

PublisherInfo		
PublisherName	:	BioMed Central
PublisherLocation	:	London
PublisherImprintName	:	BioMed Central

Mutated IKK2 inhibits endothelial cell activation

ArticleInfo		
ArticleID	:	97
ArticleDOI	:	10.1186/ar-2001-68058
ArticleCitationID	:	68058
ArticleSequenceNumber	:	54
ArticleCategory	:	Paper Report
ArticleFirstPage	:	1
ArticleLastPage	:	3
ArticleHistory	:	RegistrationDate : 2001-4-24 Received : 2001-7-26 Accepted : 2001-7-26 OnlineDate : 2001-7-26
ArticleCopyright	:	Biomed Central Ltd2001
ArticleGrants	:	

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Keywords

Adenovirus, HUVEC, IKK2, inflammation, NF- κ B

Context

The expression of many inflammatory genes in endothelial cells (ECs) is regulated by the transcription factor nuclear factor (NF)- κ B. In unstimulated cells, NF- κ B remains in the cytosol bound to the inhibitory protein, I κ B. Upon stimulation, I κ B is phosphorylated by the I κ B kinases IKK1 and IKK2. This results in I κ B degradation, and thereby allows NF- κ B to translocate to the nucleus and induce gene expression. In this study, the authors have examined the role of IKK2 in mediating inflammation, coagulation and angiogenesis, and have discussed its potential as a therapeutic target.

Significant findings

Lipopolysaccharide-induced degradation of I κ B was inhibited in human umbilical vein endothelial cells (HUVECs) that expressed dominant-negative IKK2 (dnIKK2). NF- κ B was located in the cytosol of control cells and translocated to the nucleus following stimulation with tumour necrosis factor (TNF). In contrast, NF- κ B remained in the cytosol of dnIKK2-expressing cells following TNF stimulation. Induction of vascular cell adhesion molecule (VCAM)-1, interleukin (IL)-8 and E-selectin mRNA expression by IL-1 and TNF was dramatically reduced in dnIKK2 cells compared to controls. Similarly, at the protein level, VCAM-1, E-selectin and intracellular adhesion molecule-1 expression was not induced in the dnIKK2 cells. Reduced expression of adhesion molecules was reflected functionally in reduced adhesion of the dnIKK2-expressing cells to HL-60 cells. Procoagulant activity and angiogenesis were also inhibited in the dnIKK2 cells.

Comments

This study clearly demonstrates that IKK2 plays a key role in EC NF- κ B activation. The suggestion that IKK2 is an ideal therapeutic target is questionable, however, as previous studies have shown that inhibition of NF- κ B activation is critical in determining the sensitivity of the cells to apoptosis. I κ B overexpression sensitizes ECs to TNF-mediated apoptosis, while inhibition of NF- κ B by expression of a p65 dominant negative mutant does not (see Additional information [1]). Furthermore, evidence is emerging to suggest that there is an I κ B-independent NF- κ B regulatory pathway (see Additional information [2]).

Methods

Recombinant adenovirus construction; transduction of HUVECs; immunofluorescence; northern and western blotting; electrophoretic mobility shift assay; ELISA; assays for cell adhesion, coagulation and tube formation

Additional information

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2. Schmitz ML, Bacher S, Kracht M: **I κ B-independent control of NF- κ B activity by modulatory phosphorylations.**

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1. Oitzinger W, Hofer-Warbinek R, Schmid JA, Koshelnick Y, Binder BR, de Martin R: Adenovirus-mediated expression of a mutant I κ B kinase 2 inhibits the response of endothelial cells to inflammatory stimuli. *Blood*. 2001, **97**: 1611-1617.