Phosphorylation of TBK1/IKBKE

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. ↗

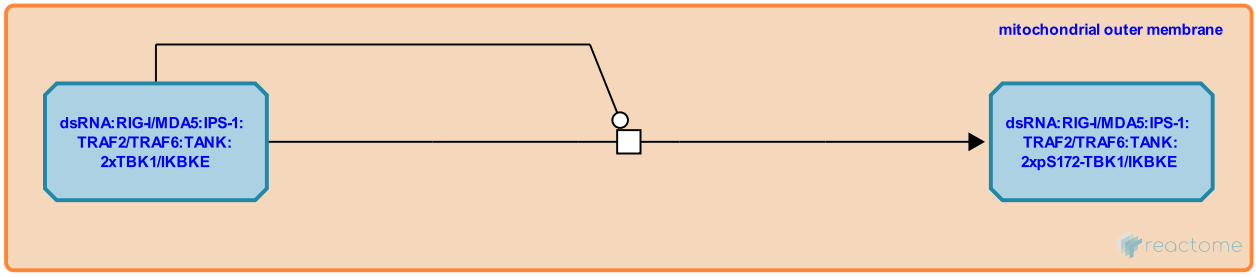
Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Phosphorylation of TBK1/IKBKE ↗

Stable identifier: R-HSA-9705323

Type: transition

Compartments: mitochondrial outer membrane



Viral nucleic acids are sensed by cellular pattern-recognition receptors (PRRs), such as RIG-I-like receptors (RLR). RLRs activate the adaptor protein called mitochondrial antiviral-signaling protein (MAVS). MAVS recruits 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 (Fitzgerald KA et al. 2003; Fang R et al. 2017). The enzymatic activity of TBK1/IKBKE is initiated by phosphorylation at Ser172 located in the T loop of the TBK1 and IKKε kinase domains, which is essential for the enhancement of kinase activity (Shimada T et al. 1999; Kishore N et al. 2002; Ma X et al. 2012; Gu L et al. 2013). TBK1 forms a homodimer (Larabi A et al. 2013; Tu D et al. 2013) and structural studies suggest that dimerization of TBK1 precludes autophosphorylation and activation in cis (Larabi A et al. 2013). IKBKE is also a dimer (Nakatsu Y et al. 2014). Other kinases such as IKKs were also implicated in TBK1/IKBKE activation (Fang R et al. 2017). Further, K63-linked polyubiquitination on Lys30 and Lys401 enhanced TBK1/IKBKE activation in HEK293 cells (Tu D et al. 2013; Zhou AY et al. 2013).

Activated TBK1 and IKBKE in turn 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).

Many viruses have evolved numerous mechanisms to evade antiviral action of type I IFNs by acting at the level of the TBK1/IKBKE kinases. For example, nonstructural protein 13 (nsp13) of severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) binds and blocks TBK1 phosphorylation, while nsp6 binds TBK1 to suppress TBK1-mediated phosphorylation of IRF3 (Xia H et al. 2020). SARS-CoV-2 membrane protein M interacts with MAVS and TBK1 thus preventing the formation of MAVS signalosome (Zheng Y et al. 2020).

Literature references

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. ↗

Inoue, J., Kanamaru, A., Tatsumi, Y., Matsumoto, M., Akira, S., Kawai, T. et al. (1999). IKK-i, a novel lipopolysaccharide-inducible kinase that is related to IkappaB kinases. *Int Immunol, 11*, 1357-62. ↗

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.