

OSTEOSCOOP

News on current events in osteoporosis and rheumatology

X-linked Vitamin D-resistant rickets: is bone PHEX guilty?

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X-linked hypophosphatemia (XLH) is the archetypal vitamin D-resistant disease in humans, and the most common form of inherited rickets, with an incidence of approximately 1 in 20 000 live births. The disease is characterized by renal phosphate (Pi) wasting with resulting hypophosphatemia, abnormal vitamin D metabolism, defective bone and cartilage mineralization, dentine defects, and stunted growth. Recently, the gene involved in the pathogenesis of XLH was identified and designated as *PHEX* (the phosphate-regulating gene with homologies to endopeptidases on the X chromosome). The murine homolog of the human disease, the *hyp*-mouse, has a phenotype identical to that evident in patients with XLH, and is due to a large deletion in the 3' region of the *Phex* gene. These findings suggest that a mutation in the *PHEX/Phex* gene is responsible for the phenotypic changes in patients with XLH and the *hyp*-mouse. Although *PHEX/Phex* expression occurs primarily in osteoblast lineage cells, transgenic *Phex* expression in *hyp*-mouse osteoblasts fails to rescue the phenotype, suggesting that *Phex* expression at other sites underlies XLH.

To establish whether abnormal *Phex* in osteoblasts and/or osteocytes alone generates the *HYP* phenotype, the authors of a recent study [1] created mice with a global *Phex* knockout and conditional osteocalcin-promoted (*OC*-promoted) *Phex* inactivation in osteoblasts and osteocytes. Serum phosphorus levels in both mouse strains and *hyp*-mice were lower than those in normal mice. Kidney cell membrane phosphate transport in all three strains was likewise reduced compared with that in normal mice. Abnormal renal phosphate transport in global or targeted *Phex* knockout was associated with increased bone production and serum FGF-23 levels and decreased kidney membrane type IIa sodium phosphate cotransporter protein, as was the case in *hyp*-mice. In addition, knockout mice and *hyp*-mice manifested comparable osteomalacia.

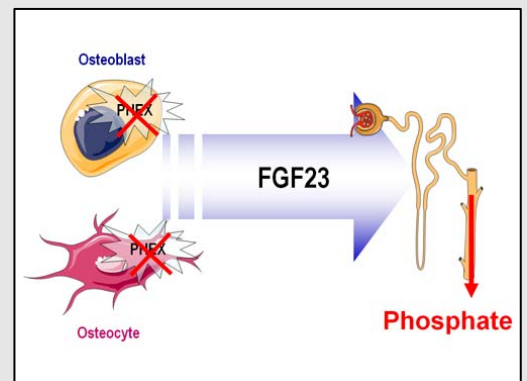
These data provide evidence that aberrant *Phex* function in osteoblasts and/or osteocytes alone is sufficient to underlie the *hyp*-mouse phenotype. Further studies are required to elucidate the precise function of *PHEX* in the bones of patients suffering from vitamin D-resistant diseases.

1. Yuan B et al. *J Clin Invest.* 2008;118:722-734.

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Osteoblasts and osteocytes express PHEX, an enzyme with homologies to endopeptidases whose mutations are responsible for X-linked hypophosphatemia. Bone-forming cells are also the source of FGF23, a circulating protein with phosphaturic effect on the kidney. Invalidation of PHEX selectively in osteoblasts and osteocytes results in increased concentrations of FGF23 and hypophosphatemia secondary to urinary phosphate loss, together with osteomalacia.

These data provide evidence that aberrant *Phex* function in osteoblasts and/or osteocytes alone is sufficient to underlie the *hyp*-mouse phenotype.



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