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IFN? production by activated T cells blocks osteoclastogenesis

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Willis Huang,[Aff1]

Aff1 University of Rochester, New York, USA

Keywords

IFN-?, osteoclast, RANK, TRAF6

Context

RANKL (receptor activator of nuclear factor [NF]-?B ligand)-activated T-cells have been implicated as a potent source of osteoclastogenic stimulation, causing bone resorption in autoimmune arthritis and other chronic inflammatory conditions. However, T cells do not exclusively activate osteoclasts; cytokines produced by activated T cells have also been shown to inhibit osteoclast formation (see Additional information [1]). In this paper, Takayanagi *et al* show that interferon (IFN)-? produced by CD3-activated T cells inhibits osteoclastogenesis and that this inhibition results from accelerated degradation of TRAF6.

Significant findings

Several *in vivo* and *in vitro* experiments together convincingly demonstrated that IFN-? inhibits osteoclastogenesis. *In vivo*, IFN-? receptor knockout (IFN-?R $^{-/-}$) mice had substantially less lipopolysaccharide (LPS)-stimulated calvarial bone resorption than wild-type mice. *In vitro*, osteoclast development was inhibited when activated T cells were added to stimulated bone marrow macrophage (BMM) cultures; this inhibitory effect was eliminated when anti-IFN-? antibody was concomitantly added. Stimulated BMMs from IFN-?R $^{-/-}$ mice formed osteoclasts even in the presence of activated T cells. Finally, direct addition of IFN-? to stimulated BMMs mimicked the inhibition of osteoclastogenesis seen with activated T cells. The intracellular signalling adaptor protein TRAF6 was found to be degraded in response to IFN-?, and constitutive expression of TRAF6 by retroviral infection rendered BMMs immune to the inhibitory effects of IFN-? on osteoclastogenesis.

Comments

These studies provide convincing proof that IFN-? from activated T cells inhibits RANK-mediated osteoclastogenesis by ubiquitination/degradation of the intracellular adaptor molecule TRAF6. These findings add more evidence to a growing body of knowledge showing that general immune responses are intimately connected with bone regulation. Nevertheless, the role of activated T cells does not seem to be exclusively anti-osteoclastogenic. A previous study (see Additional information [2]) showed that activated T cells induce osteoclastogenesis via induction of RANKL, and that induction of RANKL causes the bone resorption seen in adjuvant arthritis. The authors reconcile these seemingly contradictory findings by hypothesizing that activated T cells deliver different osteoclastogenic signals in different situations: they may promote osteoclastogenesis through induction of RANKL in some situations, and inhibit osteoclastogenesis through the induction of IFN-? in other situations. They propose that the balance of IFN-? and RANKL governs osteoclastogenesis and that differential regulation of these molecules may tip the balance toward or away from osteoclastogenesis.

Methods

Osteoclast cultures, immunoblots, immunoprecipitation

Additional information

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