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BONE

OSTEOCYTES, RANKL AND BONE LOSS

Osteocytes, former osteoblasts that become embedded within the mineralized bone matrix, are the major source of receptor activator of nuclear factor κB ligand (RANKL) for osteoclast formation and bone remodeling, two new studies in mice independently reveal.

RANKL is essential for osteoclast differentiation, but which cell type supplies RANKL for osteoclastogenesis was a source of debate. "The idea that osteoblast progenitors support osteoclast formation had become the dominant paradigm and our results challenge this paradigm," comments Charles O'Brien from the University of Arkansas for Medical Sciences, the senior researcher in the first study.

The investigators generated mice in which RANKL was conditionally deleted in various genetically defined cell populations corresponding to different stages of osteoblast and chondrocyte differentiation. They then assessed the effects on osteoclast formation and bone mass. "Our studies revealed that cells embedded within mineralized matrix, namely hypertrophic chondrocytes and osteocytes, produce the bulk of the RANKL involved in bone growth and bone remodeling, respectively," explains O'Brien. In addition, the researchers suggest that osteocytes have a role in pathological bone resorption by demonstrating that unloading-induced bone loss is prevented in mice lacking RANKL in osteocytes.

In the second study, Nakashima *et al.* showed, *in vitro*, that purified osteocytes expressed RANKL at higher levels than osteoblasts or bone marrow stromal cells. The researchers then generated mice in which RANKL was exclusively deleted in osteocytes and showed that the mice developed osteopetrosis postnatally. Senior researcher Hiroshi Takayanagi of Tokyo Medical and Dental University points out that the findings "are consistent with the concept that osteocytes are mechanosensing cells that regulate other bone cells".

The next steps, O'Brien says, will include determining whether osteocytes supply the RANKL that is involved in pathological bone loss.

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Original articles Xiong, J, *et al.* Matrix-embedded cells control osteoclast formation. *Nat. Med.* doi:10.1038/nm.2448 | Nakashima, T. *et al.* Evidence for osteocyte regulation of bone homeostasis through RANKL expression. *Nat. Med.* doi:10.1038/nm.2452