

# OSTEOSCOOP

News on current events in osteoporosis and rheumatology

## PTH and PTHrP stimulate bone formation through EphrinB2

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Animal studies provided evidence that osteoclast-derived ephrinB2 can act through its receptor, EphB4, in osteoblasts to promote osteoblast differentiation and that reverse signaling by osteoblast-derived EphB4 can suppress the formation of osteoclast precursors in a contact-dependent process. With the aim of identifying new pathways and genes regulated by PTH and PTH-related protein (PTHrP) in osteoblasts, this study [2] was carried out using a mouse marrow stromal cell line, Kusa 4b10, that acquires features of the osteoblastic phenotype in long-term culture conditions. After the appearance of functional PTH receptor 1 (PTHr1) in Kusa 4b10 cells, they were treated with either PTH or PTHrP, and RNA was subjected to whole mouse genome array. The microarray data were validated using quantitative real-time RT-PCR on independently prepared RNA samples from differentiated Kusa 4b10, UMR106 osteosarcoma cells, and primary mouse calvarial osteoblasts, as well as in vivo using RNA from metaphyseal bone after a single PTH injection.

Among the regulated genes, ephrinB2 mRNA was upregulated in response to both PTH and PTHrP. This was confirmed by quantitative real-time PCR in vitro and in vivo. Increased ephrinB2 protein was also shown in vitro by Western blotting, and immunostaining of femur sections showed ephrinB2 in both osteoclasts and osteoblasts. Blockade of ephrinB2/EphB4 interaction resulted in inhibition of mineralization of Kusa 4b10 cells.

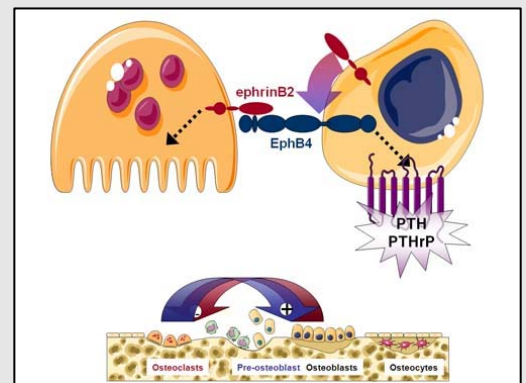
Together with the shown effect of ephrinB2 promoting osteoblast differentiation and bone formation through action on EphB4, the data raise the possibility that PTH or PTHrP might regulate ephrinB2 to act in a paracrine or autocrine manner on EphB4 or EphB2 in the osteoblast, contributing as a local event to the anabolic action of PTH or PTHrP.

1. Zhao C et al. *Cell Metab.* 2006;4:111-121.
2. Allan EH et al. *J Bone Miner Res.* 2008;23:1170-1181.

### EphrinB2 Regulation by PTH and PTHrP

Animal studies provided evidence that osteoclast-derived ephrinB2 can act through its receptor, EphB4, in osteoblasts to promote osteoblast differentiation and that reverse signaling by osteoblast-derived EphB4 can suppress the formation of osteoclast precursors in a contact-dependent process. In response to PTH or to PTH-related protein (PTHrP), osteoblasts express multiple proteins. One of them is ephrin B2.

This observation raises the possibility that PTH or PTHrP might regulate ephrinB2 to act in a paracrine or autocrine manner on EphB4 or EphB2 in the osteoblast, contributing as a local event to the anabolic action of PTH or PTHrP.



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