Role of receptor activator of nuclear factor-κB ligand and osteoprotegerin in bone cell biology

Abstract Receptor activator of nuclear factor (NF-κB) ligand (RANKL), its cellular receptor, receptor activator of NF-κB (RANK), and the decoy receptor osteoprotegerin (OPG) constitute a novel cytokine system.

RANKL produced by osteoblastic lineage cells and activated T lymphocytes is the essential factor for osteoclast formation, fusion, activation, and survival, thus resulting in bone resorption and bone loss. RANKL activates its specific receptor, RANK located on osteoclasts and dendritic cells, and its signaling cascade involves stimulation of the c-jun, NF-κB, and serine/threonine kinase PKB/Akt pathways. The effects of RANKL are counteracted by OPG which acts as a soluble neutralizing receptor. RANKL and OPG are regulated by various hormones (glucocorticoids, vitamin D, estrogen), cytokines (tumor necrosis factor α, interleukins 1, 4, 6, 11, and 17), and various mesenchymal transcription factors (such as cbfa-1, peroxisome proliferator-activated receptor γ, and Indian hedgehog). Transgenic and knock-out mice with excessive or defective production of RANKL, RANK, and OPG display the extremes of skeletal phenotypes, osteoporosis and osteopetrosis. Abnormalities of the RANKL/OPG system have been implicated in the pathogenesis of postmenopausal osteoporosis, rheumatoid arthritis, Paget’s disease, periodontal disease, benign and malignant bone tumors, bone metastases, and hypercalcemia of malignancy, while administration of OPG has been demonstrated to prevent or mitigate these disorders in animal models. RANKL and OPG are also important regulators of vascular biology and calcification and of the development of a lactating mammary gland during pregnancy, indicating a crucial role for this system in extraskeletal calcium handling. The discovery and characterization of RANKL, RANK, and OPG and subsequent studies have changed the concepts of bone and calcium metabolism, have led to a detailed understanding of the pathogenesis of metabolic bone diseases, and may form the basis of innovative therapeutic strategies.

Keywords Osteoprotegerin · Receptor activator of NF-κB ligand · Receptor activator of NF-κB · Osteoclast · Osteoporosis

Abbreviations IL: Interleukin · NF: Nuclear factor · ODAR: Osteoclast differentiation and activation receptor
Receptor activator of nuclear factor-κB ligand

RANKL was discovered in search of the cognate ligand for OPG [6, 7] and was found to be identical to a TNF ligand superfamily member that had been independently characterized by two other groups [8, 9]. Synonyms for RANKL [9] are OPG ligand [6], osteoclast differentiation factor [7], and TNF-related activation-induced cytokine [8]. RANKL is expressed in three distinct forms, including a cell-bound peptide of 317 amino acids [6, 7], a truncated ectodomain created from the cell-bound form by enzymatic cleavage by TNF-α converting enzyme-like protease at positions 140 or 145, respectively [10], and a primary secreted form [11, 12]. While the cell-bound form is most common and is expressed by many cell types [6, 7, 10], the primary secreted form is limited to activated T cells [11] and a squamous cell carcinoma cell line [12]. Various skeletal and extraskeletal cell types are capable of expressing RANKL, including stromal cells, osteoblasts, osteoclasts, mesenchymal perisosteal cells, chondrocytes, and endothelial cells [6, 7, 8, 9, 13]. Analysis of the RANKL gene promoter structure revealed response elements for vitamin D and glucocorticoids [14, 15] as well as a binding site for the osteoblastic transcription factor cbfa-1 [16].

Most studies on the effects of RANKL are based on marrow stromal- and osteoblast-derived cell-bound RANKL or a genetically engineered soluble RANKL form. In the presence of permissive levels of macrophage colony-stimulating factor, RANKL is sufficient and necessary to promote osteoclast differentiation [17, 18, 19] (Fig. 1). RANKL also stimulates osteoclast activation [19, 20, 21], survival [22], and adherence to bone surface [23] (Fig. 1). Some osteoclastogenic cytokines such as prostaglandin E₂ and transforming growth factor β may facilitate, and cooperate with, RANKL-induced osteoclast formation and activation [24, 25].

After receiving parenteral administration of RANKL, mice displayed enhanced osteoclast formation and activation, massive osteoporosis (decreased bone mass), and life-threatening hypercalcemia, all due to enhanced generation and activation of osteoclasts [6]. By contrast, an opposite phenotype with osteopetrosis (increased bone mass) and impaired tooth eruption due to the absence of mature osteoclasts was observed in mice with targeted deletion of RANKL [26].

In addition to its osteotropic effects, RANKL has important immunomodulatory functions, as is evident from the phenotype of RANKL-deficient mice which have lymph node agenesis and thymus hypoplasia [26]. At the time of its initial discovery RANKL was identified as a T cell derived cytokine required for the interactions between T cells and dendritic cells [8, 9]. In subsequent studies RANKL was found to stimulate survival of dendritic cells (by up-regulating Bcl-2 expression and preventing apoptosis), to enhance the immunostimulatory capacity of dendritic cells, and to modulate T cell activation [27, 28, 29, 30, 31].