

OSTEOSCOOP

News on current events in osteoporosis and rheumatology

Disruption of calcineurin in osteoblasts increases bone formation and reduces bone resorption

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Calcineurin is a protein phosphatase that regulates several physiological processes and is the target for cyclosporine A. Pharmacological inhibition of calcineurin by low concentrations of cyclosporin A increases osteoblast differentiation in vitro and bone mass in vivo. To determine whether calcineurin exerts direct actions on osteoblasts, the authors of a recent study [1] generated mice lacking a calcineurin regulatory subunit selectively in osteoblasts.

Microcomputed tomography analysis of tibiae at 3 months showed that these mice had dramatic increases in bone mass compared with controls. Histomorphometric analyses showed significant increases in mineral apposition rate (67%), bone volume (32%), trabecular thickness (29%), and osteoblast numbers (68%) as well as a 40% decrease in osteoclast numbers as compared with the values from control mice. In vitro, engineered osteoblasts differentiated and mineralized more rapidly than controls. Deletion of the calcineurin regulatory subunit increased expression of osteoprotegerin and decreased expression of RANKL. Coculturing calcineurin-deficient osteoblasts with wild type osteoclasts demonstrated that osteoblasts lacking calcineurin failed to support osteoclast differentiation in vitro.

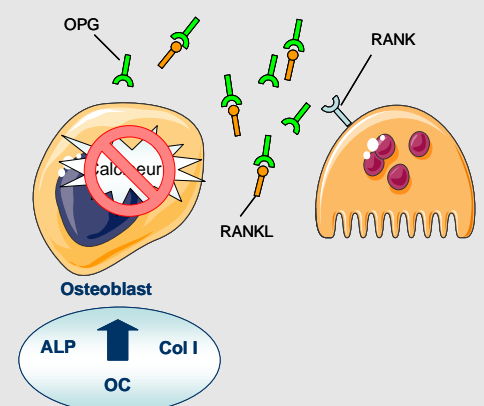
Taken together, these findings demonstrate that the inhibition of calcineurin in osteoblasts increases bone mass by directly increasing osteoblast differentiation and indirectly decreasing osteoclastogenesis. Selective inhibition of calcineurin in osteoblasts would be a useful tool to restore bone mass.

1. Yeo H et al. J Biol Chem. 2007;282:35318-35327.

Disruption of calcineurin in osteoblasts increases bone formation and reduces bone resorption

Bone-forming osteoblasts express a protein phosphatase named calcineurin. Calcineurin is the target of cyclosporin A which inhibits its activity. A recent study has demonstrated that selective inactivation of calcineurin in osteoblasts results in increased bone mass. This is the consequence of a combined effect of bone formation and resorption. Osteoblast differentiation is enhanced as evidenced by increased expression of alkaline phosphatase (ALP), osteocalcin (OC) and collagen I (col I). On the other hand, osteoclastic bone resorption is decreased because osteoblasts secrete more osteoprotegerin (OPG) but less RANKL ligand (RANKL).

Selective inhibition of calcineurin in osteoblasts would be a useful tool to restore bone mass.



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