



Inpp4b as a regulator of bone mass

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Osteoclasts are the major cell type involved in bone resorption. Unbalanced increase of osteoclasts activity decreases bone mass and favors osteoporosis. The authors of this study [1] identified a regulator of osteoclastogenesis, inositol polyphosphate 4-phosphatase type 2 α (*Inpp4b α*), a member of the PI3 kinase signaling pathway.

This phosphatase was expressed from early osteoclast differentiation to activation stage. Ex vivo expression of *Inpp4b α* repressed osteoclast differentiation, whereas inactive *Inpp4b α* mutant increased shape, number and cell differentiation rate. *Inpp4b α* affected intracellular calcium level that controlled NFATc1 nuclear localization and led to an increase in the expression of osteoclast genes differentiation. In vivo, mice deficient in *Inpp4b* showed an increased osteoclast differentiation resulting in a decreased bone mass and osteoporosis. The authors identified human INPP4B as a potential important locus for osteoporosis.

This study highlights the role of *Inpp4b* as a major modulator of osteoclastogenesis which could be involved in bone mineral density variability in mice and humans.

1. Ferron M et al. *Cell Metab.* 2011;14:466-477.

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Osteoclast differentiation, maturation, and survival is repressed by *Inpp4b α* phosphatase activity. In mice, absence of *Inpp4b* increased osteoclast differentiation, leading to an increased number of mature osteoclasts. Since osteoclasts are involved in bone resorption, this imbalance decreased bone mass and led to osteoporosis in *Inpp4b*^{-/-} KO mice. Under RANK-RANKL activation, intracellular calcium concentration increased and induced dephosphorylation and nuclear localization of NFATc1, allowing the expression of specific osteoclast markers and genes differentiation. *Inpp4b α* modulated calcium intracellular concentration affecting NFATc1 nuclear localization and its further effect on osteoclast differentiation.

