

# OSTEOSCOOP

News on current events in osteoporosis and rheumatology

## Human osteopetrosis due to RANKL mutations: the osteoclast is not guilty

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Osteopetrosis is caused by a failure of osteoclasts to resorb bone tissue, resulting in bone marrow cavities becoming occluded. Osteopetrosis is a monogenetic disease and, whenever it occurs, can be traced to a gene essential to osteoclast function. The most severe form of human osteopetrosis is the malignant, infantile, autosomal recessive variant (ARO). ARO occurs because of specific mutations in genes responsible for osteoclast function. Despite a decrease in resorption, osteoclast numbers are normal or increased. These "osteoclast-rich" cases suggest that the osteoclast defect does not affect osteoclast formation but rather lies in their mature functional capacity. Providing osteoclast precursors via bone marrow transplantation successfully treats these patients.

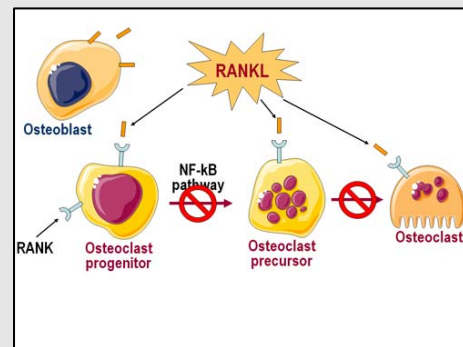
In contrast, Sobacchi et al. [1] describe examples of ARO in which osteoclasts were difficult to find (osteoclast-deplete or -poor). Several subjects studied in this report failed to improve after bone marrow transplantation. This strongly suggests that healthy marrow cells could not overcome the absence of osteoclastogenic stimuli and form healthy resorbing mature osteoclasts within the bone environment and indicates that cells of the myeloid-monocytic lineage, the osteoclast-precursor population, are not the primary cell source of this particular genetic defect. The authors showed that circulating peripheral blood mononuclear cells from the osteoclast-poor ARO subjects could form functional osteoclasts when cultured in the presence of exogenous RANK ligand (RANKL). RANKL is required for normal osteoclast formation and binds to its receptor RANK on the surface of osteoclast precursors, leading to a cascade of intracellular signaling proteins that trigger the formation and sustained activity of mature bone-resorbing osteoclasts. In these subjects, loss-of-function mutations of RANKL were found.

The observation that exogenous RANKL induced formation of functional osteoclasts from their monocytes suggests that these subjects could, theoretically, benefit from exogenous RANKL administration.

1. Sobacchi C et al. *Nat Genet.* 2007;39:360-362.

### Human osteopetrosis due to RANKL mutations: the osteoclast is not guilty

Mature osteoclasts originate from hematopoietic progenitors which differentiate progressively into multinucleated, resorbing cells. Osteoclasts and their precursors bear a membrane receptor called RANK which activates the NF- $\kappa$ B signaling pathway and is instrumental in osteoclast differentiation. Activation occurs when the ligand of RANK is present. RANKL is synthesized by osteoblasts and mesenchymal stem cells. In the case of loss-of-function mutations of RANK ligand, recruitment and activation of osteoclasts does not occur properly. This results in osteopetrosis characterized by a very low number of osteoclasts in bone. Patients suffering from this disease could, theoretically, benefit from exogenous RANKL administration.



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