

**Impaired differentiation and hyper-resorptive activity of osteoclasts in  
TREM-2 deficient individuals.**

**Marco Colonna**

TREM-2 is an immunoglobulin-like cell surface receptor associated with DAP12/KARAP that activates monocyte-derived dendritic cells *in vitro*. Recently, it has been shown that genetic defects of human DAP12/KARAP and TREM-2 result in a rare syndrome characterized by bone cysts and presenile dementia called Nasu-Hakola disease (NHD). This observation suggests that TREM-2 may function in myeloid cells other than DC, most probably osteoclasts and microglial cells, which are involved in bone modeling and brain function. Consistent with this prediction, here we show that osteoclast differentiation is dramatically arrested in TREM-2-deficient patients, resulting in large aggregates of immature osteoclasts. Remarkably, these cells exhibit hyper-resorptive activity in bone resorption assays, which may account for the development of bone cysts in NHD. These results demonstrate a critical role for TREM-2 in the differentiation of mononuclear myeloid precursors into functional multinucleated osteoclasts.

References:

1. Bouchon, A., Hernandez-Munain, C., Cella, M. & Colonna, M. A DAP12-mediated pathway regulates expression of CC chemokine receptor 7 and maturation of human dendritic cells. *J Exp Med* **194**, 1111-22. (2001).
2. Paloneva, J. et al. Mutations in two genes encoding different subunits of a receptor signaling complex result in an identical disease phenotype. *Am J Hum Genet* **71**, 656-62. (2002).
3. Teitelbaum, S.L. Bone resorption by osteoclasts. *Science* **289**, 1504-8. (2000)
4. Arron, J.R., and Choi, Y. Bone versus immune system. *Nature* 408:535-536. (2000.)