



## Cytokine-mediated Bone Resorption in Rheumatoid Arthritis

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### Cross Talk Between the Immune & Skeletal Systems

Bone remodeling is a normal, homeostatic process that is mediated by bone-forming osteoblasts and bone-resorbing osteoclasts. Factors that alter the activities of these cells can disrupt bone stability and cause an increase or a decrease in bone mass. Rheumatoid arthritis is a chronic inflammatory disorder characterized by excessive bone loss. In this disorder, T cells infiltrate tissues in the joints ❶ and release pro-inflammatory cytokines including IL-17 and TNF- $\alpha$  ❷. These cytokines stimulate the expression of TRANCE/RANK L, a critical osteoclast differentiation factor, on mesenchymal cells such as osteoblasts and bone marrow stromal cells ❸. In addition, TRANCE/RANK L is expressed by activated T cells themselves ❹. Binding of osteoblast- or T cell-expressed TRANCE/RANK L to the RANK receptor on osteoclast precursor cells promotes NFATc1-mediated osteoclast differentiation and activation ❺, leading to an increase in bone resorption ❻. Due to their ability to induce TRANCE/RANK signaling and negatively impact bone homeostasis, activated T cells are now believed to play an integral role in the pathogenesis of rheumatoid arthritis. Whether Th1 or Th17 cells are the primary regulators of this process is still under investigation.

