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The role of JNK in rheumatoid joint destruction

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Keywords

JNK , MMP, IL-1, AP-1, c-*jun*, c-*fos*

Context

The c-Jun N-terminal kinase (JNK) is a member of the mitogen-activated protein kinase (MAPK) family. JNK has been implicated in the regulated expression of matrix metalloproteinases (MMPs), which are known to play a crucial role in rheumatoid arthritis (RA)-associated joint destruction. IL-1 has been shown to activate JNK, which in turn activates the transcription factor AP-1, a key regulator of MMP production. In order to directly test the role of JNK in mediating joint disease, the authors investigated the regulation of MMP expression in synoviocytes from JNK-deficient mice and used a novel JNK inhibitor in an animal model of arthritis.

Significant findings

The JNK inhibitor SP600125 blocked JNK function and inhibited IL-1-induced phosphorylation of c-Jun in extracts of fibroblast-like synoviocytes (FLSs) isolated from RA synovial tissues. In IL-1-stimulated FLSs, SP600125 also blocked accumulation of mRNA for c-Jun (a component of AP-1), inhibited AP-1 DNA binding activity and blocked MMP1 expression. Induction of MMP3 and MMP13 by IL-1 and AP-1 binding activity were suppressed in FLSs from both JNK1-deficient mice and JNK2-deficient mice; MMP3 induction was further suppressed by SP600125, indicating that it blocks both JNK isoforms. SP600125 was investigated *in vivo* using an adjuvant arthritis animal model. JNK activity was not detected in joint lysates from SP600125-treated animals. Furthermore, inhibition of JNK in arthritic animals resulted in modest reductions in paw swelling, but significantly decreased bone and cartilage damage. MMP13 mRNA and AP-1 binding activity were also reduced in joint extracts of SP600125-treated animals.

Comments

Using a novel selective inhibitor, this study demonstrates that JNK may play a role in mediating joint destruction and that inhibition of JNK function may be of therapeutic value in the treatment of joint disease. It should be noted, however, that a MEK inhibitor also partially inhibited the IL-1-inducible effects described above, while inhibition of p38 MAPK had no effect. Given that other kinases may be involved in the mediation of IL-1-induced effects, JNK inhibition may only result in the partial resolution of joint disease. As JNK2 appears to be the important isoform in mediating matrix destruction, additional work might investigate the response of JNK2-deficient mice in a model of RA. Interestingly, in contrast to previous work using nuclear factor (NF)-?B inhibitors, inhibition of JNK had little effect on inflammation. The authors therefore suggest that these two pathways may complement each other by primarily regulating inflammation and destruction respectively. Further characterisation of SP600125 will establish whether it evokes any adverse side effects. If it proves to be well tolerated, this inhibitor could be a good candidate for human therapeutic development, and may be of particular use in combination with NF-?B blockade.

Methods

Kinase assays, JNK-deficient mice, synoviocyte isolation, western and northern analyses, electrophoretic mobility shift assays, adjuvant arthritis model

Additional information

References

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