

EFFECTS OF INFLAMMATORY MEDIATORS ON MATRIX METALLOPROTEINASE-2 EXPRESSION BY RHEUMATOID ARTHRITIS SYNOVIAL FIBROBLASTS

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RA is a chronic inflammatory disease characterized by synovial hyperplasia, invasion and destruction of bone and cartilage. In RA, angiogenesis is thought to be a key event in the expansion of the synovial lining of the joints. Angiogenesis requires proteolysis of the extracellular matrix, proliferation, and migration of endothelial cells, as well as synthesis of new matrix components. MMP-2 plays an important role in this angiogenic process.

In the present study, we investigated RA synovial fibroblast MMP-2 production in response to various stimuli. We found that MIF induced RA synovial fibroblast MMP-2 expression in a time and concentration dependent manner. MIF-induced RA synovial fibroblast MMP-2 upregulation required PKC δ , JNK and Src signaling pathways. Consistent with these results, MIF induced phosphorylation of JNK, PKC δ and c-jun. Further, we found that MMP-2 protein levels were significantly decreased in MIF gene deficient mice compared to wild type mice joint homogenates in zymosan induced arthritis. Immunohistochemistry staining revealed that synovial lining cells, endothelial cells and sublining non-lymphoid mononuclear cells expressed MMP-2 in the synovium. Consistent with these results, in antigen-induced arthritis, a model for RA, enhanced joint MMP-2 expression was also observed in wild type compared to MIF gene deficient mice. Furthermore, chemokines including ENA-78/CXCL5, gro- α /CXCL1 and RANTES/CCL5 all induced RA synovial fibroblast MMP-2 expression. These stimulatory effects were inhibited by EGCG, a constituent of green tea, suggesting that natural products, as well as pharmacological agents may interfere with inflammatory and destructive processes associated with arthritis.

Keywords: rheumatoid arthritis, synovial fibroblasts, matrix metalloproteinases, macrophage migration inhibitory factor, chemokines, epigallocatechin-3-gallate