A56 LOSS OF INTEGRIN α2β1 REDUCES TUMOUR NECROSIS FACTOR-DEPENDENT INFLAMMATORY CARTILAGE DESTRUCTION AND MATRIX METALLOPROTEINASE EXPRESSION THROUGH MODULATING EXTRACELLULAR SIGNAL-REGULATED KINASE

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10.1136/ard.2010.129593r

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. α2β1 integrin functions as a major receptor for type I collagen on a number of different cells, including fibroblasts and inflammatory cells. Although α2-deficient mice appear normal apart from mild platelet dysfunction, it was shown that α2β1 integrin contributes to the induction of matrix metalloproteinases (MMPs) in tissue remodelling. Based on the hypothesis that, under stress conditions such as chronic inflammation, α2β1 integrin may be involved in the activation of synovial cells, we investigated its role in inflammatory arthritis.

To determine the role of α2 in tumour necrosis factor (TNF)-mediated joint disease, we crossed α2-deficient mice with arthritic human TNFα 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 α2-subunit in the attachment of synovial fibroblasts to healthy and interleukin 1 (IL1)-damaged articular cartilage.

The loss of α2 integrin in hTNFtg mice resulted in improved clinical signs and symptoms compared with the hTNFtg mice arthritis score. hTNFtg/α2–/– 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 α2 integrin led to a decrease in synovial inflammation compared with hTNFtg mice. To evaluate the role of α2 for MMPs, we analysed serum levels of α2-deficient and wild-type mice and found no significant difference in MMP3 or MMP9. However, in α2–/– synovial fibroblasts, MMP3 expression was downregulated compared with wild-type synovial fibroblasts. This downregulation was similar in synovial fibroblasts from hTNFtg/α2–/– mice as in fibroblasts from hTNFtg animals. In synovial fibroblasts, loss of α2 reduced phosphorylated ERK signalling after TNFα or IL1 stimulation. In addition, we found diminished attachment of α2-deficient synovial fibroblasts, particularly after induction of proteoglycan loss in IL1-treated cartilage pieces in vitro.

Our findings suggest that, although α2β1 integrin appears to be dispensable for normal development, the loss of α2 leads to a decrease in inflammation and bone destruction in an animal model of inflammatory arthritis.

Loss of integrin α2β1 reduces tumour necrosis factor-dependent inflammatory cartilage destruction and matrix metalloproteinase expression through modulating extracellular signal-regulated kinase

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*Ann Rheum Dis*2010 69: A22-A23
doi: 10.1136/ard.2010.129593r

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