Nature Reviews Rheumatology **9**, 446 (2013); published online 9 July 2013; doi:10.1038/nrrheum.2013.111

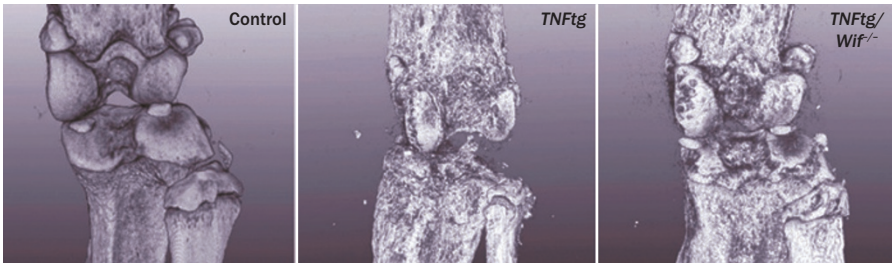
RHEUMATOID ARTHRITIS

Uncoupling bone and cartilage destruction

Wnt inhibitory factor 1 (Wif-1) might uncouple bone and cartilage destruction in inflammatory arthritis. In a mouse model of rheumatoid arthritis (RA), mice deficient in *Wif1* had more cartilage damage and less bone damage than mice with normal Wif-1 expression.

RA is associated with the destruction of both bone and cartilage. Transgenic mice overexpressing TNF (*TNFtg*) develop arthritis similar to RA, with synovial inflammation and destruction of both cartilage and bone. Michael Stock and colleagues examined chondrocytes and osteoblasts *ex vivo*, and found that TNF represses the expression of Wif-1, thereby stimulating canonical Wnt signalling. Wif-1 levels were also lower in *TNFtg* mice than in control mice, suggesting a role for Wif-1 in TNF-induced arthritis.

Using the *TNFtg* mouse, they then assessed the role of Wif-1 in arthritis. *TNFtg* mice and *Wif1*$^{-/-}$*;TNFtg* mice both developed arthritis with similar levels of inflammation. *Wif1*$^{-/-}$*;TNFtg* mice, however, had less arthritis-mediated loss of the trabecular bone than *TNFtg* mice did. More osteoclasts were found in *TNFtg* than in control mice; this increase was not observed in *Wif1*$^{-/-}$*;TNFtg* mice. Osteoblast numbers were unaffected by *Wif1* deficiency. Wif-1 might, therefore, increase osteoclast activity, thereby increasing bone loss in RA.



By contrast, more cartilage destruction and more proteoglycan loss were observed in *Wif1*$^{-/-}$*;TNFtg* mice than in *TNFtg* mice. Transient overexpression of Wif-1 in *TNFtg* mice had the opposite effect; Wif-1 decreased the arthritis-related loss of proteoglycan and articular cartilage. In this model, Wif-1 protects cartilage but does not protect bone.

Other Wnt-modulating proteins have not shown this uncoupling effect. "Wif-1 is a very interesting molecule since it controls bone and cartilage damage in opposite directions," explains Stock. "For future therapies targeting cartilage and bone damage, it will be important to understand how these two tissues interact in different types of arthritis."

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Original article Stock, M. *et al*. Wif-1-deficiency uncouples cartilage and bone destruction in TNFα-mediated experimental arthritis. *Arthritis Rheum*. doi:10.1002/art.38054