

## ROLE OF THE RANK LIGAND PATHWAY IN THE REGULATION OF BONE REMODELING

N. Franchimont

Amgen (Europe) GmbH, Luzern, Switzerland

To maintain a healthy skeleton, bone formation and bone resorption must be in equilibrium. Receptor activator of NF- $\kappa$ B ligand (RANKL), RANK, and osteoprotegerin (OPG) comprise a critical pathway in regulation of bone remodeling. The RANKL/RANK/OPG axis was discovered by genetic ablation and transgenic expression approaches. *In vivo* studies using genetically modified animals firmly established the central importance of the RANKL pathway in bone mass regulation.

RANKL is expressed on the surface of osteoblasts as a type II membrane protein or released in soluble form via proteolytic cleavage. RANKL expression is stimulated by various hormones and cytokines (e.g. parathyroid hormone, TNF, and interleukin-1). RANK, the cognate receptor of RANKL, is expressed by osteoclasts and osteoclasts progenitors. RANKL binds to RANK on the surface of precursor and mature osteoclasts and promotes the differentiation, activity, and survival of osteoclasts. In the absence of RANKL, osteoclasts fail to form, function, or survive.

To modulate the bone resorbing effects of RANKL, the body naturally produces OPG. OPG is a decoy receptor for RANKL that binds to and prevents RANKL from interacting with RANK on the surface of osteoclasts or their precursors. OPG neutralizes the effects of RANKL, thus inhibiting bone resorption. OPG is an important inhibitor of the terminal differentiation and function of osteoclasts.

Appropriate expression of RANKL, RANK, and OPG maintains a balance between the bone resorbing actions of osteoclasts and bone forming activities of osteoblasts. Since RANKL is the primary mediator of bone resorption, therapeutic inhibition of RANKL may be a useful approach for treating a broad spectrum of bone loss disorders including osteoporosis, cancer-related bone destruction, and inflammatory bone diseases.