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Invited Plenary Abstract
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Unique biological function of fibroblast growth factor (FGF) 23

Seiji Fukumoto
University of Tokyo Hospital, Tokyo, Japan

FGF23 was identified as a humoral factor involved in the development of several hypophosphatemic diseases including tumor-induced rickets/osteomalacia and autosomal dominant hypophosphatemic rickets/osteomalacia. FGF23 is the last member of FGF family and belongs to FGF19 subfamily. FGF23 decreases serum phosphate level by suppressing expression of type 2a and 2c sodium-phosphate co-transporter in brush border membrane of renal proximal tubules and lowers serum 1,25-dihydroxyvitamin D [1,25$(OH)_2$D] by modulating expression levels of enzymes for vitamin D metabolism. Because *FGF23* null mice show hyperphosphatemia and high serum 1,25$(OH)_2$D levels, FGF23 seems to be a physiological regulator of serum phosphate and 1,25$(OH)_2$D. Mutations in *FGF23* gene which enhances FGF23 activity cause autosomal dominant hypophosphatemic rickets/osteomalacia. In contrast, several missense mutations which enhance proteolytic processing of FGF23 protein and abolish biological activity of FGF23 have been found in patients with familial tumoral calcinosis characterized by hyperphosphatemia. Results so far reported indicate that FGF23 is produced by bone cells and works only in kidney. This means that there should be a specific receptor for FGF23 in kidney. Recent in vivo and in vitro investigations identified klotho as an integral molecule for FGF23 signaling. Klotho mice with disruption of *klotho* gene show high serum phosphate and 1,25$(OH)_2$D levels as *FGF23* null mice. FGF23 level in klotho mice is extremely high indicating that FGF23 can not work in these mice. In addition, introduction of klotho into several cell lines in vitro enables these cells to respond to FGF23. Furthermore, FGF receptor 1 together with klotho and FGF23 forms a complex in vitro. These results indicate that FGF23 is quite unique among other members of FGF family. First, FGF23 is a hormone regulating mineral homeostasis rather than working as a local factor involved in the modulation of cell growth and differentiation like other members of FGF23 family. Second, although many mutations of FGF receptor are reported, both activating and inactivating mutations of *FGF23* gene are known to cause human diseases as ligand for FGF receptor. Finally, FGF23 requires klotho for its signaling in addition to FGF receptor. It is likely that FGF family members have broader biological functions and mode of actions than previously recognized.