

A56 LOSS OF INTEGRIN $\alpha 2\beta 1$ REDUCES TUMOUR NECROSIS FACTOR-DEPENDENT INFLAMMATORY CARTILAGE DESTRUCTION AND MATRIX METALLOPROTEINASE EXPRESSION THROUGH MODULATING EXTRACELLULAR SIGNAL-REGULATED KINASE

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Integrins are the main receptors for cell-matrix interactions and integrin signalling is critical for a variety of cellular functions such as adhesion, cell spreading and inflammatory responses. $\alpha 2\beta 1$ integrin functions as a major receptor for type I collagen on a number of different cells, including fibroblasts and inflammatory cells. Although $\alpha 2$ -deficient mice appear normal apart from mild platelet dysfunction, it was shown that $\alpha 2\beta 1$ integrin contributes to the induction of matrix metalloproteinases (MMPs) in tissue remodelling. Based on the hypothesis that, under stress conditions such as chronic inflammation, $\alpha 2\beta 1$ integrin may be involved in the activation of synovial cells, we investigated its role in inflammatory arthritis.

To determine the role of $\alpha 2$ in tumour necrosis factor (TNF)-mediated joint disease, we crossed $\alpha 2$ -deficient mice with arthritic human TNF α transgenic (hTNFtg) mice. Clinical signs of arthritis and weight as well as the histological degree of synovitis and cartilage destruction were investigated using standard clinical evaluation and histomorphometric analysis. In addition, we analysed cytokine and MMP levels in serum and synovial fibroblasts from all genotypes and analysed changes in extracellular signal-regulated kinase (ERK) phosphorylation. We used an established in vitro assay to investigate the role of the $\alpha 2$ -subunit in the attachment of synovial fibroblasts to healthy and interleukin 1 (IL1)-damaged articular cartilage.

The loss of $\alpha 2$ integrin in hTNFtg mice resulted in improved clinical signs and symptoms compared with the hTNFtg mice arthritis score. hTNFtg/ $\alpha 2^{-/-}$ mice had less paw swelling (1.87 vs 2.66), increased grip strength (-1.83 vs -2.66) and a less pronounced weight loss. Histological analysis revealed that loss of $\alpha 2$ integrin led to a decrease in synovial inflammation compared with hTNFtg mice. To evaluate the role of $\alpha 2$ for MMPs, we analysed serum levels of $\alpha 2$ -deficient and wild-type mice and found no significant difference in MMP3 or MMP9. However, in $\alpha 2^{-/-}$ synovial fibroblasts, MMP3 expression was downregulated compared with wild-type synovial fibroblasts. This downregulation was similar in synovial fibroblasts from hTNFtg/ $\alpha 2^{-/-}$ mice as in fibroblasts from hTNFtg animals. In synovial fibroblasts, loss of $\alpha 2$ reduced phosphorylated ERK signalling after TNF α or IL1 stimulation. In addition, we found diminished attachment of $\alpha 2$ -deficient synovial fibroblasts, particularly after induction of proteoglycan loss in IL1-treated cartilage pieces in vitro.

Our findings suggest that, although $\alpha 2\beta 1$ integrin appears to be dispensable for normal development, the loss of $\alpha 2$ leads to a decrease in inflammation and bone destruction in an animal model of inflammatory arthritis.