisting of FGF23, the ectodomain of FGFR1c, and the naturally shed ectodomain of aKlotho (Chen et al. Nature 2018). Analysis of this complex revealed that the aKlotho co-receptor serves as a non-enzymatic molecular scaffold that simultaneously grips FGFR (via aKlotho's 'Receptor Binding Arm' [RBA]) and the C-tail of FGF23. In doing so, aKlotho enforces FGF23-FGFR1c proximity, thereby stabilizing the complex and enabling FGF23 signaling.

Based on the crystal structure, the Mohammadi laboratory has engineered an aKlotho variant that lacks the RBA ("Modified aKlotho"), and has confirmed that deletion of the RBA disables aKlotho from binding FGFR1c. As a result, the RBA aKlotho deletion variant cannot form the ternary complex. However, this variant retains its full ability to tether FGF23 via its C-tail. Thus, aKlotho can be used as a novel class of FGF23 inhibitors that act by trapping FGF23 into functionally inactive binary complexes which cannot form a ternary complex with FGFR1c. The inhibitory effect of the aKlotho deletion mutant has been confirmed in cell-based assays and in animal models. These seminal discoveries constitute a quantum leap towards the rational discovery and structure-based drug-design of therapeutically effective biologics for treating inherited and acquired human diseases in which elevated FGF23 serum levels play causative roles.

Background

FGF23 is a bone-derived polypeptide hormone that regulates serum phosphate and vitamin D homeostasis. It acts primarily on the proximal tubules in the kidney, where it down-regulates cell surface expression of sodium phosphate co-transporters. In doing so, FGF23 inhibits phosphate reabsorption, thereby lowering serum phosphate levels and inducing phosphaturia. FGF23 mediates its activities by binding, dimerizing and activating its three cognate FGFRs (i.e., FGFR1c, FGFR3c and FGFR4) with the help of both an obligatory co-receptor, aKlotho, and a co-factor (heparansulfate, HS). aKlotho is a single-pass transmembrane protein whose extracellular domain consists of tandem TIM barrel domains (termed KL1 and KL2) that are structurally homologous to those found in b-glycosidases. Transmembrane aKlotho is predominantly expressed in kidney distal tubules and in the parathyroid glands. Ectodomain shedding of transmembrane aKlotho in kidney distal tubules generates a soluble ectodomain of aKlotho that is found in general circulation.

Abnormally high levels of intact FGF23 are causative of phosphate-wasting diseases including X-linked hypophosphatemic rickets (XLH), autosomal dominant hypophosphatemic rickets (ADHR), and tumor-induced osteomalacia (TIO). In CKD patients, FGF23 becomes progressively elevated, rising to as much as 1000-fold above normal levels. This increase initially helps normalize

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phosphate levels during the early stages of CKD when there is still a sufficient number of functionally viable nephrons. However, as the number of functional nephrons plummets in late stage CKD, excess secreted FGF23 hormone levels are unable to drive the excretion of phosphate, and hyperphosphatemia ensues. To make matters worse, elevated circulating FGF23 exerts off-target effects in other cells and tissues, causing complications such as cardiac left ventricle hypertrophy (LVH), fibrosis and other deleterious effects. Indeed, cardiovascular complications account for at least 50% of morbidity/mortality cases in CKD patients.

Applications

- Chronic kidney disease (CKD)
- Phosphate-wasting diseases

  - X-linked hypophosphatemic rickets (XLH)
  - Autosomal dominant hypophosphatemic rickets (ADHR)
  - Tumor-induced osteomalacia (TIO)

Advantages

- Known mechanism of action (MoA): Trapping of FGF23 by modified aKlotho into functionally inactive binary complexes normalizes serum phosphate levels in phosphate wasting disorders
- Innovative & powerful therapy: For curtailing pathologic FGF23 signaling

Patents

- US8889621B2 (issued)
- US8889426B2 (issued)
- US9907830B2 (issued)

References

1. Chen, G., Liu, Y., Goetz, R. et al. , α-Klotho is a non-enzymatic molecular scaffold for FGF23 hormone signalling