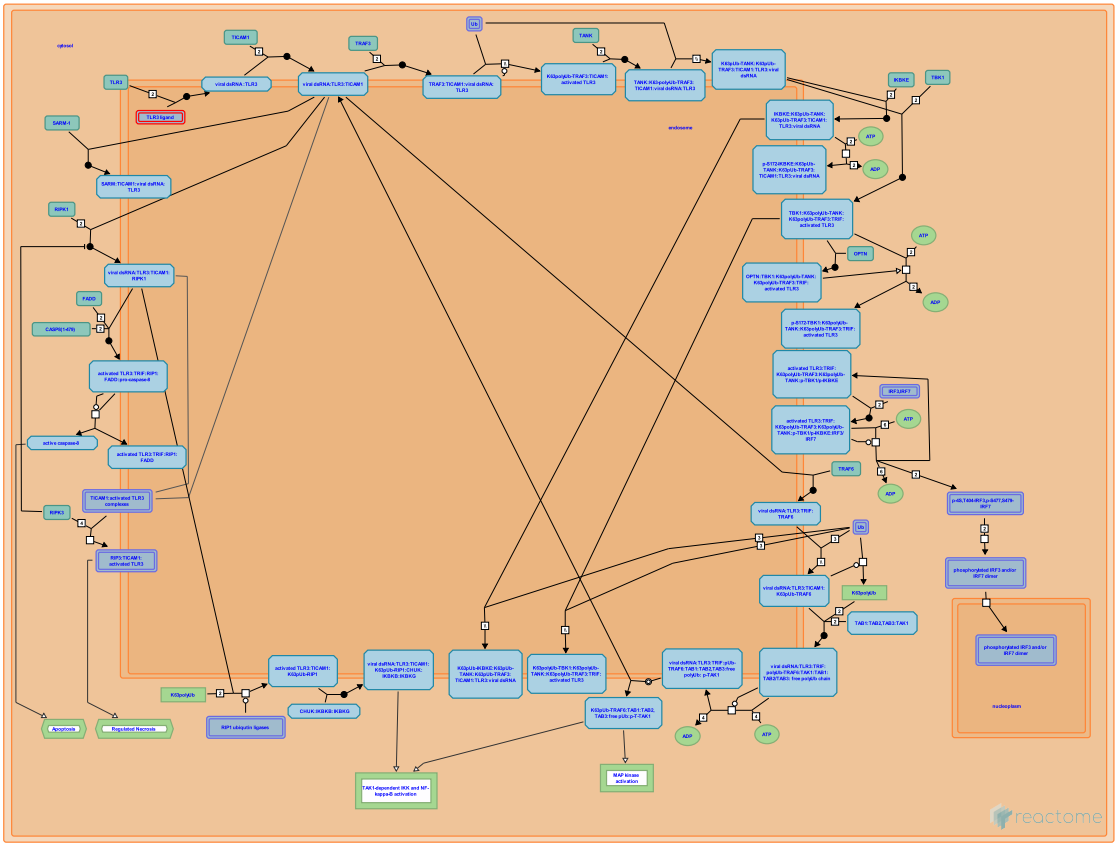
Toll Like Receptor 3 (TLR3) Cascade



Fitzgerald, KA., Franjkić, T., Gay, NJ., Gillespie, ME., Luo, F., Masci, A M., Munitić, I., Napetschnig, J., Shamovsky, V., de Martin, R.

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This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the Reactome Textbook.

29/04/2024

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. ↗

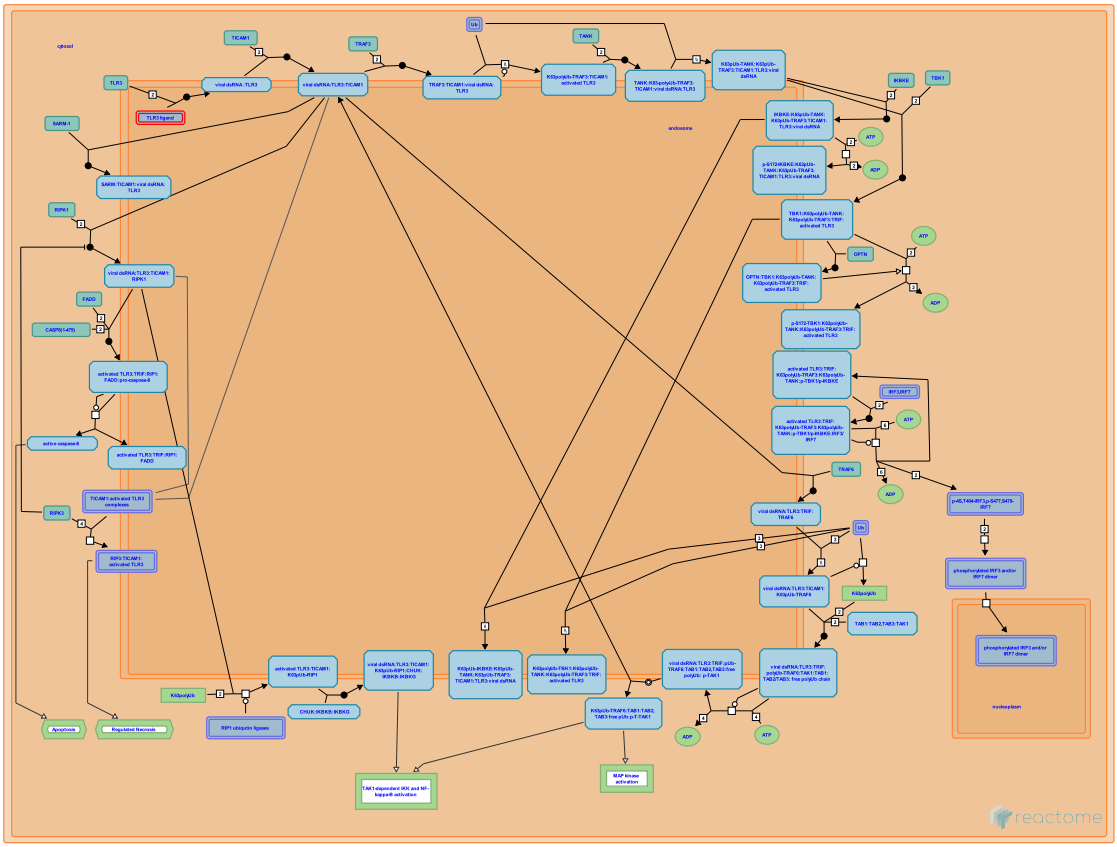
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

Toll Like Receptor 3 (TLR3) Cascade ↗

Stable identifier: R-HSA-168164



Toll-like receptor 3 (TLR3) as was shown for mammals is expressed in various tissues and cells, including myeloid dendritic cells, macrophages, respiratory and intestinal epithelium, neurons and microglial cells to induce antiviral and inflammatory responses of the innate immunity in combating viral infections.

TLR3 recognizes dsRNA in the endosome and that triggers the receptor dimerization. TLR3 recruits the adaptor TRIF (TICAM1), leading to the activation of NF-kappa-B and the production of type I interferons (IFNs). dsRNA-stimulated phosphorylation of two specific TLR3 tyrosine residues (Tyr759 and Tyr858) is essential for initiating TLR3 signaling pathways.

Literature references

O'Neill, LA., Carpenter, S. (2009). Recent insights into the structure of Toll-like receptors and post-translational modifications of their associated signalling proteins. *Biochem J, 422*, 1-10. ↗

Beyaert, R., Staal, J., Vercammen, E. (2008). Sensing of viral infection and activation of innate immunity by toll-like receptor 3. *Clin Microbiol Rev, 21*, 13-25. ↗

Sarkar, SN., Sen, GC. (2005). Transcriptional signaling by double-stranded RNA: role of TLR3. *Cytokine Growth Factor Rev, 16*, 1-14. ↗

Editions

2005-11-10	Authored	Luo, F.
2006-04-24	Reviewed	Gay, NJ.
2009-09-29	Revised	Shamovsky, V.
2011-08-12	Edited	Shamovsky, V.

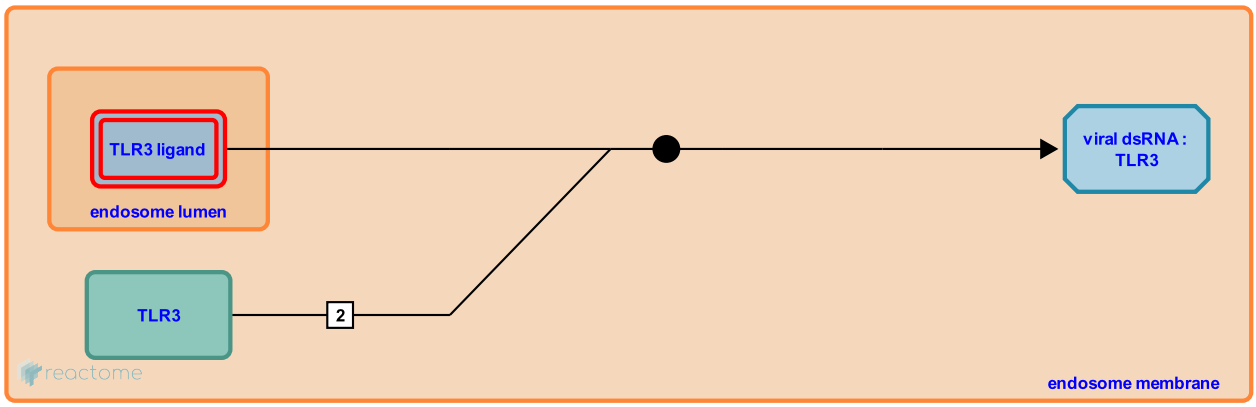
Viral dsRNA binds the Toll-Like Receptor 3 (TLR3) ↗

Location: Toll Like Receptor 3 (TLR3) Cascade

Stable identifier: R-HSA-168092

Type: binding

Compartments: endosome membrane, endosome lumen



Viral dsRNA triggers an antiviral pathway mediated by toll like receptor 3. TLR3 dimerization occurs upon ligand binding to positively charged residues on the ectodomain termini of TLR3 which are responsible for the interaction with sugar-phosphate groups of dsRNA.

Followed by: Viral dsRNA:TLR3 recruits TRIF (TICAM1)

Literature references

Davies, DR., Leonard, JN., Shiloach, J., Botos, I., Liu, L., Wang, Y. et al. (2008). Structural basis of toll-like receptor 3 signaling with double-stranded RNA. *Science, 320*, 379-81. ↗

Holt, AC., Alexopoulou, L., Medzhitov, R., Flavell, RA. (2001). Recognition of double-stranded RNA and activation of NF-kappaB by Toll-like receptor 3. *Nature, 413*, 732-8. ↗

Editions

2005-11-10	Authored	Luo, F.
2006-04-24	Reviewed	Gay, NJ.
2009-09-29	Revised	Shamovsky, V.
2012-02-19	Edited	Shamovsky, V.

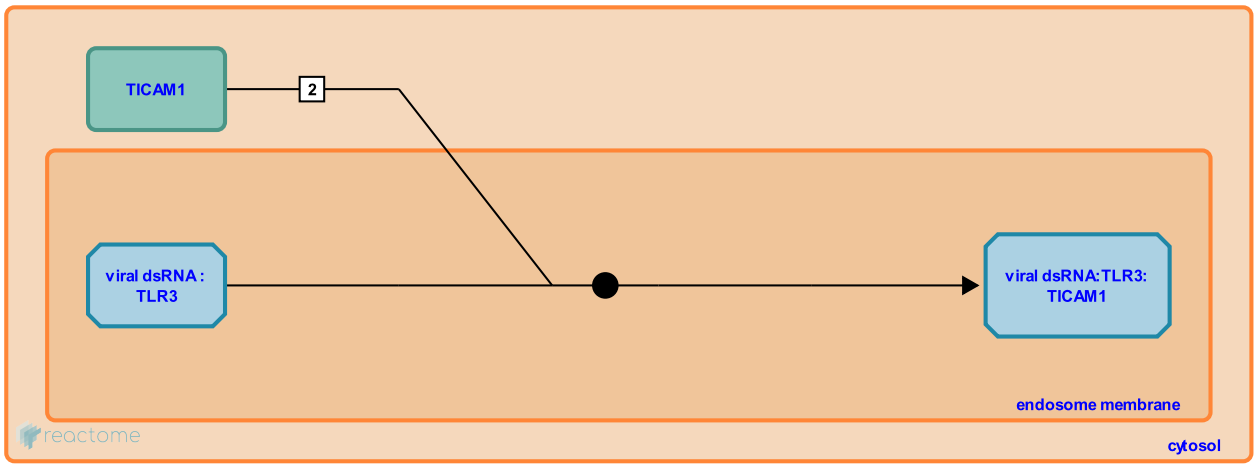
Viral dsRNA:TLR3 recruits TRIF (TICAM1) ↗

Location: Toll Like Receptor 3 (TLR3) Cascade

Stable identifier: R-HSA-168929

Type: binding

Compartments: endosome membrane, cytosol



TIR-domain-containing adaptor inducing interferon-beta (TRIF or TICAM1) was shown to play an essential role in TLR3 signaling. All poly(I:C)-induced pathways leading to NFkB and IRF3 activation were abolished in TRIF-/- mice [Yamamoto et al. 2003].

Preceded by: Viral dsRNA binds the Toll-Like Receptor 3 (TLR3)

Followed by: SARM binds viral dsRNA:TLR3:TICAM1

Literature references

Sugiyama, M., Takeuchi, O., Sanjo, H., Hoshino, K., Takeda, K., Okabe, M. et al. (2003). Role of adaptor TRIF in the MyD88-independent toll-like receptor signaling pathway. *Science, 301*, 640-3. ↗

Fitzgerald, KA., Rowe, DC., Latz, E., Barnes, BJ., Golenbock, DT., Pitha-Rowe, PM. et al. (2003). LPS-TLR4 signaling to IRF-3/7 and NF-kappaB involves the toll adapters. *J Exp Med, 198*, 1043-55. ↗

Matsumoto, M., Oshiumi, H., Funami, K., Akazawa, T., Seya, T. (2003). TICAM-1, an adaptor molecule that participates in Toll-like receptor 3-mediated interferon-beta induction. *Nat Immunol, 4*, 161-7. ↗

Editions

2005-11-10	Authored	Luo, F.
2006-04-24	Reviewed	Gay, NJ.
2009-09-29	Revised	Shamovsky, V.
2009-12-16	Edited	Shamovsky, V.
2012-11-13	Reviewed	Fitzgerald, KA.

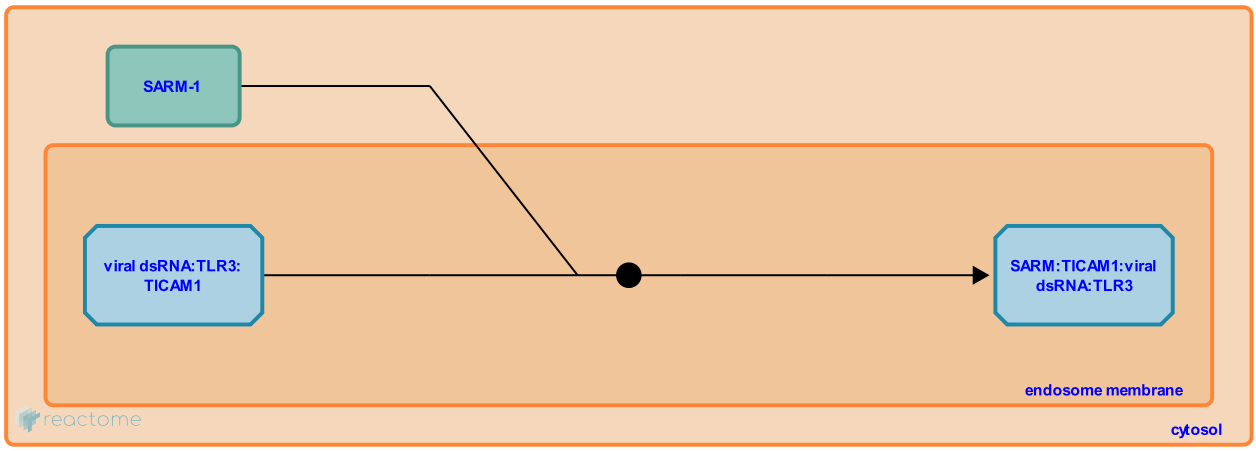
SARM binds viral dsRNA:TLR3:TICAM1 ↗

Location: Toll Like Receptor 3 (TLR3) Cascade

Stable identifier: R-HSA-9014320

Type: binding

Compartments: endosome membrane, cytosol



SARM (sterile alpha-and armadillo-motif-containing protein) is a TIR-domain-containing adaptor, which functions as a negative regulator of TRIF (TICAM1)-dependent Toll-like receptor signaling in humans. A pairwise yeast two-hybrid assay demonstrated that SARM is capable of binding directly to TICAM1 (Carty M et al. 2006). GST pulldown studies suggest that protein-protein interactions occur between the TIR domains of SARM and TICAM1 (Carlsson E et al. 2016). The complex of TICAM1:SARM is thought to inhibit downstream TRIF signaling by preventing the recruitment of TRIF effector proteins (Carty M et al. 2006).

SARM expression was shown to inhibit poly(I:C)-induced TICAM1-dependent NFkappaB activaion, RANTES production and IRF activation in human embryonic kidney HEK293 cells (Carty M et al. 2006). Moreover, suppression of endogenous SARM expression by siRNA led to enhanced TLR3- and TLR4-dependent gene induction in both transformed HEK293 and primary PBMC cells (Carty M et al. 2006), Thus, SARM associates with TICAM1 via its TIR and sterile-alpha motif (SAM) domains to block the induction of proinflammatory genes downstream TLR3.

Preceded by: Viral dsRNA:TLR3 recruits TRIF (TICAM1)

Literature references

Schröder, M., Stack, J., Moynagh, PN., Carty, M., Bowie, AG., Goodbody, R. (2006). The human adaptor SARM negatively regulates adaptor protein TRIF-dependent Toll-like receptor signaling. *Nat. Immunol., 7*, 1074-81. ↗

Editions

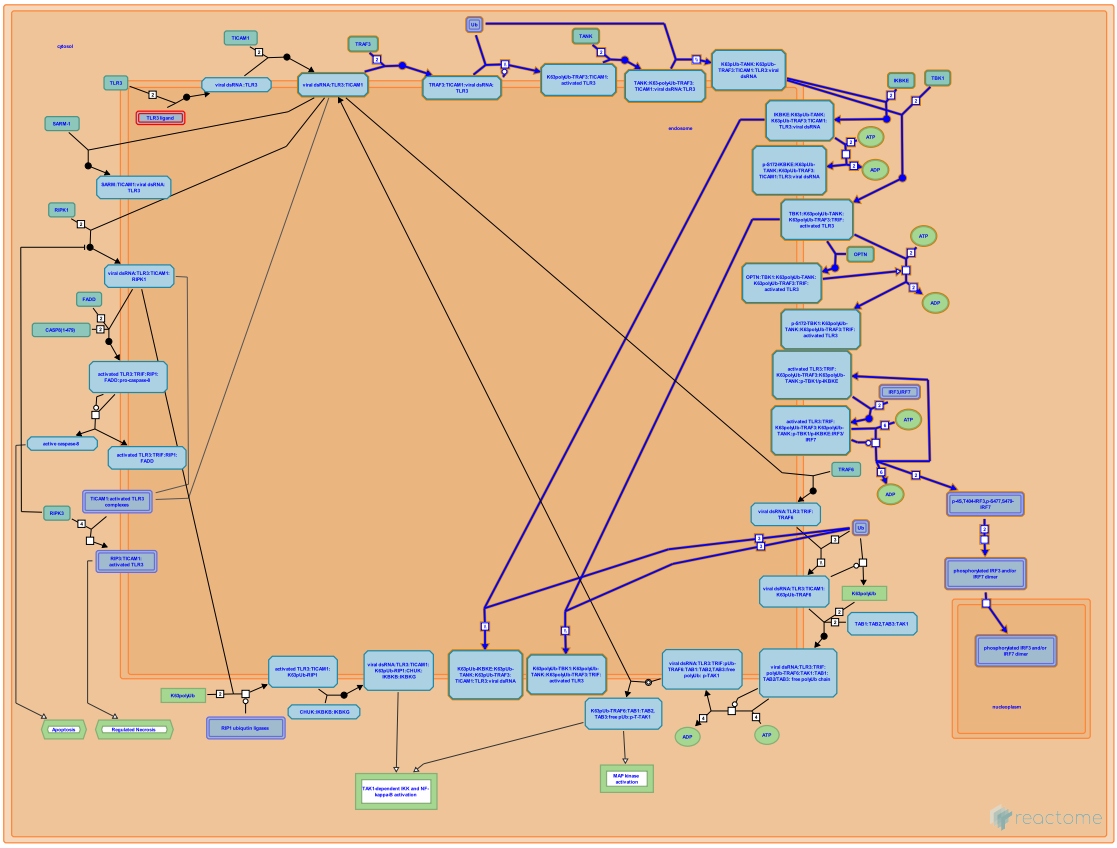
2012-05-15	Authored	Shamovsky, V.
2012-11-13	Reviewed	Fitzgerald, KA.
2012-11-19	Edited	Shamovsky, V.

TICAM1-dependent activation of IRF3/IRF7 ↗

Location: Toll Like Receptor 3 (TLR3) Cascade

Stable identifier: R-HSA-9013973

Compartments: cytosol



Cell stimulation with viral double-stranded (ds) RNA and bacterial lipopolysaccharide (LPS) activate Toll-like receptors 3 (TLR3) and TLR4, respectively, triggering the activation the activation of two IKK-related serine/threonine kinases, TANK-binding kinase 1 (TBK1) and IκB kinase ε (IKKε, IKBKE) which directly phosphorylate interferon regulatory factor 3 (IRF3) and IRF7 promoting their dimerization and translocation into the nucleus. Although both kinases show structural and functional similarities, it seems that TBK1 and IKBKE differ in their regulation of downstream signaling events of TLR3/TLR4.

IRF3 activation and interferon β (IFNβ) production by poly(I:C), a synthetic analog of dsRNA, are decreased in TBK1-deficient mouse fibroblasts, whereas normal activation was observed in the IKBKE-deficient fibroblasts. However, in double-deficient mouse fibroblasts, the activation of IRF3 is completely abolished, suggesting a partially redundant functions of TBK1 and IKKε (IKBKE) (Hemmi H et al., 2004).

The poly(I:C)-induced phosphorylation of TBK1 and IRF3 was abolished in TRIF (TICAM1)-knockout human keratinocyte HACAT cells (Bakshi S et al., 2017). TICAM1 is utilized as an adaptor protein by TLR3 and TLR4 (Yamamoto M et al., 2003).

TLR3 recruits and activates PI3 kinase (PI3K), which activates the downstream kinase, Akt, leading to full phosphorylation and activation of IRF3 (Sarkar SN et al., 2004). When PI3K is not recruited to TLR3 or its activity is blocked, IRF3 is only partially phosphorylated and fails to bind the promoter of the target gene (Sarkar SN et al., 2004).

Literature references

Takeuchi, O., Hoshino, K., Sanjo, H., Takeda, K., Sato, S., Yamamoto, M. et al. (2004). The roles of two IkappaB kinase-related kinases in lipopolysaccharide and double stranded RNA signaling and viral infection. *J Exp Med, 199*, 1641-50. ↗

Sakamoto, S., Elco, CP., Sarkar, SN., Peters, KL., Pal, S., Sen, GC. (2004). Novel roles of TLR3 tyrosine phosphorylation and PI3 kinase in double-stranded RNA signaling. *Nat Struct Mol Biol, 11*, 1060-7. ↗

Garcia-Sastre, A., Chua, MA., Ng, SL., McWhirter, SM., Tenoever, BR., Maniatis, T. (2007). Multiple functions of the IKK-related kinase IKKepsilon in interferon-mediated antiviral immunity. *Science, 315*, 1274-8. ↗

Fitzgerald, KA., Rowe, DC., McWhirter, SM., Golenbock, DT., Maniatis, T., Rosains, J. (2004). IFN-regulatory factor 3-dependent gene expression is defective in Tbk1-deficient mouse embryonic fibroblasts. *Proc Natl Acad Sci U S A, 101*, 233-8. ↗

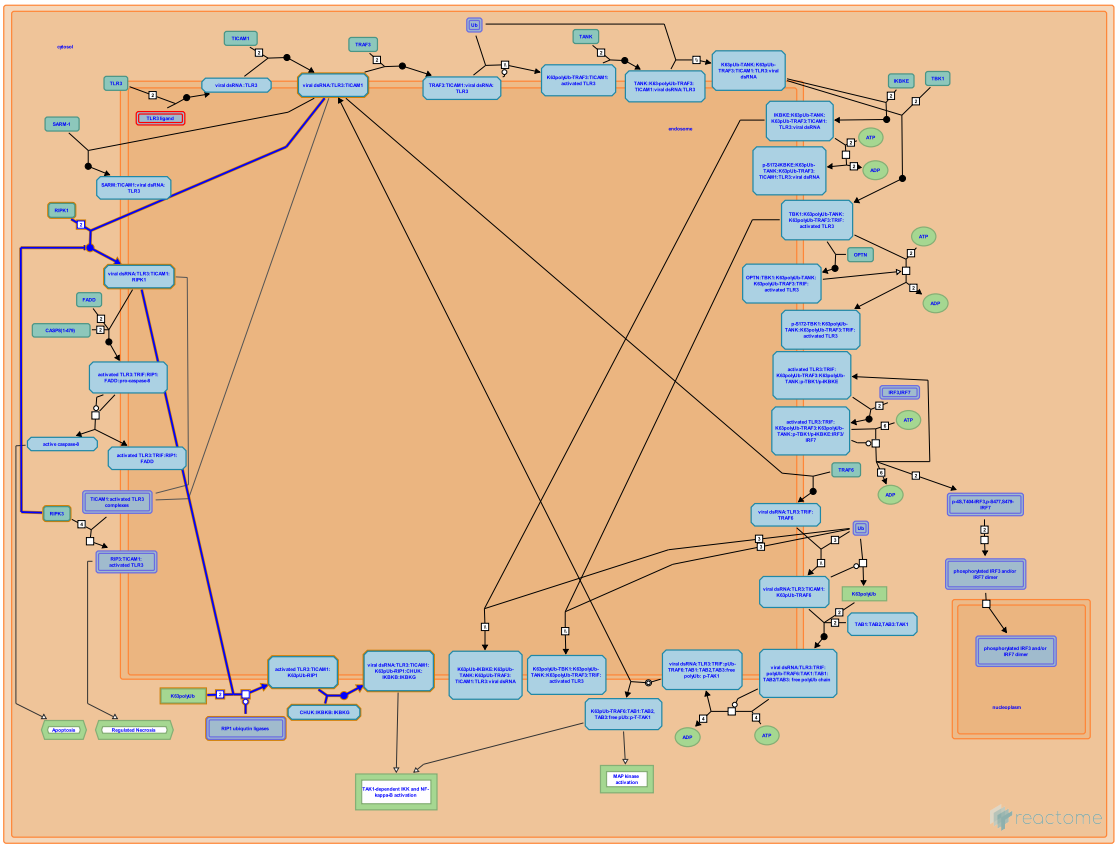
Editions

2010-06-01	Authored	Shamovsky, V.
2010-11-16	Edited	Shamovsky, V.
2010-11-30	Reviewed	Gillespie, ME.
2012-11-13	Reviewed	Fitzgerald, KA.
2014-05-16	Reviewed	Masci, A M.
2024-02-28	Reviewed	Munitić, I., Franjkić, T.

TICAM1, RIP1-mediated IKK complex recruitment ↗

Location: Toll Like Receptor 3 (TLR3) Cascade

Stable identifier: R-HSA-168927



Receptor-interacting protein 1 (RIP1) mediates the activation of interferon-alpha/beta via intermediate activation of IKK/TBK1 or NFkB pathways.

Literature references

Fitzgerald, KA., Cusson-Hermance, N., Khurana, S., Kelliher, MA., Lee, TH. (2005). Rip1 mediates the Trif-dependent toll-like receptor 3- and 4-induced NF-{kappa}B activation but does not contribute to interferon regulatory factor 3 activation. *J Biol Chem, 280*, 36560-6. ↗

Blancheteau, V., Meylan, E., Burns, K., Kelliher, M., Tschopp, J., Martinon, F. et al. (2004). RIP1 is an essential mediator of Toll-like receptor 3-induced NF-kappa B. *Nat Immunol, 5*, 503-7. ↗

Editions

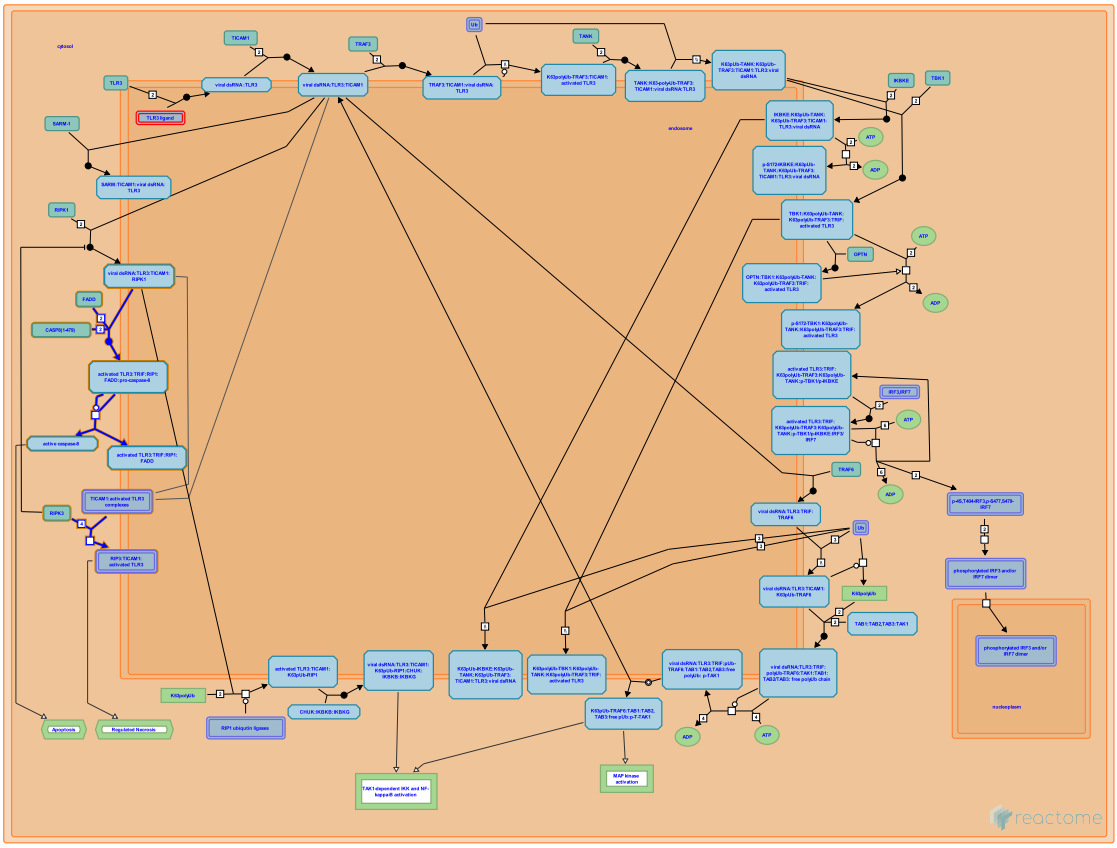
2005-11-10	Authored	Luo, F.
2006-04-24	Reviewed	Gay, NJ.
2009-09-29	Revised	Shamovsky, V.
2009-12-16	Edited	Shamovsky, V.
2012-11-13	Reviewed	Fitzgerald, KA.

TLR3-mediated TICAM1-dependent programmed cell death ↗

Location: Toll Like Receptor 3 (TLR3) Cascade

Stable identifier: R-HSA-9013957

Compartments: endosome membrane, cytosol



TLR3 and TLR4 trigger TRIF(TICAM1)-dependent programmed cell death in various human and mouse cells (Kalai M et al. 2002; Han KJ et al. 2004; Kaiser WJ and Offermann MK 2005; Estornes Y et al. 2012; He S et al. 2011). Apoptosis is a prevalent form of programmed cell death and is mediated by the activation of a set of caspases. In addition to apoptosis, TLR3/TLR4 activation induces RIP3-dependent necroptosis. These two programmed cell-death pathways may suppress each other. When the caspase activity is impaired or inhibited, certain cell types switch the apoptotic death program to necroptosis in response to various stimuli (TNF, Fas, viral infection and other stress stimuli) (Kalai M et al. 2002; Weber A et al. 2010; Feoktistova M et al. 2011, Tenev et al 2011).

Literature references

Pierrot, A., Salaun, B., Lalaoui, N., Jacquemin, G., Micheau, O., Renno, T. et al. (2012). dsRNA induces apoptosis through an atypical death complex associating TLR3 to caspase-8. *Cell Death Differ., 19*, 1482-94. ↗

Offermann, MK., Kaiser, WJ. (2005). Apoptosis induced by the toll-like receptor adaptor TRIF is dependent on its receptor interacting protein homotypic interaction motif. *J Immunol, 174*, 4942-52. ↗

Leverkus, M., Häcker, G., Kirejczyk, Z., Weber, A., Potthoff, S., Besch, R. (2010). Proapoptotic signalling through Toll-like receptor-3 involves TRIF-dependent activation of caspase-8 and is under the control of inhibitor of apoptosis proteins in melanoma cells. *Cell Death Differ., 17*, 942-51. ↗

Zachariou, A., Langlais, C., Darding, M., Tenev, T., Cain, K., Bianchi, K. et al. (2011). The Ripoptosome, a signaling platform that assembles in response to genotoxic stress and loss of IAPs. *Mol. Cell, 43*, 432-48. ↗

Zhang, J., Shu, HB., Han, KJ., Bin, LH., Su, X., Xu, LG. (2004). Mechanisms of the TRIF-induced interferon-stimulated response element and NF-kappaB activation and apoptosis pathways. *J. Biol. Chem., 279*, 15652-61. ↗

Editions

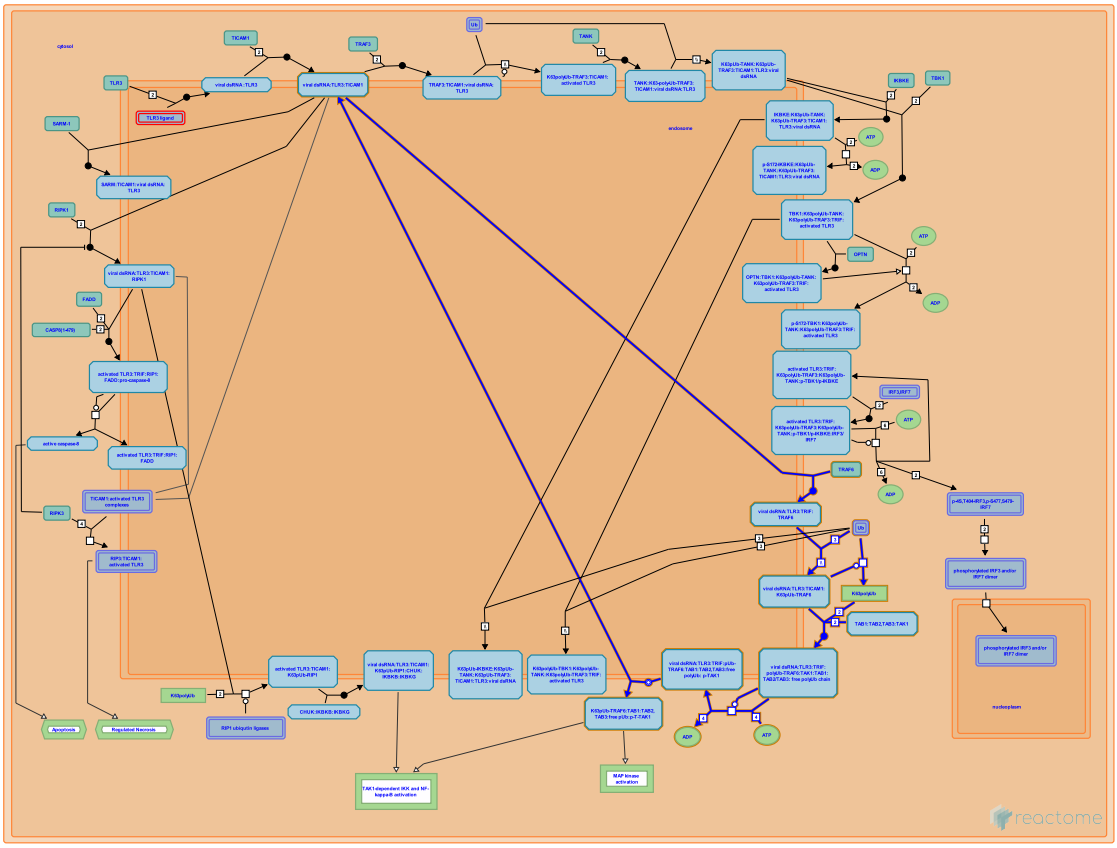
2012-05-15	Authored	Shamovsky, V.
2012-11-13	Reviewed	Fitzgerald, KA.
2012-11-19	Edited	Shamovsky, V.

TICAM1,TRAF6-dependent induction of TAK1 complex ↗

Location: Toll Like Receptor 3 (TLR3) Cascade

Stable identifier: R-HSA-9014325

Compartments: endosome membrane, cytosol



In human, together with ubiquitin-conjugating E2-type enzymes UBC13 and UEV1A (also known as UBE2V1), TRAF6 catalyses Lys63-linked ubiquitination. It is believed that auto polyubiquitination and oligomerization of TRAF6 is followed by binding the ubiquitin receptors of TAB2 or TAB3 (TAK1 binding protein 2 and 3), which stimulates phosphorylation and activation of TGF beta-activated kinase 1(TAK1).

TAK1 phosphorylates IKK alpha and IKK beta, which in turn phosphorylate NF-kB inhibitors - IkB and eventually results in IkB degradation and NF-kB translocation to the nucleus. Also TAK1 mediates JNK and p38 MAP kinases activation by phosphorylating MKK4/7 and MKK3/6 respectivly resulting in the activation of many transcription factors.

The role of TRAF6 is somewhat controversial and probably cell type specific. TRAF6 autoubiquitination was found to be dispensable for TRAF6 function to activate TAK1 pathway. These findings are consistent with the new mechanism of TRAF6-mediated NF-kB activation that was suggested by Xia et al. (2009). TRAF6 generates unanchored Lys63-linked polyubiquitin chains that bind to the regulatory subunits of TAK1 (TAB2 or TAB3) and IKK(NEMO), leading to the activation of the kinases.

Xia et al. (2009) demonstrated in vitro that unlike polyubiquitin chains covalently attached to TRAF6 or IRAK, TAB2 and NEMO-associated ubiquitin chains were found to be unanchored and susceptible to N-terminal ubiquitin cleavage. Only K63-linked polyubiquitin chains, but not monomeric ubiquitin, activated TAK1 in a dose-dependent manner. Optimal activation of the IKK complex was achieved using ubiquitin polymers containing both K48 and K63 linkages.

Furthermore, the authors proposed that the TAK1 complexes might be brougt in close proximity by binding several TAB2/3 to a single polyubiquitin chain to facilitate TAK1 kinase trans-phosphorylation. Alternativly, the possibility that polyUb binding promotes allosteric activation of TAK1 complex should be considered (Walsh et al 2008).

Literature references

Adhikari, A., Zeng, W., Chen, ZJ., Pineda, G., Sun, L., Chen, X. et al. (2009). Direct activation of protein kinases by unanchored polyubiquitin chains. *Nature.* ↗

Walsh, MC., Molnar, EE., Maurizio, PL., Choi, Y., Kim, GK. (2008). TRAF6 autoubiquitination-independent activation of the NFkappaB and MAPK pathways in response to IL-1 and RANKL. *PLoS One, 3*, e4064. ↗

Editions

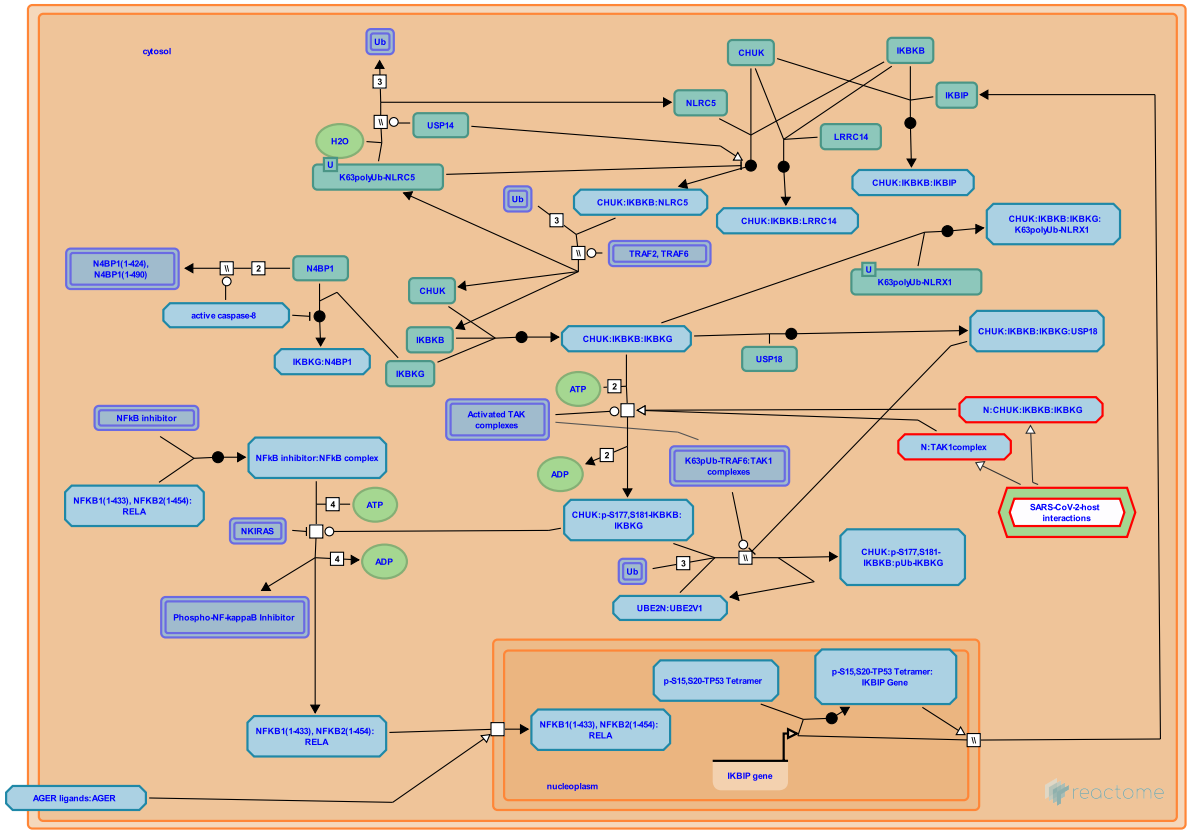
2010-06-01	Authored	Shamovsky, V.
2010-11-15	Edited	Shamovsky, V.
2010-11-30	Reviewed	Gillespie, ME.
2012-11-13	Reviewed	Fitzgerald, KA.

TAK1-dependent IKK and NF-kappa-B activation ↗

Location: Toll Like Receptor 3 (TLR3) Cascade

Stable identifier: R-HSA-445989

Compartments: nucleoplasm, cytosol



NF-kappa-B is sequestered in the cytoplasm in a complex with inhibitor of NF-kappa-B (IkB). Almost all NF-kappa-B activation pathways are mediated by IkB kinase (IKK), which phosphorylates IkB resulting in dissociation of NF-kappa-B from the complex. This allows translocation of NF-kappa-B to the nucleus where it regulates gene expression.

Literature references

Deng, L., Inoue, J., Akkaraju, GR., Hong, M., Wang, C., Chen, ZJ. (2001). TAK1 is a ubiquitin-dependent kinase of MKK and IKK. *Nature, 412*, 346-51. ↗

Kracht, M., Wolter, S., Resch, K., Dittrich-Breiholz, O., Wirth, D., Thiefes, A. et al. (2005). Simultaneous blockade of NFkappaB, JNK, and p38 MAPK by a kinase-inactive mutant of the protein kinase TAK1 sensitizes cells to apoptosis and affects a distinct spectrum of tumor necrosis factor [corrected] target genes. *J Biol Chem, 280*, 27728-41. ↗

Editions

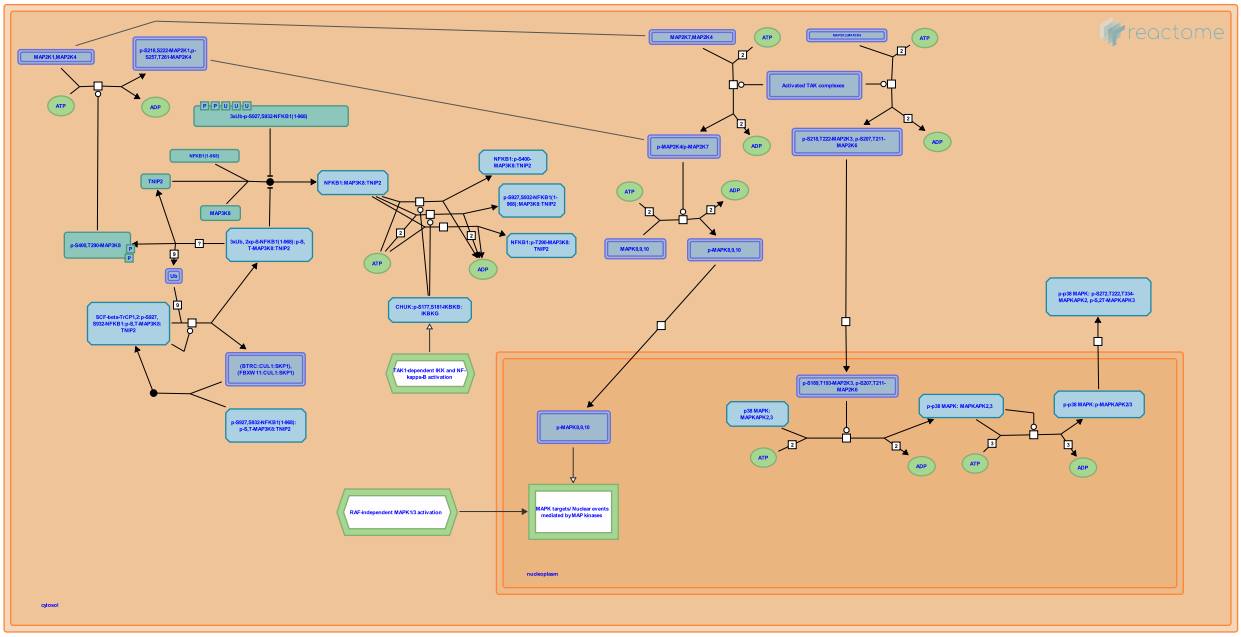
2009-12-16	Authored	Shamovsky, V.
2010-02-28	Reviewed	Gillespie, ME.
2011-08-12	Edited	Shamovsky, V.
2012-11-13	Reviewed	Fitzgerald, KA.
2012-11-16	Reviewed	Napetschnig, J.
2022-05-04	Reviewed	de Martin, R.

MAP kinase activation ↗

Location: Toll Like Receptor 3 (TLR3) Cascade

Stable identifier: R-HSA-450294

Compartments: nucleoplasm, cytosol



The mitogen activated protein kinase (MAPK) cascade, one of the most ancient and evolutionarily conserved signaling pathways, is involved in many processes of immune responses. The MAP kinases cascade transduces signals from the cell membrane to the nucleus in response to a wide range of stimuli (Chang and Karin, 2001; Johnson et al, 2002).

There are three major groups of MAP kinases

- the extracellular signal-regulated protein kinases ERK1/2,
- the p38 MAP kinase
- and the c-Jun NH-terminal kinases JNK.

ERK1 and ERK2 are activated in response to growth stimuli. Both JNKs and p38-MAPK are activated in response to a variety of cellular and environmental stresses. The MAP kinases are activated by dual phosphorylation of Thr and Tyr within the tripeptide motif Thr-Xaa-Tyr. The sequence of this tripeptide motif is different in each group of MAP kinases: ERK (Thr-Glu-Tyr); p38 (Thr-Gly-Tyr); and JNK (Thr-Pro-Tyr).

MAPK activation is mediated by signal transduction in the conserved three-tiered kinase cascade: MAPKKKK (MAP4K or MKKKK or MAPKKK Kinase) activates the MAPKKK. The MAPKKKs then phosphorylates a dual-specificity protein kinase MAPKK, which in turn phosphorylates the MAPK.

The dual specificity MAP kinase kinases (MAPKK or MKK) differ for each group of MAPK. The ERK MAP kinases are activated by the MKK1 and MKK2; the p38 MAP kinases are activated by MKK3, MKK4, and MKK6; and the JNK pathway is activated by MKK4 and MKK7. The ability of MAP kinase kinases (MKKs, or MEKs) to recognize their cognate MAPKs is facilitated by a short docking motif (the D-site) in the MKK N-terminus, which binds to a complementary region on the MAPK. MAPKs then recognize many of their targets using the same strategy, because many MAPK substrates also contain D-sites.

The upstream signaling events in the TLR cascade that initiate and mediate the ERK signaling pathway remain unclear.

Literature references

Chang, L., Karin, M. (2001). Mammalian MAP kinase signalling cascades. *Nature, 410*, 37-40. ↗

Davis, RJ., Flavell, RA., Dong, C. (2002). MAP kinases in the immune response. *Annu Rev Immunol, 20*, 55-72. ↗

Gerondakis, S., Banerjee, A. (2007). Coordinating TLR-activated signaling pathways in cells of the immune system. *Immunol Cell Biol, 85*, 420-4. ↗

Bardwell, L., Bardwell, AJ., Frankson, E. (2009). Selectivity of docking sites in MAPK kinases. *J Biol Chem, 284*, 13165-73. ↗

Editions

2009-12-16	Authored	Shamovsky, V.
2010-02-28	Reviewed	Gillespie, ME.
2010-02-28	Edited	Shamovsky, V.

Table of Contents