

OSTEOSCOOP

News on current events in osteoporosis and rheumatology

A subunit of v-ATPase controls osteoclast fusion and bone formation

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Matrix-producing osteoblasts and bone-resorbing osteoclasts maintain bone homeostasis. Osteoclasts are multinucleated, giant cells of hematopoietic origin formed by the fusion of mononuclear pre-osteoclasts derived from myeloid cells. Fusion-mediated giant cell formation is critical for osteoclast maturation; without it, bone resorption is inefficient. One gene predominantly expressed in osteoclasts, is the d2 isoform of vacuolar (H⁺) ATPase (v-ATPase) V₀ domain (Atp6v0d2). What is the function of this protein?

To answer this question, Lee et al. [1] inactivated this protein in mice. They observed that, in these animals, there was a markedly increased bone mass due to defective osteoclasts and enhanced bone formation. Atp6v0d2 deficiency did not affect differentiation or the v-ATPase activity of osteoclasts, a function mandatory for acidification of the microenvironment of osteoclasts which allows solubilisation of hydroxyapatite. Rather, Atp6v0d2 was required for efficient pre-osteoclast fusion. Increased bone formation was probably due to osteoblast-extrinsic factors, produced by mutant osteoclasts or their immediate precursors, as Atp6v02 was not expressed in osteoblasts and their differentiation *ex vivo* was not altered in the absence of Atp6v02.

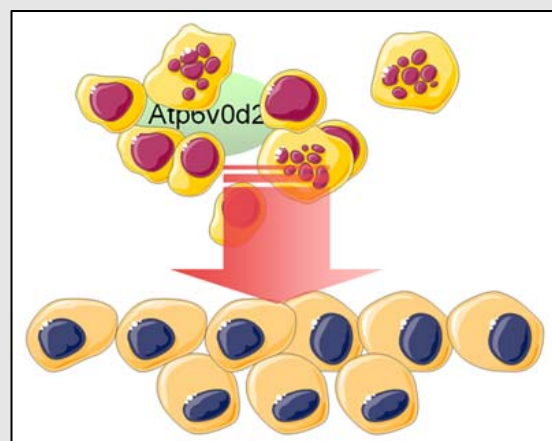
These results identify Atp6v0d2 as a regulator of osteoclast fusion and bone formation, and provide genetic data showing that it is possible to simultaneously inhibit osteoclast maturation and stimulate bone formation by therapeutically targeting the function of a single gene.

1. Lee S-H et al. *Nat Med.* 2006;12:1403-1409.

v-ATPase V₀ subunit d2 is important for osteoclast fusion and bone formation

This protein is expressed selectively in osteoclasts and its precursors. In the absence of this protein, the fusion of preosteoclasts into multinucleated osteoclasts is impaired and the number of mature, bone-resorbing osteoclasts is decreased. In contrast, the number of bone-forming osteoblasts is increased. The signal for increased bone formation originates likely from osteoclasts but is presently to be discovered.

Targeting this ATPase subunit would be an attractive way to reduce bone resorption and to increase bone formation.



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