

# OSTEOSCOOP

News on current events in osteoporosis and rheumatology

## Beta-Arrestin2 regulates RANKL and Ephrins in response to bone remodeling

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Together with the local RANKL/RANK/OPG system which is crucial for the crosstalk between osteoblasts and osteoclasts, other mediators recently described are the ephrins (Efn), expressed at the surface of the osteoclasts, and the ephrin receptors (Eph), present on osteoblasts. The specific binding of EfnB2 to EphB4 induced osteoblast differentiation and reciprocal inhibition of osteoclast differentiation (see *Osteoscoop Newsletter N°18*).

Beta-arrestins regulate intracellular signaling by G-protein-coupled receptors, including the PTH/PTH-related protein (PTHrP) receptor. In a recent study [1], the authors evaluated the role of beta-arrestin2 on the development and activity of bone marrow (BM) osteoclasts (OCs) and Ephrins ligand (Efn), and receptor (Eph) levels in bone in response to PTH and the changes of bone microarchitecture in wildtype (WT) and beta-arrestin2 knockout mice in models of bone remodeling: a low-calcium diet and ovariectomy.

The number of PTH-stimulated OCs was increased in BM cultures from beta-arrestin2 knockout mice, because of a higher RANKL/OPG ratio, without directly influencing osteoclast activity. In vivo, high PTH levels induced by a low-calcium diet led to greater changes in TRACP5b levels in beta-arrestin2 knockout animals compared with WT. Low-calcium diet caused a loss of BMD and bone microarchitecture, which was most prominent in beta-arrestin2 knockout mice. PTH downregulated Efn and Eph genes in beta-arrestin2 knockout mice, but not WT. After ovariectomy, vertebral trabecular bone volume fraction and trabecular number were lower in beta-arrestin2 knockout mice compared with WT. Histomorphometry showed that OC number was higher in ovariectomy-beta-arrestin2 knockout animals compared with WT.

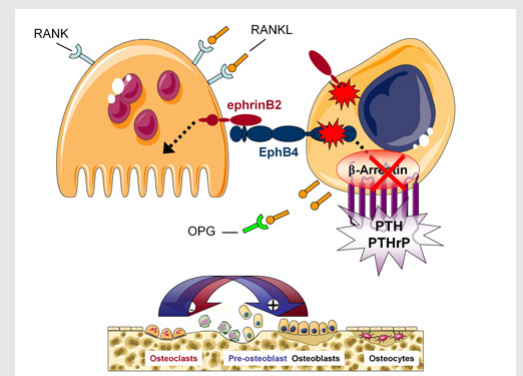
These results indicate that beta-arrestin2 inhibits osteoclastogenesis in vitro, which resulted in decreased bone resorption in vivo by regulating RANKL/OPG production and ephrins mRNAs. Beta-arrestins are important for the control of bone remodeling in response to PTH and estrogen deprivation.

1. Pierroz DD et al. *J Bone Miner Res.* 2009;24:775–784.

### Beta-Arrestin2 regulates RANKL and Ephrins in response to bone remodeling

Both the RANK/RANKL/OPG system and the Ephrin B2/EphB4 system are important in cellular crosstalk between osteoblasts and osteoclasts and in bone remodeling. PTH and PTHrP are important modulators of bone remodeling and they share a common receptor. Beta arrestin is an intracellular protein which modulates the PTH receptor signaling. In the absence of beta-arrestin, PTH stimulates osteoclastogenesis because of an increased RANKL over OPG ratio. Moreover, PTH down regulates EphB4 and EphrinB2 in the absence of beta arrestin.

Beta arrestins are therefore important inhibitors of bone resorption by controlling RANKL/OPG and Ephrin/Eph signaling



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