A177 ANTIBODIES AGAINST SYNDECAN-4 REDUCE CARTILAGE DESTRUCTION AND THE PROGRESSION AFTER ONSET IN RA-LIKE DISEASE OF HTNF TRANSGENIC MICE

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Background 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, the authors used the human tumour necrosis factor α (TNF α) 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-estruction and/or improve the phenotype after onset of the disease in this animal model of human rheumatoid arthritis.

Methods Expression of syndecan-4 was investigated by immunohistochemistry in the hind-paws of 8-/12-week-old hTNFtg mice and wild type controls. In addition, synovial fibroblasts were isolated and analysed for syndecan-4-expression by reverse transcriptase PCR. For functional analyses, the authors generated blocking-antibodies against syndecan-4. To investigate their effect on TNF α mediated-destructive-arthritis, hTNFtg mice were injected with the antibodies or with IgG-control twice weekly for 4-week prophylactically (age 4–8 weeks) and for disease treatment (age 8–12 weeks) into their hind paws. Evaluation of disease severity included clinical parameters (weight, arthritis-score, grip-strength) as well as histomorphometric analysis of toluidine-blue-stained paraffin sections.

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 30-fold higher expression of syndecan-4 than wild type controls. Administration of the anti-syndecan-4 antibodies but not of IgG-control in pretreated 8-week-old hTNFtg mice clearly ameliorated the clinical signs of arthritis 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. Significantly reduced cartilage damage in the anti-syndecan-4

treated hTNFtg mice was accompanied by a striking reduction in the expression of matrix metalloproteinase 3 (MMP3). The treatment with anti-syndecan-4 in 12-week-old hTNFtg mice after onset of the arthritic disease prevented the mice from massive joint-destruction, and improved the severe cartilage-damage. The treatment also showed a clear reduction of inflammation in the paws compared to the untreated.

Conclusions This 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, My data suggest that inhibition of syndecan-4 can not only prevent cartilage damage, but also reduces the severity after onset of the disease.