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Bidirectional ephrinB2-EphB4 signaling controls bone homeostasis

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Various molecules coordinate osteoclast function with that of osteoblasts, such as the RANK/RANKL pathway. However, molecules that mediate osteoclast-osteoblast interactions by simultaneous signal transduction in both cell types have not yet been identified.

Zhao et al [1] show that osteoclasts express a gene encoding the membrane protein ephrinB2, while osteoblasts express the ephrin receptor EphB4. Using directed mutagenesis, they demonstrate that reverse signaling through ephrinB2 into osteoclast precursors suppresses osteoclast differentiation. In addition, forward signaling through EphB4 into osteoblasts enhances osteogenic differentiation, and overexpression of EphB4 in osteoblasts increases bone mass in transgenic mice.

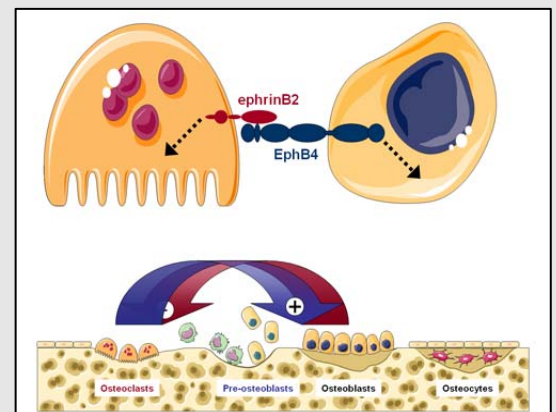
Termination of osteoclastic bone resorption has to be followed by osteoblastic bone formation, which refills resorption lacunae with new bone. A bidirectional interaction between ephrinB ligands expressed on osteoclasts and Eph receptors on osteoblasts can dynamically enhance the transition from resorption to a reversal phase occurring at each resorption cycle. An osteoclast-free area might be maintained by ephrinB reverse signaling to osteoclast precursors. Furthermore, continuous bone formation by osteoblasts over the several months required to refill resorption lacunae might be self-maintained by ephrin-Eph interactions on osteoblasts.

These data demonstrate that ephrin-Eph bidirectional signaling links two major molecular mechanisms for cell differentiation, one in osteoclasts and the other in osteoblasts, thereby maintaining bone homeostasis.

1. Zhao C. et al. *Cell Metab.* 2006;4:111-121.

Ephrin-Eph signaling and bone homeostasis

Osteoclasts are responsible for bone resorption of a localized area of bone, and when they cease their activity, osteoblasts are attracted to the resorption site, where they proliferate, differentiate, and then reform new bone. Ephrin-Eph forward signaling from osteoclasts to osteoblasts is involved in driving the formation of new bone, whereas Eph-ephrin reverse signaling from osteoblasts to osteoclasts might be responsible for the cessation of bone resorption by osteoclasts.



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