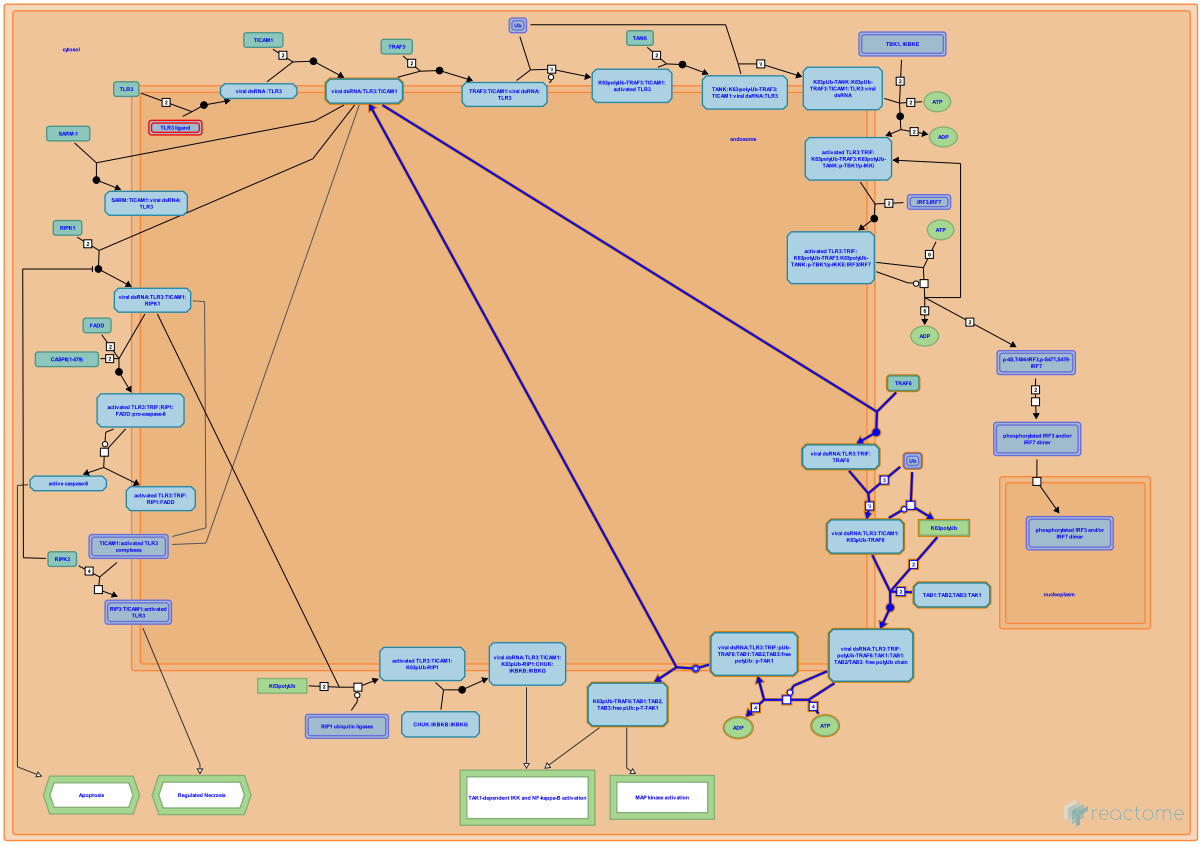
TICAM1,TRAF6-dependent induction of TAK1 complex



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08/08/2022

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. ↗

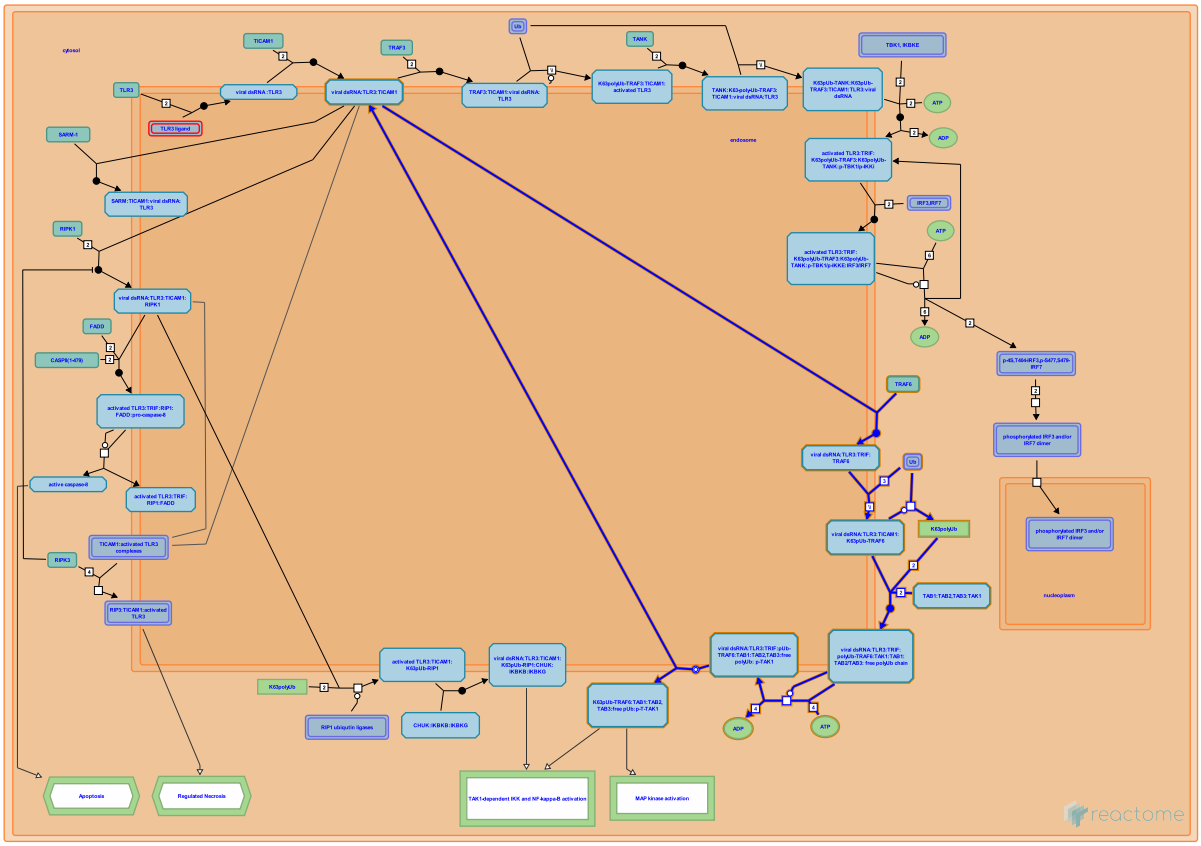
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

TICAM1,TRAF6-dependent induction of TAK1 complex ↗

Stable identifier: R-HSA-9014325

Compartments: cytosol, endosome membrane



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. Al-

ternativly, 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.

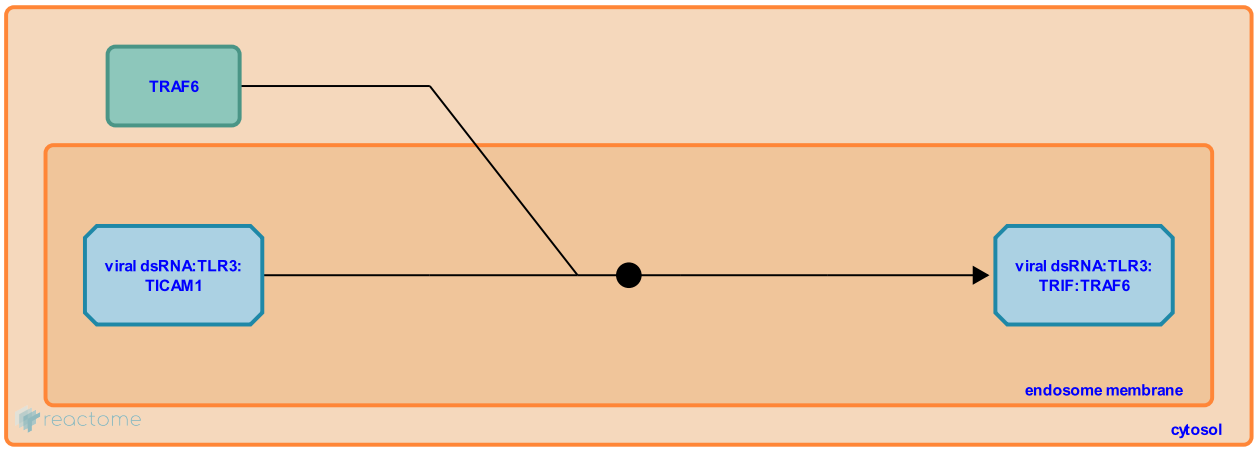
Viral dsRNA:TLR3:TICAM1 complex recruits TRAF6 ↗

Location: TICAM1,TRAF6-dependent induction of TAK1 complex

Stable identifier: R-HSA-177694

Type: binding

Compartments: endosome membrane, cytosol



TRAF6 is recruited to the N-terminal domain of TICAM1 and this event is followed by auto polyubiquitination and oligomerization of TRAF6.

Followed by: Auto ubiqitination of TRAF6 bound to viral dsRNS:TLR3:TICAM1 complex

Literature references

Matsumoto, M., Hatakeyama, S., Oshiumi, H., Funami, K., Seya, T., Sasai, M. et al. (2010). Direct binding of TRAF2 and TRAF6 to TICAM-1/TRIF adaptor participates in activation of the Toll-like receptor 3/4 pathway. *Mol Immunol* . ↗

Deng, L., Pickart, C., Spencer, E., You, J., Wang, C., Slaughter, C. et al. (2000). Activation of the IkappaB kinase complex by TRAF6 requires a dimeric ubiquitin-conjugating enzyme complex and a unique polyubiquitin chain. *Cell, 103*, 351-61. ↗

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

2009-09-29	Revised	Shamovsky, V.
2009-12-16	Authored, Edited	Shamovsky, V.
2012-11-13	Reviewed	Fitzgerald, KA.

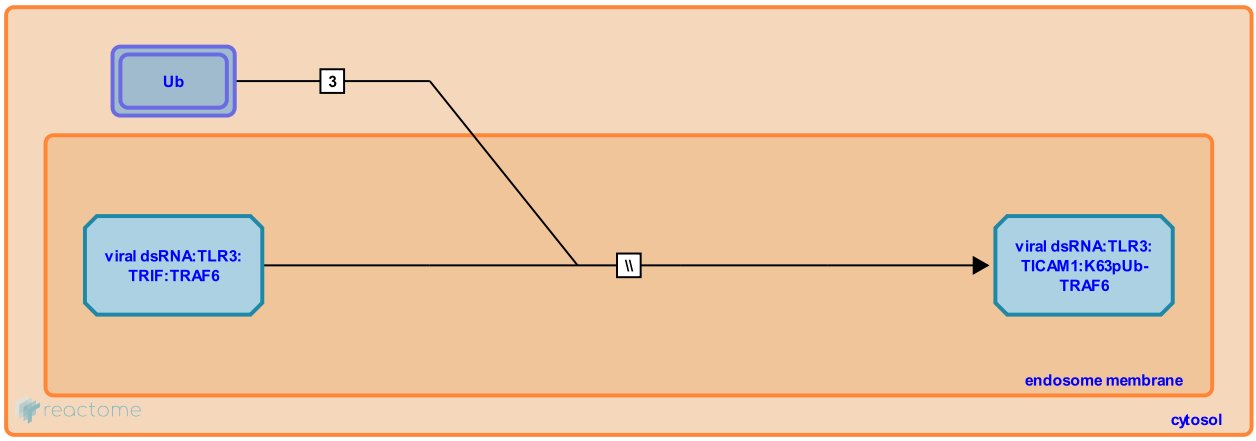
Auto ubiqitination of TRAF6 bound to viral dsRNS:TLR3:TICAM1 complex ↗

Location: TICAM1,TRAF6-dependent induction of TAK1 complex

Stable identifier: R-HSA-450259

Type: omitted

Compartments: endosome membrane, cytosol



TRAF6 possesses ubiquitin ligase activity and undergoes K-63-linked auto-ubiquitination. In the first step, ubiquitin is activated by an E1 ubiquitin activating enzyme. The activated ubiquitin is transferred to a E2 conjugating enzyme (a heterodimer of proteins Ubc13 and Uev1A) forming the E2-Ub thioester. Finally, in the presence of ubiquitin-protein ligase E3 (TRAF6, a RING-domain E3), ubiquitin is attached to the target protein (TRAF6 on residue Lysine 124) through an isopeptide bond between the C-terminus of ubiquitin and the epsilon-amino group of a lysine residue in the target protein. In contrast to K-48-linked ubiquitination that leads to the proteosomal degradation of the target protein, K-63-linked polyubiquitin chains act as a scaffold to assemble protein kinase complexes and mediate their activation through proteosome-independent mechanisms. This K63 polyubiquitinated TRAF6 activates the TAK1 kinase complex.

Preceded by: Viral dsRNA:TLR3:TICAM1 complex recruits TRAF6

Followed by: Activated TRAF6 synthesizes unanchored polyubiquitin chains upon TLR3 stimulation

Literature references

Lamothe, B., Wu, H., Darnay, BG., Besse, A., Campos, AD., Webster, WK. (2007). Site-specific Lys-63-linked tumor necrosis factor receptor-associated factor 6 auto-ubiquitination is a critical determinant of I kappa B kinase activation. *J Biol Chem, 282*, 4102-12. ↗

Editions

2009-12-16	Authored	Shamovsky, V.
2010-02-28	Edited	Shamovsky, V.
2010-03-02	Reviewed	Gillespie, ME.
2012-11-13	Reviewed	Fitzgerald, KA.

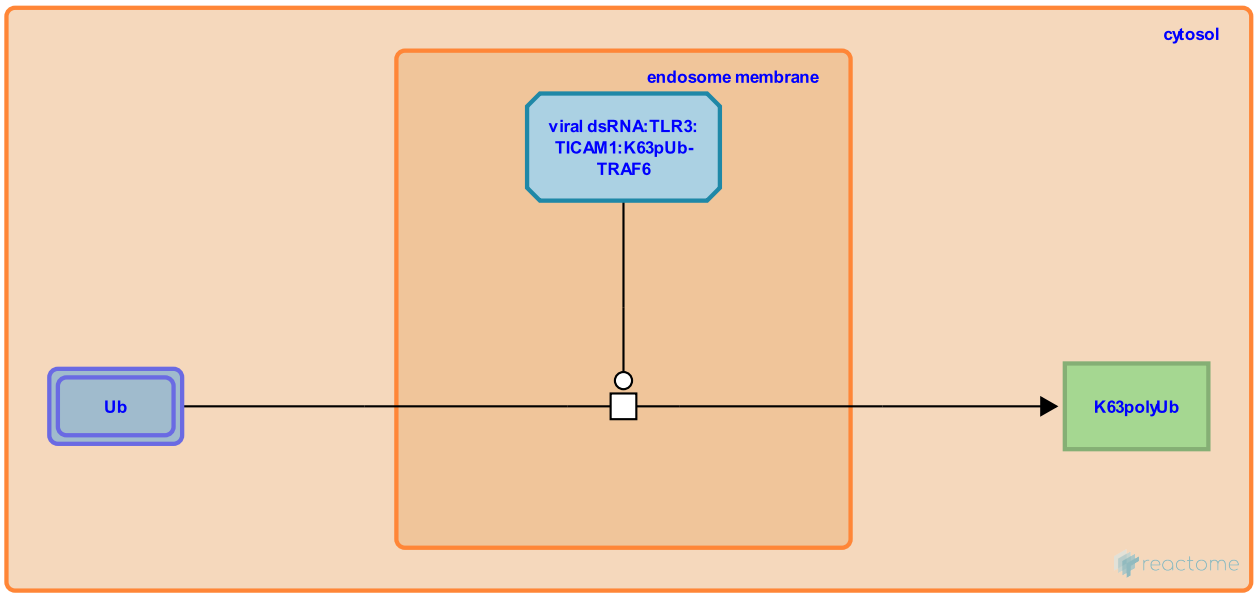
Activated TRAF6 synthesizes unanchored polyubiquitin chains upon TLR3 stimulation ↗

Location: TICAM1,TRAF6-dependent induction of TAK1 complex

Stable identifier: R-HSA-9628444

Type: transition

Compartments: endosome membrane, cytosol



E3 ubiquitin ligase TRAF6 generates free K63 -linked polyubiquitin chains that non-covalently associate with ubiquitin receptors of TAB2/TAB3 regulatory proteins of the TAK1 complex, leading to the activation of the TAK1 kinase.

Preceded by: Auto ubiqitination of TRAF6 bound to viral dsRNS:TLR3:TICAM1 complex

Followed by: Activated TLR3:TRIF:K63pUb-TRAF6 recruits TAK1complex

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*. ↗

Editions

2009-12-16	Authored	Shamovsky, V.
2010-02-28	Edited	Shamovsky, V.
2010-03-02	Reviewed	Gillespie, ME.

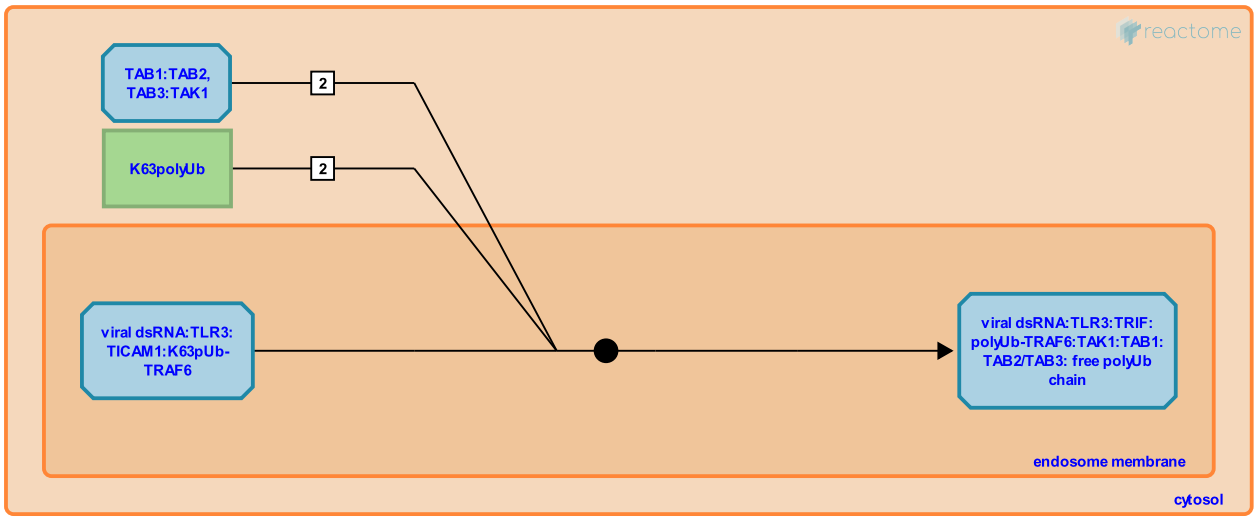
Activated TLR3:TRIF:K63pUb-TRAF6 recruits TAK1complex ↗

Location: TICAM1,TRAF6-dependent induction of TAK1 complex

Stable identifier: R-HSA-177690

Type: binding

Compartments: endosome membrane, cytosol



TAK1-binding protein 2 (TAB2) and/or TAB3, as part of a complex that also contains TAK1 and TAB1, binds polyubiquitinated TRAF6. The TAB2 and TAB3 regulatory subunits of the TAK1 complex contain C-terminal Npl4 zinc finger (NZF) motifs that recognize with Lys63-pUb chains (Kanayama et al. 2004). The recognition mechanism is specific for Lys63-linked ubiquitin chains [Kulathu Y et al 2009]. TAK1 can be activated by unattached Lys63-polyubiquitinated chains when TRAF6 has no detectable polyubiquitination (Xia et al. 2009) and thus the synthesis of these chains by TRAF6 may be the signal transduction mechanism.This binding leads to autophosphorylation and activation of TAK1.

Preceded by: Activated TRAF6 synthesizes unanchored polyubiquitin chains upon TLR3 stimulation

Followed by: Activation of recruited TAK1 within the activated TLR3 complex

Literature references

Jiang, Z., Nie, H., Li, X., Williams, BR., Zamanian-Daryoush, M., Silva, AM. (2003). Poly(I-C)-induced Toll-like receptor 3 (TLR3)-mediated activation of NFkappa B and MAP kinase is through an interleukin-1 receptor-associated kinase (IRAK)-independent pathway employing the signaling components TLR3-TRAF6-TAK1-TAB2-PKR. *J Biol Chem, 278*, 16713-9. ↗

Xu, M., Adhikari, A., Chen, ZJ. (2007). Ubiquitin-mediated activation of TAK1 and IKK. *Oncogene, 26*, 3214-26. ↗

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*. ↗

Deng, L., Seth, RB., Kanayama, A., Shaito, A., Hong, M., Chiu, YH. et al. (2004). TAB2 and TAB3 activate the NF-kappaB pathway through binding to polyubiquitin chains. *Mol Cell, 15*, 535-48. ↗

Editions

2006-04-24	Reviewed	Gay, NJ.
2009-12-16	Authored, Edited, Revised	Shamovsky, V.
2012-11-13	Reviewed	Fitzgerald, KA.

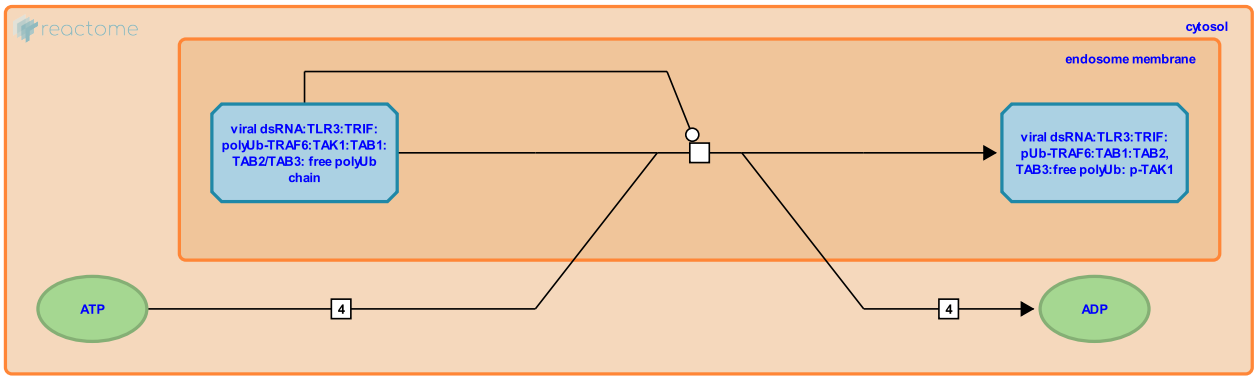
Activation of recruited TAK1 within the activated TLR3 complex ↗

Location: TICAM1,TRAF6-dependent induction of TAK1 complex

Stable identifier: R-HSA-177692

Type: transition

Compartments: endosome membrane, cytosol



TAK1 complex consists of transforming growth factor-beta (TGFB)-activated kinase (TAK1) and TAK1-binding protein 1 (TAB1), TAB2 and TAB3. TAK1 requires TAB1 for its kinase activity (Shibuya et al. 1996, Sakurai et al. 2000). TAB1 promotes TAK1 autophosphorylation at the kinase activation lobe, probably through an allosteric mechanism (Brown et al. 2005, Ono et al. 2001). The TAK1 complex is regulated by polyubiquitination. Binding of TAB2 and TAB3 to Lys63-linked polyubiquitin chains leads to the activation of TAK1 by an uncertain mechanism. Binding of multiple TAK1 complexes to the same polyubiquitin chain may promote oligomerization of TAK1, facilitating TAK1 autophosphorylation and subsequent activation of its kinase activity (Kishimoto et al. 2000). The binding of TAB2/3 to polyubiquitinated TRAF6 may facilitate polyubiquitination of TAB2/3 by TRAF6 (Ishitani et al. 2003), which might result in conformational changes within the TAK1 complex that lead to TAK1 activation. Another possibility is that TAB2/3 may recruit the IKK complex by binding to ubiquitinated NEMO; polyubiquitin chains may function as a scaffold for higher order signaling complexes that allow interaction between TAK1 and IKK (Kanayama et al. 2004).

Preceded by: Activated TLR3:TRIF:K63pUb-TRAF6 recruits TAK1complex

Followed by: Phosphorylated TAK1 dissociates from the TLR3 receptor complex

Literature references

Jiang, Z., Nie, H., Li, X., Williams, BR., Zamanian-Daryoush, M., Silva, AM. (2003). Poly(I-C)-induced Toll-like receptor 3 (TLR3)-mediated activation of NFkappa B and MAP kinase is through an interleukin-1 receptor-associated kinase (IRAK)-independent pathway employing the signaling components TLR3-TRAF6-TAK1-TAB2-PKR. *J Biol Chem, 278*, 16713-9. ↗

Xu, M., Adhikari, A., Chen, ZJ. (2007). Ubiquitin-mediated activation of TAK1 and IKK. *Oncogene, 26*, 3214-26. ↗

Kawai, T., Takeuchi, O., Sanjo, H., Takeda, K., Ninomiya-Tsuji, J., Sato, S. et al. (2005). Essential function for the kinase TAK1 in innate and adaptive immune responses. *Nat Immunol, 6*, 1087-95. ↗

Shim, JH., Steckel, M., Xiao, C., Yamada, G., Ghosh, S., Paschal, AE. et al. (2005). TAK1, but not TAB1 or TAB2, plays an essential role in multiple signaling pathways in vivo. *Genes Dev, 19*, 2668-81. ↗

Kishimoto, K., Ninomiya-Tsuji, J., Matsumoto, K. (2000). TAK1 mitogen-activated protein kinase kinase kinase is activated by autophosphorylation within its activation loop. *J Biol Chem, 275*, 7359-64. ↗

Editions

2006-04-24	Reviewed	Gay, NJ.
2009-12-16	Authored, Edited, Revised	Shamovsky, V.
2012-11-13	Reviewed	Fitzgerald, KA.

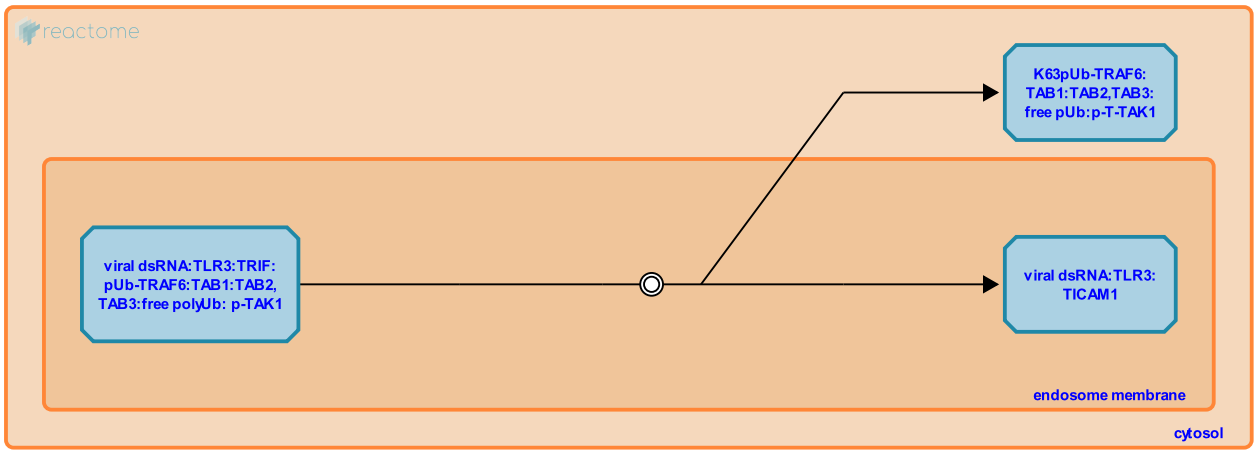
Phosphorylated TAK1 dissociates from the TLR3 receptor complex ↗

Location: TICAM1,TRAF6-dependent induction of TAK1 complex

Stable identifier: R-HSA-847070

Type: dissociation

Compartments: endosome membrane, cytosol



Phosphorylated TAK1 complexed with TRAF6-TAB1-TAB2/TAB3 leaves the activated TLR4 complex and translocates to the cytosol

Preceded by: Activation of recruited TAK1 within the activated TLR3 complex

Literature references

Jiang, Z., Nie, H., Li, X., Williams, BR., Zamanian-Daryoush, M., Silva, AM. (2003). Poly(I-C)-induced Toll-like receptor 3 (TLR3)-mediated activation of NFkappa B and MAP kinase is through an interleukin-1 receptor-associated kinase (IRAK)-independent pathway employing the signaling components TLR3-TRAF6-TAK1-TAB2-PKR. *J Biol Chem, 278*, 16713-9. ↗

Jiang, Z., Ninomiya-Tsuji, J., Li, X., Matsumoto, K., Qian, Y. (2002). Interleukin-1 (IL-1) receptor-associated kinase-dependent IL-1-induced signaling complexes phosphorylate TAK1 and TAB2 at the plasma membrane and activate TAK1 in the cytosol. *Mol Cell Biol, 22*, 7158-67. ↗

Editions

2010-05-21	Authored, Edited	Shamovsky, V.
2010-05-28	Reviewed	Gillespie, ME.
2012-11-13	Reviewed	Fitzgerald, KA.

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