

OSTEOSCOOP

News on current events in osteoporosis and rheumatology

Constitutive activity of the osteoblast calcium-sensing receptor promotes loss of cancellous bone

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Remodeling of the skeleton is a physiological process crucial for the maintenance of skeletal integrity and systemic calcium homeostasis. Local extracellular calcium concentration ($[Ca^{2+}]_e$) fluctuates dramatically within bone multicellular units, from ~ 0.5 mM during bone formation, when the extracellular matrix is being mineralized, to ≥ 2 mM during bone resorption and matrix degradation. Osteoblasts sense and respond to fluctuations in $[Ca^{2+}]_e$ independently of systemic factors: high $[Ca^{2+}]_e$ promote osteoblast chemotaxis, proliferation, maturation, gene expression, and matrix mineralization. Osteoblasts express the calcium receptor (CaR) that detects and responds to changes in $[Ca^{2+}]_e$. Important physiological functions of the CaR have been shown in the parathyroid and kidney cells.

To determine whether enhanced CaR signaling could modulate remodelling and thereby bone mass in vivo, Dvorak et al. [1] generated transgenic mice with a constitutively active mutant CaR (Act-CaR) targeted to their mature osteoblasts. Longitudinal microcomputed tomography of cancellous bone revealed reduced bone volume and density, accompanied by a diminished trabecular network, in the Act-CaR mice. The bone loss was secondary to an increased number and activity of osteoclasts. Bone formation rate was unchanged in the transgenic mice. Constitutive signaling of the CaR in mature osteoblasts resulted in increased expression of RANK ligand, the major stimulator of osteoclast differentiation and activation. The phenotype of Act-CaR mice is not due to systemic changes in serum $[Ca^{2+}]$ or parathyroid hormone (PTH) levels.

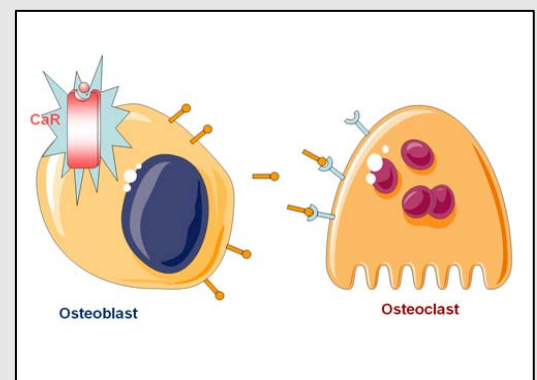
This elegant study provides the first in vivo evidence that increased signaling by the CaR in mature osteoblasts can enhance bone resorption, and further propose that fluctuations in the $[Ca^{2+}]$ within the bone microenvironment may modulate remodeling via the CaR.

1. Dvorak MM et al. *Endocrinology*.doi:10.1210/en.2007-0147.

Activation of the osteoblast calcium receptor modulates bone remodelling

Osteoblasts are able to sense fluctuations of the extracellular calcium concentration through activation of a calcium receptor ("calcium sensor") expressed at their surface.

Activation of the calcium receptor enhances the expression of RANKL by osteoblasts. Interaction of RANKL with RANK expressed by osteoclasts promotes activation of bone-resorbing cells.



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