**INTRODUCTION**

- X-linked hypophosphatemia (XLH) is a rare skeletal disorder due to mutation in PHEX gene leading to increased levels of fibroblast growth factor 3 (FGF23) (1,2).
- Hypophosphatemia and low levels of active vitamin D due to high FGF23 result in skeletal and osteo-articular abnormalities (1,2).
- The conventional substitutive treatment (parathyroid hormone (PTH)), analog) is associated with severe long-term side effects (1,2).
- Monoclonal antibody against FGF23 has been approved for XLH but still requiring high-cost lifelong therapy (3,7).

**AIM**

- Proof-of-concept of gene therapy: one injection to rescue the bone phenotype in a murine model of XLH.

**METHOD**

- Gene therapy approach for XLH:
  - Adenovirus vector (AAV) + C-terminal tail FGF23 (Fig. 6).
  - Liver-targeting vector (AAV)
  - blood
  - kidney
  - binding FGF1-
  - blocking FGF23 pathway
  - restoration of NaPi2a co-transporter and phosphatase reabsorption
  - phosphatase to bone

- Why C-terminal tail FGF23?
  - It is biologically inactive, but it is capable to bind to FGFRI (the main receptor of FGF23), thus block the action of native FGF23

**Study design: in-vivo approach**

- 3 groups of mice microinjected with:
  - AAV
  - AAV-FFG23
  - AAV-FFG23

**RESULTS**

1. Restoration of NaPi2a co-transporter in the kidney

- One-month-old Hyp-Dx mice were injected with AAV expressing sp7-FFG23/sp7-FFG23 (AAV-FFG23) and sacrificed three months after injection
- PBS-injected WT and Hyp-Dux mice served as controls
- AAV-FFG23 treatment led to the restoration of expression of the NaPi2a transporter mRNA (Fig. 1) as well as of the NaPi2a transporter protein in kidney obtained with immunohistochemistry (Fig. 2, arrows).

2. Correction of bone abnormalities

- The treatment rescued signs of saccular aortic aneurysm in terms of morphology (Fig. 6A) and saccular score (Fig. 6B) of multiple aneurysms and irregular cortical bone are present in untreated Hyp-Dx mice and indicated by red arrows on Fig. 6A, but completely disappear after AA-V-FFG23 treatment (Fig. 6A).

**CONCLUSIONS**

1. Through the restoration of NaPi2a co-transporter in kidney, the AAV-FFG23 gene therapy corrects the abnormal skeletal phenotype in Hyp-Dx mice:
   - bone mineralization and microstructure
   - bone elongation and growth
   - osteo-articular manifestations

2. Our project opens new perspectives on the treatment of skeletal diseases by gene therapy targeting the liver

**REFERENCES**


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