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ODF/RANKL independent osteoclast differentiation

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Lisa Childs,[Aff1]

Aff1 University of Rochester, USA

Keywords

BMMf, ODF/RANKL, osteoclast differentiation, TNF-a

Context

Osteoblasts/bone marrow stromal cells express ODF on the surface of osteoclast precursors. The interaction of ODF with RANK (receptor activator of NF-?B) transduces a signal to initiate osteoclast differentiation via the NF-?B pathway. The involvement of ODF in osteoclastogenesis is supported by the fact that the soluble decoy receptor OPG (osteoprotegerin)/OCIF (osteoclastogenesis inhibitory factor) blocks the survival and activity of osteoclasts induced by osteoblasts/stromal cells or sODF. This suggests that the ODF interaction with RANK is important in regulating the number of osteoclasts and may be a therapeutic target for bone metabolism disorders including arthritis, osteoporosis and orthopedic osteolysis. TNF-a has also been implicated in inflammatory bone diseases and transduces signals through its two receptors, leading to the activation of NF-?B. This study examined both the ability of TNF-a to stimulate osteoclast differentiation and the pathway involved in mediating the induction. To determine whether and how TNF-a is able to induce osteoclastogenesis in bone marrow macrophages (BMMFs).

Significant findings

After three days, murine bone marrow cultures were composed of macrophages as assessed by immunohistochemical staining. These BMMfs were induced to form multinucleated $TRAP^+$ osteoclast-like cells when cultured with either sODF or murine TNF-a in combination with M-CSF. $TRAP^+$ cells were formed in cultures with murine TNF-a in a dose-dependent manner; IL-1a and vitamin D3 did not induce osteoclastogenesis. Cultured BMMfs expressed levels of TNF-R1, TNF-R2, c-fms, and RANK similar to those expressed by purified osteoclasts and were able to signal through the NF-?B pathway. Inhibition of ODF or RANK reduced the number of $TRAP^+$ cells formed in cultures treated with sODF but not those treated with TNF-a. The effect of TNF-a was found to be mediated by both TNF-Rs, since the addition of blocking antibodies eliminated $TRAP^+$ cell formation. TNF-a treatment also increased the survival of the $TRAP^+$ cells in the absence of M-CSF; this survival was not diminished in the

presence of OPG. Although TNF-a induced $TRAP^+$ cell formation, pit forming activity was only found in BMMf cultures treated with TNF-a and IL-1a.

Comments

This paper makes the very interesting observation, that tumor necrosis factor alpha (TNF-a) can induce osteoclast differentiation *in vitro* through a mechanism independent of ODF (osteoclast differentiation factor also known as RANKL [receptor activator of NF-?B ligand]). The idea of ODF-independent osteoclastogenesis is controversial since, *in vivo*, ODF appears to be absolutely required for osteoclastogenesis. However, the authors tested their hypothesis only in an *in vitro* culture system; *in vivo* work is needed to fully comprehend the nature of TNF-a and ODF signaling. Understanding the relationship between TNF-a and bone metabolism will lead to more effective therapeutics to treat inflammatory bone diseases such as arthritis, osteoporosis, and orthopedic osteolysis.

Methods

Murine bone marrow was isolated and the adherent cells were removed and cultured for three days in the presence of various cytokines and inhibitors. Osteoclastogenesis was measured by staining for tartrate-resistant acid phosphatase (TRAP) and counting the number of multinucleated $TRAP^+$ cells. BMMfs were characterized according to cell surface receptor mRNA expression by RT-PCR. Osteoclast function was assayed with a pit formation assay in which bone marrow cells were plated on dentine slices with macrophage colony stimulating factor (M-CSF) for six days and stained for TRAP or with hematoxylin. $TRAP^+$ cells and the number of resorption pits were counted. The survival of osteoclasts was determined by culturing with TNF-a, interleukin (IL)-1a, or sODF in the absence of M-CSF for three days then counting the number of $TRAP^+$ cells remaining.

References

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