TBK1, IKBKE form homodimers

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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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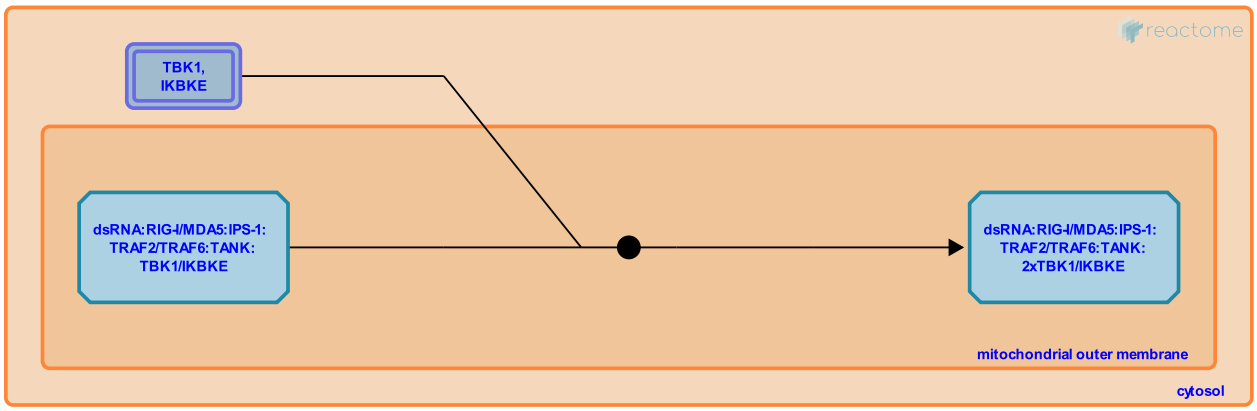
Stable identifier: R-HSA-9705145

Type: binding

Compartments: mitochondrial outer membrane



TBK1 (tumor necrosis factor (TNF) receptor-associated factor (TRAF) family member-associated NF-κB activator (TANK)-binding kinase 1) and its close homolog inhibitor-kappa-B kinase (IKK) epsilon (IKKε or IKBKE) are serine/threonine-protein kinases that trigger phosphorylation of interferon regulatory factor 3 (IRF3) and IRF7 and subsequent expression of type I interferons (IFNs; IFN-α/β). Type I IFNs can induce the expression of numerous antiviral genes called interferon-stimulated genes (ISGs). Structural studies revealed a dimeric assembly of TBK1 stabilized by an extensive network of interactions among its kinase, ubiquitin-like (ULD) and scaffold/dimerization (SDD) domains (Larabi A et al. 2013; Tu D et al. 2013). IKBKE was also reported to form dimers (Nakatsu Y et al. 2014). Even though the contacts that stabilize the TBK1 dimer are largely conserved in IKKε (IKBKE), studies reported differences in activation mechanisms between TBK1 and IKBKE (Larabi A et al. 2013; Tu D et al. 2013; Nakatsu Y et al. 2014). While the C-terminal region was required for dimerization of IKBKE and downstream signaling, a C-terminally truncated fragment of TBK1 formed a dimer both in vitro and in vivo and was able to induce IRF3 phosphorylation (Nakatsu Y et al. 2014). Mutants that interfere with TBK1 dimerization showed significantly reduced trans-autophosphorylation upon expression in human embryonic kidney 293 (HEK293) cells (Larabi A et al. 2013). An intact TBK1 dimer was modified by K63-linked polyubiquitination on lysine 30 and lysine 401, and these modifications were required for TBK1 activation in HEK293 cells (Tu D et al. 2013). Similar findings were reported for IKBKE (Zhou AY et al. 2013). Further, interferon-β expression was ablated in TBK1-/- mouse embryo fibroblasts (MEFs) cells reconstituted with dimerization defective TBK1 mutants (Tu D et al. 2013). Structural studies suggest that TBK1 dimerization is required for kinase activation via transautophosphorylation at Ser172 of dimeric TBK1 (Larabi A et al. 2013; Tu D et al. 2013; Ma X et al. 2012). However, dimerization of TBK1 was not required for TBK1 downstream activity once the activation loop was phosphorylated (Ma X et al. 2012; Larabi A et al. 2013). These observations are supported by findings that amyotrophic lateral sclerosis (ALS)-associated TBK1 mutations in ULD or SDD displayed defects in dimerization of TBK1 without losing kinase activity (Ye J et al. 2019). The Reactome event shows homodimer formation of TBK1 and/or IKBKE in the RIG-I-like receptors (RLRs):mitochondrial antiviral-signaling protein (MAVS) signaling pathway.

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Editions

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