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IKK? and synovial inflammation

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Keywords

Adenaovirus, NF-?B, synovial inflammation

Context

Nuclear factor-?B (NF-?B) binding sites are present in the promoter regions of many genes involved in the pathophysiology of joint inflammation and tissue destruction. Various stimuli such as IL-1 and TNF-a lead to the binding of NF-?B to decameric DNA sequences in the nucleus after phosphorylation of its inhibitor I?B by I?B kinase (IKK). A subunit of the IKK complex, IKK? is thought to be the primary pathway for proinflammatory stimuli resulting in NF-?B activation. This study evaluates the effects of IKK? overproduction and inhibition, on inflammation in rat ankle joints using gene transfer of recombinant adenoviral vectors encoding IKK? (Ad.IKK?) or a dominant negative IKK? (Ad.IKK?-dn).

Significant findings

Following 48 hours injection of Ad.IKK? into the ankles of normal rats, elevated IKK activity was found in recovered synovial tissues. Interestingly, a modest increase in IKK activity was observed in contralateral noninjected knees. Seven days after Ad.IKK? transfer, rats developed clinical signs of arthritis such as paw swelling and marked synovial inflammation. Ad.IKK?-dn gene transfer was found to block IKK function, NF-?B translocation and significantly decrease paw swelling 1 week following injection. However, no significant radiologic changes were observable in these joints relative to arthritic controls receiving an adenoviral vector encoding green fluorescent protein.

Comments

The authors use gene transfer technologies to study the role of IKK? on inflammation *in vivo*. Consistent with the hypothesis that IKK? has a preponderant role in regulating inflammation adenoviral mediated IKK? overexpression induced a severe synovitis in the ankles of rats. However, delivery of Ad.IKK?-dn in the adjuvant arthritis model was less striking. As suggested by the authors, this may be the result of NF-?B-independent matrix metalloproteinase activation pathways. Alternatively, it may reflect a limitation of gene transfer *in vivo*, particularly with respect to delivery of a gene the product of which is not secreted. Because Ad.IKK?-dn acts intracellularly, it is only possible to directly inhibit IKK? activity in those cells infected by the virus. The modest therapeutic effect may reflect a limitation of the accessibility of the gene transfer vector to activated cells within the synovial stroma and thereby perhaps underrepresents the therapeutic potential for IKK? inhibition.

Methods

Adenoviral constructs, immunohistochemistry, histologic analysis, EMSA

Additional information

References

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