**T_{REG} CELLS BLOCK
BONE LOSS IN VIVO**

Stimulation of regulatory T (T_{REG}) cells protects against bone destruction induced by tumor necrosis factor (TNF), according to research by Zaiss *et al.* published in *The Journal of Immunology*.

The investigators previously showed that T_{REG} cells directly suppress the differentiation of osteoclasts *in vitro*. To separate the potential *in vivo* effects of T_{REG} cells on bone from their immunoregulatory effects, in the current study they used a human TNF-transgenic mouse model of inflammatory arthritis, which is non-T-cell-dependent and is characterized by excessive local and systemic bone loss.

Irradiated TNF-transgenic mice reconstituted with bone marrow from mice overexpressing the transcription factor FOXP3 had increased numbers of T_{REG} cells. These recipient mice were effectively protected from TNF-induced local joint destruction and from systemic bone loss, effects that were mediated by the influence of T_{REG} cells on osteoclast differentiation. By contrast, mice that received bone marrow from donors lacking T_{REG} cells showed increased bone loss as a result of enhanced osteoclastogenesis.

A pharmacological approach was also used to expand T_{REG} cells, by use of an anti-CD28 superagonist antibody. *In vivo* treatment with this antibody protected against TNF-induced bone loss in TNF-transgenic mice, and, notably, also increased systemic bone density in wild-type mice.

Supporting the notion that T_{REG} cells control bone destruction in humans, the authors reported that levels of FOXP3⁺ T cells inversely correlate with serum markers of osteoclastogenesis in the peripheral blood of patients with rheumatoid arthritis and normal controls.

Together, the findings suggest that increasing the activity of T_{REG} cells could represent a therapeutic strategy to prevent inflammation-induced structural bone damage in patients with rheumatoid arthritis.

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Original article Zaiss, M. M. *et al.* Regulatory T cells protect from local and systemic bone destruction in arthritis. *J. Immunol.* **184**, 7238–7246 (2010)