Nature Reviews Rheumatology **8**, 123 (2012); published online 7 February 2012; doi:10.1038/nrrheum.2012.12

BONE

RBP-J PREVENTS BONE EROSION

TNF has a crucial role in the progression of inflammatory arthritis and is implicated in pathological bone resorption. The regulatory mechanisms that restrain and prevent bone loss caused by the proinflammatory activities of TNF, however, remain unknown. Now, Lionel Ivashkiv and colleagues have published in *The Journal of Experimental Medicine* that the transcription factor RBP-J (recombinant recognition sequence binding protein at the J_K site) suppresses TNF-induced osteoclastogenesis and inflammatory bone resorption.

"Using complementary genetic approaches in which RBP-J was specifically knocked out in osteoclast precursors or activated using a transgenic approach enabled the *in vivo* role of RBP-J to be tested in mouse models of bone loss," explains Ivashkiv. High numbers of osteoclasts were observed in mice lacking RBP-J, whereas forced activation of RBP-J in osteoclast precursors suppressed inflammatory bone resorption; neither of these interventions affected homeostatic bone remodeling. Interestingly, in the absence of RBP-J, TNF-induced osteoclastogenesis and bone resorption occurred independently of the major inducer of osteoclastogenesis RANKL. Ivashkiv and colleagues confirmed these findings in human primary osteoclasts, which implicates RBP-J as a regulator of human inflammatory bone erosion.

Furthermore, the authors went on to determine the mechanism by which RBP-J suppresses TNF: RBP-J inhibits activation of NFATc1 (nuclear factor of activated T cells, cytoplasmic 1)—the master regulator of osteoclastogenesis. RBP-J blocks activation of c-Fos (a positive regulator of NFATc1) and also prevents degradation of the transcriptional repressor IRF-8 (a negative regulator). RBP-J therefore seems to be a key regulator of the positive and negative pathways that control osteoclastogenesis and bone erosion during inflammation.

Ivashkiv and co-workers now plan to "develop new ways of increasing RBP-J activity during inflammation to suppress bone destruction in inflammatory diseases; such therapy could be safely combined with current immunosuppressive treatments."

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Original article Zhao, B. *et al.* TNF-induced osteoclastogenesis and inflammatory bone resorption are inhibited by transcription factor RBP-J. *J. Exp. Med.* doi:10.1084/jem.20111566