SUPPRESSION OF ARTHRITIC BONE DESTRUCTION BY ADENOVIRUS-MEDIATED DOMINANT NEGATIVE RAS GENE TRANSFER TO SYNOVIOCYTES AND OSTEOCLASTS

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Objective.
To determine the role of Ras-mediated signaling pathways in synovial cell activation and bone destruction in arthritic joints.

Methods.
The E11 rheumatoid synovial cell line and primary synovial fibroblast-like cells (SFCs) from patients with rheumatoid arthritis (RA) were gene-transferred by replication-deficient adenovirus vector carrying the dominant-negative mutant of ras gene (AxRasDN). The effects of RasDN overexpression on cellular proliferation, interleukin (IL)-1-induced activation of mitogen-activated protein kinases (extracellular signal-regulated kinase [ERK], p38, c-Jun N-terminal kinase [JNK]), and IL-6 production by synovial cells were analyzed. The in vivo effects of Ras inhibition on synovial cell activation and arthritic bone destruction were analyzed by injection of AxRasDN into ankle joints of rats with adjuvant arthritis.

Results.
AxRasDN markedly reduced the proliferation of RA SFCs. IL-1, a proinflammatory cytokine involved in the RA pathology, induced activation of ERK activation, p38 and JNK in the cells. Adenovirus vector-mediated RasDN overexpression suppressed ERK activation, but not p38 or JNK activation in SFCs. IL-6 is also an important proinflammatory cytokine, and RasDN inhibited IL-1-induced IL-6 production by RA SFCs at both transcriptional and protein levels. Injection of AxRasDN into ankle joints of rats with adjuvant arthritis ameliorated inflammation and suppressed bone destruction in the affected joints.

Conclusion.
Ras-mediated signaling pathways are involved in the activation of RA SFCs and the destruction of bone in arthritic joints, suggesting that inhibition of Ras signaling can be a novel approach for RA treatment that targets both synovial cell activation and bone destruction in the RA joint.