

OSTEOSCOOP

News on current events in osteoporosis and rheumatology

CD40 ligand is a modulator of osteoclastogenesis

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Patients with X-linked hyper-IgM syndrome (XHIM), an inherited immune deficiency disorder caused by mutations in the gene encoding CD40 ligand (CD40L), have prominent osteopenia, leading to low-energy fractures, of unknown mechanism. This clinical observation prompted the investigators to ask whether CD40L deficiency may contribute to an imbalance in bone mineral homeostasis [1]. In this study, they show that, compared with age- and sex-matched normal controls, XHIM patients have significantly lower bone mineral density (BMD) and have elevated levels of N-terminal telopeptides of type I collagen (NTX), a urinary marker indicative of osteoclast activity. Recognizing that activated T cells express surface receptor activator of NF- κ B ligand (RANKL) and can induce osteoclast differentiation of myeloid cells expressing RANK, they assessed the capacity of wild-type T cells and CD40L^{-/-} T cells to induce osteoclastogenesis *in vitro*. Relative to wild-type T cells, activated CD40L^{-/-} T cells from both humans and mice promoted robust osteoclast differentiation of myeloid cells. Whereas activated CD40L^{-/-} T cells had normal expression of RANKL, they were deficient in IFN- γ production. In subsequent studies, they cultured activated CD40L^{-/-} T cells in the presence of IFN- γ , and found that the osteoclastic capacity of CD40L^{-/-} T cells could be greatly diminished. IFN- γ signaling leads to the proteosomal degradation of tumor necrosis factor receptor-associated factor 6 (TRAF6), which is recruited following RANK stimulation and activates intracellular pathways downstream. IFN- γ can therefore have an inhibitory effect on RANK intracellular signaling and osteoclast activity.

These results show that CD40L can influence RANKL signaling through T cell priming, and thus they demonstrate a regulatory role for CD40L in bone mineralization that is absent in patients with X-linked hyper-IgM syndrome.

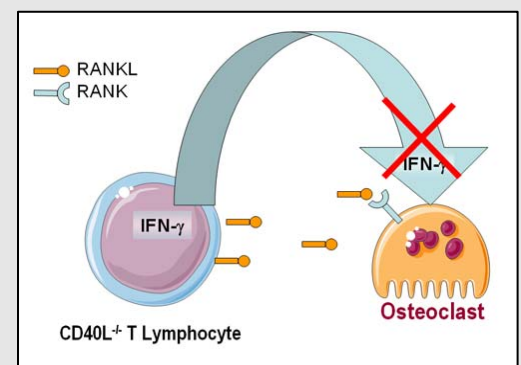
1. Lopez-Granados E et al. *Proc Natl Acad Sci USA*. 2007;104: 5056-5061.

CD40 ligand is a modulator of osteoclastogenesis

Activated T cells express surface receptor activator of NF- κ B ligand (RANKL) and can induce osteoclast differentiation of myeloid cells expressing RANK.

T cells also secrete Interferon gamma (IFN- γ) which acts on downstream RANK stimulation by its ligand in osteoclasts and inhibits RANK intracellular signaling and osteoclast activity

In CD40^{-/-} T lymphocytes, RANK ligand synthesis is normal but IFN- γ production is deficient. In this situation, osteoclastogenesis is increased and results in osteopenia



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