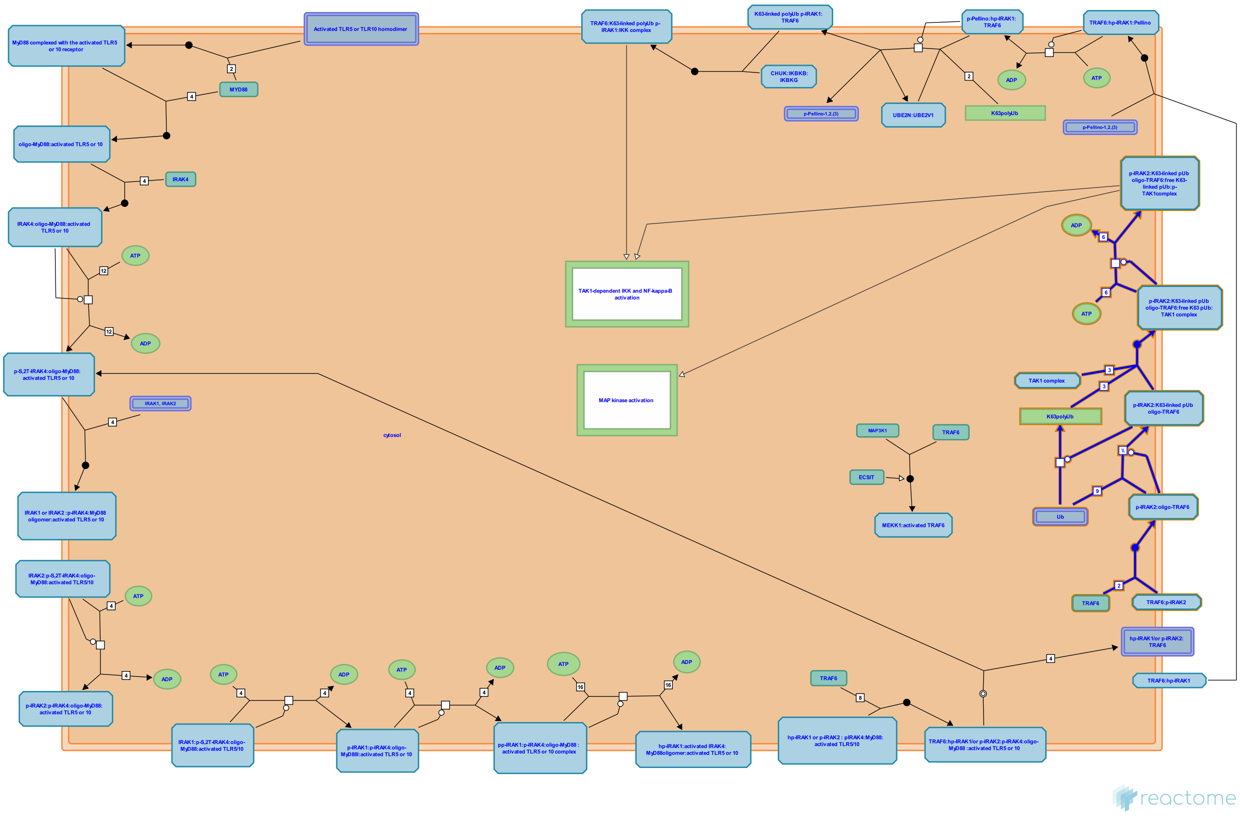
reactome

IRAK2 mediated activation of TAK1 complex



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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]().

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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.

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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. ↗

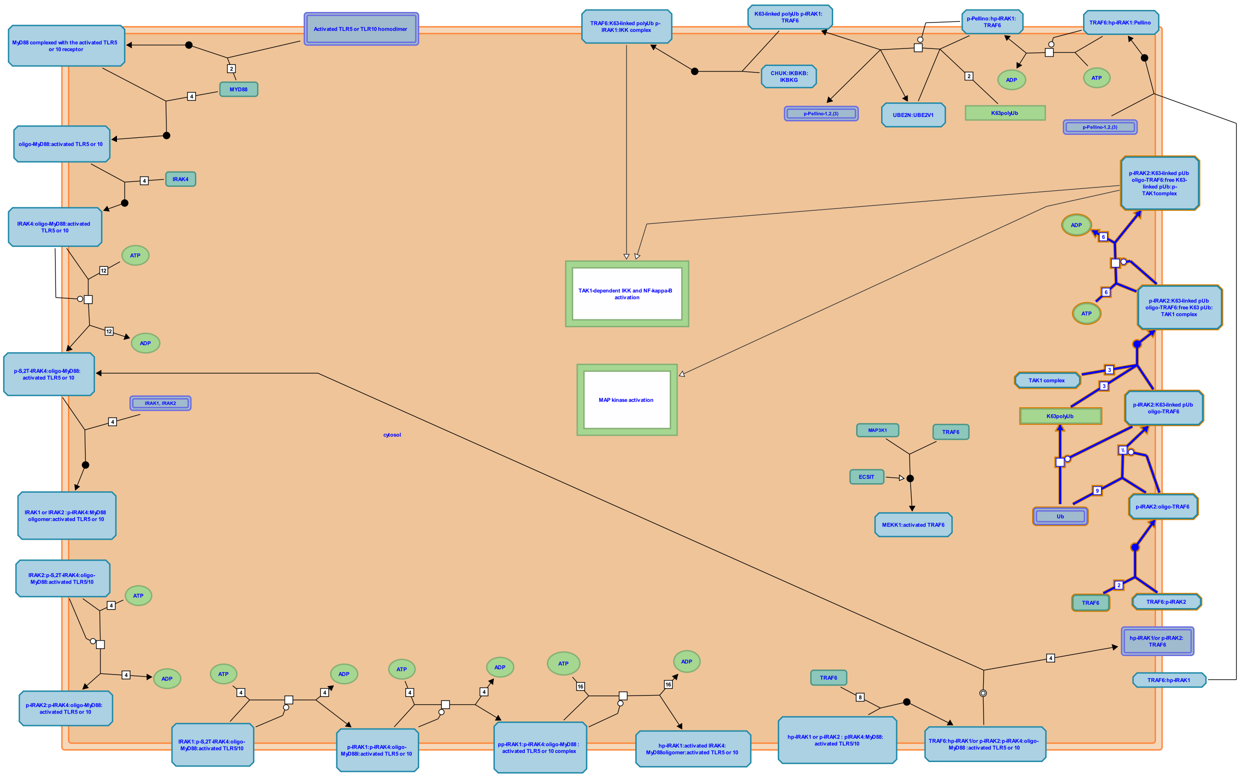
Reactome database release: 88

This document contains 1 pathway and 5 reactions (see Table of Contents)

IRAK2 mediated activation of TAK1 complex ↗

Stable identifier: R-HSA-937042

Compartments: cytosol, plasma membrane



Although IRAK-1 was originally thought to be a key mediator of TRAF6 activation in the IL1R/TLR signaling (Dong W et al. 2006), recent studies showed that IRAK-2, but not IRAK-1, led to TRAF6 polyubiquitination (Keating SE et al 2007). IRAK-2 loss-of-function mutants, with mutated TRAF6-binding motifs, could no longer activate NF-kB and could no longer stimulate TRAF-6 ubiquitination (Keating SE et al 2007). Furthermore, the proxyvirus protein A52 - an inhibitor of all IL-1R/TLR pathways to NF-kB activation, was found to interact with both IRAK-2 and TRAF6, but not IRAK-1. Further work showed that A52 inhibits IRAK-2 functions, whereas association with TRAF6 results in A52-induced MAPK activation. The strong inhibition effect of A52 was also observed on the TLR3-NFkB axis and this observation led to the discovery that IRAK-2 is recruited to TLR3 to activate NF-kB (Keating SE et al 2007). Thus, A52 possibly inhibits MyD88-independent TLR3 pathways to NF-kB via targeting IRAK-2 as it does for other IL-1R/TLR pathways, although it remains unclear how IRAK-2 is involved in TLR3 signaling.

IRAK-2 was shown to have two TRAF6 binding motifs that are responsible for initiating TRAF6 signaling transduction (Ye H et al 2002).

Literature references

Szymak, J., Keating, SE., Bowie, AG., Flannery, SM. (2011). Human interleukin-1 receptor-associated kinase-2 is essential for Toll-like receptor-mediated transcriptional and post-transcriptional regulation of tumor necrosis factor alpha. *J. Biol. Chem., 286*, 23688-97. ↗

Maloney, GM., Bowie, AG., Keating, SE., Moran, EM. (2007). IRAK-2 participates in multiple toll-like receptor signaling pathways to NFkappaB via activation of TRAF6 ubiquitination. *J Biol Chem, 282*, 33435-43. ↗

Zou, T., Liu, Z., Liu, Y., Xiao, H., Peng, J., Chen, L. et al. (2006). The IRAK-1-BCL10-MALT1-TRAF6-TAK1 cascade mediates signaling to NF-kappaB from Toll-like receptor 4. *J Biol Chem, 281*, 26029-40. ↗

Vologodskaia, M., Kobayashi, T., Wu, H., Cirilli, M., Lamothe, B., Arron, JR. et al. (2002). Distinct molecular mechanism for initiating TRAF6 signalling. *Nature, 418*, 443-7. ↗

Editions

2010-06-01	Authored	Shamovsky, V.
2010-11-30	Reviewed	Gillespie, ME.
2012-11-06	Edited	Shamovsky, V.
2012-11-16	Reviewed	Napetschnig, J.

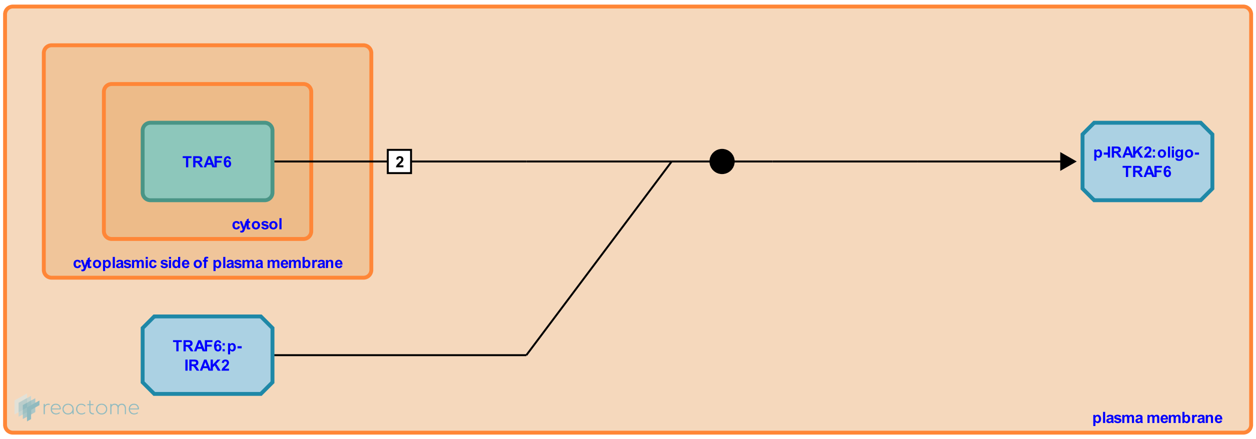
IRAK2 induces TRAF6 oligomerization ↗

Location: IRAK2 mediated activation of TAK1 complex

Stable identifier: R-HSA-936963

Type: binding

Compartments: plasma membrane, cytosol



The mechanism by which IRAK-2 induces TRAF6 E3 ligase activity remains to be deciphered, but one possibility is that IRAK-2 may direct TRAF6 oligomerization.

Followed by: Auto ubiquitination of oligo-TRAF6 bound to p-IRAK2

Literature references

Maloney, GM., Bowie, AG., Keating, SE., Moran, EM. (2007). IRAK-2 participates in multiple toll-like receptor signaling pathways to NFkappaB via activation of TRAF6 ubiquitination. *J Biol Chem, 282*, 33435-43. ↗

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2012-11-16	Reviewed	Napetschnig, J.

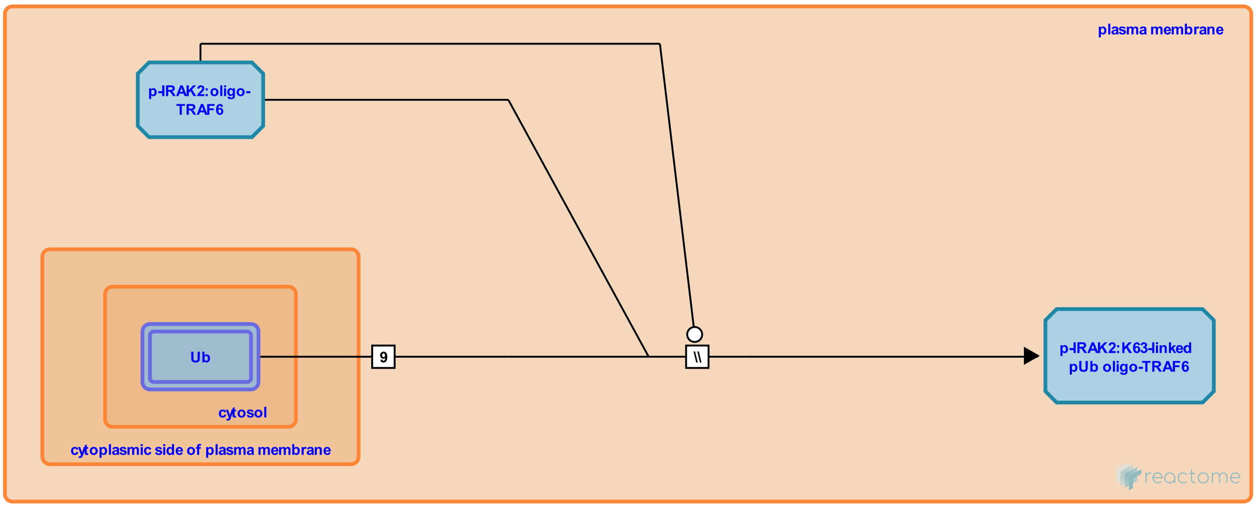
Auto ubiquitination of oligo-TRAF6 bound to p-IRAK2 ↗

Location: IRAK2 mediated activation of TAK1 complex

Stable identifier: R-HSA-936942

Type: omitted

Compartments: plasma membrane, cytosol



TRAF6 possesses ubiquitin ligase activity and undergoes K-63-linked auto-ubiquitination after its oligomerization. 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: IRAK2 induces TRAF6 oligomerization

Followed by: Activated TRAF6 synthesizes unanchored polyubiquitin chains, Activated TRAF6:p-IRAK2 interacts with TAK1 complex

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. ↗

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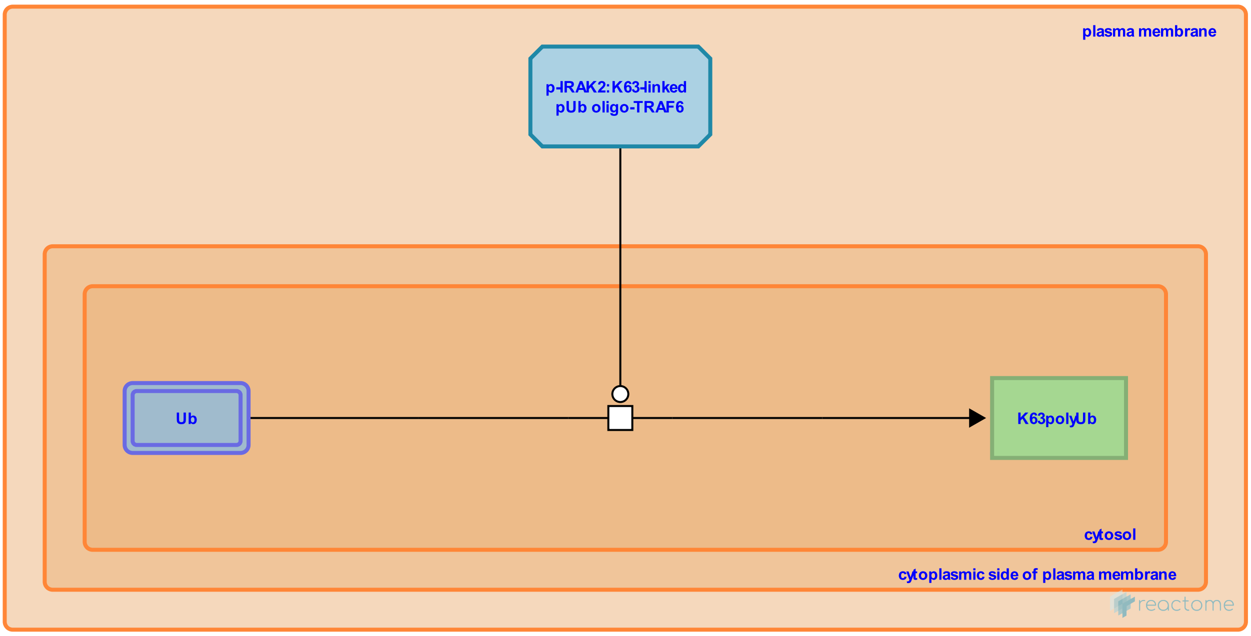
Activated TRAF6 synthesizes unanchored polyubiquitin chains ↗

Location: IRAK2 mediated activation of TAK1 complex

Stable identifier: R-HSA-936986

Type: transition

Compartments: cytosol



Polyubiquitinated TRAF6 (as E3 ubiquitin ligase) 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 ubiquitination of oligo-TRAF6 bound to p-IRAK2

Followed by: Activated TRAF6:p-IRAK2 interacts with TAK1 complex

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*. ↗

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2012-11-13	Reviewed	Fitzgerald, KA.
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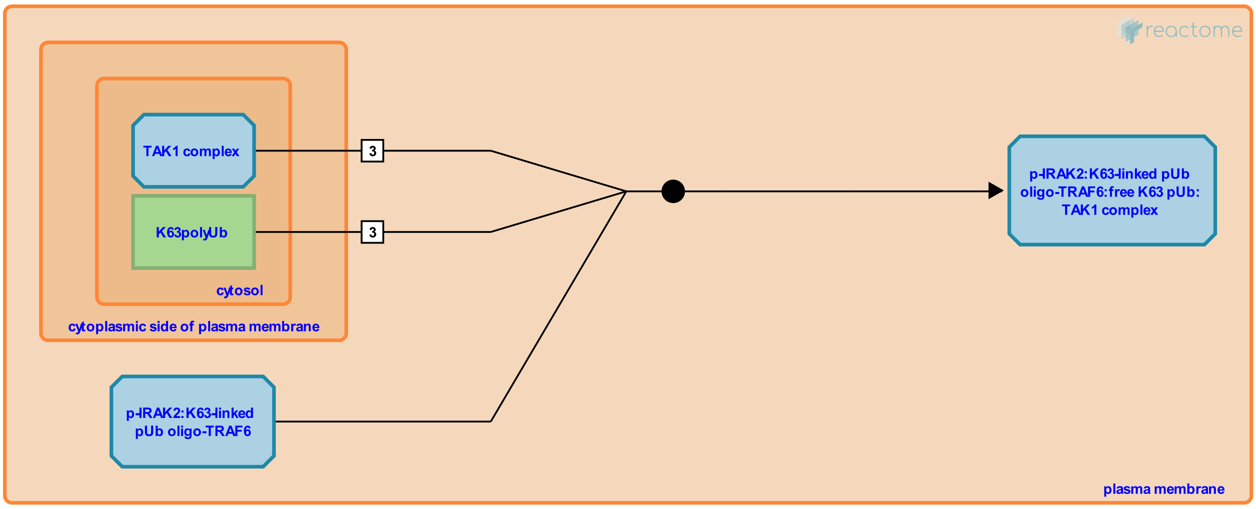
Activated TRAF6:p-IRAK2 interacts with TAK1 complex ↗

Location: IRAK2 mediated activation of TAK1 complex

Stable identifier: R-HSA-936960

Type: binding

Compartments: plasma 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.

As a de-ubiquitinating/de-ISGylating enzyme, severe acute respiratory syndrome coronavirus type 1 (SARS-CoV-1) 1a-encoded papain-like protease (PLPro or nsp3) antagonizes the host type I interferon (IFN) response by removing Lys63-linked ubiquitin chains of TRAF3 and TRAF6 (Li SW et al. 2016).

Preceded by: Activated TRAF6 synthesizes unanchored polyubiquitin chains, Auto ubiquitination of oligo-TRAF6 bound to p-IRAK2

Followed by: Auto phosphorylation of TAK1 bound to p-IRAK2:pUb oligo-TRAF6: free K63 pUb:TAB1:TAB2/TAB3

Literature references

Kishida, S., Shibuya, H., Takaesu, G., Ninomiya-Tsuji, J., Matsumoto, K., Yamaguchi, K. et al. (2000). TAB2, a novel adaptor protein, mediates activation of TAK1 MAPKKK by linking TAK1 to TRAF6 in the IL-1 signal transduction pathway. *Mol Cell, 5*, 649-58. ↗

Bremm, A., Kulathu, Y., Hofmann, K., Komander, D., Akutsu, M. (2009). Two-sided ubiquitin binding explains specificity of the TAB2 NZF domain. *Nat. Struct. Mol. Biol., 16*, 1328-30. ↗

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. ↗

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2012-11-16	Reviewed	Napetschnig, J.

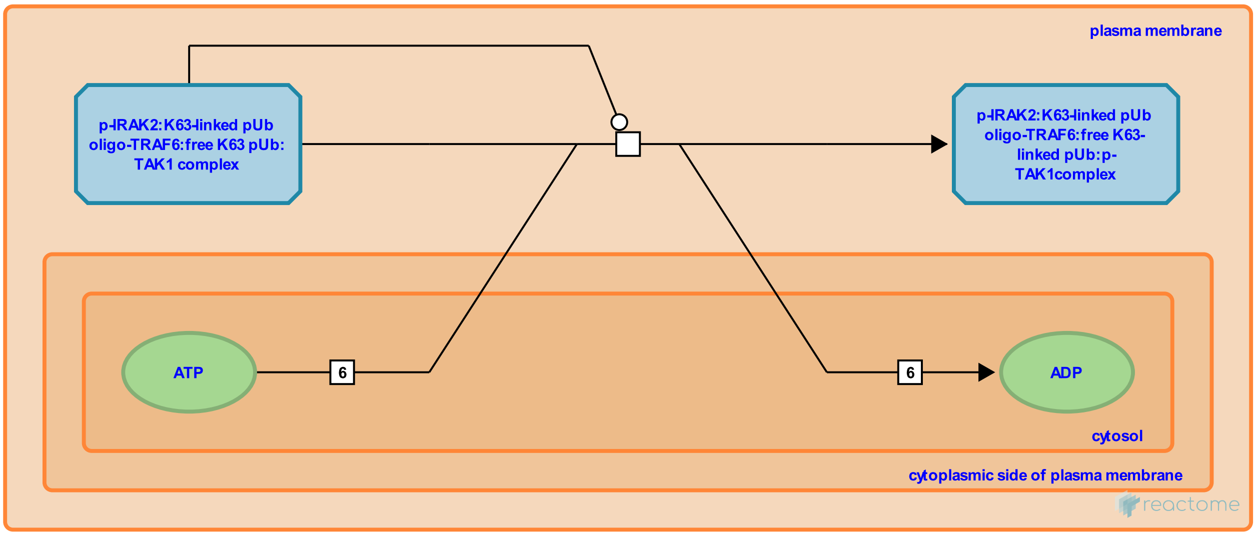
Auto phosphorylation of TAK1 bound to p-IRAK2:pUb oligo-TRAF6: free K63 pUb:TAB1:TAB2/TAB3 ↗

Location: IRAK2 mediated activation of TAK1 complex

Stable identifier: R-HSA-936991

Type: transition

Compartments: plasma membrane, cytosol



The 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 TRAF6:p-IRAK2 interacts with TAK1 complex

Literature references

Sugita, T., Sakurai, H., Mizukami, J., Miyoshi, H. (2000). Phosphorylation-dependent activation of TAK1 mitogen-activated protein kinase kinase kinase by TAB1. *FEBS Lett., 474*, 141-5. ↗

Ohtomo, T., Suzuki, M., Hisamoto, N., Sugamata, Y., Ono, K., Sato, S. et al. (2001). An evolutionarily conserved motif in the TAB1 C-terminal region is necessary for interaction with and activation of TAK1 MAPKKK. *J. Biol. Chem., 276*, 24396-400. ↗

Shibuya, H., Shirakabe, K., Ueno, N., Nishida, E., Matsumoto, K., Gotoh, Y. et al. (1996). TAB1: an activator of the TAK1 MAPKKK in TGF-beta signal transduction. *Science, 272*, 1179-82. ↗

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. ↗

Dunster, NJ., Brown, K., Vial, SC., Dedi, N., Cheetham, GM., Long, JM. (2005). Structural basis for the interaction of TAK1 kinase with its activating protein TAB1. *J. Mol. Biol., 354*, 1013-20. ↗

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