9 PROTECTIVE ROLE OF SYNDECAN-4 IN EXPERIMENTAL COLITIS

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10.1136/annrheumdis-2011-201238.9

Background Syndecan-4 (sdc4) is a transmembrane heparan sulfate proteoglycan that in addition to functioning as an adhesion molecule can bind cytokines and impact on inflammation. Modulation of inflammatory signals by sdc4 may occur either through mere binding of cytokines, in which case sdc4 acts as decoy receptor or through initiation of sdc4-dependent signalling following sdc4 complex formation. While arthritic cartilage damage is decreased in sdc4-deficient mice most likely due to reduced sdc4 signaling, osteopontin-mediated liver damage has been shown to be increased in these mice due to the lack of sdc4 decoy receptor function. Based on this dual and in part opposing effects of sdc4, the aim of this study was to investigate if the loss of sdc4 changes the natural course of murine experimental colitis.

Methods Experimental Colitis was induced in sdc4^{-/-} mice and in C57BL/6 WT mice by DSS. The course of colitis was monitored by weight loss as well as assessment of colon length and blinded histological scoring of colonic changes at the end of the experiment. In addition, sdc4^{-/-} and C57BL/6 WT mice were orally gavaged with 5×10⁸ colony-forming units (CFU) of *Citrobacter rodentium*. Fecal excretion of *C. rodentium* and changes of body weight were monitored. At day 21 postinfection, inflammatory changes of the colon were evaluated histologically.

Results Beginning from day 5 after start of DSS-administration, sdc4^{-/-} mice lost dramatically more body weight compared to WT animals (day 8: 24.8%±1.9 vs 9.2%±3.1; p=0.008). In accordance with the increased loss of body weight, the colon length of sdc4^{-/-} mice was significantly shortened (63.3 mm±2.4 vs 74.8±2.3; p=0.01) and the histological damage according to the Dieleman-Score was markedly aggravated (16AU±3.7 vs 3.4AU±0.2; p=0.016). At day 19 postinfection, the fecal excretion of *C. rodentium* in sdc4^{-/-} was prolonged compared to WT animals (2.5×10⁵±6.8×10³ vs 9.6×10³±6.5×10²; p=0.01). Histological damage of colonic mucosa, reflected by lengthening of crypts, was increased in Sdc4^{-/-} mice (14.3AU±1.3 vs 10.2AU±0.9; p=0.03).

Conclusions The data suggest that like in inflammatory liver damage, sdc4 exerts protective effects in intestinal inflammation. Future studies are needed to explore the underlying mechanisms and to determine if these effects are due to a decoy receptor function of sdc4 or whether sdc4 complex formation and signalling is involved.