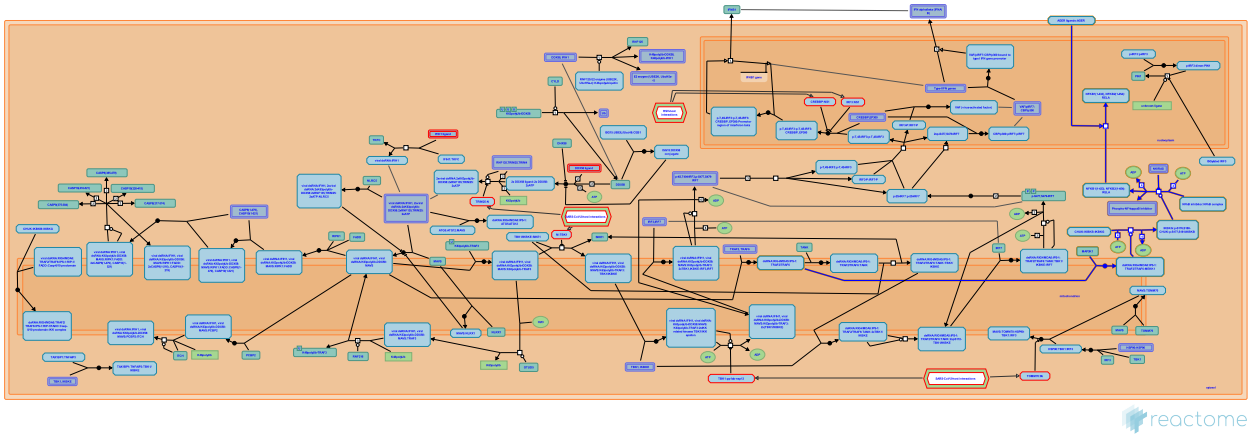
TRAF6 mediated NF-kB activation



Akira, S., D'Eustachio, P., Fitzgerald, KA., Garapati, P V., Jin, L., Kawai, T., Mocarski, ES., Napetschnig, J., Shamovsky, V., Upton, JW., Wu, J., de Martin, R.

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04/05/2024

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. ↗

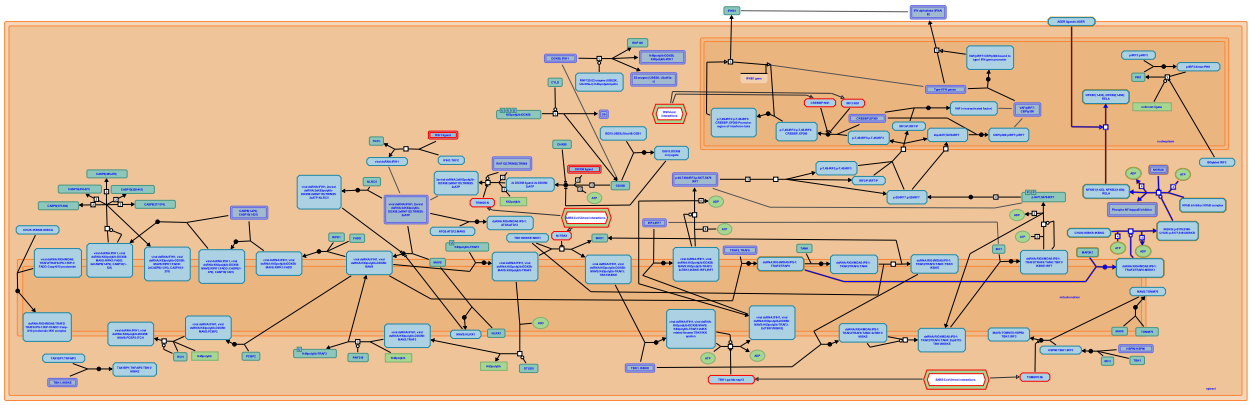
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

TRAF6 mediated NF-kB activation ↗

Stable identifier: R-HSA-933542

Compartments: mitochondrial outer membrane, cytosol



The TRAF6/TAK1 signal activates a canonical IKK complex, resulting in the activation of NF-kB as well as MAPK cascades leading to the activation of AP-1. Although TRAF6/TAK1 has been implicated in Tool like receptor (TLR) mediated cytokine production, the involvement of these molecules in the regulation of type I IFN induction mediated by RIG-I/MDA5 pathway is largely unknown. According to the study done by Yoshida et al RIG-I/IPS-1 pathway requires TRAF6 and MAP3K, MEKK1 to activate NF-kB and MAP Kinases for optimal induction of type I IFNs.

Literature references

Kobayashi, T., Kawai, T., Yoshioka, T., Yoshida, H., Takaesu, G., Yoshida, R. et al. (2008). TRAF6 and MEKK1 play a pivotal role in the RIG-I-like helicase antiviral pathway. *J Biol Chem, 283*, 36211-20. ↗

Editions

2010-08-02	Authored, Edited	Garapati, P V.
2010-10-30	Reviewed	Akira, S., Kawai, T.

Interaction of MEKK1 with TRAF6 ↗

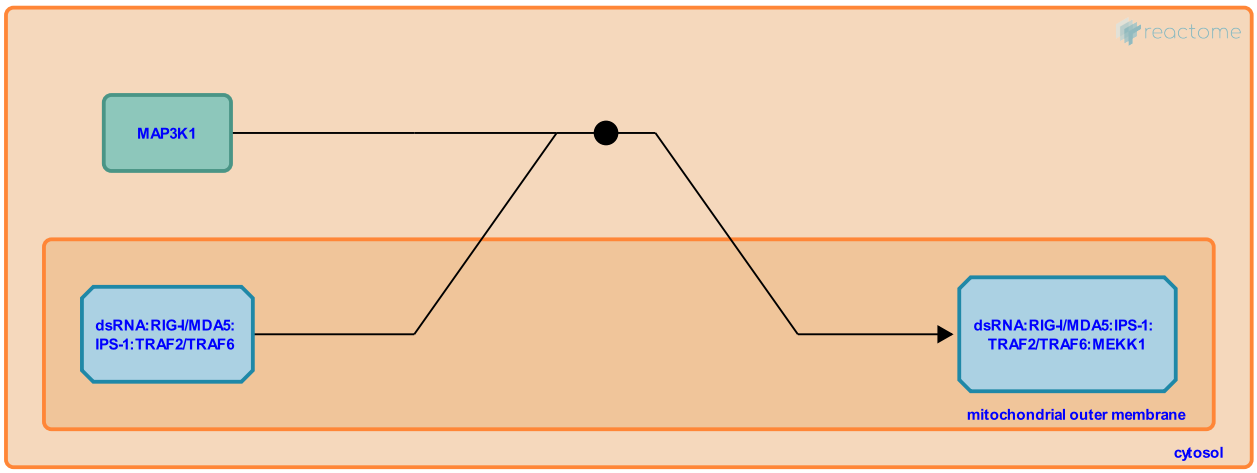
Location: TRAF6 mediated NF-kB activation

Stable identifier: R-HSA-933528

Type: binding

Compartments: cytosol, mitochondrial outer membrane

Inferred from: Interaction of MEKK1 with TRAF6 (Mus musculus)



TRAF6 requires MEKK1 (MAP3K1) to activate NF-kB and MEKK1 may interact with TRAF6, which in turn contributes to the activation of IKK and MAPKK, leading to the activation of NF-kB and AP-1. (Yoshida et al)

Followed by: Activation of IKK by MEKK1

Editions

2010-08-02	Authored, Edited	Garapati, P V.
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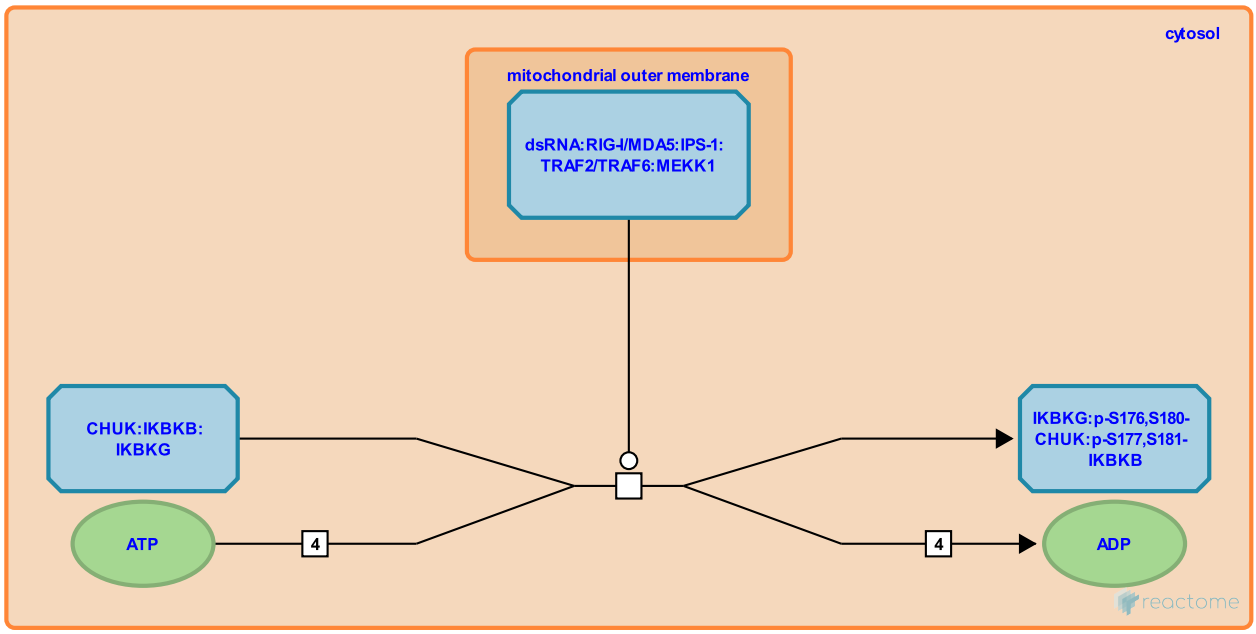
Activation of IKK by MEKK1 ↗

Location: TRAF6 mediated NF-kB activation

Stable identifier: R-HSA-933530

Type: transition

Compartments: cytosol, mitochondrial outer membrane



In Human, IKKs - IkB kinase (IKK) complex serves as the master regulator for the activation of NF-kB by various stimuli. It contains two catalytic subunits, IKK alpha and IKK beta, and a regulatory subunit, IKKgamma/NEMO. The activation of IKK complex and NFkB mediated antiviral responce are dependent on the phosphorylation of IKK alpha/beta at its activation loop and the ubiquitination of NEMO.[Solt et al 2009]; [Li et al 2002]. NEMO ubiquitination by TRAF6 is required for optimal activation of IKKalpha/beta; it's remained unclear if NEMO subunit undergoes K63-linked or linear ubiquitination.

This basic trimolecular complex is referred to as the IKK complex. Each catalytic IKK subunit has a N-term kinase domain a leucine zipper (LZ) motifs, a helix-loop-helix (HLH) and a C-ter NEMO binding domain (NBD). IKK catalytic subunits are dimerized through their LZ motifs.

IKK beta is the major IKK catalytic subunit for NF-kB activation. MEKK1 can activate both IKK-alpha (IKKA) and IKK-beta (IKKB) in vivo. MEKK1 phosphorylates Ser-176 and Ser-180 in IKKA and Ser-177 and Ser-181 in IKKB activation loop and thus activate the IKK kinase activity, leading to the IkB alpha phosphorylation and NF-kB activation.

Preceded by: Interaction of MEKK1 with TRAF6

Followed by: Active IKK Complex phosphorylates NF-kappa-B inhibitor

Literature references

Marcu, KB., Li, X., Hanidu, A., Savitt, A., Aro, P., Mische, S. et al. (2002). IKKalpha, IKKbeta, and NEMO/IKKgamma are each required for the NF-kappa B-mediated inflammatory response program. *J Biol Chem, 277*, 45129-40. ↗

Dang, LC., Lee, FS., Peters, RT., Maniatis, T. (1998). MEKK1 activates both IkappaB kinase alpha and IkappaB kinase beta. *Proc Natl Acad Sci U S A, 95*, 9319-24. ↗

May, MJ., Madge, LA., Solt, LA. (2009). The nemo binding domains of both IKKalpha and IKKbeta regulate IKK complex assembly and classical NFkappaB activation. *J Biol Chem*. ↗

Lee, FS., Hagler, J., Chen, ZJ., Maniatis, T. (1997). Activation of the IkappaB alpha kinase complex by MEKK1, a kinase of the JNK pathway. *Cell, 88*, 213-22. ↗

Editions

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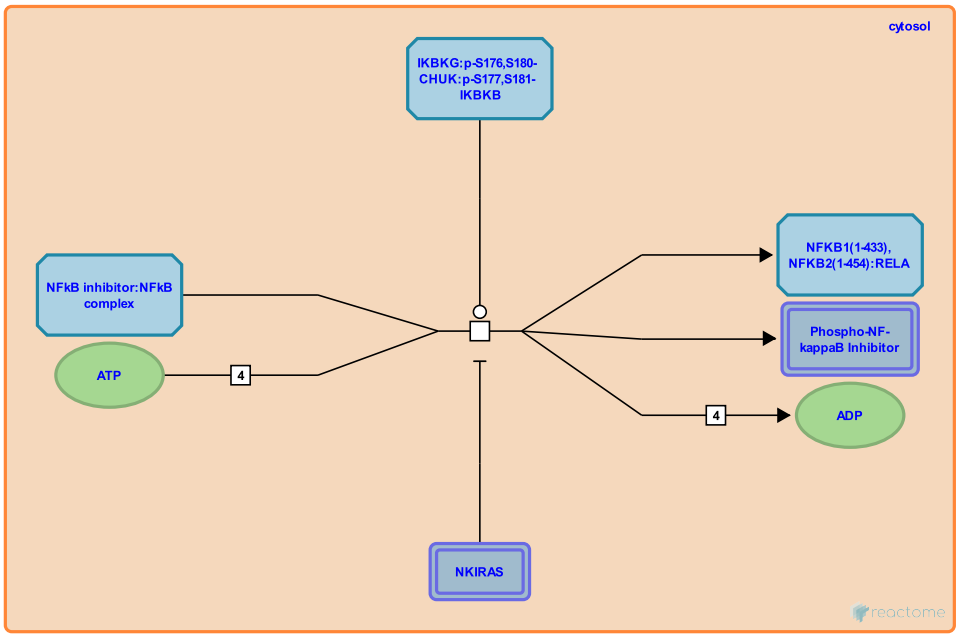
Active IKK Complex phosphorylates NF-kappa-B inhibitor ↗

Location: TRAF6 mediated NF-kB activation

Stable identifier: R-HSA-168140

Type: transition

Compartments: cytosol



In human, IkBs (NFKBIA, NFKBIB or NFKBIE) are inhibitory proteins that sequesters NF-kappa-B in the cytoplasm, by masking a nuclear localization signal, located just at the C-terminal end of the RelA (p65) subunit of the RelA:NFKB1 heterodimer.

A key event in NF-kappa-B activation involves phosphorylation of IkB by an IkB kinase (IKK). The phosphorylation and ubiquitination of IkB kinase complex is mediated by two distinct pathways, either the classical or alternative pathway. In the classical NF-kappa-B signaling pathway, the activated IKK (IkB kinase) complex, predominantly acting through IKK beta (IKKb, IKBKB) in an IKK gamma (IKBKG, NEMO)-dependent manner, catalyzes the phosphorylation of IkBs (at sites equivalent to Ser32 and Ser36 of human NFKBIA (IkB-alpha) or Ser19 and Ser22 of NFKBIB (IkB-beta)). Once phosphorylated, IkB undergoes ubiquitin-mediated degradation, releasing NF-kappa-B.

Preceded by: Activation of IKK by MEKK1

Followed by: NF-kappa-B complex is transported from cytosol to nucleus

Literature references

Yazdi, S., Stein, M., Naumann, M. (2017). Double phosphorylation-induced structural changes in the signal-receiving domain of IκBα in complex with NF-κB. *Proteins, 85*, 17-29. ↗

Karin, M., Hacker, H. (2006). Regulation and function of IKK and IKK-related kinases. *Sci STKE, 2006*, re13. ↗

Esteban, M., Alcami, J., Gil, J. (2000). Activation of NF-kappa B by the dsRNA-dependent protein kinase, PKR involves the I kappa B kinase complex. *Oncogene, 19*, 1369-78. ↗

Editions

2009-09-29	Revised	Shamovsky, V.
2009-12-16	Edited	Shamovsky, V.
2011-12-08	Reviewed	D'Eustachio, P.
2012-02-19	Reviewed	Upton, JW., Mocarski, ES.
2012-11-13	Reviewed	Fitzgerald, KA.
2012-11-16	Reviewed	Napetschnig, J.

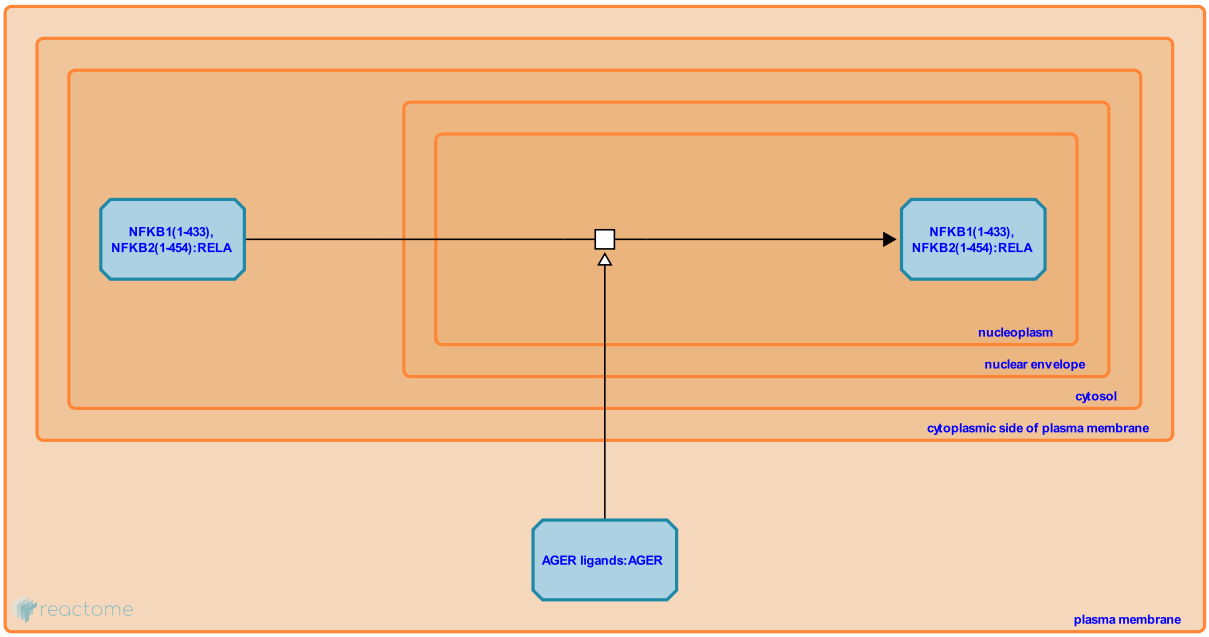
NF-kappa-B complex is transported from cytosol to nucleus ↗

Location: TRAF6 mediated NF-kB activation

Stable identifier: R-HSA-168166

Type: transition

Compartments: nucleoplasm, cytosol



Though the signaling cascade is unclear, several pieces of experimental data suggest that activation of AGER leads to sustained activation and upregulation of NFkappaB, measured as NFkappaB translocation to the nucleus, and increased levels of de novo synthesized NFkappaB.
NFkB is a family of transcription factors that play pivotal roles in immune, inflammatory, and antiapoptotic responses. There are five NF-kB/Rel family members, p65 (RelA), RelB, c-Rel, p50/p105 (NF-kappa-B1) and p52/p100 (NF-kappa-B2). All members of the NFkB family contain a highly conserved DNA-binding and dimerization domain called Rel-homology region (RHR). The RHR is responsible for homo- or heterodimerization. Therefore, NF-kappa-B exists in unstimulated cells as homo or heterodimers; the most common heterodimer is p65/p50. NF-kappa-B is sequestered in the cytosol of unstimulated cells through the interactions with a class of inhibitor proteins called IkBs, which mask the nuclear localization signal of NF-kB and prevent its nuclear translocation. Various stimuli induce the activation of the IkB kinase (IKK) complex, which then phosphorylates IkBs. The phosphorylated IkBs are ubiquitinated and then degraded through the proteasome-mediated pathway. The degradation of IkBs releases NF-kappa-B and and it can be transported into nucleus where it induces the expression of target genes.

Preceded by: Active IKK Complex phosphorylates NF-kappa-B inhibitor

Literature references

Chen, ZJ. (2005). Ubiquitin signalling in the NF-kappaB pathway. *Nat Cell Biol, 7*, 758-65. ↗

Karin, M., Bonizzi, G. (2004). The two NF-kappaB activation pathways and their role in innate and adaptive immunity . *Trends Immunol, 25*, 280-8. ↗

Esteban, M., Alcami, J., Gil, J. (2000). Activation of NF-kappa B by the dsRNA-dependent protein kinase, PKR involves the I kappa B kinase complex. *Oncogene, 19*, 1369-78. ↗

Editions

2009-09-29	Revised	Shamovsky, V.
2009-12-16	Authored	Shamovsky, V.
2011-12-08	Reviewed	D'Eustachio, P.
2012-02-19	Reviewed	Upton, JW., Mocarski, ES.
2012-11-13	Reviewed	Fitzgerald, KA.
2012-11-16	Reviewed	Napetschnig, J.
2013-05-17	Edited	Shamovsky, V.
2013-05-22	Reviewed	Jin, L., Wu, J.
2022-05-04	Reviewed	de Martin, R.

Table of Contents