Recruitment of TBK1/IKK epsilon to K63-pUb-TANK:K63-pUb-TRAF3:TRIF:activated TLR3 followed by their phosphorylation

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Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

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Literature references

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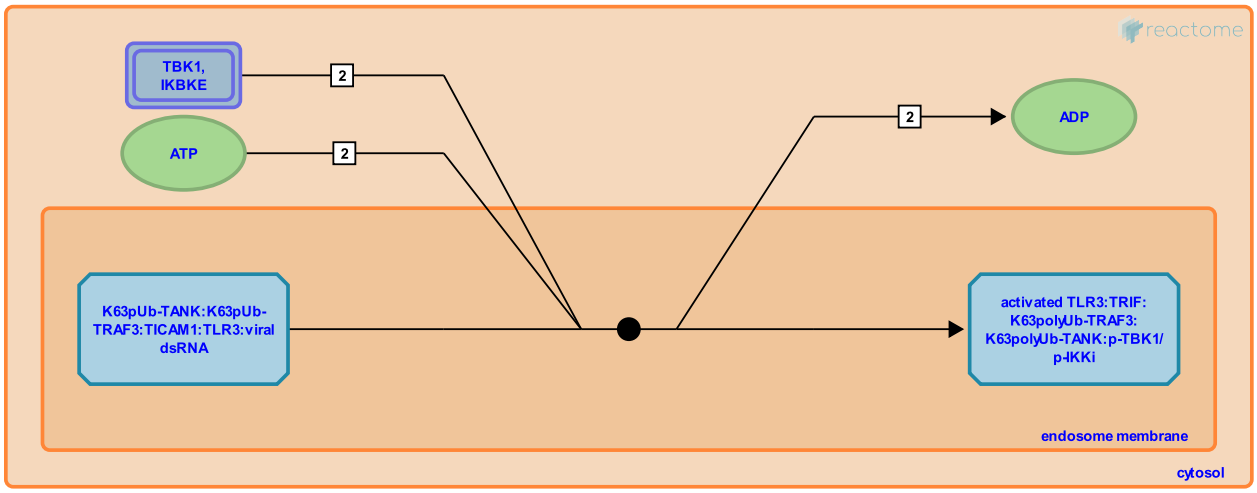
Stable identifier: R-HSA-9013986

Type: binding

Compartments: endosome membrane, cytosol



Upon stimulation by pathogen-associated inflammatory signals, TANK-binding kinase 1 (TBK1) and inhibitor of kappaB kinase epsilon (IKKi) induce type I interferon expression and modulate nuclear factor kappa B (NFkB) signaling (Fitzgerald KA et al. 2003; Hemmi H et al. 2004). The structural studies of TBK1 revealed a dimeric assembly which is mediated by several interfaces involving kinase domain (KD), a ubiquitin-like domain (ULD), and an alpha-helical scaffold dimerization domain (SDD) of TBK1 (Larabi A et al. 2013; Tu D et al. 2013). ULD of TBK1 and IKKi was involved in the control of kinase activation, substrate presentation and downstream signaling (Ikeda F et al 2007; Tu D et al. 2013). An intact TBK1 dimer was a subject to K63-linked polyubiquitination on lysines 30 and 401 (Tu D et al. 2013). Activation of TBK1 rearranged the KD into an active conformation while maintaining the overall dimer conformation (Larabi A et al. 2013). The ubiquitination sites and dimer contacts are conserved in the close homolog IKKi (Tu D et al. 2013). The activation of TBK1 and IKKi may occur through autophosphorylation or via activity of a distinct protein kinase (Clark et al. 2009). Other studies demonstrated an essential role of TRAF3 in the activation of TBK1 (Hacker et al 2006). TBK1 and IKKi were found to interact with scaffold proteins TANK (TRAF family member associated NFkB activator), NAP1 (NAK-associated protein 1), SINTBAD (similar to NAP1 TBK1 adaptor) which connect TBK1/IKKi to pathogen-activated signaling cascades (Pomerantz JL and Baltimore D 1999; Guo B and Cheng G 2007; Gatot JC et al. 2007; Ryzhakov G and Randow F 2007; Goncalves A et al. 2011).

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Editions

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