

**A114 ANTIBODIES AGAINST SYNDECAN-4 REDUCE  
CARTILAGE DESTRUCTION IN RA-LIKE DISEASE OF HTNF  
TRANSGENIC MICE**

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**Background** Syndecan-4 is a transmembrane heparansulfate proteoglycan and one out of four members of the syndecan family described in mammals. Several studies have implicated syndecan-4 in cell-matrix adhesion, cell migration, differentiation and proliferation, but its specific function in inflammatory pathologies remains unclear. Here, we used the human tumour necrosis factor  $\alpha$  (TNF $\alpha$ ) transgenic (hTNFtg) mouse to analyse the expression and function of syndecan-4 in chronic destructive arthritis and answer the question whether inhibition of syndecan-4 by specific antibodies may prevent cartilage destruction in this animal model of human RA.

**Methods** Expression of syndecan-4 was investigated by immunohistochemistry in the hind-paws of 8-week-old hTNFtg mice and wild type controls. In addition, synovial fibroblasts were isolated and analysed for syndecan-4 expression by RT-PCR. For functional analyses, we generated blocking antibodies against syndecan-4. To investigate their effect on TNF $\alpha$  mediated destructive arthritis, hTNFtg mice were injected with the antibodies or with IgG control antibodies twice weekly for 4 weeks into their hind paws. Evaluation of disease severity included clinical parameters (weight, arthritis score, grip strength) as well as histomorphometric analysis of toluidin-blue stained paraffin sections and staining of disease-relevant MMPs

**Results** As seen in immunohistochemistry, there was a strong expression of syndecan-4 in the synovial membranes of hTNFtg mice, whereas only negligible staining for syndecan-4 was found in synovial tissues of wild type animals. In vitro, synovial fibroblasts isolated from hTNFtg mice showed more than 36.5-fold higher expression of syndecan-4 than wild type controls. Administration of the anti-syndecan-4 antibodies but not of IgG control clearly ameliorated the clinical signs of arthritis ( $p < 0.05$  at week 8) and protected the treated joints from cartilage damage. At histomorphometric analysis, this was evident for all analysed parameters but seen most prominently for area of distained cartilage (IgG control 23% vs anti-syndecan-4 2%,  $p < 0.05$  at week 8). Significantly reduced cartilage damage in the anti-syndecan-4 treated hTNFtg mice was accompanied by a striking reduction in the expression of MMP3.

**Conclusions** Our findings indicate that syndecan-4 is involved prominently in fibroblast-mediated cartilage damage in hTNFtg mice by regulating the expression of disease-relevant MMPs. More importantly, however, the data also suggest that inhibition of syndecan-4 can prevent cartilage damage in this in vivo

model of human RA and that syndecan-4, therefore, may constitute a novel promising target for the treatment of this disease.