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SUMO-2/3 belongs to the small ubiquitin-related modifier family of proteins that have been implicated in many biological functions such as intracellular protein transport, control of gene expression and stability of proteins. The authors have previously shown that elevated expression of SUMO-1 in rheumatoid arthritis (RA) synovial fibroblasts (RASf) confers the resistance against Fas-induced apoptosis through SUMO-1/SENp1-dependent mechanisms. Based on these findings, the authors set out to analyse the expression of SUMO-2/3 in human RA and in a tumour necrosis factor α (TNF α)-dependent animal model of the disease and to study the regulation of apoptosis and disease-specific matrix metalloproteinase (MMP) expression by SUMO-2/3.

Synovial tissue samples were obtained from patients with RA and osteoarthritis (OA) and used for histological analysis as well as for the isolation of synovial fibroblasts. The expression of SUMO-2/3 in RASf versus OA synovial fibroblasts (OASf) and in fibroblasts from hTNFtg and wild-type mice was compared by western blot analysis and immunohistochemistry using specific antibodies. RASf/OASf were transfected with siRNA against SUMO-2/3 by lipofectamine. Apoptosis was induced by stimulation with 100ng/ml Fas ligand over 13h and the apoptotic response was measured using the Apo-ONE Homogenous Caspase-3/7 assay. MMP-1 and MMP-3 expression in synovial fibroblasts was measured using MMP ELISAs. The authors found a clear upregulation of SUMO-2/3 protein expression in all RA synovial tissue samples compared with OA control samples. SUMO-2/3 expression was most prominent in the superficial lining layer and in the sublining. Knockdown of SUMO-2/3 by specific siRNA for both proteins sensitised RASf to Fas-induced apoptosis compared with mock siRNA. In addition, the TNF α and interleukin 1 β (IL1 β)-induced MMP-3 upregulation was further elevated after knockdown of SUMO-2/3. Interestingly, the authors found no effect on MMP-1 expression.

Using tissue sections of hTNFtg mice, a clear upregulation of SUMO-2/3 protein expression compared with wild-type mice was observed. Analysing synovial fibroblasts of these mice, the authors could show that the protein levels of free SUMO-2/3 was increased in hTNFtg compared with wild-type synovial fibroblasts.

Our data suggest that post-translational modifications of target proteins by SUMO-2/3 in RASf contribute to the resistance of these cells against Fas-induced apoptosis. Furthermore, our data indicate that SUMO-2/3 is involved in the regulation of TNF α - and IL1 β -induced MMP-3 production. The authors therefore hypothesise that SUMO-2/3 are novel players contributing to specific features in the stable activation of RASf and, thus, to the disease process of RA.

A74 UPREGULATED SUMO-2/3 EXPRESSION IS INVOLVED IN THE REGULATION OF APOPTOSIS AND MATRIX METALLOPROTEINASE EXPRESSION IN RHEUMATOID ARTHRITIS SYNOVIAL FIBROBLASTS

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