11 THE TRANS-ENDOTHELIAL MIGRATION OF MURINE SYNOVIAL FIBROBLASTS OF HTNF TRANSGENIC MICE IS CONTROLLED BY JAM-C

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Background and objectives Recent studies demonstrated the potential of rheumatoid arthritis fibroblast-like synoviocytes (RA-FLS) to migrate long distances via the bloodstream and invade distant cartilage in the SCID mouse model of disease. While the mechanisms of trans-endothelial migration of RA-FLS are largely unclear the junctional adhesion molecule C (JAM-C) has become of interest due to its involvement in trans-endothelial migration of leucocytes. Here, the authors used the

hTNFtg mouse as a model for human RA and studied the role of JAM-C in the transmigration of FLS derived from these mice.

Materials and methods The expression of JAM-C on wild-type and hTNFtg FLS was investigated by western-blot analysis and immunocytochemistry. The transmigratory capacity of these cells was studied in a transmigration assay using murine endothelioma cells (bEnd.5) as an endothelial barrier and IL-1alpha treated murine cartilage tissue as chemoattractant stimulus. Functional analyses included the knock down of JAM-C expression by siRNA against murine JAM-C as well as its neutralisation by blocking antibodies.

Results The authors found the expression of JAM-C on the surface of both wild-type and hTNFtg FLS which is prominently located on sites of cell-cell interactions. Moreover, Western blot data revealed an elevated expression of JAM-C in FLS from hTNFtg mice. Transmigration experiments demonstrated a significantly higher potential of hTNFtg FLS to migrate through the endothelial monolayer than FLS from wild-type mice (+40%, p≤0,05), and cartilage explants pretreated with IL-1α enhanced the migratory capacity of hTNFtg FLS. Interestingly, siRNA-mediated knock down of JAM-C expression on hTNFtg FLS resulted in a reduction of transmigration of about 40% compared to mock control (p≤0,01). Likewise, the neutralisation of JAM-C by blocking antibodies against murine JAM-C reduced the number of transmigrated hTNFtg FLS on a similar level.

Conclusion Our data demonstrate that the inflammatory environment within the joints of hTNFtg mice induces an upregulation of JAM-C on FLS, which is characteristic for human RA-FLS. Moreover, they indicate that this environment supports the development of a trans-migrating phenotype of FLS able to get through endothelial barriers. JAM-C seems to be involved functionally in the transmigration and, thus, in extravasation of FLS and, therefore targeting JAM-C may be a promising therapeutic strategy for RA.