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DEGRADATION OF A CARTILAGE-LIKE MATRIX BY RHEUMATOID SYNOVIAL FIBROBLASTS IS INHIBITED BY GENE TRANSFER WITH A CELL SURFACE-TARGETED PLASMIN INHIBITOR. W H van der Laan, H K Ronday, J M Grimbergen, L GM Huisman, F C Breedveld, J M te Koppele, T WJ Huizinga, P HA Quax, J H Verheijen Leiden, The Netherlands

Joint destruction in rheumatoid arthritis (RA), is a result of degradation and invasion of the articular cartilage by the pannus tissue. Previously, we showed that cartilage degradation by rheumatoid synovial fibroblasts *in vitro* is plasmin-mediated, indicating that plasmin may be involved in fibroblast-dependent cartilage destruction at the invasive front of the pannus. Efficient and specific inhibition of this proces may be achieved by targeting plasmin inhibition to the cell surface of invading fibroblasts.

In the present study, the effects of gene transfer with plasmin inhibitors on cartilage matrix degradation by synovial fibroblasts were investigated.

Synovial fibroblasts were infected with a replication-deficient adenoviral vector encoding an hybrid protein consisting of a potent plasmin inhibitor, bovine pancreas trypsin inhibitor (BPTI), linked to the receptor-binding aminoterminal fragment (ATF) of urokinase-type plasminogen activator (uPA). Gene transfer with vectors encoding only the ATF or BPTI parts were used to study the effects of uPA receptor-binding and plasmin inhibition separately. A radiolabeled cartilage-like matrix was used to study fibroblast-dependent cartilage degradation *in vitro*.

ATF.BPTI gene transfer resulted in a 76% decrease of matrix degradation ($p<0.0001$). BPTI gene transfer slightly inhibited degradation (31%; $p=0.02$), and ATF gene transfer did not inhibit degradation at all. Interference with binding of ATF.BPTI to the receptor by a specific receptor-blocking antibody after ATF.BPTI gene transfer resulted in an inhibition level similar to that observed after BPTI gene transfer.

These results show that fibroblast-dependent cartilage matrix degradation can be inhibited significantly by gene transfer with a plasmin inhibitor. This effect can be markedly improved by targeting plasmin inhibition to the cell surface. *In vivo* studies will be carried out to investigate whether this concept can be applied as a therapeutic strategy in RA.

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