TBK1 or IKBKE forms homodimers

D'Eustachio, P., Ramos, CH., Shamovsky, V.

European Bioinformatics Institute, New York University Langone Medical Center, Ontario Institute for Cancer Research, Oregon Health and Science University.

06/05/2024

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.

The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

Literature references

Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics, 18*, 142. ↗

Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

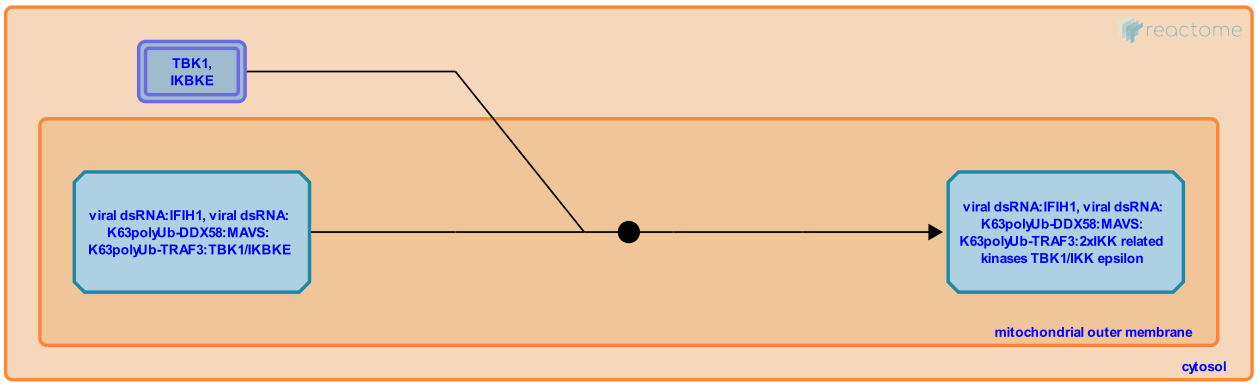
Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

TBK1 or IKBKE forms homodimers ↗

Stable identifier: R-HSA-9705137

Type: binding

Compartments: mitochondrial outer membrane



RIG-I-like receptors (RLRs) recognize RNAs from various RNA viruses and activate the mitochondrial antiviral-signaling protein (MAVS) adaptor protein. MAVS recruits the serine/threonine protein kinase TBK1 (tumor necrosis factor (TNF) receptor-associated factor (TRAF) family member-associated NF-κB activator (TANK)-binding kinase 1) and/or its close homolog inhibitor-kappa-B kinase (IKK) epsilon (IKKε or IKBKE) via TRAFs. Imunoprecipitation combined with mass spectrometry (MS)-based proteomic assays identified interactors of endogenous TBK1, such as TANK and NAP1, in SeV or HHV-1 (HSV-1)-infected human acute monocytic leukemia cells (THP-1) cells (Shang L et al. 2018). TBK1 and IKBKE trigger phosphorylation of interferon regulatory factor 3 (IRF3) and IRF7 and subsequent expression of type I interferons (IFNs; IFN-α/β). Both TBK1 and IKBKE directly phosphorylate IRF3 and IRF7 targeting identical residues within the C-terminal signal-responsive domain (McWhirter SM et al. 2004; tenOever BR et al. 2004). Type I IFNs can induce the expression of numerous antiviral genes called interferon-stimulated genes (ISGs). Structural studies revealed a dimeric assembly of TBK1 that is stabilized by an extensive network of interactions among the kinase, ubiquitin-like (ULD) and scaffold/dimerization (SDD) domains of TBK1 (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 homodimer 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 activation via transautophosphorylation at Ser172 of dimeric TBK1 (Larabi A et al. 2013; Tu D et al. 2013; Ma X et al. 2012). However, familial 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). These observations suggest that TBK1 dimerization is not required for kinase activation. Rather, dimerization seems to increase protein stability and enables efficient kinase-substrate interactions (Ye J et al. 2019).

Literature references

Kimura, H., Kubota, T., Matsuoka, M., Otsuki, N., Kato, H., Noda, M. et al. (2014). Functionally distinct effects of the C-terminal regions of IKKε and TBK1 on type I IFN production. *PLoS One, 9*, e94999. ↗

Helgason, E., Dueber, EC., Ma, X., Bowman, KK., Lee, MW., Phung, QT. et al. (2012). Molecular basis of Tank-binding kinase 1 activation by transautophosphorylation. *Proc. Natl. Acad. Sci. U.S.A., 109*, 9378-83. ↗

Devos, JM., Nanao, MH., Ng, SL., Round, A., Larabi, A., Panne, D. et al. (2013). Crystal structure and mechanism of activation of TANK-binding kinase 1. *Cell Rep, 3*, 734-46. ↗

Editions

2020-12-25	Authored	Shamovsky, V.
2021-01-27	Reviewed	D'Eustachio, P.
2021-02-22	Edited	Shamovsky, V.
2021-04-19	Reviewed	Ramos, CH.