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Renal Klotho in mineral metabolism

AKADEMISK AVHANDLING

som för avläggande av medicine licentiatexamen vid Karolinska
Institutet offentligen försvaras i C1:87, Karolinska
Universitetssjukhuset, Huddinge

Fredagen den 21 mars, 2014, klockan 09.00

av

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Stockholm 2014

ABSTRACT

Calcium and phosphorous are critical elements in a number of physiological processes, including maintenance of bone structure, cell signaling and energy metabolism. Their endocrine regulation is tightly controlled through a number of feedback mechanisms involving parathyroid hormone (PTH), vitamin D and the recently discovered fibroblast growth factor 23 (FGF23). The kidney is a key organ in maintaining normal serum levels of calcium and inorganic phosphorous, and disturbances in mineral metabolism are commonly observed in patients with chronic kidney disease (CKD). Klotho is a membrane-bound protein expressed in the renal tubules that acts as a co-receptor for FGF23. In addition, Klotho can be shedded from the cell surface to extra-cellular compartments and function as a hormone with effects on mineral metabolism independent of FGF23. During the progression of CKD the expression of Klotho rapidly declines, and accumulating evidence point to lack of Klotho as a pathogenic factor driving clinical complications in CKD. The main focus of this thesis has been to elucidate the role of renal Klotho in mineral metabolism and on systemic effects.

In **Study I** we generated distal tubule-specific Klotho knockout mice (*Ksp-KL^{-/-}*) by employing cre-lox recombination. *Ksp-KL^{-/-}* mice were hyperphosphatemic with elevated serum Fgf23 levels, indicating that distal tubular Klotho affects phosphate reabsorption in the proximal tubules. The exact mechanism of this proposed distal-to-proximal tubular signaling remains unknown.

In **Study II** we generated mice with Klotho deleted throughout the nephron (*Six2-KL^{-/-}*). *Six2-KL^{-/-}* mice were infertile, kyphotic, growth retarded and had a decreased life span, closely resembling the phenotype seen in systemic *Klotho* knockout mice. Also the serum and urine biochemistries, low serum Klotho levels as well as profound histological abnormalities were indistinguishable from systemic *Klotho* knockout mice, unraveling the kidney as the principle contributor to circulating Klotho and mediator of Klotho anti-ageing traits.

Taken together, the studies presented in this licentiate thesis substantially contribute to the understanding of renal Klotho function.