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TANK-binding kinase 1 activates NF-?B

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Keywords

IKK, NF-?B, TANK, TBK1, TRAF2

Context

The involvement of the tumour necrosis factor receptor (TNFR)-associated factor (TRAF) family of proteins in NF-?B and c-Jun amino-terminal kinase (JNK) activation by pro-inflammatory cytokines has been well documented. NF-?B activation by TRAFs occurs through NF-?B-inducing kinase (NIK), and the I?B kinase (IKK), leading to I?B phosphorylation and degradation. TRAF associated NF-?B activator (TANK) is a TRAF-binding protein which can activate NF-?B in a TRAF-dependent fashion yet inhibits NF-?B activation by pro-inflammatory cytokines. This article describes the identification of a TANK-binding kinase, TBK1, which mediates the TANK/TRAF-dependent activation of NF-?B and proposes that TANK and TBK1 can compete with pro-inflammatory receptor complexes in the activation of NF-?B. To clarify the seemingly contradictory role of TANK in the NF-?B pathway by identifying and characterising other molecules which interact with TANK.

Significant findings

Transfection of dominant-negative components of the TRAF/NF-?B pathway inhibited NF-?B activation by a constitutively active N-terminal portion of TANK (TANK 1-190), suggesting that the activation of NF-?B by TANK proceeds via TRAF2, NIK and the IKKs. A yeast two-hybrid screen, using TANK 1-190 as bait yielded TBK1, which could activate NF-?B when overexpressed: the dominant-negative form of TBK1 could block NF-?B activation by TANK, and NF-?B activation by TBK1 was also dependent on NIK and the IKKs as well as on TRAF2.

Co-precipitation of TRAF2, TBK1 and TANK (full length and 1-190) was demonstrated, indicating that these proteins can form a ternary complex. Cotransfection of an N-terminal mutant of TANK (1-168, which cannot bind TRAFs) prevented TBK1-induced NF-?B activity. Thus the ternary complex formed between these proteins seems to be necessary for TBK1-mediated activation of NF-?B. TBK1 transfection caused phosphorylation of TANK and TRAF2, although this was not necessary for complex formation.

Importantly, TBK1 did not inhibit TNF/IL-1/CD40L-induced activation of NF-?B (indicating that it lies on a distinct pathway) and it was able to overcome the ability of full length TANK to inhibit CD40L-induced NF-?B activity (indicating that TANK interacts with both pathways). Finally, a dominant-negative TBK1 had no effect on the TANK/TRAF2-induced activation of JNK.

Comments

The data presented in this paper are clear and the experiments are well designed. Constitutively active and dominant-negative forms of NF-?B pathway members demonstrate that TANK acts as an activator of the NF-?B pathway that competes with pro-inflammatory cytokine receptors for activation of the pathway. The authors themselves note that caution must be used in the interpretation of overexpression studies such as these, but the data are well controlled and convincing. It is interesting that initial overexpression studies did not reveal a clear role for TANK (indeed the results appeared contradictory). Similar studies performed using TANK and TBK1, however, provided clarification. Identification of TBK1-dependent activators of NF-?B will significantly increase our understanding of the physiological role that this transcription factor plays in inflammation and should yield new potential targets for anti-inflammatory therapies.

Methods

Methods used included identification of TBK1 by yeast two-hybrid screening, co-transfection of wild-type and mutant forms of NF-?B pathway members with NF-?B reporters and co-immunoprecipitation of TRAF2/TANK/TBK1. Also, *in vitro* kinase assays for JNK activity and electrophoretic gel mobility shift assays (EMSA) for NF-?B activity were performed. The signalling studies were performed in 293 cells.

Additional information

There are a couple of interesting articles on the identification of TANK (Cheng *et al, Genes Dev* 1996, **10**:963-973 [Abstract]; Rothe *et al, Proc Nat Ass Sci USA* 1996, **93**:8241-8246 [Abstract)

References

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