SYNOVIAL FIBROBLASTS REPRESENT AN IMPORTANT SOURCE OF MATRIX DEGRADING ENZYMES MEDIATING JOINT DESTRUCTION IN RHEUMATOID ARTHRITIS. 

In our search for new pathways for the activation of synovial fibroblasts we have detected endogenous retroviral sequences, like the line 1 element (L1). 

To study the functional role of L1 we transduced synovial fibroblasts with L1 constructs and showed that L1 induces a number of crucial transcription factors for the activation of these cells. Most significant was the induction of p38 δ. At present p38 δ has not been explored in detail, although several interesting pathways have been examined. The fact that p38 δ phosphorylates various transcription factors, including ATF-2, Elk-1, and SAP-1, and that it could be shown that the ATF-2 pathway is potentially linked to the induction of certain oncogenes as well as to the production of matrix degrading metalloproteinases has put this molecule at the focus of our interest.

Because inhibition of p38 α and β has been the centre of interest for new therapeutic targets by the industry we studied the expression of the different isoforms at sites of joint destruction and showed that synovial cells appear to be activated not only by a cytokine dependent pathway but also by a cytokine independent pathway. The latter fact may explain the observation that anticytokine treatments of rheumatoid arthritis do not abolish joint destruction completely.

REFERENCES


