FGF23 (and Klotho): what’s new?

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Introduction to FGF23

- FGF23 synthesized by osteocytes
- FGF-R: tyrosine kinase receptor
  - FGFR-1/2/3/4
- Klotho: cofactor
  - Anti-aging protein
  - Tissue-specific expression
  - Kidney and parathyroid gland

Calcium and phosphate metabolism

1-25 vitamin D

Stimulating effect / Inhibiting effect

FGF23: phosphorylation pathways

- Klotho-dependent and Klotho-independent activation of the phosphorylation pathways
  - Erk 1/2 and Akt pathway
  - Calcineurin-NFAT pathway

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FGF23: 3 main ‘historical’ actions

- Proximal tubule
  - Npt inhibition 2a-2c
  - 1α hydroxylase inhibition
  - 24 hydroxylase stimulation
- Parathyroid
  - PTH inhibition
  - 1α hydroxylase stimulation

Hypophosphatemia, PTH and 1-25 OH vitamin D inhibition

FGF23: an endocrine FGF with off-target effects

- Kidney
- Heart & Cardiomyocytes
- Immune system
- FGF23 inhibition 2a-2c
- 1α hydroxylase inhibition
- 24 hydroxylase stimulation

FGF23 as a inhibitor of bone mineralization

- Model of genetic hyperphosphatemia (GALNT3 mutation)
- Low intact FGF23 levels
- High C-terminal FGF23 levels
- Familial tumoral calcinosis

FGF23 as an inhibitor of osteoclast biology

- Comparison of mineralization in vitro in preosteoblastic cells from a patient with GALNT3 mutation (low intact FGF23 levels) and from controls
- Higher capability to form mineralization

Biphasic effects of FGF23 on osteoclast biology

- An expression of FGF-R1
- An activation of Erk and Akt
- Inhibition of osteoclast differentiation
- Effects driven through FGF-R
Klotho expression in long bones regulates FGF23 production during renal failure

- Murine model: targeted deletion of Klotho in long bones
- Two main results
- Long bones from these mice did not increase FGF23 expression after adenine diet or 5/6th nephrectomy
- FGF23-treated bone cells required Klotho to increase FGF23 expression and induce Erk phosphorylation

New insights: FGF23 physiology in the central nervous system

Impact of FGF23 on neuronal morphology and synaptic density

- In vitro model of primary murine hippocampal cultures
- Incubation with FGF23 + α-Klotho
- Enhanced number of primary neurites
- And reduced arborization
  $\Rightarrow$ Resulting in a less complex neuronal morphology

New insights: FGF23 and adipose tissue

And the fat lady sings about phosphate and calcium...

Towards new endocrine regulations...

- High adiponectin levels
- Suppressed Klotho renal expression
- Decreased FGF23 levels
- Caused renal loss of calcium

New insights: FGF23 and (pediatric) CKD
The paradigm: both FGF23 and Klotho are deregulated early in CKD

Recombinant growth hormone increases FGF23 levels
- Similar results of an open label prospective study in Pediatric Endocrinology, Birmingham, Alabama
  - 23 children with GH deficiency
  - Clinical trial: C terminal FGF23 before and one year after rhGH
  - Increased FGF23, TmP/GFR and phosphorus after rhGH
  - The increase of FGF23 remained significant after adjustment on age and phosphorus

FGF23 increases early in pediatric CKD

FGF23 as a risk factor of CKD progression

New insights: FGF23 and infections in CKD
FGF23 as an inhibitor of extra-renal 1-alpha hydroxylase in monocytes

Data obtained in monocytes from healthy donors, but similar data obtained in PD cells from pediatric patients undergoing chronic PD

New insights: FGF23 and cardiovascular disease in CKD

FGF23 and cardiomyocytes: a Klotho-independent effect

- Klotho is not expressed in CM, but FGF-R1 and 4 are
- Signaling pathways
  - Through FGF-R signaling
  - Through PLCγ and NFAT
  - No activation of Akt
- Intramyocardial and intravenous injection of FGF23 induces ventricular hypertrophy in mice
  - Wild type
  - Klotho deficient mice: high FGF23 and LVH

FGF23 and left ventricular hypertrophy

- Increased FGF 23 levels and left ventricular hypertrophy
  - Epidemiological prospective
    - CRIC cohort, 1070 CKD adults
  - Increased FGF 23 levels at baseline and increased risk for onset of LVH
    - RR= 2.4
- Rat cardiomyocytes + FGF23
  - Hypertrophy, dose-dependent
  - Reactivation fetal genes
  - Increased markers for LVH

FGF23 and LVH in pediatric CKD

German autopsy study
17 dialysis, 17 KTx, 24 controls
67% LVH in patients
Induction of cardiac FGF23-FGFR4 expression as well as a decreased Klotho expression is associated with LVH
LVH depends on FGF23 but also on Klotho levels: loss of Klotho in CKD breaks one’s heart!

- Heterozygous Klotho deficient mice
- Klotho-deficient CKD mice display aggravated cardiac fibrosis as compared to WT-CKD mice
- Transgenic expression of soluble Klotho improves cardiomyopathy in Klotho-deficient CKD mice

Anti FGF23 antibodies: can they be relevant in CKD?

Antibodies against FGF23 improve hyperparathyroidism...
- Early decreased PTH levels
- But increased phosphate, calcium and 1-25 D levels

But they also increase mortality...

FGF23 and cardiomyocytes: a potential therapeutic target
- FGFR inhibitors in a rat model of CKD (5/6th nephrectomy)
  - Decreased LVH
  - No modification of blood pressure

From prevention to treatment...
- FGFR blockade can improve LVH in animal models
So... should we trash anti FGF23 antibodies?

**FGF23 and human diseases**

Wolf et al, JASN 2010

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**Hypophosphatemic rickets**

*The revolution in 2014: KRN23 in patients, short-term*

- Adults with XLH
- 38 patients receiving KRN23 or placebo, IV or sc
- Single dose

**Hypophosphatemic rickets**

*The revolution in 2015: KRN23 in patients, ‘long-term’*

- Adults with XLH
- 28 patients receiving KRN23: 0.05 to 0.6 mg/kg every 28 days (SC)
- Then extension study 22 patients receiving 0.1 to 1 mg/kg every 28 days (SC)

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**Conclusion**

Shroff, Pediatric Nephrology 2013

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**Back in the real life of a CKD patient…**

*Phosphate is a/the vascular toxin/silent killer*

Scialla, Kidney International 2013

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**Vascular calcifications**

Shroff, Pediatric Nephrology 2013
Phosphate and longevity

Klotho null mice

FGF23, Klotho and CKD in 2017

- Both low Klotho and high FGF23 levels are deleterious in CKD for LVH
- Both low 25-D and high FGF23 levels are deleterious in CKD for infections
- FGF23 has become a therapeutic target in genetic hypophosphatemic diseases: the ongoing revolution!
- However FGF23 antibodies have proved to be deleterious in CKD
- A potential role for drugs modulating FGF-R and for recombinant Klotho in the future?
- Clinical practice: target phosphate

Conversion mg/dL: 0.323 mmol/L

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