

# OSTEOSCOOP

News on current events in osteoporosis and rheumatology

## Pathological role of osteoclast costimulation in arthritis-induced bone loss

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Osteoclasts, multinucleated cells of hematopoietic origin that degrade the bone matrix, are regulated by immunoregulatory molecules under both physiological and pathological conditions. Combined deficiency of Fc receptor common  $\gamma$  subunit (FcR $\gamma$ ) and DNAX-activation protein 12 (DAP12) results in a complete lack of osteoclasts. In addition to RANK, the receptor for RANK ligand (RANKL), the Ig-like receptors associated with FcR $\gamma$  and DAP12 have been recognized as essential receptors for osteoclastogenesis. This observation established that Ig-like receptors function as osteoclast costimulatory receptors, which are crucial for bone homeostasis under physiological conditions.

Abnormal T cell immune responses induce aberrant expression of inflammatory cytokines such as TNF- $\alpha$ , leading to osteoclast-mediated bone erosion and osteoporosis in autoimmune arthritis. However, the mechanism underlying enhanced osteoclastogenesis in arthritis is not completely understood. A recent study [1] showed that TNF- $\alpha$  contributes to inflammatory bone loss by enhancing the osteoclastogenic potential of osteoclast precursor cells through inducing paired Ig-like receptor-A (PIR-A), a costimulatory receptor for RANK. In fact, bone erosion and osteoporosis, but not inflammation, caused by aberrant TNF- $\alpha$  expression were improved in mice deficient in Fc receptor common  $\gamma$  subunit or  $\beta_2$ -microglobulin, in which the expression of PIR-As and PIR-A ligands is impaired, respectively.

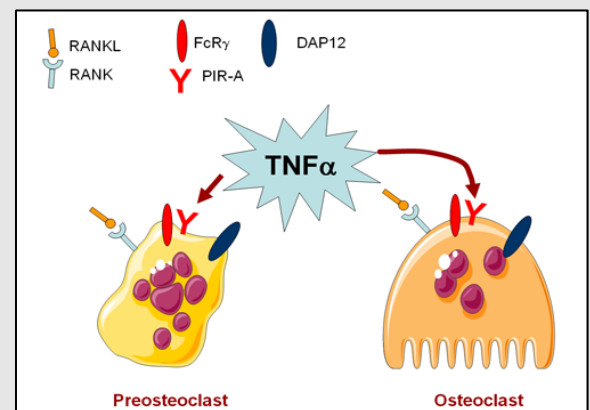
These results establish the pathological role of costimulatory receptors for RANK in bone loss in arthritis and may provide a molecular basis for the future therapy of inflammatory diseases.

1. Ochi S et al. *Proc Natl Acad Sci U S A*. 2007;104: 11394-11399

### Pathological role of osteoclast costimulation in arthritis-induced bone loss

The RANK-RANKL signaling pathway plays a key role in osteoclast recruitment and activation. In addition to RANK, the Ig-like receptors associated with FcR $\gamma$  and DAP12 have been recognized as essential receptors for osteoclastogenesis. This observation established that Ig-like receptors function as osteoclast costimulatory receptors. TNF- $\alpha$  contributes to inflammatory bone loss by enhancing the osteoclastogenic potential of osteoclast precursor cells through inducing paired Ig-like receptor-A (PIR-A), a costimulatory receptor for RANK.

These results establish the pathological role of costimulatory receptors for RANK in bone loss in arthritis and may provide a molecular basis for the future therapy of inflammatory diseases.



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