Karolinska Institutet

Institutionen för klinisk vetenskap, intervention och teknik, Enheten för medicinska njursjukdomar

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
Risul Amin
M.Sc.

Huvudhandledare:
Docent Tobias Agervald Larsson
Karolinska Institutet
Institutionen för klinisk vetenskap, intervention och teknik

Bihandledare:
Docent Annika Östman Wernerson
Karolinska Institutet
Institutionen för laboratoriemedicin

Doktor Hannes Olauson
Karolinska Institutet
Institutionen för klinisk vetenskap, intervention och teknik

Betygsnämnd:
Docent Ylva Pernow
Karolinska Institutet
Institutionen för molekylär medicin och kirurgi

Docent Louise Nordfors
Karolinska Institutet
Institutionen för klinisk vetenskap, intervention och teknik

Professor Bengt Fellström
Uppsala Universitet
Institutionen för medicinska vetenskaper

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.