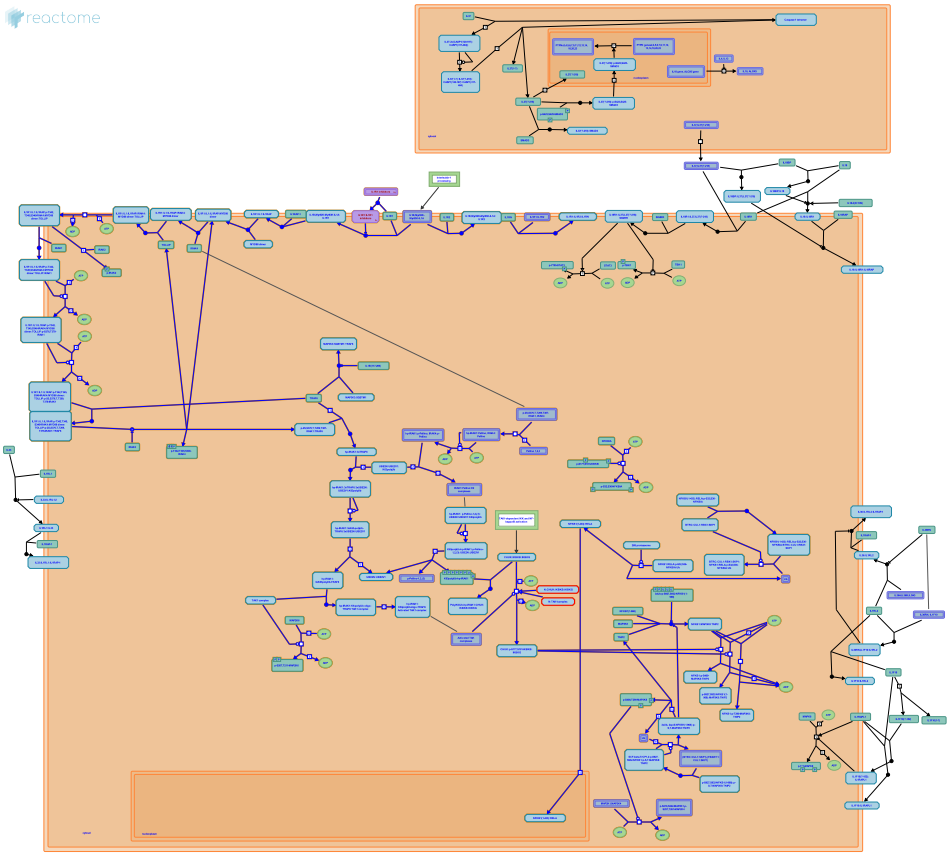
Interleukin-1 signaling



DeCicco-Skinner, KL., Fitzgerald, KA., Garapati, P V., Gillespie, ME., Jassal, B., Jupe, S., Kufer, TA., Luo, F., Messina, F., Napetschnig, J., Niarakis, A., Pinteaux, E., Ray, KP., Rittinger, K., Roncagalli, R., Shamovsky, V., Shoichet, BK., Wong, E., de Martin, R.

European Bioinformatics Institute, New York University Langone Medical Center, Ontario Institute for Cancer Research, Oregon Health and Science University.

14/05/2024

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.

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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. ↗

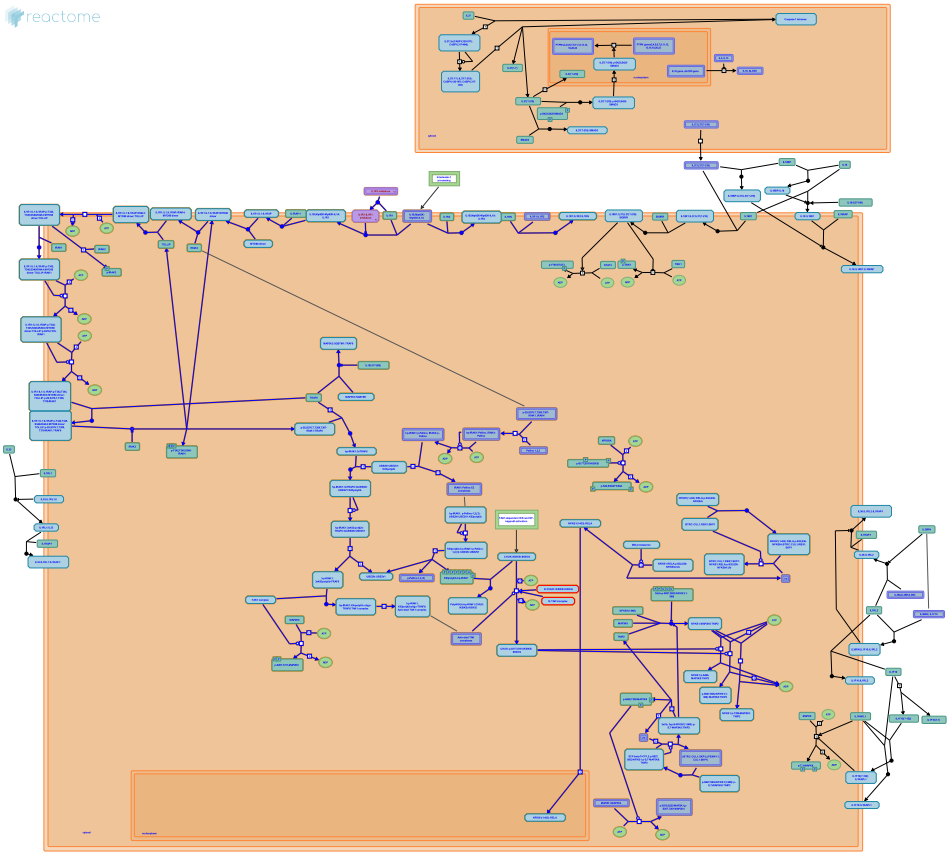
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

Interleukin-1 signaling ↗

Stable identifier: R-HSA-9020702



Interleukin 1 (IL1) signals via Interleukin 1 receptor 1 (IL1R1), the only signaling-capable IL1 receptor. This is a single chain type 1 transmembrane protein comprising an extracellular ligand binding domain and an intracellular region called the Toll/Interleukin-1 receptor (TIR) domain that is structurally conserved and shared by other members of the two families of receptors (Xu et al. 2000). This domain is also shared by the downstream adapter molecule MyD88. IL1 binding to IL1R1 leads to the recruitment of a second receptor chain termed the IL1 receptor accessory protein (IL1RAP or IL1RAcP) enabling the formation of a high-affinity ligand-receptor complex that is capable of signal transduction. Intracellular signaling is initiated by the recruitment of MyD88 to the IL-1R1/IL1RAP complex. IL1RAP is only recruited to IL1R1 when IL1 is present; it is believed that a TIR domain signaling complex is formed between the receptor and the adapter TIR domains. The recruitment of MyD88 leads to the recruitment of Interleukin-1 receptor-associated kinase (IRAK)-1 and -4, probably via their death domains. IRAK4 then activates IRAK1, allowing IRAK1 to autophosphorylate. Both IRAK1 and IRAK4 then dissociate from MyD88 (Brikos et al. 2007) which remains stably complexed with IL-1R1 and IL1RAP. They in turn interact with Tumor Necrosis Factor Receptor (TNFR)-Associated Factor 6 (TRAF6), which is an E3 ubiquitin ligase (Deng et al. 2000). TRAF6 is then thought to auto-ubiquinate, attaching K63-polyubiquitin to itself with the assistance of the E2 conjugating complex Ubc13/Uev1a. K63-pUb-TRAF6 recruits Transforming Growth Factor (TGF) beta-activated protein kinase 1 (TAK1) in a complex with TAK1-binding protein 2 (TAB2) and TAB3, which both contain nuclear zinc finger motifs that interact with K63-polyubiquitin chains (Ninomiya-Tsuji et al. 1999). This activates TAK1, which then activates inhibitor of NF-kappaB (IkappaB) kinase 2 (IKK2 or IKKB) within the IKK complex, the kinase responsible for phosphorylation of IkappaB. The IKK complex also contains the scaffold protein NF-kappa B essential modulator (NEMO). TAK1 also couples to the upstream kinases for p38 and c-jun N-terminal kinase (JNK). IRAK1 undergoes K63-linked polyubiquination; Pellino E3 ligases are important in this process. (Butler et al. 2007; Ordureau et al. 2008). The activity of these proteins is greatly enhanced by IRAK phosphorylation (Schauvliege et al. 2006), leading to K63-linked polyubiquitination of IRAK1. This recruits NEMO to IRAK1, with NEMO binding to polyubiquitin (Conze et al. 2008).

TAK1 activates IKKB (and IKK), resulting in phosphorylation of the inhibitory IkB proteins and enabling translocation of NFkB to the nucleus; IKKB also phosphorylates NFkB p105, leading to its degradation and the subsequent release of active TPL2 that triggers the extracellular-signal regulated kinase (ERK)1/2 MAPK cascade. TAK1 can also trigger the p38 and JNK MAPK pathways via activating the upstream MKKs3, 4 and 6. The MAPK pathways activate a number of downstream kinases and transcription factors that co-operate with NFkB to induce the expression of a range of TLR/IL-1R-responsive genes. There are reports suggesting that IL1 stimulation increases nuclear localization of IRAK1 (Bol et al. 2000) and that nuclear IRAK1 binds to the promoter of NFkB-regulated

gene and IkBa, enhancing binding of the NFkB p65 subunit to NFkB responsive elements within the IkBa promoter. IRAK1 is required for IL1-induced Ser-10 phosphorylation of histone H3 in vivo (Liu et al. 2008). However, details of this aspect of IRAK1 signaling mechanisms remain unclear. Interleukin-18 is another Interleukin-1 related cytokine which signals through IL18R and IL18RAP subunit receptors (which share homology with IL1R and IL1RAP in the cytokine signaling cascade). Later it follows a MYD88/IRAK1/TRAF6 cascade signaling until reach the NFKB activation (Moller et al. 2002). Interleukin 33, 36, 37 and 38 are relatively recently discovered Interleukin-1 related citokines which are also able to signal through IL1 receptor subunits or other as IL18R, IL37R (Schmitz et al. 2005, Yi et al. 2016, Lunding et al. 2015, van de Veendorck et al. 2012, Lin et al. 2001).

Literature references

Vosshenrich, CA., Di Santo, JP. (2002). Interleukin signaling. *Curr Biol, 12*, R760-3. ↗

Kracht, M., Wasiliew, P., Weber, A. (2010). Interleukin-1 (IL-1) pathway. *Sci Signal, 3*, cm1. ↗

Editions

2010-05-17	Reviewed	Pinteaux, E.
2010-05-17	Authored	Ray, KP.
2017-11-09	Edited	Jupe, S.

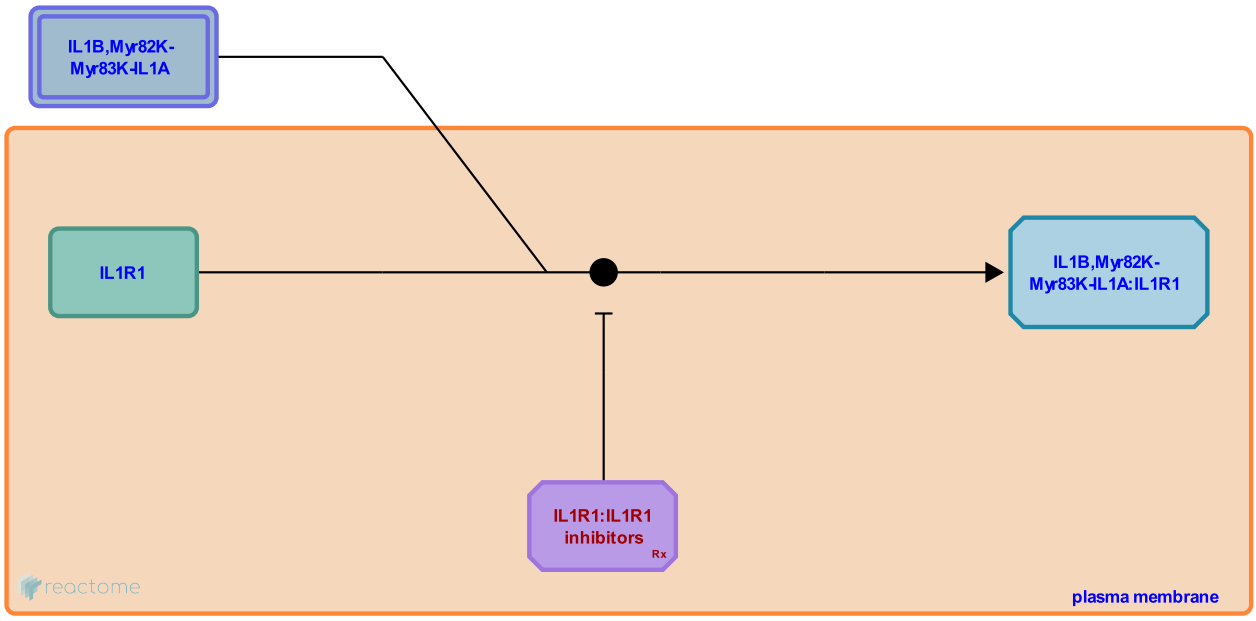
IL1B,Myr82K-Myr83K-IL1A:IL1R1 ↗

Location: Interleukin-1 signaling

Stable identifier: R-HSA-445753

Type: binding

Compartments: plasma membrane, extracellular region



Interleukin-1 receptor type 1 (IL1R1) is the receptor responsible for transmitting the inflammatory effects of Interleukin-1 (IL1).

Literature references

Kronheim, SR., Urdal, DL., Deeley, M., Cantrell, M., Gillis, S., Hopp, TP. et al. (1986). The cell surface receptors for interleukin-1 alpha and interleukin-1 beta are identical. *Nature, 324*, 266-8. ↗

Mantovani, A., Shanebeck, K., Colotta, F., Re, F., Slack, JL., Alderson, MR. et al. (1993). Interleukin 1 signaling occurs exclusively via the type I receptor. *Proc Natl Acad Sci U S A, 90*, 6155-9. ↗

Editions

2010-05-17	Edited	Jupe, S.
2010-05-17	Reviewed	Pinteaux, E.
2010-05-17	Authored	Ray, KP.

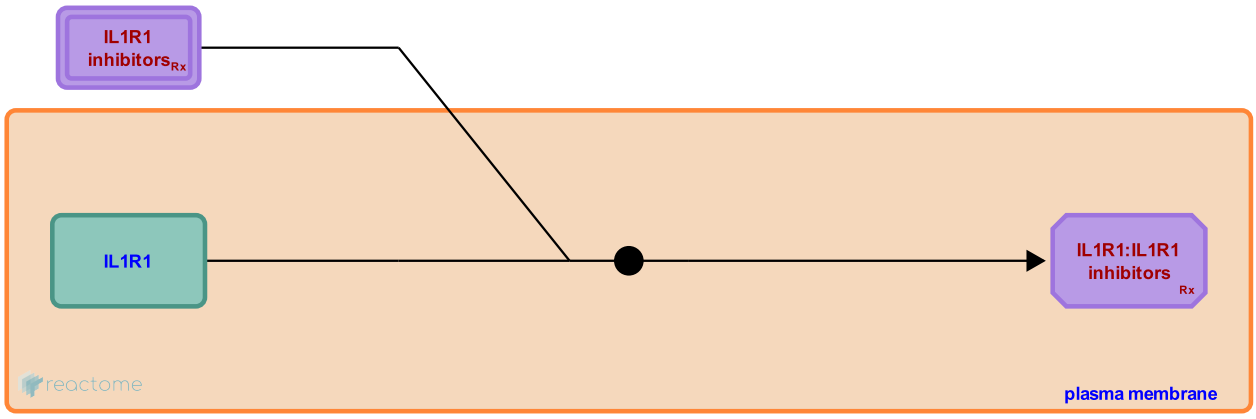
IL1R1 binds IL1R1 inhibitors ↗

Location: Interleukin-1 signaling

Stable identifier: R-HSA-9681763

Type: binding

Compartments: plasma membrane, extracellular region



The IL1 family includes two agonists, IL1α and IL1β, and a naturally occurring receptor antagonist, IL1Ra. IL1Ra is produced locally in various tissues in response to infection or inflammation (Arend & Gabay 2000). Anakinra (Kineret) is a recombinant form of IL1Ra that competitively inhibit the local inflammatory effects of IL1 (Seckinger et al. 1990) and is approved for the treatment of rheumatoid arthritis (RA) in combination with methotrexate (Drevlow et al. 1996, Cohen et al. 2002, Fleischmann et al. 2003). Isunakinra (EBI 005) is a fusion protein containing domains from IL1β and the IL1 receptor antagonist (IL1Ra or anakinra) developed as a topical therapy for dry eye disease (Goldstein et al. 2017). It blocks IL1R1 signalling with higher affinity than anakinra (Kovalchin et al. 2018). These IL1R1 inhibitors may be investigated for their role in blocking inflammatory cytokines produced in the "cytokine storm syndrome" caused by COVID-19 (Cron & Chatham 2020).

Literature references

Sheppard, J., Martel, JR., Korenfeld, M., Durham, TA., Tauber, J., Furfine, E. et al. (2017). Multicenter Study of a Novel Topical Interleukin-1 Receptor Inhibitor, Isunakinra, in Subjects With Moderate to Severe Dry Eye Disease . *Eye Contact Lens, 43*, 287-296. ↗

Arend, WP., Gabay, C. (2000). Physiologic role of interleukin-1 receptor antagonist. *Arthritis Res., 2*, 245-8. ↗

Seckinger, P., Thompson, RC., Raisz, LG., Dayer, JM., Alander, C., Klein-Nulend, J. (1990). Natural and recombinant human IL-1 receptor antagonists block the effects of IL-1 on bone resorption and prostaglandin production. *J. Immunol., 145*, 4181-4. ↗

Editions

2020-04-06	Authored, Edited	Jassal, B.
2020-05-14	Reviewed	Shoichet, BK.

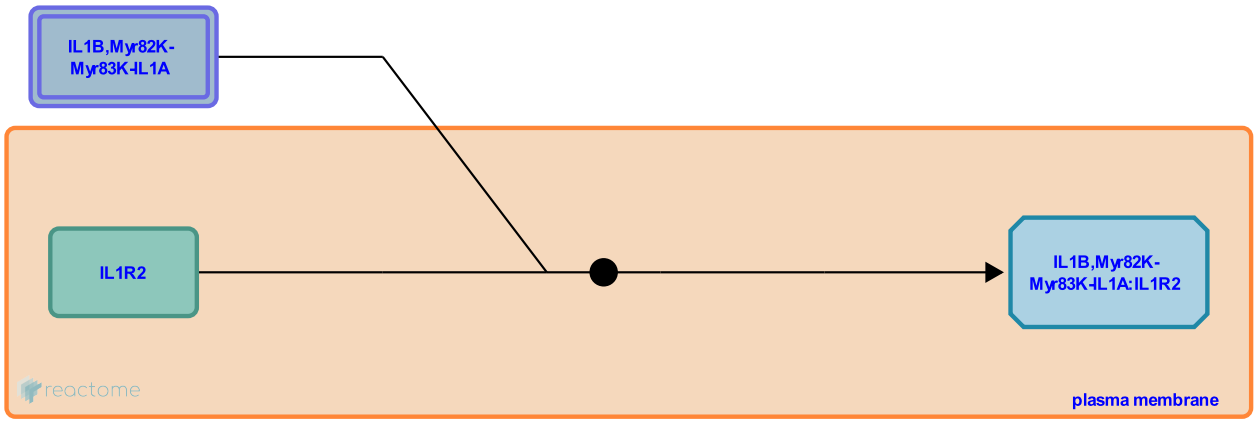
Interleukin-1 receptor type 2 binds Interleukin 1 ↗

Location: Interleukin-1 signaling

Stable identifier: R-HSA-446130

Type: binding

Compartments: plasma membrane, extracellular region



Interleukin-1 receptor type 2 (IL1R2) binds Interleukin-1 but does not participate in any signaling processes. IL1R2 is thought to be a decoy receptor, removing or neutralizing Interleukin-1 that could otherwise stimulate the type 1 receptor.

Literature references

Brunton, LL., Lupton, SD., Grubin, CE., Mosley, B., Jenkins, NA., McMahan, CJ. et al. (1991). A novel IL-1 receptor, cloned from B cells by mammalian expression, is expressed in many cell types. *EMBO J., 10*, 2821-32. ↗

Mantovani, A., Colotta, F., Polentarutti, N., Re, F., Bertini, R., Dower, SK. et al. (1993). Interleukin-1 type II receptor: a decoy target for IL-1 that is regulated by IL-4. *Science, 261*, 472-5. ↗

Editions

2010-05-17	Edited	Jupe, S.
2010-05-17	Reviewed	Pinteaux, E.
2010-05-17	Authored	Ray, KP.

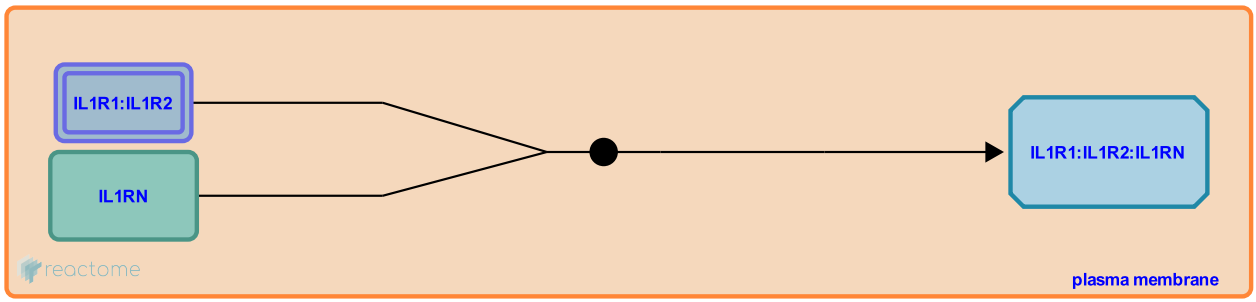
IL1 receptor antagonist protein binds Interleukin 1 receptors ↗

Location: Interleukin-1 signaling

Stable identifier: R-HSA-445757

Type: binding

Compartments: plasma membrane



The interleukin 1 receptor antagonist protein (ILRAP or IL1RN) is a member of the IL1 family that binds to IL1R1 (and with much lower affinity IL1R2) but does not elicit a signaling response. By competing with IL1 for IL1R1 binding ILRAP acts as a natural antagonist, inhibiting the biological actions of both agonist forms of IL1 (IL1 alpha and IL1 beta).

Literature references

Bienkowski, MJ., Deibel MR, Jr., Laborde, AL., McEwan, RN., Slightom, JL., Tomich, CS. et al. (1990). Purification, cloning, expression and biological characterization of an interleukin-1 receptor antagonist protein. *Nature, 344*, 633-8. ↗

Eisenberg, SP., Dripps, DJ., Brandhuber, BJ., Thompson, RC. (1991). Interleukin-1 (IL-1) receptor antagonist binds to the 80-kDa IL-1 receptor but does not initiate IL-1 signal transduction. *J Biol Chem, 266*, 10331-6. ↗

Editions

2010-05-17	Edited	Jupe, S.
2010-05-17	Reviewed	Pinteaux, E.
2010-05-17	Authored	Ray, KP.

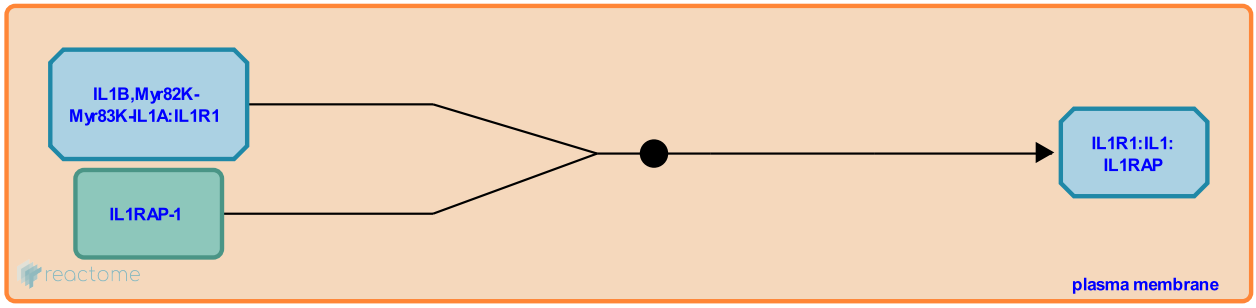
Interleukin-1 receptor type 1: Interleukin 1 binds Interleukin-1 receptor accessory protein, membrane associated isoform ↗

Location: Interleukin-1 signaling

Stable identifier: R-HSA-445752

Type: binding

Compartments: plasma membrane, extracellular region



Interleukin receptor 1 type 1 when bound to interleukin 1 binds interleukin 1 receptor accessory protein, essential for eliciting a signaling cascade.

Literature references

Cao, Z., Gao, X., Li, S., Huang, J. (1997). Recruitment of IRAK to the interleukin 1 receptor complex requires interleukin 1 receptor accessory protein. *Proc Natl Acad Sci U S A, 94*, 12829-32. ↗

Editions

2010-05-17	Edited	Jupe, S.
2010-05-17	Reviewed	Pinteaux, E.
2010-05-17	Authored	Ray, KP.

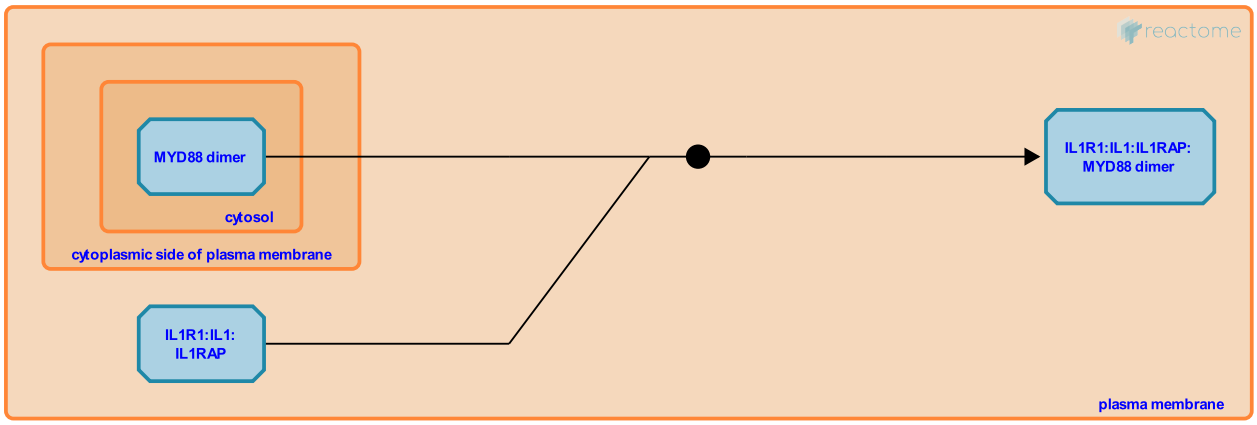
IL1R1:IL1:IL1RAP binds MYD88 homodimer ↗

Location: Interleukin-1 signaling

Stable identifier: R-HSA-450133

Type: binding

Compartments: plasma membrane, cytosol



MYD88 is a cytoplasmic adaptor protein that is recruited to the intracellular region of the IL1 receptor complex following IL1 stimulation. MYD88 binds to the complex of the two receptor chains and subsequently to IL-1 receptor-associated kinase 4 (IRAK4). This complex is the minimum required for signaling (Brikos et al. 2007).

Literature references

Henzel, WJ., Wesche, H., Li, S., Cao, Z., Shillinglaw, W. (1997). MyD88: an adapter that recruits IRAK to the IL-1 receptor complex. *Immunity, 7*, 837-47. ↗

Begum, S., Brikos, C., O'Neill, LA., Wait, R., Saklatvala, J. (2007). Mass spectrometric analysis of the endogenous type I interleukin-1 (IL-1) receptor signaling complex formed after IL-1 binding identifies IL-1RAcP, MyD88, and IRAK-4 as the stable components. *Mol Cell Proteomics, 6*, 1551-9. ↗

Editions

2010-05-17	Edited	Jupe, S.
2010-05-17	Reviewed	Pinteaux, E.
2010-05-17	Authored	Ray, KP.

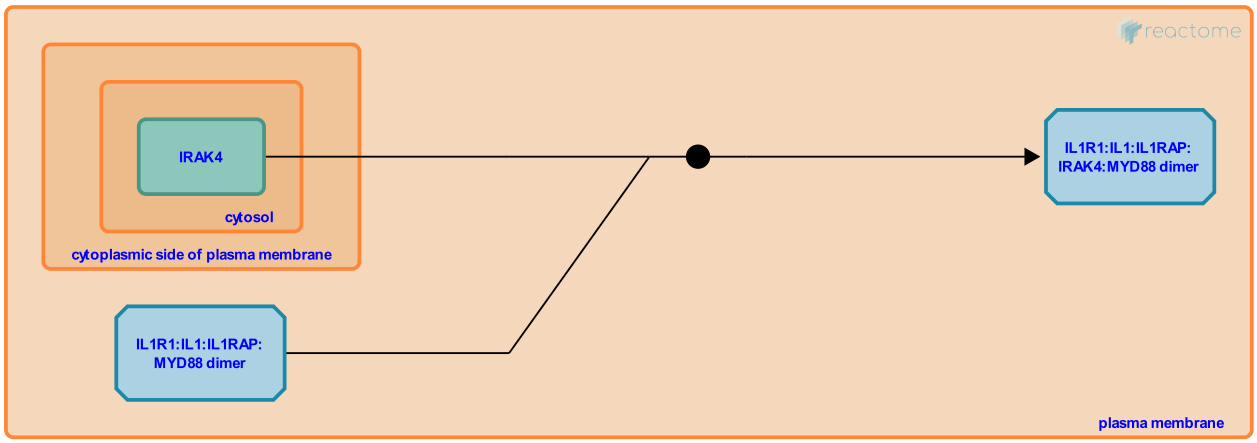
IL1R1:IL1:IL1RAP:MYD88 homodimer binds IRAK4 ↗

Location: Interleukin-1 signaling

Stable identifier: R-HSA-446648

Type: binding

Compartments: plasma membrane, cytosol



MYD88 is a cytoplasmic adaptor protein that is recruited to the intracellular region of the IL1 receptor complex following IL1 stimulation. MYD88 binds to the complex of the two receptor chains and subsequently to IL-1 receptor-associated kinase 4 (IRAK4). This complex is the minimum required for signaling (Brikos et al. 2007).

Literature references

Brissoni, B., Janssens, S., Olivos, N., Burns, K., Beyaert, R., Tschopp, J. (2003). Inhibition of interleukin 1 receptor/Toll-like receptor signaling through the alternatively spliced, short form of MyD88 is due to its failure to recruit IRAK-4. *J Exp Med, 197*, 263-8. ↗

Begum, S., Brikos, C., O'Neill, LA., Wait, R., Saklatvala, J. (2007). Mass spectrometric analysis of the endogenous type I interleukin-1 (IL-1) receptor signaling complex formed after IL-1 binding identifies IL-1RAcP, MyD88, and IRAK-4 as the stable components. *Mol Cell Proteomics, 6*, 1551-9. ↗

Editions

2010-05-17	Edited	Jupe, S.
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2010-05-17	Authored	Ray, KP.

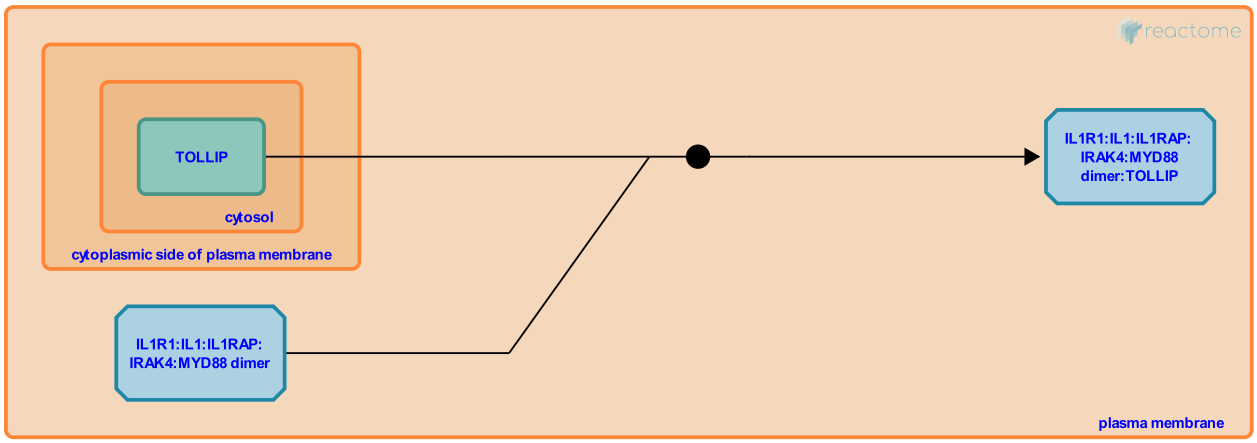
The Interleukin 1 receptor complex binds Tollip ↗

Location: Interleukin-1 signaling

Stable identifier: R-HSA-446868

Type: binding

Compartments: plasma membrane, cytosol



Toll-interacting protein (TOLLIP) binds to IRAK1 and IL-1RAP within the receptor complex. TOLLIP has the capacity to act as an ubiquitin-binding receptor for ubiquitinated IL1R1, linking IL1R to endosomal degradation.

Literature references

Maschera, B., Volpe, F., Plumpton, C., Martinon, F., Ray, KP., Burns, K. et al. (2000). Tollip, a new component of the IL-1RI pathway, links IRAK to the IL-1 receptor. *Nat Cell Biol, 2*, 346-51. ↗

Editions

2010-05-17	Edited	Jupe, S.
2010-05-17	Reviewed	Pinteaux, E.
2010-05-17	Authored	Ray, KP.

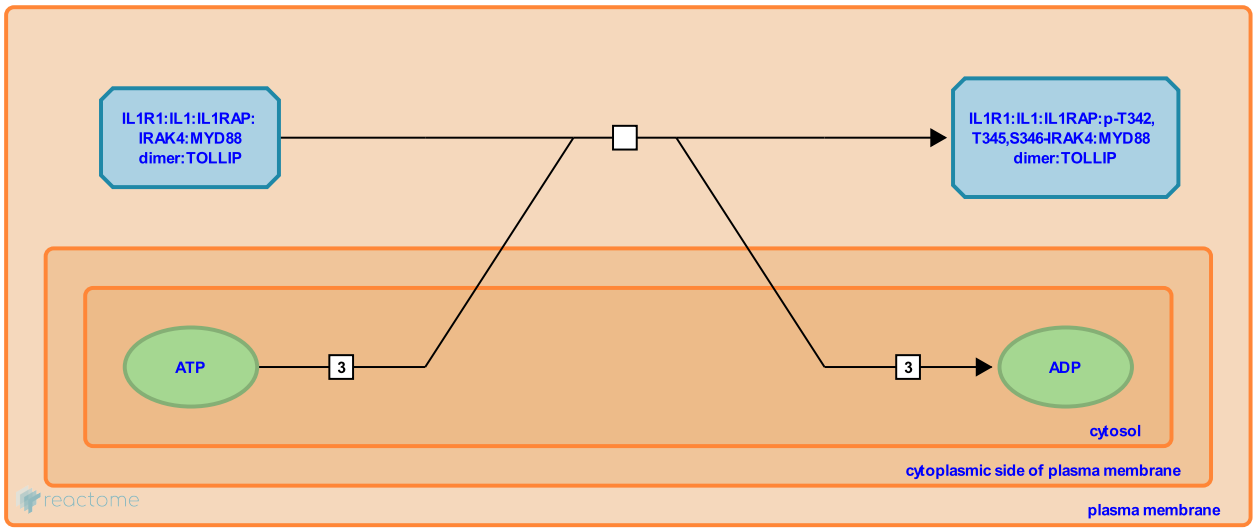
IRAK4 is activated by autophosphorylation ↗

Location: Interleukin-1 signaling

Stable identifier: R-HSA-446634

Type: transition

Compartments: plasma membrane, cytosol



IRAK4 is activated by autophosphorylation at 3 positions within the kinase activation loop, Thr-342, Thr-345 and Ser-346.

Literature references

Dahlstrand, E., Wang, A., Ocain, TD., Li, Z., Addona, T., Xu, Y. et al. (2007). Regulation of IRAK-4 kinase activity via autophosphorylation within its activation loop. *Biochem Biophys Res Commun, 352*, 609-16. ↗

Editions

2010-05-17	Edited	Jupe, S.
2010-05-17	Reviewed	Pinteaux, E.
2010-05-17	Authored	Ray, KP.

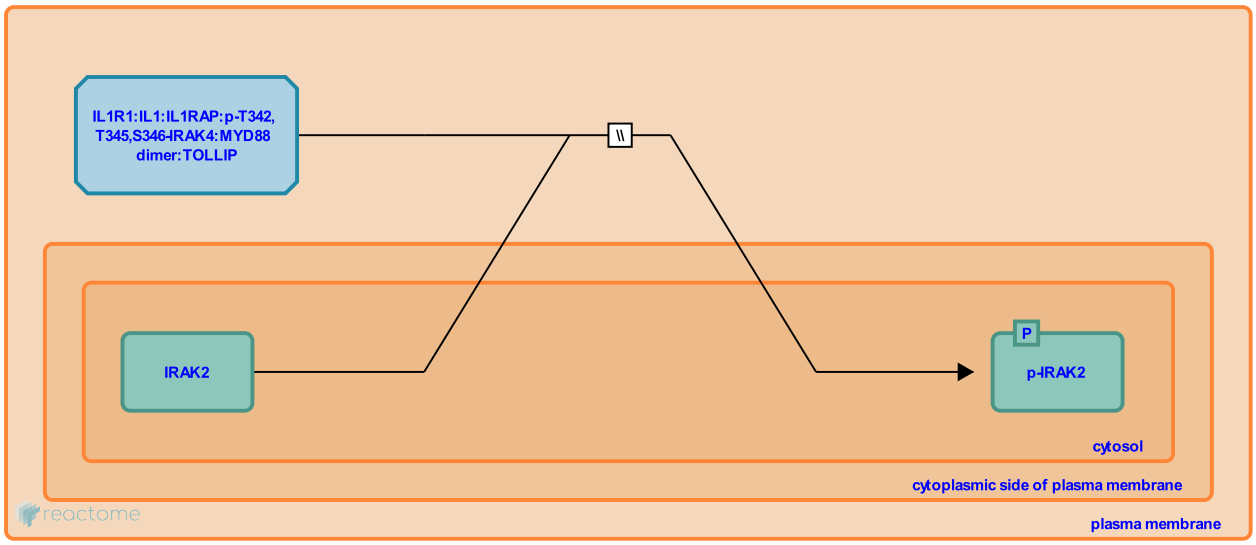
IRAK2 is phosphorylated downstream of IRAK4 following IL1 receptor activation ↗

Location: Interleukin-1 signaling

Stable identifier: R-HSA-446684

Type: omitted

Compartments: plasma membrane



IRAK2 has been implicated in IL1R and TLR signaling by the observation that IRAK2 can associate with MyD88 and Mal (Muzio et al. 1997). Like IRAK1, IRAK2 is activated downstream of IRAK4 (Kawagoe et al. 2008). It has been suggested that IRAK1 activates IRAK2 (Wesche et al. 1999) but IRAK2 phosphorylation is observed in IRAK1–/– mouse macrophages while IRAK4 deficiency abrogates IRAK2 phosphorylation (Kawagoe et al. 2008), suggesting that activated IRAK4 phosphorylates IRAK2 as it does IRAK1. IL6 production in response to IL1beta is impaired in embryonic fibroblasts from IRAK1 or IRAK2 knockout mice and abrogated in IRAK1/2 dual knockouts (Kawagoe et al. 2007) suggesting that IRAK1 and IRAK2 are both involved in IL1R signaling downstream of IRAK4.

Literature references

Kumagai, Y., Kawai, T., Takeuchi, O., Saitoh, T., Matsushita, K., Sato, S. et al. (2008). Sequential control of Toll-like receptor-dependent responses by IRAK1 and IRAK2. *Nat Immunol, 9*, 684-91. ↗

Editions

2010-05-17	Edited	Jupe, S.
2010-05-17	Reviewed	Pinteaux, E.
2010-05-17	Authored	Ray, KP.

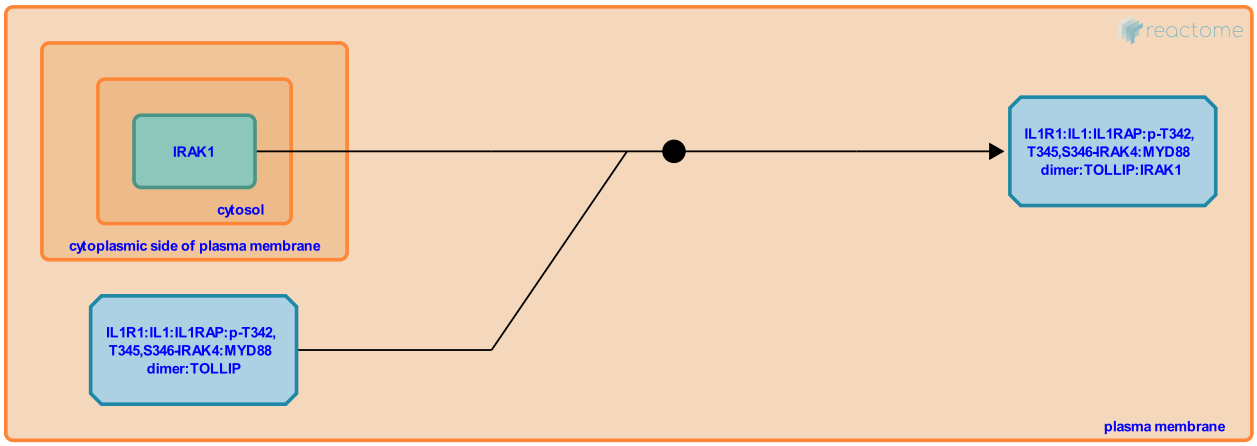
IRAK1 binds to MYD88 within the IL1R complex ↗

Location: Interleukin-1 signaling

Stable identifier: R-HSA-446692

Type: binding

Compartments: plasma membrane, cytosol



MYD88 recruits unphosphorylated, inactive IRAK1 to the IL1 receptor complex.

Literature references

Henzel, WJ., Wesche, H., Li, S., Cao, Z., Shillinglaw, W. (1997). MyD88: an adapter that recruits IRAK to the IL-1 receptor complex. *Immunity, 7*, 837-47. ↗

Henzel, WJ., Cao, Z., Gao, X. (1996). IRAK: a kinase associated with the interleukin-1 receptor. *Science, 271*, 1128-31. ↗

Editions

2010-05-17	Edited	Jupe, S.
2010-05-17	Reviewed	Pinteaux, E.
2010-05-17	Authored	Ray, KP.

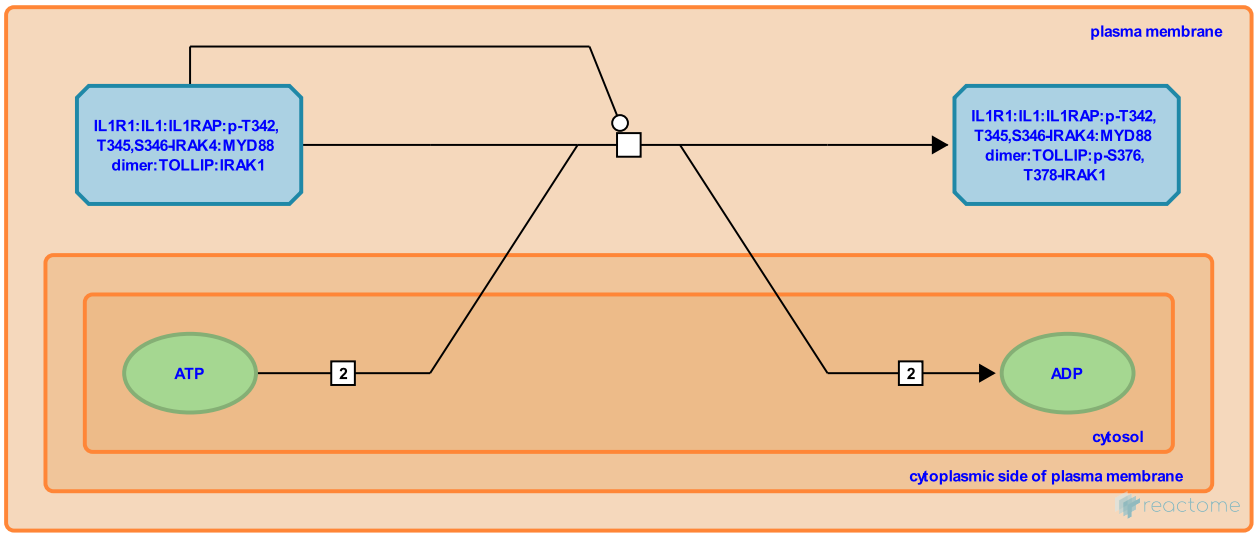
IRAK4 phosphorylates IRAK1 ↗

Location: Interleukin-1 signaling

Stable identifier: R-HSA-446694

Type: transition

Compartments: plasma membrane, cytosol



MyD88 recruits unphosphorylated IRAK1 to the signaling complex. IRAK1 is then rapidly activated and autophosphorylates in a region that is outside the kinase domain (Cao et al. 1996). Several pieces of evidence suggest that IRAK4 triggers IRAK1 activation by phosphorylating its kinase activation loop, leading to IRAK1 autophosphorylation (Suzuki et al. 2002): in vitro kinase assays indicate that IRAK1 can be a direct substrate of IRAK4 (Li et al. 2002); IRAK1 phosphorylation by IRAK4 is independent of and precedes IRAK1 activation and autophosphorylation; IRAK1 autophosphorylation is partially inhibited in cells overexpressing a kinase-inactive IRAK4 protein (Li et al. 2002).

Literature references

Wesche, H., Li, S., Fontana, EJ., Strelow, A. (2002). IRAK-4: a novel member of the IRAK family with the properties of an. *Proc Natl Acad Sci U S A, 99*, 5567-72. ↗

Editions

2010-05-17	Edited	Jupe, S.
2010-05-17	Reviewed	Pinteaux, E.
2010-05-17	Authored	Ray, KP.

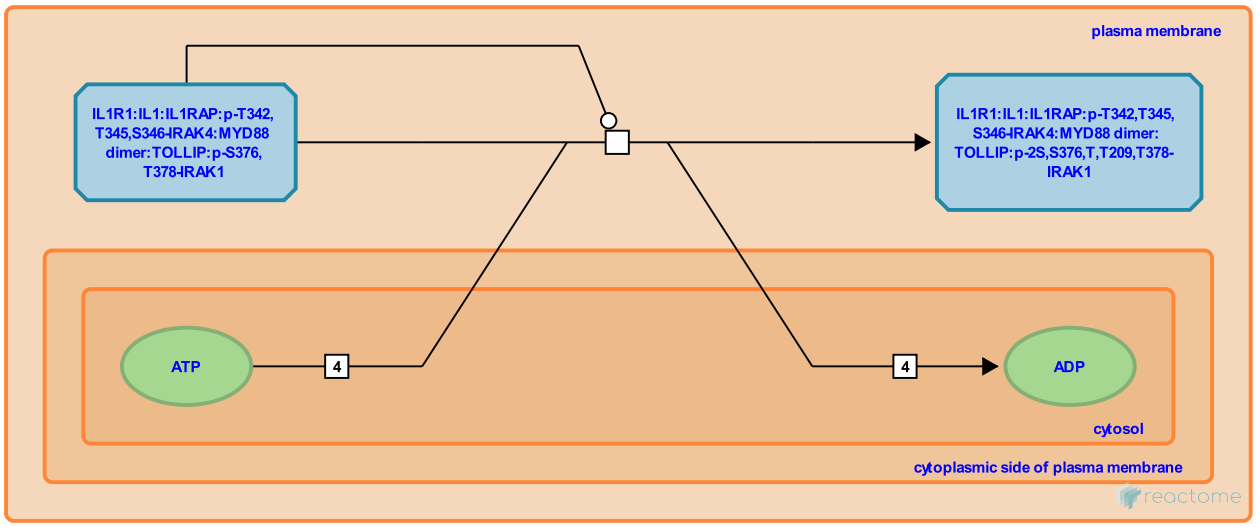
IRAK4-activated IRAK1 autophosphorylates ↗

Location: Interleukin-1 signaling

Stable identifier: R-HSA-446701

Type: transition

Compartments: plasma membrane, cytosol



A series of sequential phosphorylation events lead to full or hyper-phopshorylation of IRAK1. Under in vitro conditions these are all autophosphorylation events. First, Thr-209 is phosphorylated resulting in a conformational change of the kinase domain. Next, Thr-387 in the activation loop is phosphorylated, leading to full enzymatic activity. Several additional residues are phosphorylated in the proline-, serine-, and threonine-rich (ProST) region between the N-terminal death domain and kinase domain. Hyperphosphorylation of this region leads to dissociation of IRAK1 from the upstream adapters MyD88 and Tollip. The significance of these phosphorylation events is not clear; the kinase activity of IRAK1 is dispensable for IL1-induced NFkB and MAP kinase activation (Knop & Martin, 1999), unlike that of IRAK4 (Suzuki et al. 2002; Kozicak-Holbro et al. 2007), so IRAK1 is believed to act primarily as an adaptor for TRAF6 (Conze et al. 2008).

Literature references

Wesche, H., Li, S., Martin, MU., Knop, J., Neumann, D., Cao, P. et al. (2004). Sequential autophosphorylation steps in the interleukin-1 Receptor-associated Kinase-1 Regulate its Availability as an Adapter in Interleukin-1 Signaling. *J Biol Chem, 279*, 5227-36. ↗

Editions

2010-05-17	Edited	Jupe, S.
2010-05-17	Reviewed	Pinteaux, E.
2010-05-17	Authored	Ray, KP.

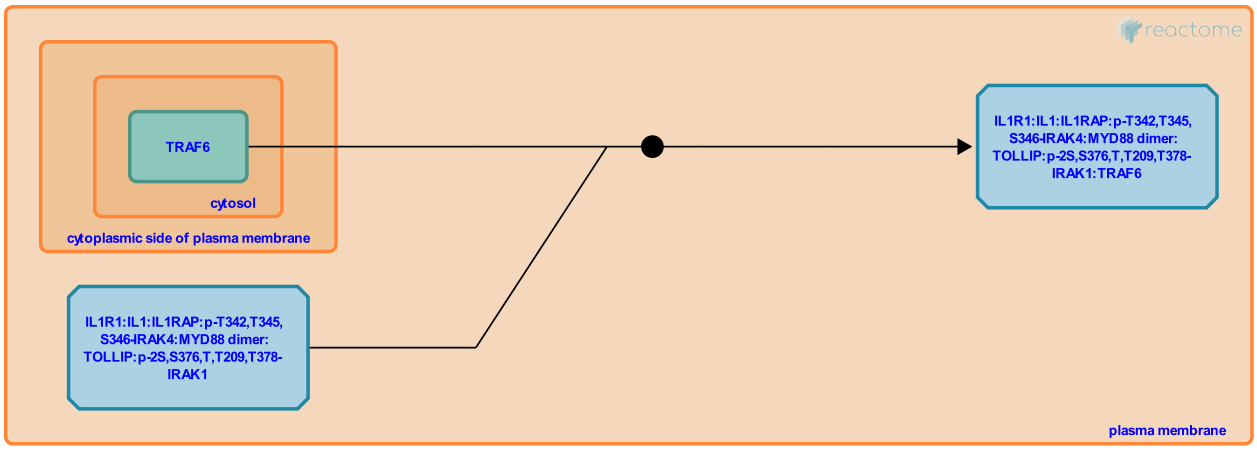
Hyperphosphorylated IRAK1 associates with TRAF6 ↗

Location: Interleukin-1 signaling

Stable identifier: R-HSA-446862

Type: binding

Compartments: plasma membrane, cytosol



Hyperphosphorylated IRAK1, still within the receptor complex, binds TRAF6 through multiple regions including the death domain, the undefined domain and the C-terminal C1 domain (Li et al. 2001). The C-terminal region of IRAK-1 contains three potential TRAF6-binding sites; mutation of the amino acids (Glu544, Glu587, Glu706) in these sites to alanine greatly reduces activation of NFkappaB (Ye et al. 2002).

Literature references

Cao, Z., Kurama, T., Xiong, J., Takeuchi, M., Goeddel, DV. (1996). TRAF6 is a signal transducer for interleukin-1. *Nature, 383*, 443-6. ↗

Editions

2010-05-17	Edited	Jupe, S.
2010-05-17	Reviewed	Pinteaux, E.
2010-05-17	Authored	Ray, KP.

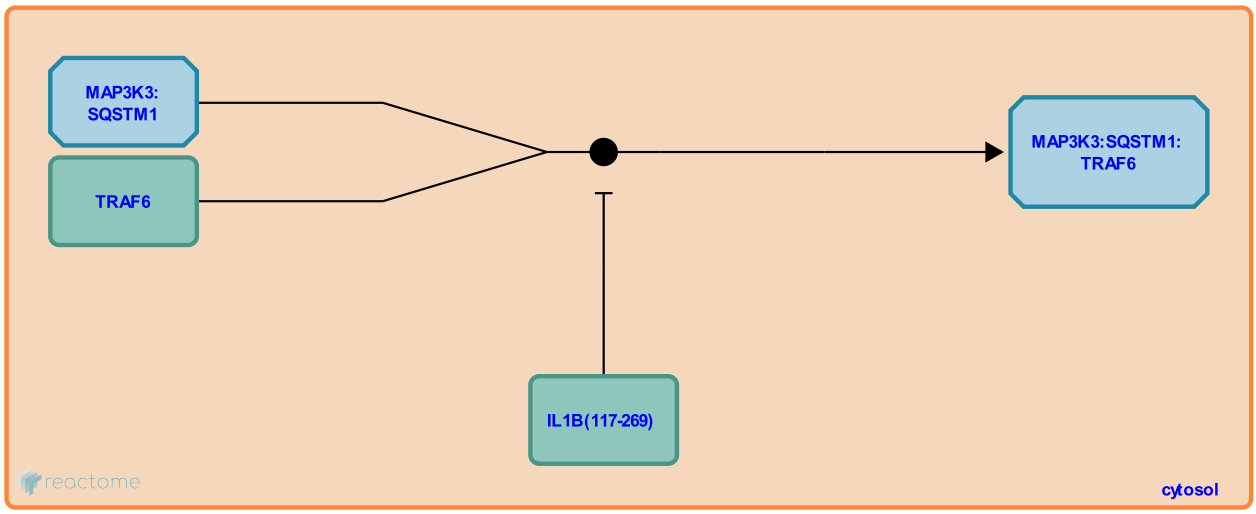
p62:MEKK3 binds to TRAF6 ↗

Location: Interleukin-1 signaling

Stable identifier: R-HSA-507719

Type: binding

Compartments: cytosol



p62, MEKK3 and TRAF6 co-localize in cytoplasmic aggregates that are thought to be centres for organizing TRAF6-regulated NF-kappaB signaling and the assembly of polyubiquinated proteins sorting to sequestosomes and proteasomes. p62/Sequestosome-1 is a scaffold protein involved in the regulation of autophagy, trafficking of proteins to the proteasome and activation of NF-kB. p62 binds the basic region of MEKK3. MEKK3 is known to bind TRAF6 in response to IL1B (Huang et al. 2004). Recently p62 was shown to be required for the association of MEKK3 with TRAF6. RNA knockdown of p62 inhibited IL1B and MEKK3 activation of NF-kB. IL1B stimulation resulted in dissociation of MEKK3 from p62:TRAF6 (Nakamura et al. 2010).

Literature references

Siderovski, DP., Nakamura, K., Johnson, GL., Kimple, AJ. (2010). PB1 domain interaction of p62/sequestosome 1 and MEKK3 regulates NF-kappaB activation. *J Biol Chem, 285*, 2077-89. ↗

Editions

2010-05-17	Edited	Jupe, S.
2010-05-17	Reviewed	Pinteaux, E.
2010-05-17	Authored	Ray, KP.

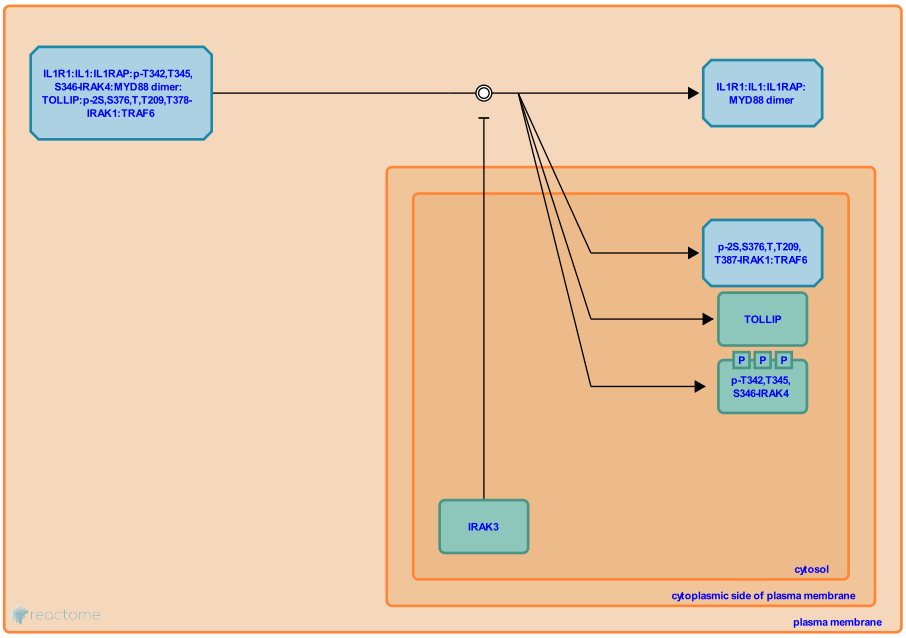
TRAF6 binding leads to IRAK1:TRAF6 release ↗

Location: Interleukin-1 signaling

Stable identifier: R-HSA-446894

Type: dissociation

Compartments: plasma membrane, cytosol



MyD88 and Tollip only bind to non-phosphorylated IRAK1 (Wesche et al. 1997) so hyper-phosphorylated IRAK1 is predisposed to release from the receptor complex, a key step in this signaling cascade. It is believed that the interaction of IRAK1 with TRAF6 enables the release of IRAK1:TRAF6 from the receptor (Gottipati et al. 2007). Though released from the receptor complex, IRAK1:TRAF6 remains associated with the membrane, perhaps due to subsequent interaction with the TAK1 complex (Dong et al. 2006). Interleukin-1 receptor-associated kinase 3 (IRAK3 or IRAK-M) prevents the dissociation of IRAK1 and IRAK4 from the MYD88 oligomeric signaling complex called the Myddosome (Kobayashi K et al. 2002).

Literature references

Rao, NL., Gottipati, S., Fung-Leung, WP. (2008). IRAK1: a critical signaling mediator of innate immunity. *Cell Signal, 20*, 269-76. ↗

Editions

2010-05-17	Edited	Jupe, S.
2010-05-17	Reviewed	Pinteaux, E.
2010-05-17	Authored	Ray, KP.

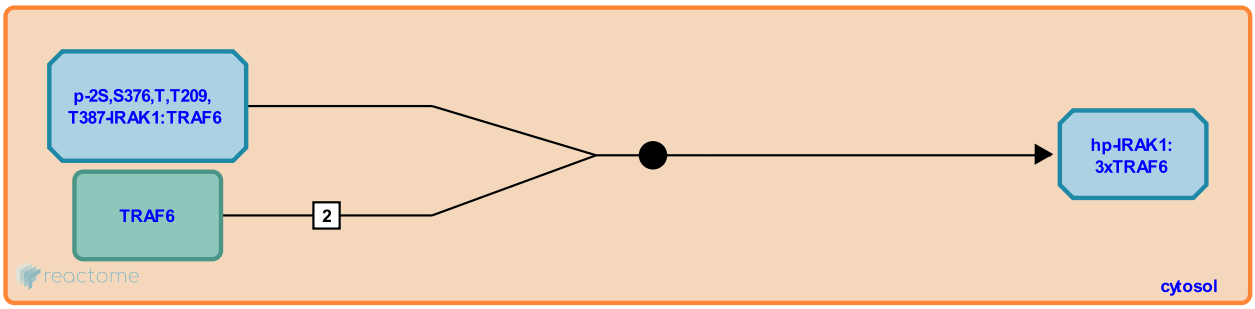
IRAK1 induces oligomerisation of TRAF6 ↗

Location: Interleukin-1 signaling

Stable identifier: R-HSA-450173

Type: binding

Compartments: cytosol



TRAF6 oligomerization is induced by IRAK1. The TRAF6 oligomer consists of more than two molecules of TRAF6; thermodynamic data for TRAF2 strongly suggests that it is functionally a trimer (Rawlings et al. 2006). TRAF6 is represented here as a trimer, though the extent and significance of TRAF6 oligomerization is unclear. Oligomerisation may be assisted by TIFA (TRAF-interacting protein with a FHA domain; Takatsuna et al. 2003).

Literature references

Muroi, M., Tanamoto, K. (2008). TRAF6 distinctively mediates MyD88- and IRAK-1-induced activation of NF-kappaB. *J Leukoc Biol, 83*, 702-7. ↗

Editions

2010-05-17	Edited	Jupe, S.
2010-05-17	Reviewed	Pinteaux, E.
2010-05-17	Authored	Ray, KP.

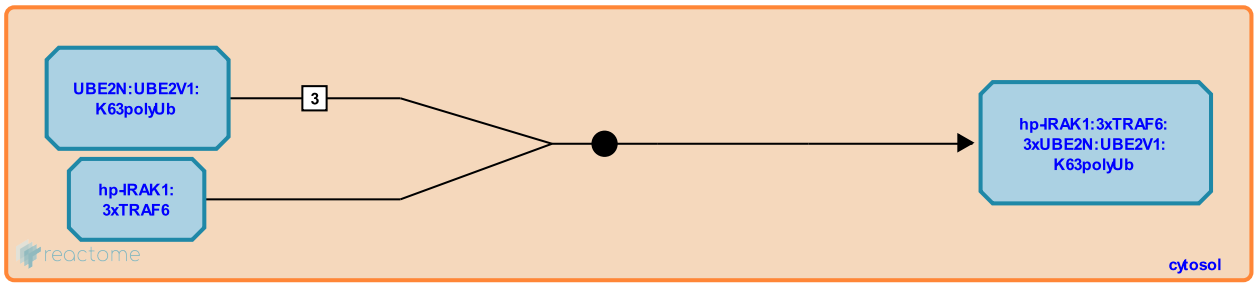
hp-IRAK1:3xTRAF6 binds UBE2N:UBE2V1:K63-polyUb ↗

Location: Interleukin-1 signaling

Stable identifier: R-HSA-8948015

Type: binding

Compartments: cytosol



Activated ubiquitin is transferred to a heterodimeric E2 conjugating enzyme UBE2N (Ubc13) and UBEE2V1 (Uev1A) forming an E2-Ub thioester.

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

2010-05-17	Authored	Ray, KP.
2010-09-06	Reviewed	Pinteaux, E.
2016-11-08	Edited	Jupe, S.

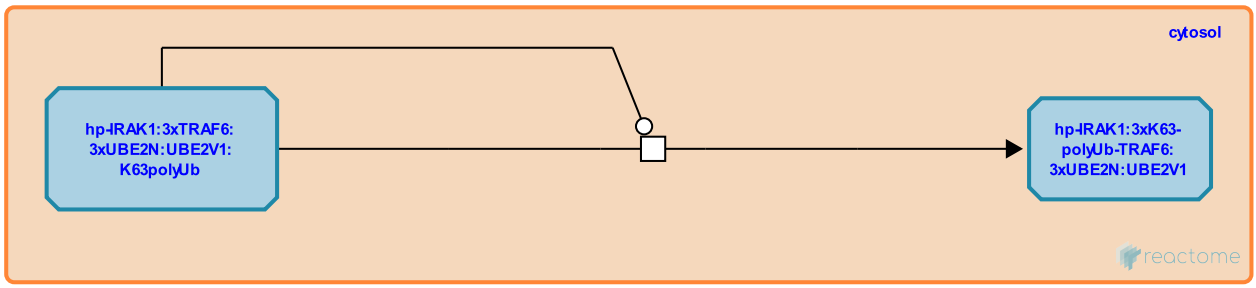
TRAF6 is K63 poly-ubiquitinated ↗

Location: Interleukin-1 signaling

Stable identifier: R-HSA-446877

Type: transition

Compartments: 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.

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

2010-05-17	Edited	Jupe, S.
2010-05-17	Reviewed	Pinteaux, E.
2010-05-17	Authored	Ray, KP.

UBE2N:UBE2V1 dissociates from hp-IRAK1:3xK63-polyUb-TRAF6:3xUBE2N:UBE2V1

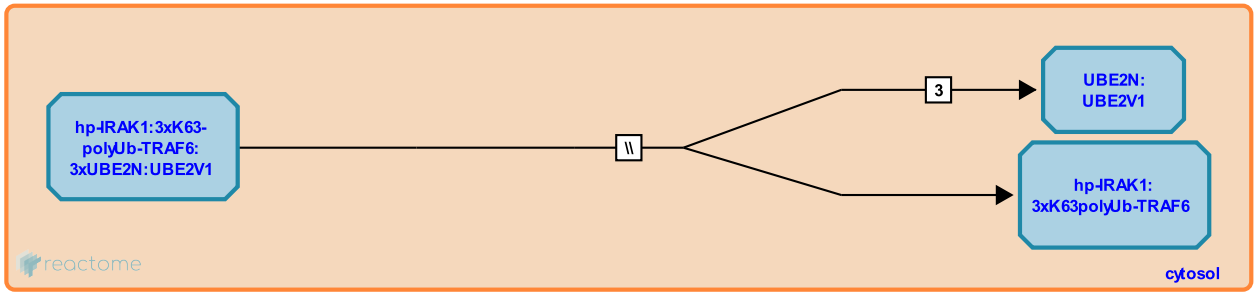
↗

Location: Interleukin-1 signaling

Stable identifier: R-HSA-8948018

Type: omitted

Compartments: cytosol



Following the TRAF6-mediated transfer of ubiquitin from the E2 conjugating enzyme UBE2N:UBE2V1 it dissociates.

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

2010-05-17	Authored	Ray, KP.
2010-09-06	Reviewed	Pinteaux, E.
2016-11-14	Edited	Jupe, S.

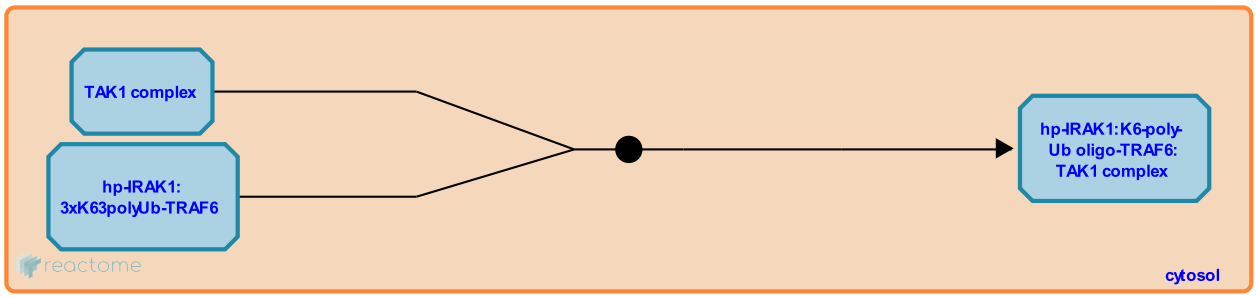
Polyubiquitinated TRAF6 binds the TAK1 complex ↗

Location: Interleukin-1 signaling

Stable identifier: R-HSA-446870

Type: binding

Compartments: 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).

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. ↗

Editions

2010-05-17	Edited	Jupe, S.
2010-05-17	Reviewed	Pinteaux, E.
2010-05-17	Authored	Ray, KP.

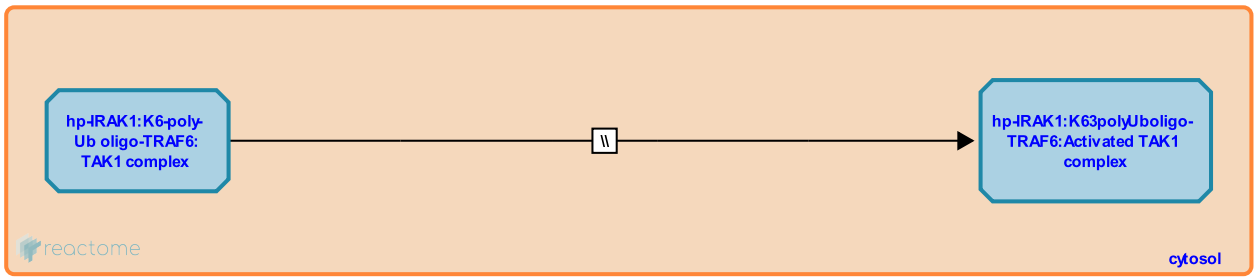
TAK1 is activated within the TAK1 complex ↗

Location: Interleukin-1 signaling

Stable identifier: R-HSA-450187

Type: omitted

Compartments: 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).

Literature references

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

2010-05-17	Edited	Jupe, S.
2010-05-17	Reviewed	Pinteaux, E.
2010-05-17	Authored	Ray, KP.

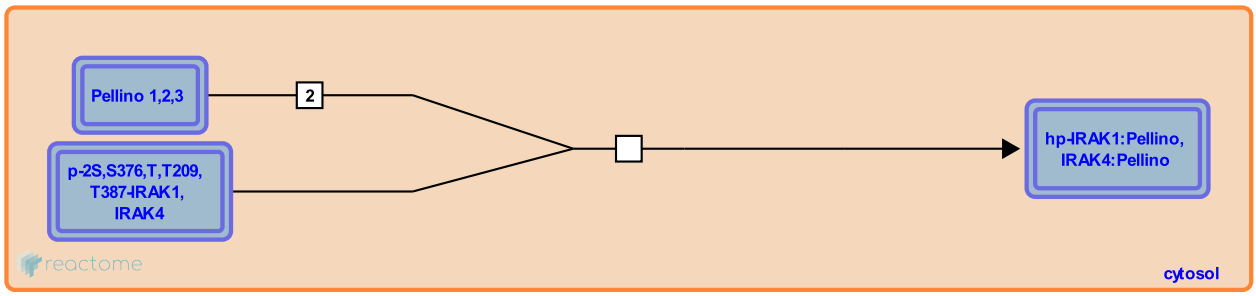
hp-IRAK1,hp-IRAK4 bind Pellino1,2,3

Location: Interleukin-1 signaling

Stable identifier: R-HSA-450690

Type: transition

Compartments: cytosol



IRAK1 and 4 interact with Pellino-1 (Jiang et al. 2003), 2 (Strellow et al. 2003) and 3 (Butler et al. 2005, 2007). Pellinos may act as scaffolding proteins, bringing signaling complexes into proximity. They are E3 ubiquitin ligases capable of ubiquitinating IRAK1, believed to mediate IL-1-stimulated formation of K63-polyubiquitinated IRAK1 in cells.

Though not clearly demonstrated and therefore not shown here, the current models of IRAK1 involvement suggest it would be within a complex including TRAF6.

Literature references

Hanly, JA., Butler, MP., Moynagh, PN. (2007). Kinase-active interleukin-1 receptor-associated kinases promote poly-ubiquitination and degradation of the Pellino family: direct evidence for PELLINO proteins being ubiquitin-protein isopeptide ligases. *J Biol Chem, 282*, 29729-37.

Johnson, HJ., Li, X., Jiang, Z., Nie, H., Bird, TA., Qin, J. (2003). Pellino 1 is required for interleukin-1 (IL-1)-mediated signaling through its interaction with the IL-1 receptor-associated kinase 4 (IRAK4)-IRAK-tumor necrosis factor receptor-associated factor 6 (TRAF6) complex. *J Biol Chem, 278*, 10952-6.

Hanly, JA., Butler, MP., Moynagh, PN. (2005). Pellino3 is a novel upstream regulator of p38 MAPK and activates CREB in a p38-dependent manner. *J Biol Chem, 280*, 27759-68.

Wesche, H., Strelow, A., Kollewe, C. (2003). Characterization of Pellino2, a substrate of IRAK1 and IRAK4. *FEBS Lett, 547*, 157-61.

Peggie, M., Ordureau, A., Carrick, E., Morrice, N., Windheim, M., Smith, H. et al. (2008). The IRAK-catalysed activation of the E3 ligase function of Pellino isoforms induces the Lys63-linked polyubiquitination of IRAK1. *Biochem J , 409*, 43-52.

Editions

2010-05-17	Edited	Jupe, S.
2010-05-17	Reviewed	Pinteaux, E.
2010-05-17	Authored	Ray, KP.

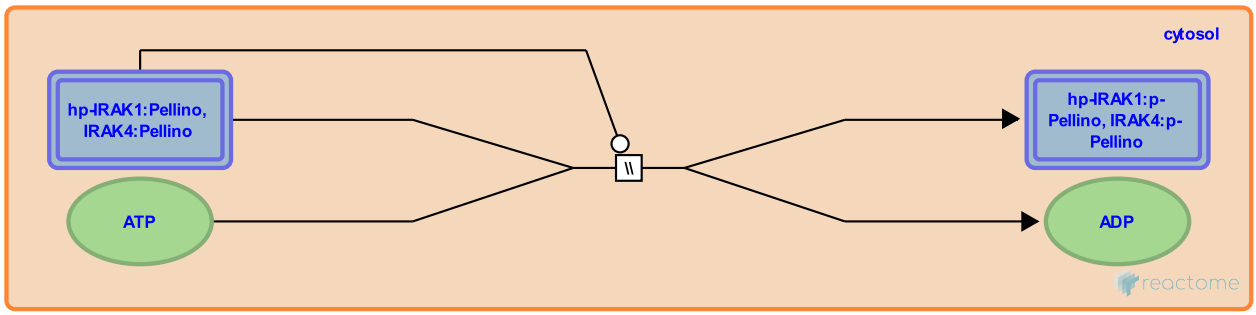
hp-IRAK1, hp-IRAK4 4 phosphorylate Pellino-1 and 2. ↗

Location: Interleukin-1 signaling

Stable identifier: R-HSA-450827

Type: omitted

Compartments: cytosol



IRAK1 and 4 can phosphorylate Pellino-1 and -2 and probably -3. Phosphorylation enhances the E3 ligase activity of Pellino-1 in conjunction with several different E2-conjugating enzymes (Ubc13-Uev1a, UbcH4, or UbcH5a/5b). Phosphorylation at any of several different sites or a combination of other sites leads to full activation of Pellino-1 E3 ubiquitin ligase activity.

Though not shown here, the current models of IRAK1 involvement suggest it is part of a complex that includes TRAF6.

Literature references

Peggie, M., Campbell, DG., Carrick, E., Smith, H., Vandermoere, F., Cohen, P. (2009). Identification of the phosphorylation sites on the E3 ubiquitin ligase Pellino that are critical for activation by IRAK1 and IRAK4. *Proc Natl Acad Sci U S A, 106*, 4584-90. ↗

Wesche, H., Strelow, A., Kollewe, C. (2003). Characterization of Pellino2, a substrate of IRAK1 and IRAK4. *FEBS Lett, 547*, 157-61. ↗

Editions

2010-05-17	Edited	Jupe, S.
2010-05-17	Reviewed	Pinteaux, E.
2010-05-17	Authored	Ray, KP.

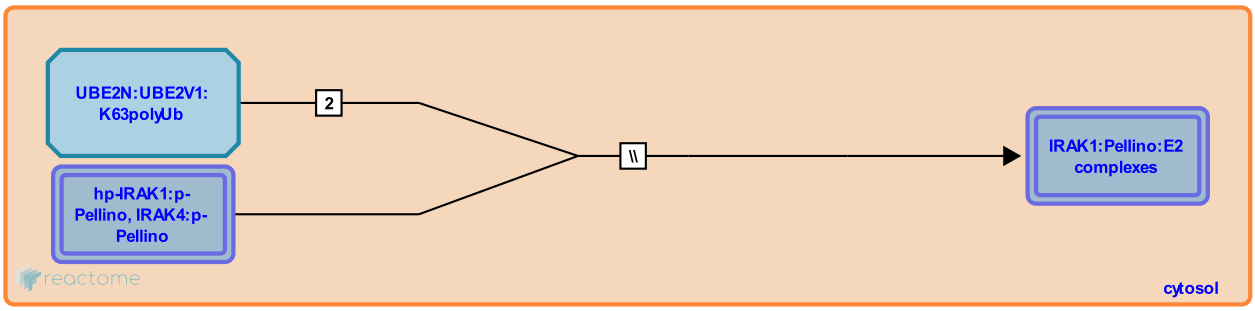
hp-IRAK1:p-Pellino, IRAK4:p-Pellino bind UBE2N:UBE2V1 ↗

Location: Interleukin-1 signaling

Stable identifier: R-HSA-8948063

Type: omitted

Compartments: cytosol



IL1 induces the poly-ubiquitination and degradation of IRAK1. Pellino1-3 possess E3 ligase activity and are believed to directly catalyse polyubiquitylation of IRAK1 (Xiao et al. 2008; Butler et al. 2007; Ordureau et al. 2008). They are capable of catalysing the formation of K63- and K48-linked polyubiquitin chains; the type of linkage is controlled by the collaborating E2 enzyme. All the Pellino proteins can combine with the E2 heterodimer UBE2N:UBE2V1 (Ubc13:Uev1a) to catalyze K63-linked ubiquitylation (Ordureau et al. 2008). IRAK1 polyubiquitination was originally thought to tag IRAK1 for proteolysis by the proteasome, but more recently has been shown to involve K63-linked, not K48-linked polyubiquitination (Windheim et al. 2008; Conze et al. 2008), which is believed to have a scaffoling function. IRAK1 is ubiquitinated on K134 and K180; mutation of these sites impairs IL1R-mediated ubiquitination of IRAK1 (Conze et al. 2008). Some authors have proposed a role for TRAF6 as the E3 ubiquitin ligase that catalyzes polyubiquitination of IRAK1 (Conze et al. 2008) but this view has been refuted (Windheim et al. 2008, Xiao et al. 2008). The current consensus is that Pellino proteins are the physiologically-relevant IRAK1 E3 ubiquitin ligases.

Literature references

Peggie, M., Ordureau, A., Carrick, E., Morrice, N., Windheim, M., Smith, H. et al. (2008). The IRAK-catalysed activation of the E3 ligase function of Pellino isoforms induces the Lys63-linked polyubiquitination of IRAK1. *Biochem J , 409*, 43-52. ↗

Editions

2010-05-17	Authored	Ray, KP.
2010-09-06	Reviewed	Pinteaux, E.

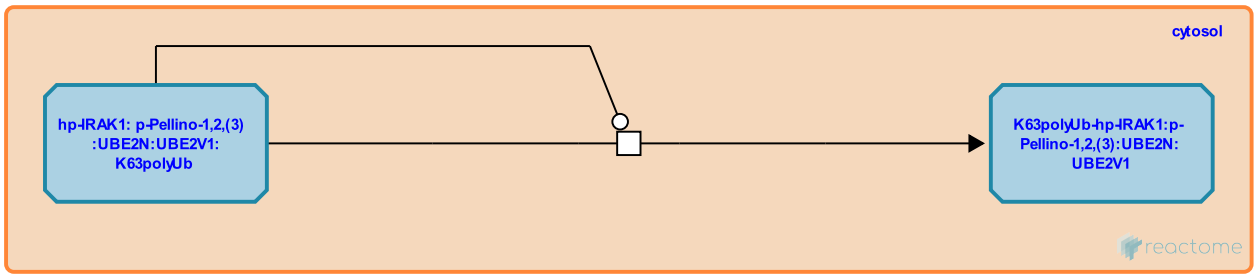
Pellino ubiquitinates IRAK1 ↗

Location: Interleukin-1 signaling

Stable identifier: R-HSA-451418

Type: transition

Compartments: cytosol



IL1 induces the poly-ubiquitination and degradation of IRAK1. This was believed to be K48-linked polyubiquitination, targeting IRAK1 for proteolysis by the proteasome, but recently IL-1R signaling has been shown to lead to K63-linked polyubiquitination of IRAK1 (Windheim et al. 2008; Conze et al. 2008), and demonstrated to have a role in the activation of NF-kappaB. IRAK1 is ubiquitinated on K134 and K180; mutation of these sites impairs IL1R-mediated ubiquitylation of IRAK1 (Conze et al. 2008). Some authors have proposed a role for TRAF6 as the E3 ubiquitin ligase that catalyzes polyubiquitination of IRAK1 (Conze et al. 2008) but this view has been refuted (Windheim et al. 2008; Xiao et al. 2008). There is stronger agreement that Pellino proteins have a role as IRAK1 E3 ubiquitin ligases.
Pellino1-3 possess E3 ligase activity and are believed to directly catalyse polyubiquitylation of IRAK1 (Xiao et al. 2008; Butler et al. 2007; Ordureau et al. 2008). They are capable of catalysing the formation of K63- and K48-linked polyubiquitin chains; the type of linkage is controlled by the collaborating E2 enzyme. All the Pellino proteins can combine with the E2 heterodimer UBE2N:UBE2V1 (Ubc13:Uev1a) to catalyze K63-linked ubiquitylation (Ordureau et al. 2008).

Literature references

Peggie, M., Ordureau, A., Carrick, E., Morrice, N., Windheim, M., Smith, H. et al. (2008). The IRAK-catalysed activation of the E3 ligase function of Pellino isoforms induces the Lys63-linked polyubiquitination of IRAK1. *Biochem J , 409*, 43-52. ↗

Editions

2010-05-17	Edited	Jupe, S.
2010-05-17	Reviewed	Pinteaux, E.
2010-05-17	Authored	Ray, KP.

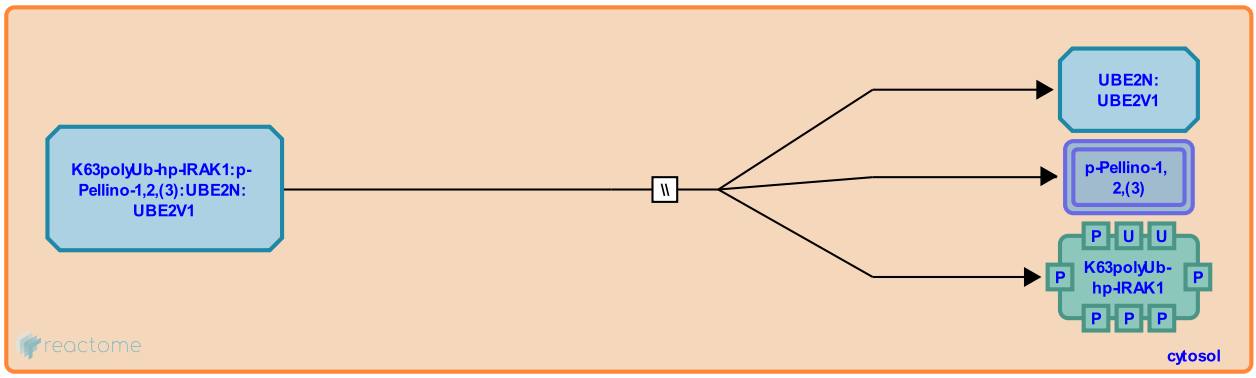
K63polyUb-IRAK1 dissociates ↗

Location: Interleukin-1 signaling

Stable identifier: R-HSA-8948066

Type: omitted

Compartments: cytosol



Pellino1, 2 and possibly 3 are believed to directly catalyse polyubiquitylation of IRAK1 (Xiao et al. 2008; Butler et al. 2007; Ordureau et al. 2008). Following ubiquitination IRAK1 dissociates.

Literature references

Peggie, M., Ordureau, A., Carrick, E., Morrice, N., Windheim, M., Smith, H. et al. (2008). The IRAK-catalysed activation of the E3 ligase function of Pellino isoforms induces the Lys63-linked polyubiquitination of IRAK1. *Biochem J , 409*, 43-52. ↗

Editions

2010-05-17	Authored	Ray, KP.
2010-09-06	Reviewed	Pinteaux, E.
2016-11-14	Edited	Jupe, S.

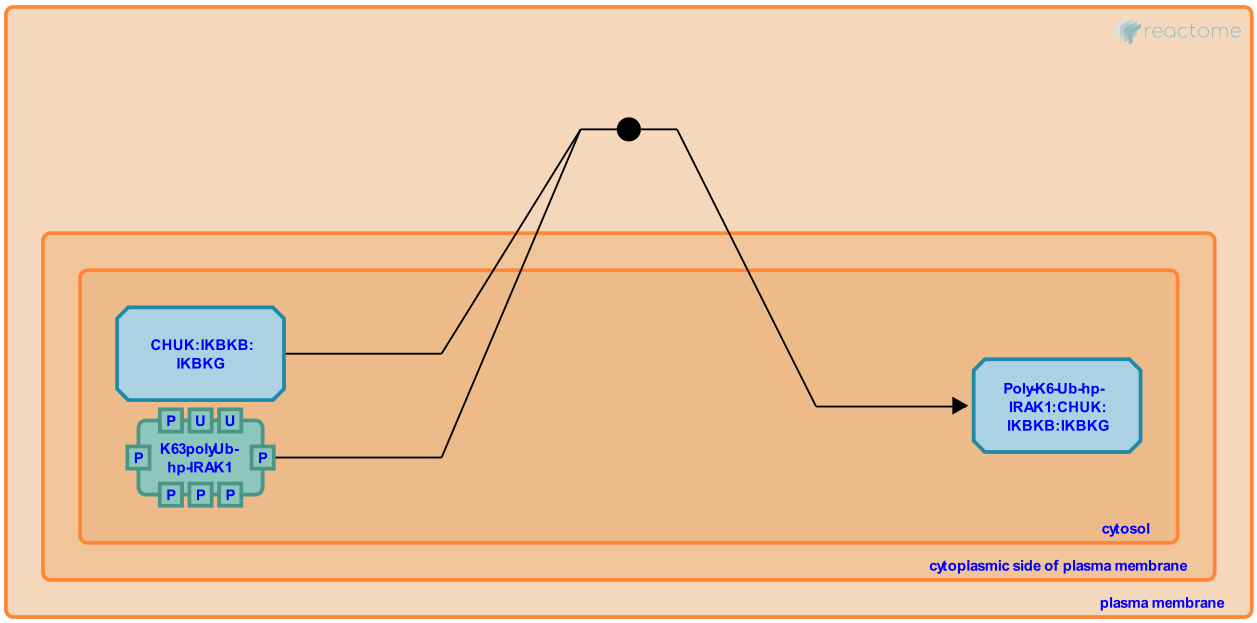
NEMO binds polyubiquitinated IRAK1 ↗

Location: Interleukin-1 signaling

Stable identifier: R-HSA-451561

Type: binding

Compartments: plasma membrane, cytosol



NF-kappa-B essential modulator (NEMO, also known as IKKG abbreviated from Inhibitor of nuclear factor kappa-B kinase subunit gamma) is the regulatory subunit of the IKK complex which phosphorylates inhibitors of NF-kappa-B leading to dissociation of the inhibitor/NF-kappa-B complex. NEMO binds to K63-pUb chains (Ea et al. 2006; Wu et al. 2006), linking K63-pUb-hp-IRAK1 with the IKK complex. Models of IL-1R dependent activation of NF-kappaB suggest that the polyubiquitination of both TRAF6 and IRAK1 within a TRAF6:IRAK1 complex and their subsequent interactions with the TAK1 complex and IKK complex respectively brings these complexes into proximity, facilitating the TAK1-catalyzed activation of IKK (Moynagh, 2008).

Literature references

Peggie, M., Stafford, M., Windheim, M., Cohen, P. (2008). Interleukin-1 (IL-1) induces the Lys63-linked polyubiquitination of IL-1 receptor-associated kinase 1 to facilitate NEMO binding and the activation of IkappaBalpha kinase . *Mol Cell Biol, 28*, 1783-91. ↗

Editions

2010-05-17	Edited	Jupe, S.
2010-05-17	Reviewed	Pinteaux, E.
2010-05-17	Authored	Ray, KP.

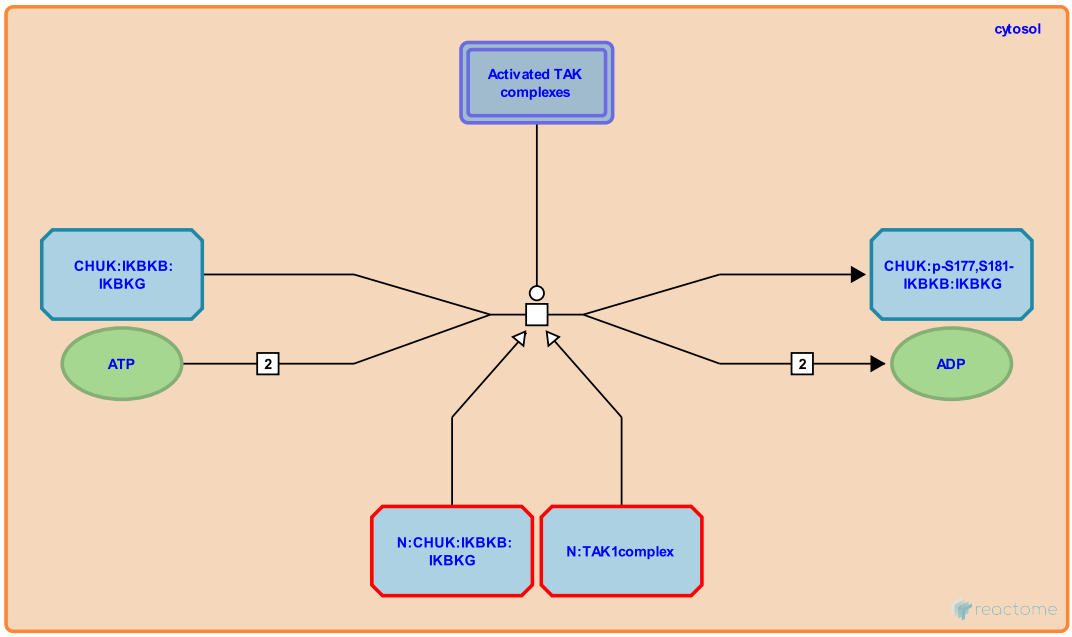
Activated TAK1 mediates phosphorylation of the IKK Complex ↗

Location: Interleukin-1 signaling

Stable identifier: R-HSA-168184

Type: transition

Compartments: cytosol



In humans, the IkB kinase (IKK) complex serves as the master regulator for the activation of NF-kappa-B by various stimuli. The IKK complex contains two catalytic subunits, IKK alpha (IKKa, IKK1 or CHUK) and IKK beta (IKKb, IKK2, IKBKB) associated with a regulatory subunit NEMO (IKK gamma or IKBKG). Each catalytic IKK subunit has an N-terminal kinase domain and leucine zipper (LZ) motifs, a helix-loop-helix (HLH) and a C-terminal NEMO binding domain (NBD). IKK catalytic subunits are dimerized through their LZ motifs. In the classical or canonical NF-kappa-B pathway, the activation of the IKK complex is dependent on the phosphorylation of IKKb (IKBKB) at its activation loop and the ubiquitination of IKBKG (NEMO) (Solt et al 2009; Li et al 2002). IKKb (IKBKB) is phosphorylated at Ser177 and Ser181 (Wang et al. 2001). IKBKG (NEMO) ubiquitination by TRAF6 is required for optimal activation of the IKK kinase activity; it is unclear if NEMO subunit undergoes K63-linked or linear ubiquitination. Activated IKK complex phosphorylates IkB alpha (IkBa or NFKBIA) on Ser32 and Ser36 leading to K48-linked ubiquitination and proteasome-dependent degradation of IkB alpha. This leads to the release of active NF-kappa-B dimers.

This Reactome event shows phosphorylation of IKK beta (IKBKB) by TGF-β–activated kinase 1 (TAK1), encoded by the MAP3K7 gene. TAK1 functions downstream of receptor signaling complexes in TLR, TNF-alpha and IL-1 signaling pathways (Xu & Lei 2021). TAK1 appears to be essential for IL-1-induced NF-kappa-B activation since a specific TAK1 inhibitor (5Z)-7-oxozeaenol prevents NF-kappa-B activation in human umbilical vein endothelial cells (HUVEC) (Lammel 2020); also, it prevents NF-kappa-B-mediated TNF production in human myeloid leukaemia U937 cells (Rawlins et al. 1999). TAK1 functions through assembling the TAK1 complex consisting of the coactivators TAB1 and either TAB2 or TAB3 (Shibuya et al. 1996, Sakurai et al. 2000; Xu & Lei 2021). TAB1 promotes TAK1 autophosphorylation at the kinase activation lobe (Sakurai et al. 2000; Brown et al. 2005). The TAK1 complex is regulated by polyubiquitination. The binding of TAB2 or TAB3 to polyubiquitinated TRAF6 may facilitate polyubiquitination of TAB2, -3 by TRAF6 (Ishitani et al. 2003), which in turn results in conformational changes within the TAK1 complex. TAB2 or -3 is recruited to K63-linked polyubiquitin chains of receptor interacting protein (RIP) kinase RIP1 (RIPK1) via the Zinc finger domain of TAB2 or TAB3. RIPK1 functions as an essential component of inflammatory and immune signaling pathways. Ubiquitination of RIPK1 follows the recruitment of TRADD and TRAF2 or -5 (the latter functions as the E3 ubiquitin ligase, but also cIAP1,-2 can ubiquitinate RIPK1 as a response to TNF receptor engagement (Varfolomeev et al. 2008). The IKK complex is also recruited ubiquitin (Ub) chains via its Ub binding domain. Polyubiquitin chains may function as a scaffold for higher order signaling complexes bringing the TAK1 and IKK complexes in close proximity and allowing TAK1 to phosphorylate IKBKB (IKK2) (Kanayama et al. 2004).

The alternative (non-canonical) pathway can be activated via CD40, LTßR, BAFF, RANK, and is therefore limited to cells which express these receptors. It leads to NIK-mediated phosphorylation of IKKa (IKK1, CHUK), which phosphorylates the NFKB2 (p52) precursor p100, leading to the ubiquitin-dependent degradation of its C-terminal part (processing of p100 to the mature p52 subunit) and releasing the NFKB2:RelB complex (Sun 2017). In non-stimulated cells NIK is constitutively degraded by the cIAP1/2:TRAF2:TRAF3 Ub ligase complex; following stimulation, the complex is recruited to the respective receptor comlex where cIAPs ubiquitinates TRAF3, resulting it its degradation and stabilization of NIK. NIK then phosphorylates and activates IKK1 (CHUK), leading to the NFKB2:RelB complex activation (Sun 2017). TRAF3 deubiquitylation by OTUD7B downregulates the NIK-mediated NF-kappa-B activation. (Hu et al 2013). In addition, TAK1 has been shown to interact with NIK and with IKK2, and TAK1 can be stimulated by anti-apoptotic protein, XIAP (Hofer-Warbinek et al. 2000). XIAP is an NF-kB dependent gene, therefore its expression represents a positive regulatory circuit. NIK is also involved in the classical pathway, and is activated by TAK1 in the IL-1 signalling pathway (Ninomiya-Tsui et al. 1999) and Hemophilus influenzae-induced TLR2 signalling pathway (Shuto et al. 2001).

RNA-induced liquid phase separation of SARS-CoV-2 nucleocapsid (N) protein serves as a platform to enhance the interaction between TAK1 and IKK complexes promoting NF-kappa-B-dependent inflammatory responses (Wu Y et al. 2021).

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

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

Israel, A. (2010). The IKK complex, a central regulator of NF-kappaB activation. *Cold Spring Harb Perspect Biol, 2*, a000158. ↗

Editions

2005-11-10	Authored	Luo, F.
2009-09-29	Revised	Shamovsky, V.
2009-12-16	Edited	Shamovsky, V.
2011-04-28	Reviewed	Kufer, TA.
2011-06-06	Reviewed	Rittinger, K., Wong, E.
2012-11-13	Reviewed	Fitzgerald, KA.
2012-11-16	Reviewed	Napetschnig, J.
2022-02-18	Reviewed	Messina, F.
2022-05-04	Reviewed	de Martin, R.

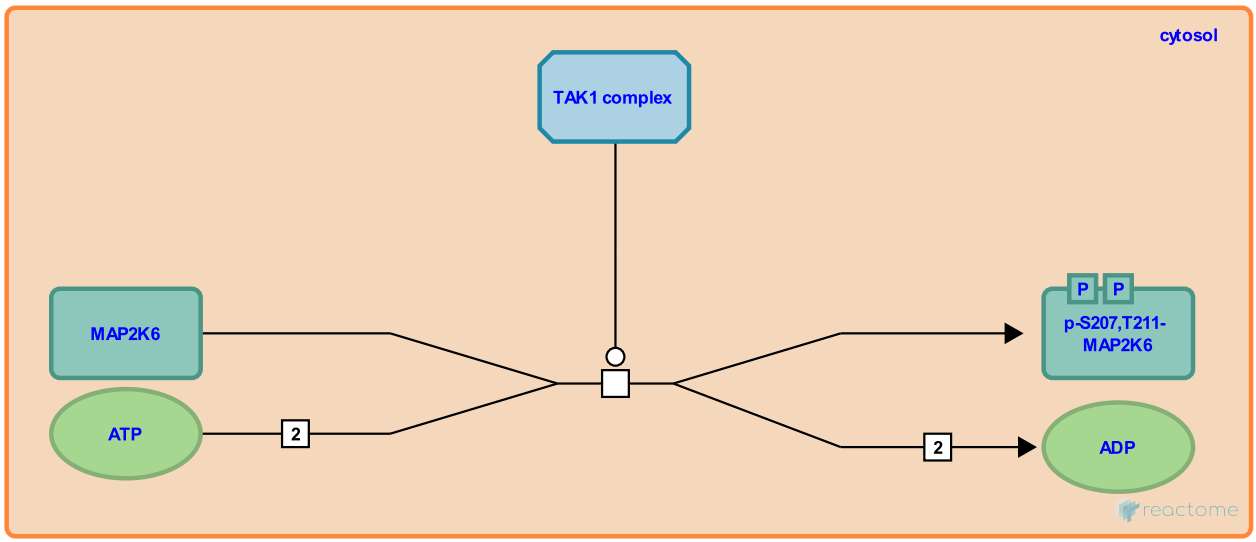
TAK1 phosphorylates MKK6 ↗

Location: Interleukin-1 signaling

Stable identifier: R-HSA-727819

Type: transition

Compartments: cytosol



Within the TAK1 complex (TAK1 plus TAB1 and TAB2/3) activated TAK1 phosphorylates IKKB, MAPK kinase 6 (MKK6) and other MAPKs to activate the NFkappaB and MAPK signaling pathways. TAB2 within the TAK1 complex can be linked to polyubiquitinated TRAF6; current models of IL-1 signaling suggest that the TAK1 complex is linked to TRAF6, itself complexed with polyubiquitinated IRAK1 which is linked via NEMO to the IKK complex. The TAK1 complex is also essential for NOD signaling; NOD receptors bind RIP2 which recruits the TAK1 complex (Hasegawa et al. 2008).

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. ↗

Editions

2010-05-17	Edited	Jupe, S.
2010-05-17	Authored	Ray, KP.
2011-04-28	Reviewed	Kufer, TA.
2011-06-06	Reviewed	Rittinger, K., Wong, E.

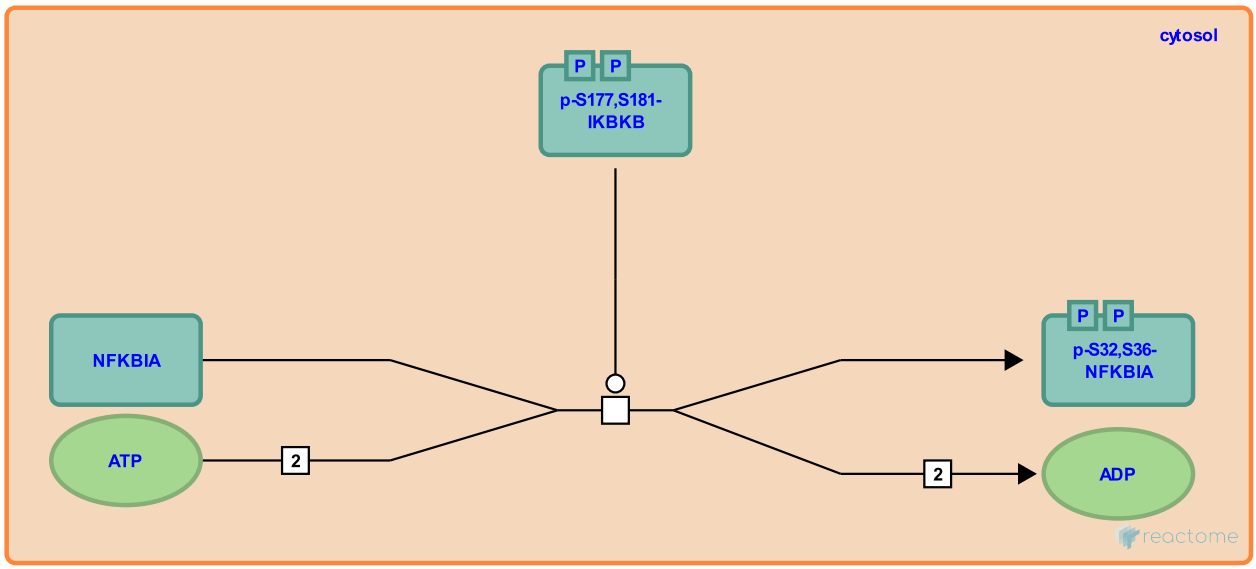
IKBA is phosphorylated by Phospho IKKB kinase ↗

Location: Interleukin-1 signaling

Stable identifier: R-HSA-209087

Type: transition

Compartments: cytosol



Human IKBA, orthologue of Drosophila Cactus (CACT), is phosphorylated by activated IKKB kinase at residues Ser32 and Ser36.

Literature references

Bennett, BL., Rao, A., Barbosa, M., Shevchenko, A., Young, DB., Mann, M. et al. (1997). IKK-1 and IKK-2: cytokine-activated IkappaB kinases essential for NF-kappaB activation. *Science, 278*, 860-6. ↗

Wu, C., Ghosh, S. (2003). Differential phosphorylation of the signal-responsive domain of I kappa B alpha and I kappa B beta by I kappa B kinases. *J Biol Chem, 278*, 31980-7. ↗

Editions

2010-05-17	Edited	Jupe, S.
2010-05-17	Reviewed	Pinteaux, E.
2010-05-17	Authored	Ray, KP.

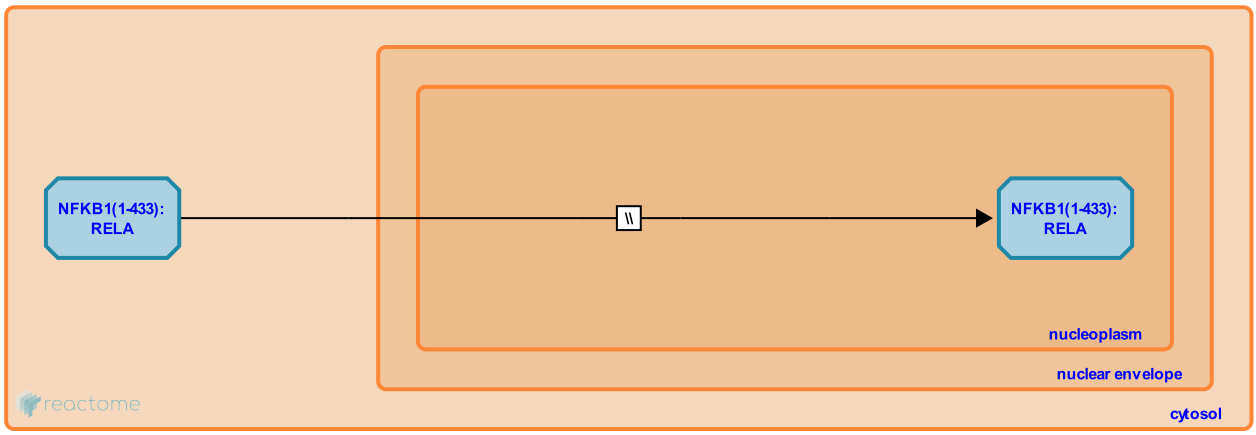
NFKB1:RELA translocates from the cytosol to the nucleus ↗

Location: Interleukin-1 signaling

Stable identifier: R-HSA-2730894

Type: omitted

Compartments: nucleoplasm, cytosol



The released NF-kB transcription factor (p50/p65) with unmasked nuclear localization signal (NLS) moves in to the nucleus. Once in the nucleus, NF-kB binds DNA and regulate the expression of genes encoding cytokines, cytokine receptors, and apoptotic regulators.

Literature references

Gilmore, TD. (2006). Introduction to NF-kappaB: players, pathways, perspectives. *Oncogene, 25*, 6680-4. ↗

Editions

2012-08-22	Edited	Garapati, P V.
2012-12-21	Authored	Niarakis, A.
2013-02-13	Reviewed	Roncagalli, R.

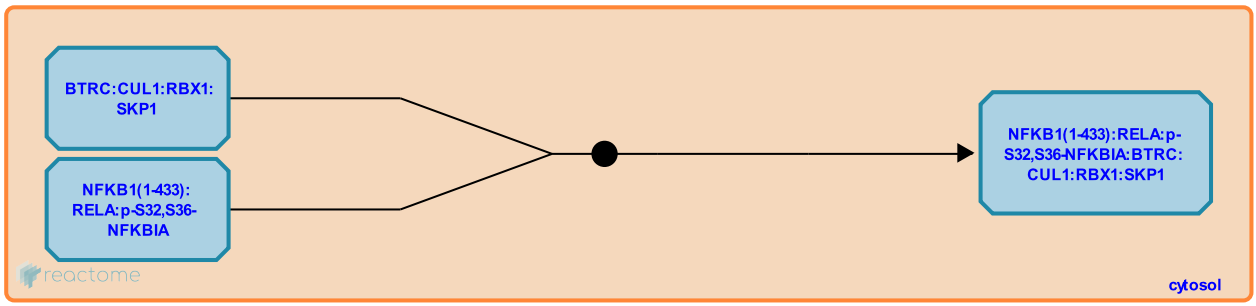
SCF Beta-TrCP complex binds to NFKB p50:p65: phospho IKBA complex ↗

Location: Interleukin-1 signaling

Stable identifier: R-HSA-209125

Type: binding

Compartments: cytosol



Human beta-TrCP forms part of the SCF E3 ubiquitin ligase complex which binds to phosphorylated residues Ser32 and Ser 36 at the IKK target motif in IKBA complex with P65:P50 heterodimer.

Literature references

Strack, P., Elledge, SJ., Beer-Romero, P., Chu, CY., Winston, JT., Harper, JW. (1999). The SCFbeta-TRCP-ubiquitin ligase complex associates specifically with phosphorylated destruction motifs in IkappaBalpha and beta-catenin and stimulates IkappaBalpha ubiquitination in vitro. *Genes Dev, 13*, 270-83. ↗

Matsumoto, M., Hatakeyama, S., Shirane, M., Hattori, K., Nakayama, K. (1999). Molecular dissection of the interactions among IkappaBalpha, FWD1, and Skp1 required for ubiquitin-mediated proteolysis of IkappaBalpha. *J Biol Chem, 274*, 29641-7. ↗

Scherer, D., Chen, Z., Hagler, J., Palombella, VJ., Ballard, D., Maniatis, T. et al. (1995). Signal-induced site-specific phosphorylation targets I kappa B alpha to the ubiquitin-proteasome pathway. *Genes Dev, 9*, 1586-97. ↗

Jiang, J., Spencer, E., Chen, ZJ. (1999). Signal-induced ubiquitination of IkappaBalpha by the F-box protein Slimb/beta-TrCP. *Genes Dev, 13*, 284-94. ↗

Margottin, F., Bachelerie, F., Kohl, A., Benarous, R., Concordet, JP., Durand, H. et al. (1999). Inducible degradation of IkappaBalpha by the proteasome requires interaction with the F-box protein h-betaTrCP. *J Biol Chem, 274*, 7941-5. ↗

Editions

2010-05-17	Edited	Jupe, S.
2010-05-17	Reviewed	Pinteaux, E.
2010-05-17	Authored	Ray, KP.

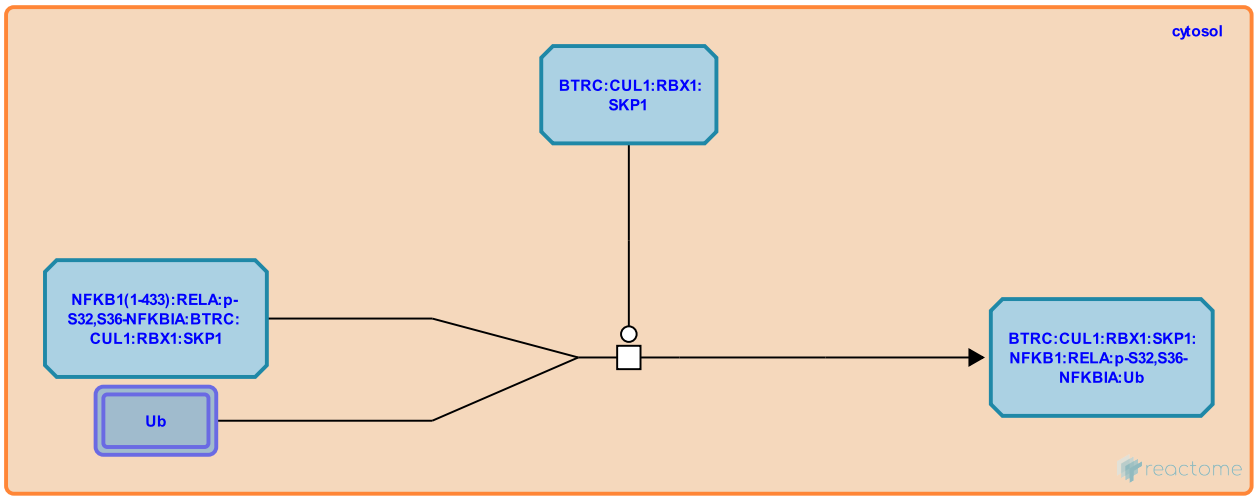
Beta-TrCP ubiquitinates NFKB p50:p65:phospho IKBA complex ↗

Location: Interleukin-1 signaling

Stable identifier: R-HSA-209063

Type: transition

Compartments: cytosol



SCF (Beta-TrCP) ubiquitinates phosphorylated I kappa B alpha.

Literature references

Strack, P., Elledge, SJ., Beer-Romero, P., Chu, CY., Winston, JT., Harper, JW. (1999). The SCFbeta-TRCP-ubiquitin ligase complex associates specifically with phosphorylated destruction motifs in IkappaBalpha and beta-catenin and stimulates IkappaBalpha ubiquitination in vitro. *Genes Dev, 13*, 270-83. ↗

Matsumoto, M., Hatakeyama, S., Shirane, M., Hattori, K., Nakayama, K. (1999). Molecular dissection of the interactions among IkappaBalpha, FWD1, and Skp1 required for ubiquitin-mediated proteolysis of IkappaBalpha. *J Biol Chem, 274*, 29641-7. ↗

Scherer, D., Chen, Z., Hagler, J., Palombella, VJ., Ballard, D., Maniatis, T. et al. (1995). Signal-induced site-specific phosphorylation targets I kappa B alpha to the ubiquitin-proteasome pathway. *Genes Dev, 9*, 1586-97. ↗

Jiang, J., Spencer, E., Chen, ZJ. (1999). Signal-induced ubiquitination of IkappaBalpha by the F-box protein Slimb/beta-TrCP. *Genes Dev, 13*, 284-94. ↗

Andersen, JS., Mann, M., Lavon, I., Manning, AM., Hatzubai, A., Amit, S. et al. (1998). Identification of the receptor component of the IkappaBalpha-ubiquitin ligase. *Nature, 396*, 590-4. ↗

Editions

2010-05-17	Edited	Jupe, S.
2010-05-17	Reviewed	Pinteaux, E.
2010-05-17	Authored	Ray, KP.

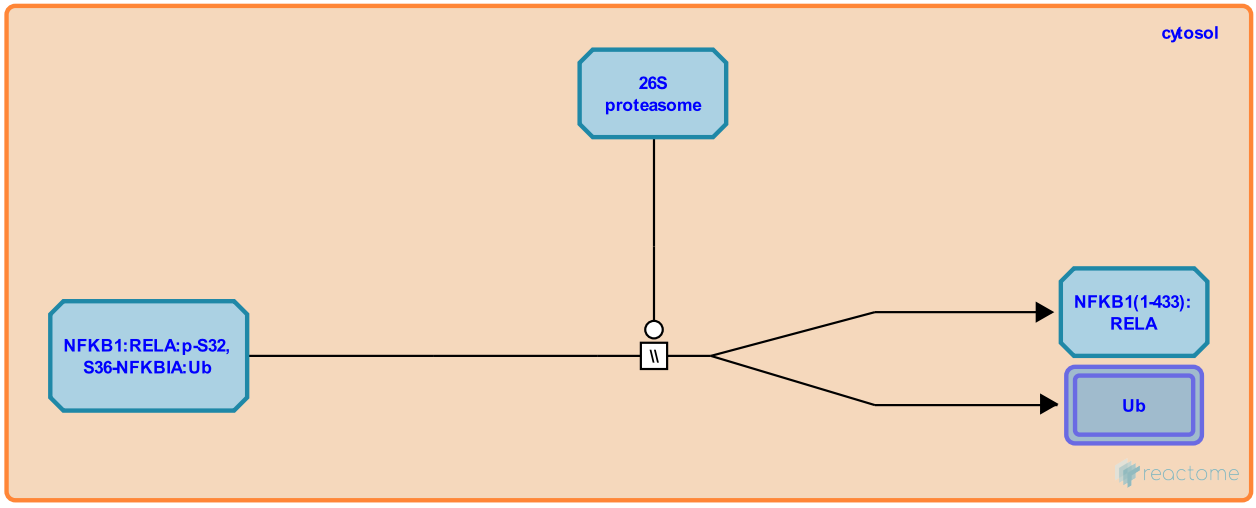
Ubiquitinated and phosphorylated IKBA binds to and is degraded by the proteasome complex ↗

Location: Interleukin-1 signaling

Stable identifier: R-HSA-209061

Type: omitted

Compartments: cytosol



Ubiquitinated IKBA is degraded by the proteasome complex.

Literature references

Matsumoto, M., Hatakeyama, S., Shirane, M., Hattori, K., Nakayama, K. (1999). Molecular dissection of the interactions among IkappaBalpha, FWD1, and Skp1 required for ubiquitin-mediated proteolysis of IkappaBalpha. *J Biol Chem, 274*, 29641-7. ↗

Scherer, D., Chen, Z., Hagler, J., Palombella, VJ., Ballard, D., Maniatis, T. et al. (1995). Signal-induced site-specific phosphorylation targets I kappa B alpha to the ubiquitin-proteasome pathway. *Genes Dev, 9*, 1586-97. ↗

Jiang, J., Spencer, E., Chen, ZJ. (1999). Signal-induced ubiquitination of IkappaBalpha by the F-box protein Slimb/beta-TrCP. *Genes Dev, 13*, 284-94. ↗

Margottin, F., Bachelerie, F., Kohl, A., Benarous, R., Concordet, JP., Durand, H. et al. (1999). Inducible degradation of IkappaBalpha by the proteasome requires interaction with the F-box protein h-betaTrCP. *J Biol Chem, 274*, 7941-5. ↗

Boisclair, M., Auger, KR., Beer-Romero, P., Parsons, T., Theodoras, A., Strack, P. et al. (2000). SCF(beta-TRCP) and phosphorylation dependent ubiquitinationof I kappa B alpha catalyzed by Ubc3 and Ubc4. *Oncogene, 19*, 3529-36. ↗

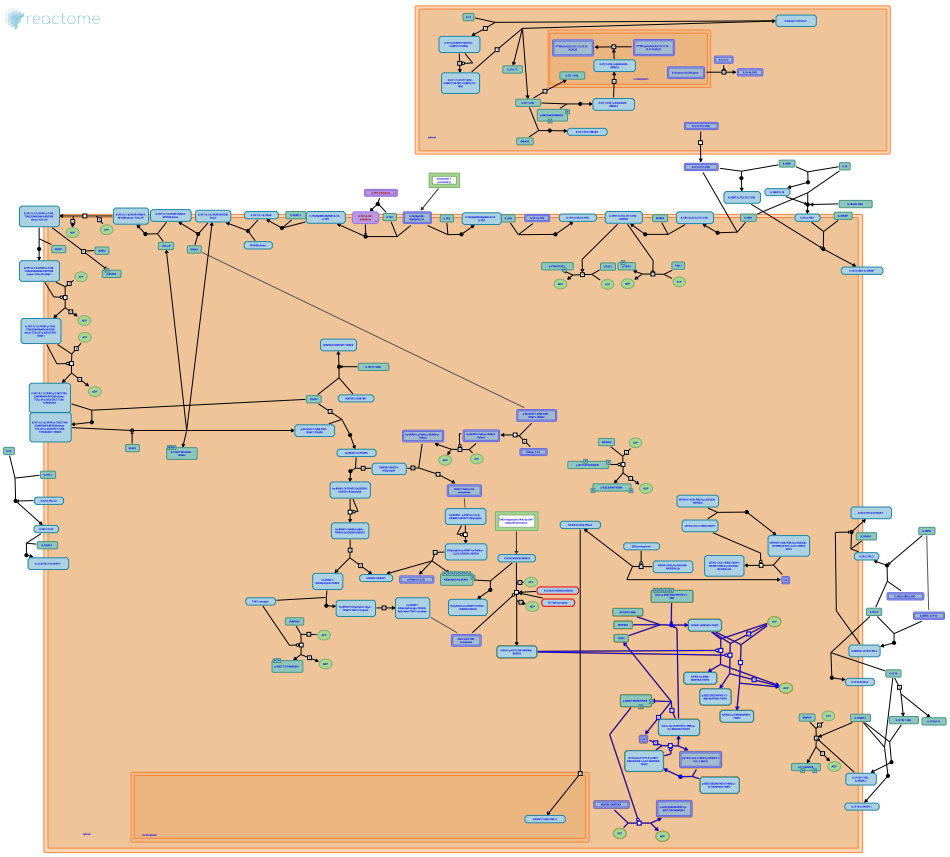
Editions

2010-05-17	Edited	Jupe, S.
2010-05-17	Reviewed	Pinteaux, E.
2010-05-17	Authored	Ray, KP.

MAP3K8 (TPL2)-dependent MAPK1/3 activation ↗

Location: Interleukin-1 signaling

Stable identifier: R-HSA-5684264



Tumor progression locus-2 (TPL2, also known as COT and MAP3K8) functions as a mitogen-activated protein kinase (MAPK) kinase kinase (MAP3K) in various stress-responsive signaling cascades. MAP3K8 (TPL2) mediates phosphorylation of MAP2Ks (MEK1/2) which in turn phosphorylate MAPK (ERK1/2) (Gantke T et al., 2011).

In the absence of extra-cellular signals, cytosolic MAP3K8 (TPL2) is held inactive in the complex with ABIN2 (TNIP2) and NFkB p105 (NFKB1) (Beinke S et al., 2003; Waterfield MR et al., 2003; Lang V et al., 2004). This interaction stabilizes MAP3K8 (TPL2) but also prevents MAP3K8 and NFkB from activating their downstream signaling cascades by inhibiting the kinase activity of MAP3K8 and the proteolysis of NFkB precursor protein p105. Upon activation of MAP3K8 by various stimuli (such as LPS, TNF-alpha, and IL-1 beta), IKBKB phosphorylates NFkB p105 (NFKB1) at Ser927 and Ser932, which trigger p105 proteasomal degradation and releases MAP3K8 from the complex (Beinke S et al., 2003, 2004; Roget K et al., 2012). Simultaneously, MAP3K8 is activated by auto- and/or transphosphorylation (Gantke T et al. 2011; Yang HT et al. 2012). The released active MAP3K8 phosphorylates its substrates, MAP2Ks. The free MAP3K8, however, is also unstable and is targeted for proteasome-mediated degradation, thus restricting prolonged activation of MAP3K8 (TPL2) and its downstream signaling pathways (Waterfield MR et al. 2003; Cho J et al., 2005). Furthermore, partially degraded NFkB p105 (NFKB1) into p50 can dimerize with other NFkB family members to regulate the transcription of target genes.

MAP3K8 activity is thought to regulate the dynamics of transcription factors that control an expression of diverse genes involved in growth, differentiation, and inflammation. Suppressing the MAP3K8 kinase activity with selective inhibitors, such as C8-chloronaphthyridine-3-carbonitrile, caused a significant reduction in TNFalpha production in LPS- and IL-1beta-induced both primary human monocytes and human blood (Hall JP et al. 2007). Similar results have been reported for mouse LPS-stimulated RAW264.7 cells (Hirata K et al. 2010). Moreover, LPS-stimulated macrophages derived from Map3k8 knockout mice secreted lower levels of pro-inflammatory cytokines such as TNFalpha, Cox2, Pge2 and CXCL1 (Dumitru CD et al. 2000; Eliopoulos AG et al. 2002). Additionally, bone marrow-derived dendritic cells (BMDCs) and macrophages from Map3k8 knockout mice showed significantly lower expression of IL-1beta in response to LPS, poly IC and LPS/MDP (Mielke et al., 2009). However, several other studies seem to contradict these findings and Map3k8 deficiency in mice has been also reported to enhance pro-inflammatory profiles. Map3k8 deficiency in LPS-stimulated macrophages was associated with an increase in nitric oxide synthase 2 (NOS2) expression (López-Peláez et al., 2011). Similarly, expression of IRAK-M, whose function

is to compete with IL-1R-associated kinase (IRAK) family of kinases, was decreased in Map3k8-/- macrophages while levels of TNF and IL6 were elevated (Zacharioudaki et al., 2009). Moreover, significantly higher inflammation level was observed in 12-O-tetradecanoylphorbol-13-acetate (TPA)-treated Map3k8-/- mouse skin compared to WT skin (DeCicco-Skinner K. et al., 2011). Additionally, MAP3K8 activity is associated with NFkB inflammatory pathway. High levels of active p65 NFkB were observed in the nucleus of Map3k8 -/- mouse keratinocytes that dramatically increased within 15-30 minutes of TPA treatment. Similarly, increased p65 NFkB was observed in Map3k8-deficient BMDC both basally and after stimulation with LPS when compared to wild type controls (Mielke et al., 2009). The data opposes the findings that Map3k8-deficient mouse embryo fibroblasts and human Jurkat T cells with kinase domain-deficient protein have a reduction in NFkB activation but only when certain stimuli are administered (Lin et al., 1999; Das S et al., 2005). Thus, it is possible that whether MAP3K8 serves more of a pro-inflammatory or anti-inflammatory role may depend on cell- or tissue type and on stimuli (LPS vs. TPA, etc.) (Mielke et al., 2009; DeCicco-Skinner K. et al., 2012).

MAP3K8 has been also studied in the context of carcinogenesis, however the physiological role of MAP3K8 in the etiology of human cancers is also convoluted (Vougioukalaki M et al., 2011; DeCicco-Skinner K. et al., 2012).

Literature references

Ley, SC., Brender, C., Handley, M., Belich, M., Janzen, J., Papoutsopoulou, S. et al. (2012). Coordinate regulation of TPL-2 and NF-?B signaling in macrophages by NF-?B1 p105. *Mol. Cell. Biol., 32,* 3438-51. ↗

Ley, SC., Sriskantharajah, S., Gantke, T. (2011). Regulation and function of TPL-2, an I?B kinase-regulated MAP kinase kinase kinase. *Cell Res., 21,* 131-45. ↗

Da Silva Xavier, G. (2012). The Role of Tpl2 Protein Kinase in Carcinogenesis and Inflammation, Advances in Protein Kinases.

Editions

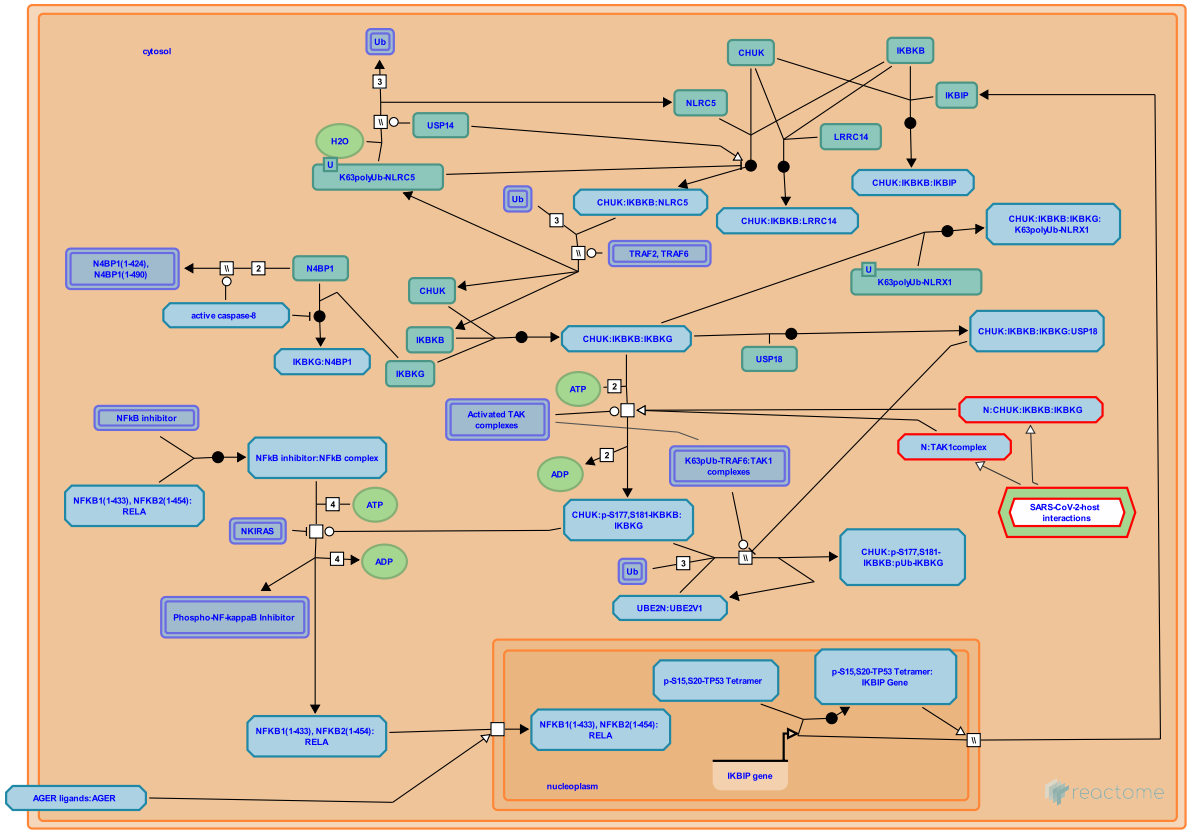
2015-04-14	Reviewed	Jupe, S.
2015-05-13	Authored	Shamovsky, V.
2015-08-21	Reviewed	DeCicco-Skinner, KL.
2015-08-25	Edited	Shamovsky, V.

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

Location: Interleukin-1 signaling

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.

Table of Contents