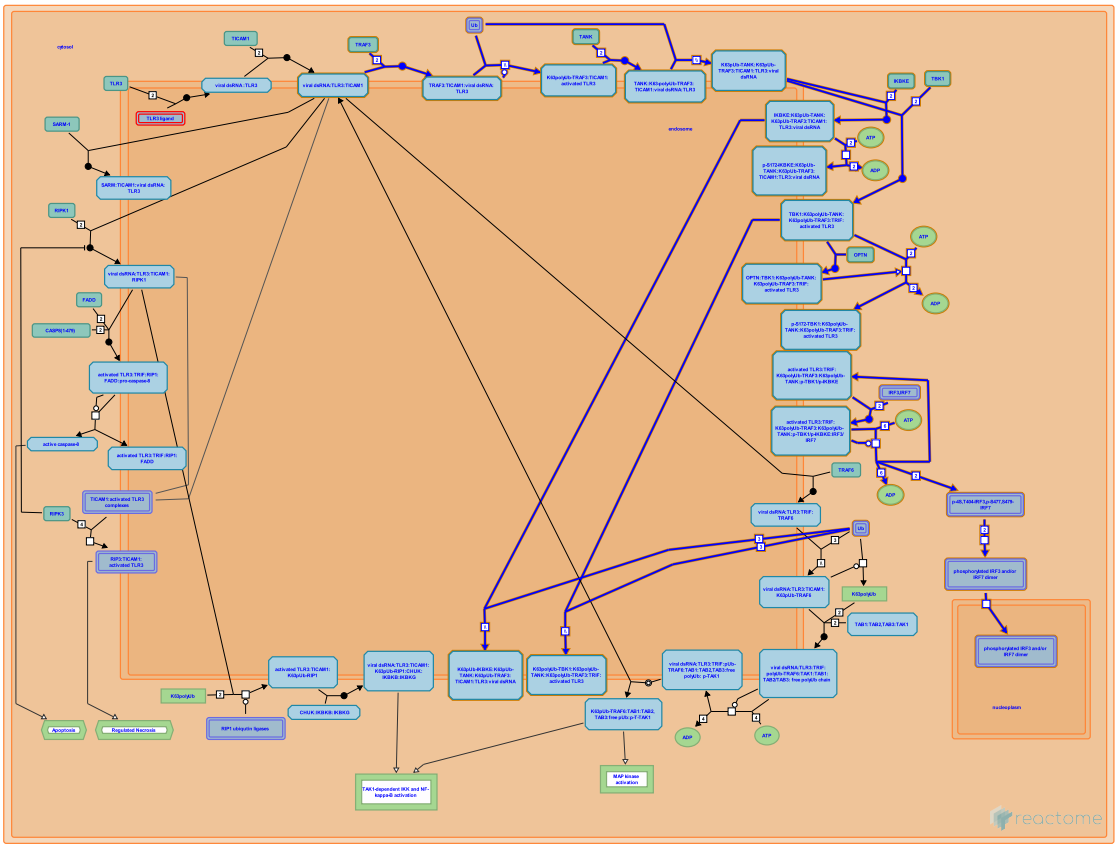
TICAM1-dependent activation of IRF3/IRF7



D'Eustachio, P., Fitzgerald, KA., Franjkić, T., Gay, NJ., Gillespie, ME., Masci, A M., Munitić, I., Shamovsky, V., de Bono, B.

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10/04/2024

Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.
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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. ↗

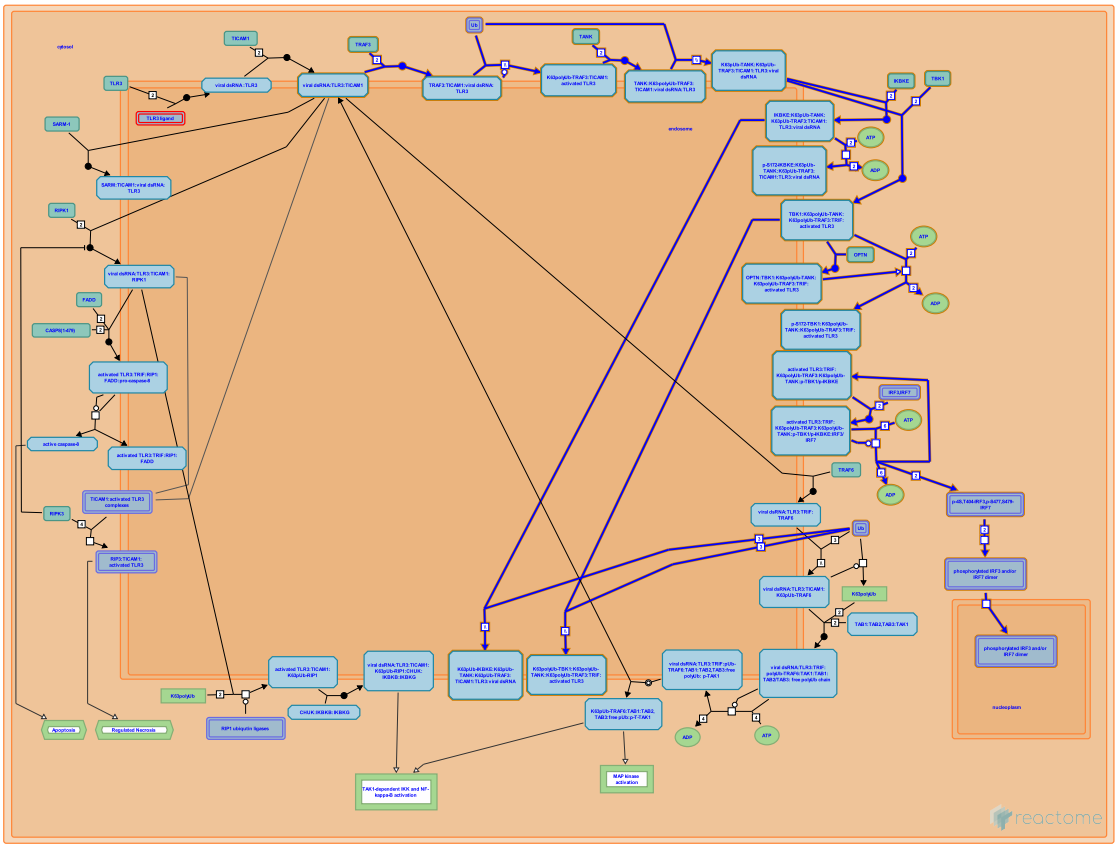
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

TICAM1-dependent activation of IRF3/IRF7 ↗

Stable identifier: R-HSA-9013973

Compartments: cytosol



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

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

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

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

Literature references

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

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

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

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

Editions

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

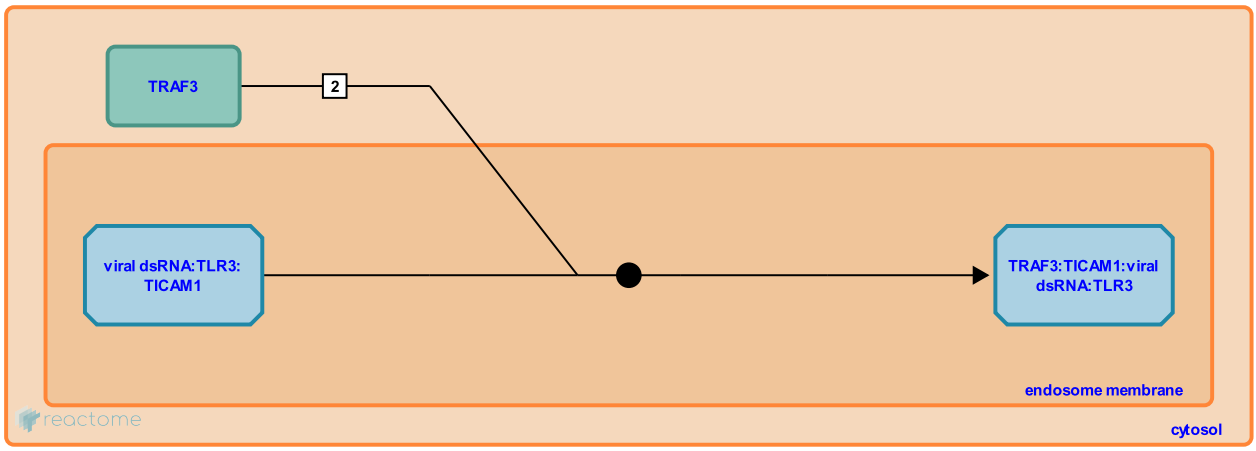
TRAF3 binds to TRIF:activated TLR3 complex ↗

Location: TICAM1-dependent activation of IRF3/IRF7

Stable identifier: R-HSA-9013992

Type: binding

Compartments: endosome membrane, cytosol



Tumor necrosis factor (TNF) receptor associated factor 3 (TRAF3) is a ubiquitin ligase recruited to both MYD88- and TRIF-assembled signalling complexes (Hacker H et al., 2006). However, TRAF3 controls the production of interferon and proinflammatory cytokines in different ways (Tseng PH et al., 2010). Positive or negative type of regulation is dictated by TRAF3 subcellular distribution and its mode of ubiquitination. Thus, TRIF-mediated signaling initiated on endosomes triggers TRAF3 self-ubiquitination through noncanonical (K63-linked) polyubiquitination, which is essential for activation of IRF3/7 and the interferon response. In contrast, during MyD88-dependent signaling initiated from plasma membrane TRAF3 functions as a negative regulator of inflammatory cytokines and mitogen-activated protein kinases (MAPKs), unless it undergoes degradative (K48-linked) polyubiquitination mediated by TRAF6 and a pair of the ubiquitin ligases cIAP1 and cIAP2. The degradation of TRAF3 is essential for MAPK activation via TAK1 and MEKK1 (Tseng PH et al., 2010).

Followed by: Auto-ubiquitination of TRAF3 within activated TLR3 complex

Literature references

Mino, T., Matsuzawa, A., Karin, M., Zhang, W., Tseng, PH., Vignali, DA. (2010). Different modes of ubiquitination of the adaptor TRAF3 selectively activate the expression of type I interferons and proinflammatory cytokines. *Nat Immunol, 11*, 70-5. ↗

Perry, A., Saha, SK., Oganesyan, G., He, JQ., Guo, B., Shahangian, A. et al. (2006). Critical role of TRAF3 in the Toll-like receptor-dependent and -independent antiviral response. *Nature, 439*, 208-11. ↗

Hsu, LC., Raz, E., Häcker, G., Karin, M., Kamps, MP., Mann, M. et al. (2006). Specificity in Toll-like receptor signalling through distinct effector functions of TRAF3 and TRAF6. *Nature, 439*, 204-7. ↗

Editions

2012-04-26	Authored	Shamovsky, V.
2012-05-25	Reviewed	D'Eustachio, P.
2012-05-25	Edited	Shamovsky, V.
2012-11-13	Reviewed	Fitzgerald, KA.
2014-05-16	Reviewed	Masci, A M.

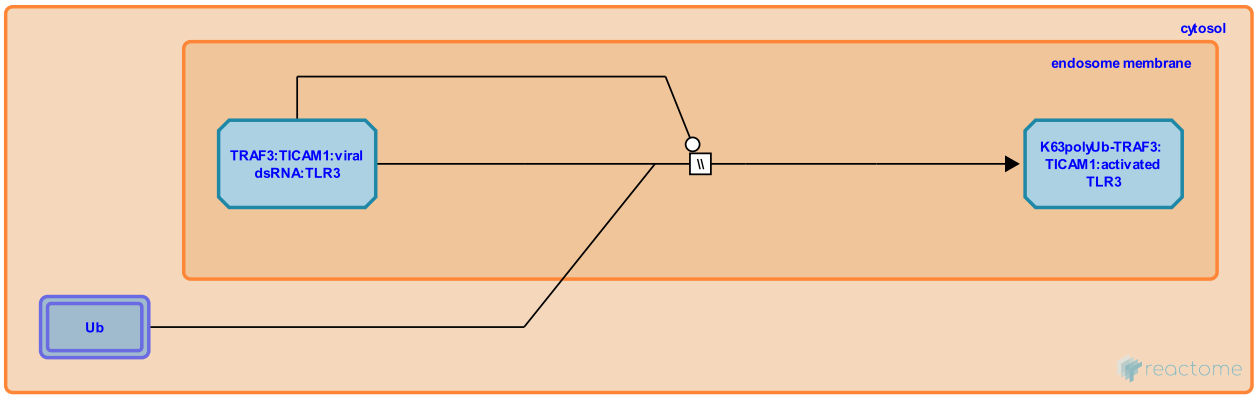
Auto-ubiquitination of TRAF3 within activated TLR3 complex ↗

Location: TICAM1-dependent activation of IRF3/IRF7

Stable identifier: R-HSA-9013974

Type: omitted

Compartments: endosome membrane, cytosol



TRIF(TICAM1) signaling activates TRAF3 self-mediated polyubiquitination trough Lys-63 of ubiquitin. The ubiquitinated TRAF3 in turn activates the interferon response (Tseng PH et al. 2010).

Preceded by: TRAF3 binds to TRIF:activated TLR3 complex

Followed by: TANK binds K63-poly-Ub-TRAF3:TICAM1:activated TLR3

Literature references

Mino, T., Matsuzawa, A., Karin, M., Zhang, W., Tseng, PH., Vignali, DA. (2010). Different modes of ubiquitination of the adaptor TRAF3 selectively activate the expression of type I interferons and proinflammatory cytokines. *Nat Immunol, 11*, 70-5. ↗

Editions

2012-04-26	Authored	Shamovsky, V.
2012-05-25	Reviewed	D'Eustachio, P.
2012-05-25	Edited	Shamovsky, V.
2012-11-13	Reviewed	Fitzgerald, KA.
2014-05-16	Reviewed	Masci, A M.

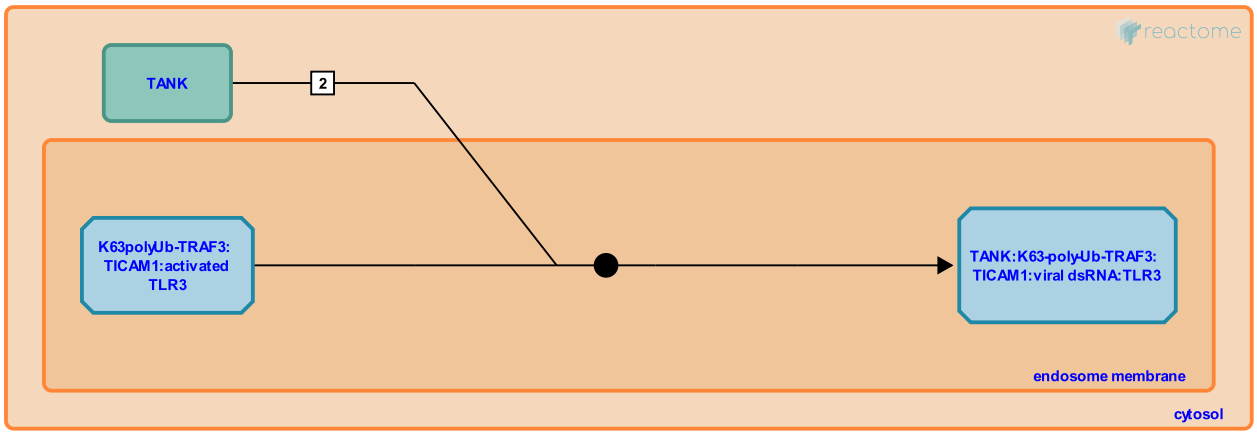
TANK binds K63-poly-Ub-TRAF3:TICAM1:activated TLR3

Location: TICAM1-dependent activation of IRF3/IRF7

Stable identifier: R-HSA-9013985

Type: binding

Compartments: endosome membrane, cytosol



TRAF family member-associated NFkB activator (TANK or ITRAF) is a TRAF-binding protein that has been implicated in RLR, TNFR and IL-1R/TLR signaling pathways in mammals (Rothe M et a.l 1996; Pomerantz JL and Baltimore D 1999; Li C et al. 2002; Guo B and Cheng G 2007; Konno H 2009). TANK was shown to interact with TBK1, IKK epsilon, IPS-1, TRIF (TICAM1), IRF3 and is thought to be a part of the TRAF3-containing complex (Pomerantz JL and Baltimore D 1999; Guo B and Cheng G 2007; Gatot JC et al. 2007). Upon microbe stimulation TANK is believed to induce IRF-dependent type I IFN production in mammalian cells by linking kinase TBK1 or IKK epsilon with upstream mediators TRAF3/6 (Guo B and Cheng G 2007; Gatot JC et al. 2007). In addition, TANK is thought to act synergistically with IKK epsilon or TBK1 to link them to IKK complex via interaction with NEMO (IKK gamma), where TBK1/IKK epsilon may modulate NFkB activation (Chariot A et al. 2002). TANK influence on NFkB activation was found to occur via either positive or negative regulation (Guo B and Cheng G 2007, Konno H et al. 2009; Pomerantz JL and Baltimore D 1999; Kawagoe T et al. 2009).

Two other adaptor proteins NAK-associated protein 1 (NAP1) and SINTBAD (not shown here) have been implicated in TBK1/IKKepsilon-mediated activation of IRF3 (Sasai M et al. 2005; Ryzhakov G and Randow F 2007). Structural and functional studies showed that TANK, NAP1 and SINTBAD share a common region which mediates association with the coiled-coil 2 in TBK1 (Ryzhakov G and Randow F 2007; Goncalves A et al. 2011; Larabi A et al. 2013; Tu D et al. 2013). TANK, NAP1 and SINTBAD were found to compete for TBK1 binding (Ryzhakov G and Randow F 2007; Goncalves A et al. 2011), TBK1 is thought to form alternative complexes with each adaptor TANK, NAP1 or SINTBAD, rather than a single large multiprotein complex containing all three adaptors (Goncalves A et al. 2011; Larabi A et al. 2013).

Preceded by: Auto-ubiquitination of TRAF3 within activated TLR3 complex

Followed by: TANK is ubiquitinated within TANK:K63polyUb-TRAF3:TICAM1:TLR3:viral dsRNA

Literature references

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

Guo, B., Cheng, G. (2007). Modulation of the interferon antiviral response by the TBK1/IKKi adaptor protein TANK. *J Biol Chem, 282*, 11817-26.

Editions

2014-05-16	Reviewed	Masci, A M.
2014-05-16	Authored, Edited	Shamovsky, V.

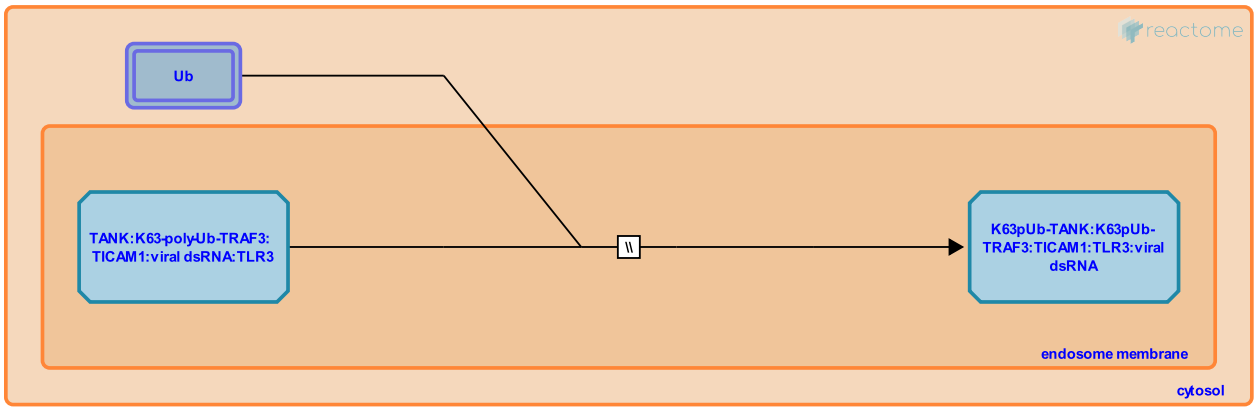
TANK is ubiquitinated within TANK:K63polyUb-TRAF3:TICAM1:TLR3:viral dsRNA

Location: TICAM1-dependent activation of IRF3/IRF7

Stable identifier: R-HSA-9013990

Type: omitted

Compartments: endosome membrane, cytosol



Upon stimulation by pathogen-associated inflammatory signals TANK associates with TRAF3 which may result in K63-linked ubiquitination of TANK (Gatot JC et al. 2007). How the ubiquitination of TANK contributes to the activation of TBK1 and/or IKKepsilon remains unclear.

Preceded by: TANK binds K63-poly-Ub-TRAF3:TICAM1:activated TLR3

Followed by: TBK1 binds K63-pUb-TANK:K63-pUb-TRAF3:TRIF:activated TLR3 , IKKε (IKBKE) binds K63-pUb-TANK:K63-pUb-TRAF3:TRIF:activated TLR3

Literature references

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

Editions

2014-05-16	Reviewed	Masci, A M.
2014-05-16	Authored, Edited	Shamovsky, V.

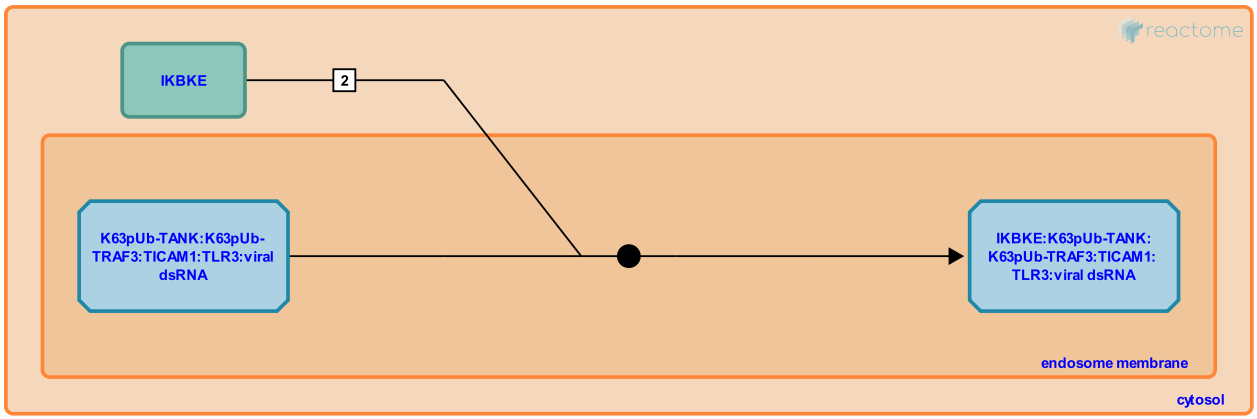
IKKε (IKBKE) binds K63-pUb-TANK:K63-pUb-TRAF3:TRIF:activated TLR3

Location: TICAM1-dependent activation of IRF3/IRF7

Stable identifier: R-HSA-9828204

Type: binding

Compartments: endosome membrane, cytosol



Pathogen-induced inflammatory signaling pathways lead to the activation of inhibitor of kappaB kinase epsilon (IKKε, IKBKE) and its close homolog TANK-binding kinase 1 (TBK1). Both TBK1 and IKKε (IKBKE) are serine/threonine kinases, which induce type I interferon production and modulate nuclear factor kappa-B (NF-kappa-B) signaling (Fitzgerald KA et al., 2003; Hemmi H et al., 2004; Taft J et al., 2021; Wegner J et al., 2023).

This Reactome event shows recruitment of IKKε (IKBKE) to the activated TLR3 complex, followed by homodimerization of IKKε (Zhou AY et al., 2013; Nakatsu Y et al., 2014).

Both TBK1 and IKKε (IKBKE) are regulated through similar activation mechanisms involving phosphorylation and ubiquitination (Ikeda F et al., 2007; Tu D et al., 2013; Zhou AY et al., 2013). Structural studies of TBK1 reveal a dimeric assembly that is mediated by several interfaces involving an N-terminal kinase domain (KD), a ubiquitin-like domain (ULD), and an alpha-helical scaffold dimerization domain (SDD) of TBK1 (Larabi A et al., 2013; Tu D et al., 2013). Although there is no structural data on dimerization of IKKε (IKBKE), the dimer contacts are conserved in IKBKE and TBK1 (Tu D et al., 2013). The C-terminal region of IKKε contributes to the dimer formation (Nakatsu Y et al., 2014).

Activated IKKε (IKBKE) and TBK1 phosphorylate interferon (IFN) regulatory factor 3 (IRF3) and IRF7 leading to type I interferon (IFN) production (Fitzgerald KA et al., 2003; Hemmi H et al., 2004; Hacker H & Karin M 2006; Taft J et al., 2021; Wegner J et al., 2023). IKKε and TBK1 exhibit functional redundancy with the ability to compensate for each other's functions (Fitzgerald KA et al., 2003; Taft J et al., 2021; Wegner J et al., 2023). For instance, TBK1 has been shown to downregulate the protein expression of IKKε (IKBKE) in human myeloid cells and increased IKKε expression compensated for the loss of TBK1 ensuring efficient type I IFN responses in conditions of TBK1 deficiency (Wegner J et al., 2023). These findings are supported by studies using genetically modified mice (Eren RO et al., 2024).

Preceded by: TANK is ubiquitinated within TANK:K63polyUb-TRAF3:TICAM1:TLR3:viral dsRNA

Followed by: IKKε (IKBKE) is phosphorylated within the activated TLR3 complex

Literature references

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

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

Maniatis, T., Golenbock, DT., McWhirter, SM., Latz, E., Rowe, DC., Liao, SM. et al. (2003). IKKepsilon and TBK1 are essential components of the IRF3 signaling pathway. *Nat Immunol, 4*, 491-6. ↗

Schlee, M., Hunkler, C., Wegner, J., Ciupka, K., Hartmann, G. (2023). Increased IKK protein stability ensures efficient type I interferon responses in conditions of TBK1 deficiency. *Front Immunol, 14*, 1073608. ↗

Devos, JM., Nanao, MH., Ng, SL., Round, A., Larabi, A., Panne, D. et al. (2013). Crystal structure and mechanism of activation of TANK-binding kinase 1. *Cell Rep, 3*, 734-46. ↗

Editions

2023-02-10	Authored	Shamovsky, V.
2024-02-28	Reviewed	Munitić, I., Franjkić, T.
2024-02-28	Edited	Shamovsky, V.

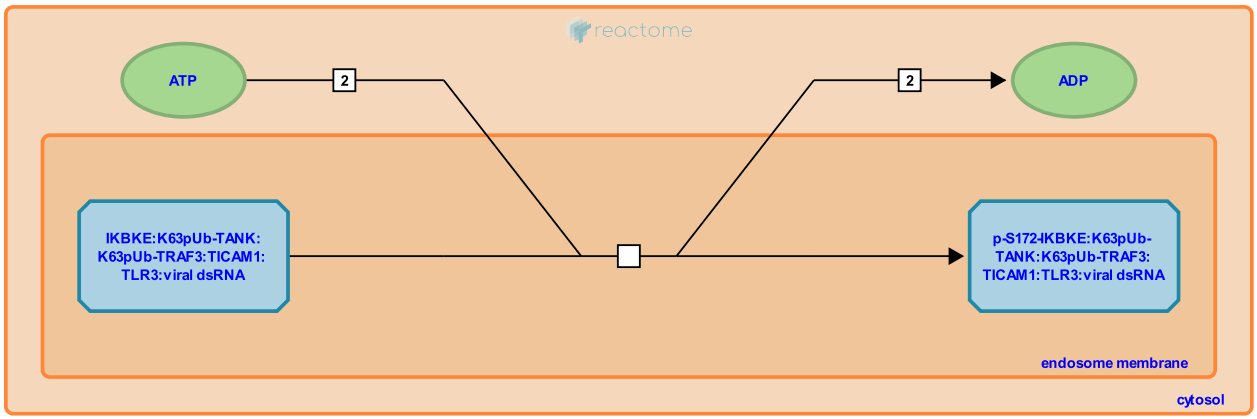
IKKε (IKBKE) is phosphorylated within the activated TLR3 complex ↗

Location: TICAM1-dependent activation of IRF3/IRF7

Stable identifier: R-HSA-9830706

Type: transition

Compartments: endosome membrane, cytosol



Inhibitor of kappaB kinase epsilon (IKKε, IKBKE) and its close homolog TANK-binding kinase I (TBK1) are activated downstream of pattern-recognition receptor activation upon infection (Fitzgerald KA et al., 2003; Hemmi H et al., 2004; Hacker H & Karin M 2006; Taft J et al., 2021; Wegner J et al., 2023). Activity of IKKε (IKBKE), like that of TBK1, is regulated by the phosphorylation of a serine residue 172 (S172) within the activation loop of the N-terminal kinase domain (KD) (Clark et al., 2009). The activation of IKKε, like TBK1, may occur through autophosphorylation or via activity of a distinct protein kinase (Clark et al., 2009).

Structural studies of TBK1 reveal a dimeric assembly which is mediated by several interfaces involving the N-terminal KD, a ubiquitin-like domain (ULD), and an alpha-helical scaffold dimerization domain (SDD) of TBK1, thus supporting a model of trans-autophosphorylation (Larabi A et al., 2013; Tu D et al., 2013). IKKε forms homodimers upon co-expression of tagged monomers in human embryonic kidney 293 (HEK293) cells (Nakatsu Y et al., 2014). The ULDs of TBK1 and IKKε are involved in the control of kinase activation, substrate presentation, and downstream signaling (Ikeda F et al., 2007; Tu D et al., 2013). Upon activation, IKKε (IKBKE) is modified by K63-linked polyubiquitination on lysines 30 and 401 (Zhou AY et al. 2013). The ubiquitination sites and dimer contacts are conserved in IKKε and TBK1 (Tu D et al., 2013; Zhou AY et al., 2013). These findings suggest that both IKKε and TBK1 are regulated through similar activation mechanisms involving dimerization, phosphorylation, and ubiquitination. Activated IKKε (IKBKE) and TBK1 phosphorylate interferon (IFN) regulatory factor 3 (IRF3) and IRF7 leading to IFN production (Fitzgerald KA et al., 2003; Hemmi H et al., 2004; Hacker H & Karin M 2006; Taft J et al., 2021; Wegner J et al., 2023).

In this Reactome reaction, IKKε (IKBKE) is trans-autophosphorylated at S172 within the activated TLR3 complex.

Preceded by: IKKε (IKBKE) binds K63-pUb-TANK:K63-pUb-TRAF3:TRIF:activated TLR3

Followed by: IRF3/IRF7 recruitment to p-TBK1/p-IKK epsilon bound to the activated TLR3

Literature references

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

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

Maniatis, T., Golenbock, DT., McWhirter, SM., Latz, E., Rowe, DC., Liao, SM. et al. (2003). IKKepsilon and TBK1 are essential components of the IRF3 signaling pathway. *Nat Immunol, 4*, 491-6. ↗

Devos, JM., Nanao, MH., Ng, SL., Round, A., Larabi, A., Panne, D. et al. (2013). Crystal structure and mechanism of activation of TANK-binding kinase 1. *Cell Rep, 3*, 734-46. ↗

Editions

2023-02-10	Authored	Shamovsky, V.
2024-02-28	Reviewed	Munitić, I., Franjkić, T.
2024-02-28	Edited	Shamovsky, V.

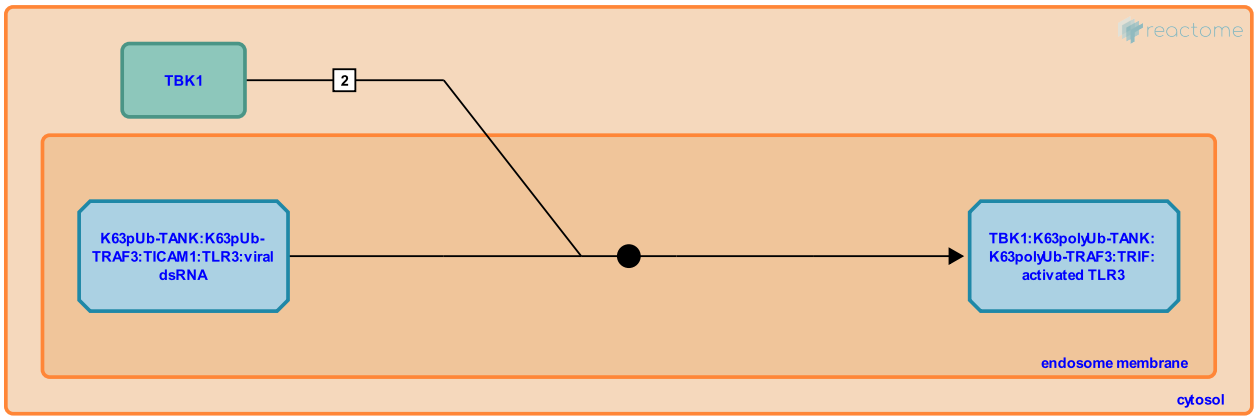
TBK1 binds K63-pUb-TANK:K63-pUb-TRAF3:TRIF:activated TLR3 ↗

Location: TICAM1-dependent activation of IRF3/IRF7

Stable identifier: R-HSA-9828196

Type: binding

Compartments: endosome membrane, cytosol



Upon stimulation by pathogen-associated inflammatory signals, TANK-binding kinase 1 (TBK1) and its close homolog, inhibitor of kappaB kinase epsilon (IKKε, IKBKE), induce type I interferon (IFN) expression and modulate nuclear factor-kappa-B (NF-kappa-B) signaling (Fitzgerald KA et al., 2003; Hemmi H et al., 2004; Taft J et al., 2021; Wegner J et al., 2023).

This Reactome event shows recruitment of TBK1 to the activated Toll-like receptor 3 (TLR3) complex.

TBK1 and IKKε (IKBKE) are found to interact with scaffold proteins TANK (TRAF family member associated NF-kappa-B activator), NAP1 (NAK-associated protein 1), and SINTBAD (similar to NAP1 TBK1 adaptor), which connect TBK1 and IKKε to pathogen-activated signaling complexes such as TLR3 (Pomerantz JL and Baltimore D 1999; Guo B and Cheng G 2007; Gatot JC et al., 2007; Ryzhakov G and Randow F 2007; Goncalves A et al., 2011). In addition, studies demonstrate an essential role for the E3 ubiquitin ligase TRAF3 in the activation of TBK1 (Oganesyan G et al., 2006; Hacker H et al 2006). Further, structural studies of TBK1 revealed a dimeric assembly that is mediated by several interfaces involving an N-terminal kinase domain (KD), a ubiquitin-like domain (ULD), and an alpha-helical scaffold dimerization domain (SDD) of TBK1 (Larabi A et al., 2013; Tu D et al., 2013). The ULDs of TBK1 and IKKε are involved in the control of kinase activation, substrate presentation, and downstream signaling (Ikeda F et al., 2007; Tu D et al., 2013). TBK1 dimer is a subject to K63-linked polyubiquitination on lysines 30 and 401 (Tu D et al., 2013). Activation of TBK1 rearranges the KD into an active conformation while maintaining the overall dimer conformation (Larabi A et al., 2013). The ubiquitination sites and dimer contacts are conserved in the close homolog IKKε (IKBKE) (Tu D et al., 2013). The activation of TBK1 and IKKε may occur through autophosphorylation or via activity of a distinct protein kinase (Clark et al., 2009).

Preceded by: TANK is ubiquitinated within TANK:K63polyUb-TRAF3:TICAM1:TLR3:viral dsRNA

Followed by: TBK1 is phosphorylated within the activated TLR3 complex

Literature references

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

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

Maniatis, T., Golenbock, DT., McWhirter, SM., Latz, E., Rowe, DC., Liao, SM. et al. (2003). IKKepsilon and TBK1 are essential components of the IRF3 signaling pathway. *Nat Immunol, 4*, 491-6. ↗

Devos, JM., Nanao, MH., Ng, SL., Round, A., Larabi, A., Panne, D. et al. (2013). Crystal structure and mechanism of activation of TANK-binding kinase 1. *Cell Rep, 3*, 734-46. ↗

Editions

2023-02-10	Authored	Shamovsky, V.
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2024-02-28	Edited	Shamovsky, V.

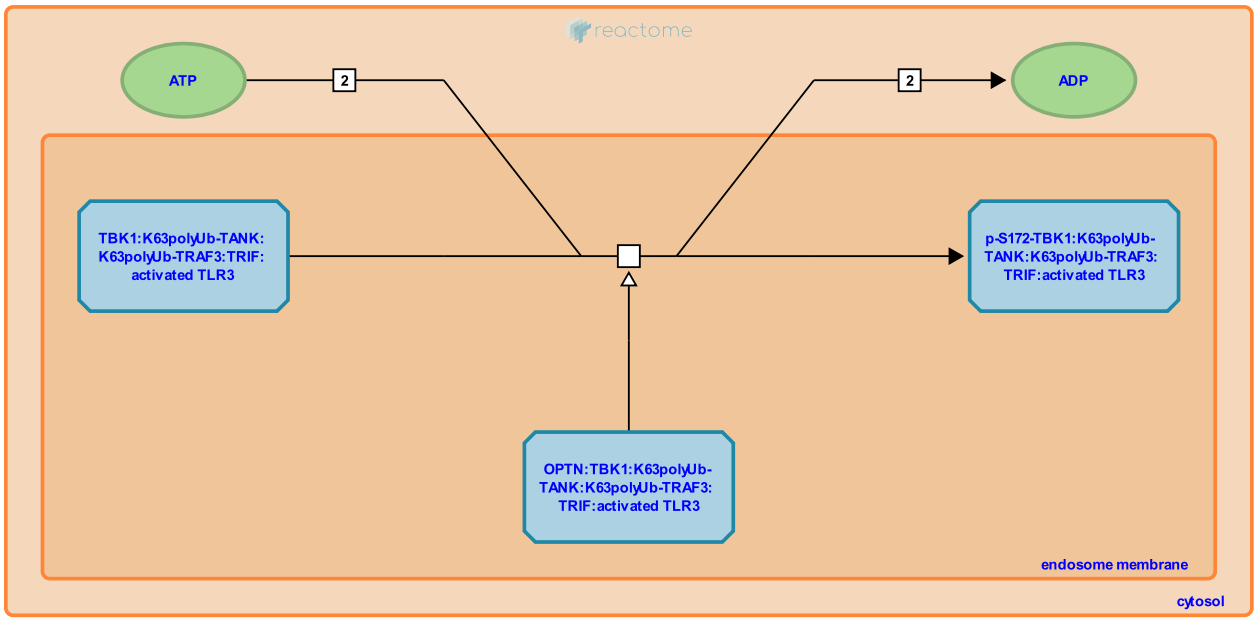
TBK1 is phosphorylated within the activated TLR3 complex ↗

Location: TICAM1-dependent activation of IRF3/IRF7

Stable identifier: R-HSA-9828205

Type: transition

Compartments: endosome membrane, cytosol



TANK-binding kinase I (TBK1) and its close homolog inhibitor of kappaB kinase epsilon (IKKε or IKBKE) are serine/threonine protein kinases, that are activated by pattern-recognition receptors upon infection. Activity of both TBK1 and IKKε (IKBKE) is regulated by the phosphorylation of a serine residue 172 (S172) within the activation loop of the N-terminal kinase domain (KD) (Clark et al., 2009). The activation of TBK1 and IKKε may occur through autophosphorylation or via activity of a distinct protein kinase (Clark et al., 2009). Structural studies of TBK1 reveal a dimeric assembly which is mediated by several interfaces involving an N-terminal KD, a ubiquitin-like domain (ULD), and an alpha-helical scaffold dimerization domain (SDD) of TBK1 thus supporting a model of trans-autophosphorylation (Larabi A et al., 2013; Tu D et al., 2013). The ULD of TBK1 (and IKKε) is involved in the control of kinase activation, substrate presentation and downstream signaling (Ikeda F et al., 2007; Tu D et al., 2013). Upon activation, TBK1 is modified by K63-linked polyubiquitination on lysines 30 (K30) and K401 (Tu D et al., 2013). Ubiquitination of TBK1 leads to conformational changes that facilitate activation of the N-terminal KD while maintaining the overall dimer conformation (Larabi A et al., 2013). The ubiquitination and phosphorylation sites, as well as dimer contacts, are conserved in the close homolog IKKε (IKBKE) suggesting that both kinases are regulated through similar activation mechanisms (Tu D et al., 2013; Zhou AY et al., 2013). Activated TBK1 then phosphorylates IRF3 and IRF7.

TBK1, K63-polyubiquitinated on K30 and K401, interacts with ubiquitin-binding adaptor protein optineurin (OPTN), which regulates the activity of TBK1 (Pourcelot M et al., 2016).

This Reactome event shows TBK1 phosphorylation within the activated TLR3 complex.

Preceded by: TBK1 binds K63-pUb-TANK:K63-pUb-TRAF3:TRIF:activated TLR3

Followed by: IRF3/IRF7 recruitment to p-TBK1/p-IKK epsilon bound to the activated TLR3

Literature references

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

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

Arnoult, D., Vazquez, A., Pourcelot, M., Silva Da Costa, L., Zemirli, N., Loyant, R. et al. (2016). The Golgi apparatus acts as a platform for TBK1 activation after viral RNA sensing. *BMC Biol, 14*, 69. ↗

Maniatis, T., Golenbock, DT., McWhirter, SM., Latz, E., Rowe, DC., Liao, SM. et al. (2003). IKKepsilon and TBK1 are essential components of the IRF3 signaling pathway. *Nat Immunol, 4*, 491-6. ↗

Devos, JM., Nanao, MH., Ng, SL., Round, A., Larabi, A., Panne, D. et al. (2013). Crystal structure and mechanism of activation of TANK-binding kinase 1. *Cell Rep, 3*, 734-46. ↗

Editions

2023-02-10	Authored	Shamovsky, V.
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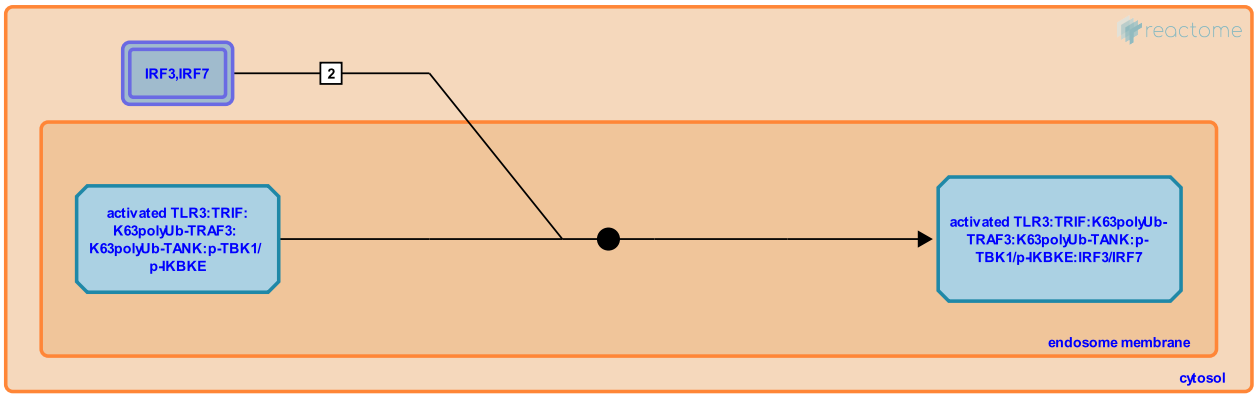
IRF3/IRF7 recruitment to p-TBK1/p-IKK epsilon bound to the activated TLR3 ↗

Location: TICAM1-dependent activation of IRF3/IRF7

Stable identifier: R-HSA-9013979

Type: binding

Compartments: endosome membrane, cytosol



SH2-containing protein tyrosine phosphatase 2 (SHP-2) has been shown to inhibit the TRIF-dependent production of proinflammatory cytokines and type I interferon in LPS or poly(I-C)-stimulated mouse peritoneal macrophages. SHP-2 overexpression also inhibited TRIF-induced IFN-luciferase reporter gene expression in human embryonic kidney HEK293 cells. Experiments with truncated SHP-2 or truncated TBK1 mutants revealed that C-terminal domain of SHP-2 associates with N-terminal domain of TBK1 when coexpressed in HEK293 cells. Furthermore, SHP-2 is thought to prevent TBK1-mediated downstream substrate phosphorylation in tyrosine phosphatase activity independent manner by binding to kinase domain of TBK1 (An H et al. 2006).
Two members of the interferon regulatory factor (IRF) family IRF3 and IRF7 are the major modulators of IFN gene expression (Hemmi H et al. 2004). Activation of IRF3 and IRF7, which is mediated by TBK1/IKK protein kinases, promotes IFN gene expression and the production of IFN developing an effective antiviral immune response (Hemmi H et al. 2004).

Irf-3 deficient mice were found to be more vulnerable to virus infection. Mouse cells defective in IRF3 and IRF7 expression totally fail to induce IFN genes in response to viral infection. It was shown on mice and mouse cells that both IRF3 and IRF7 have non redundant and distinct roles (Sato M et al. 2000). IRF3 is expressed at a basal level in normally growing cells and is a major factor in the early induction phase of IFN-alpha/beta production, while the IRF7 gene expression is induced upon IFNs stimulation and IRF7 is involved in the late induction phase.

Preceded by: TBK1 is phosphorylated within the activated TLR3 complex, IKKε (IKBKE) is phosphorylated within the activated TLR3 complex

Followed by: Phosphorylation of IRF-3/IRF7 and their release from the activated TLR3 complex

Literature references

Hiscott, J., Lin, R., Pitha-Rowe, PM., Heylbroeck, C. (1998). Virus-dependent phosphorylation of the IRF-3 transcription factor regulates nuclear translocation, transactivation potential, and proteasome-mediated degradation. *Mol Cell Biol, 18*, 2986-96. ↗

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

Zhang, Y., Cao, X., Zhao, W., Hou, J., Liu, S., Zheng, Y. et al. (2006). SHP-2 phosphatase negatively regulates the TRIF adaptor protein-dependent type I interferon and proinflammatory cytokine production. *Immunity, 25*, 919-28. ↗

Fujita, T., Inagaki, F., Takahashi, K., Yoneyama, M., Mori, M., Ito, T. (2004). Identification of Ser-386 of interferon regulatory factor 3 as critical. *J Biol Chem, 279*, 9698-702. ↗

Editions

2005-08-16	Authored	de Bono, B.
2006-04-24	Reviewed	Gay, NJ.
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2014-05-16	Reviewed	Masci, A M.
2014-05-16	Edited	Shamovsky, V.

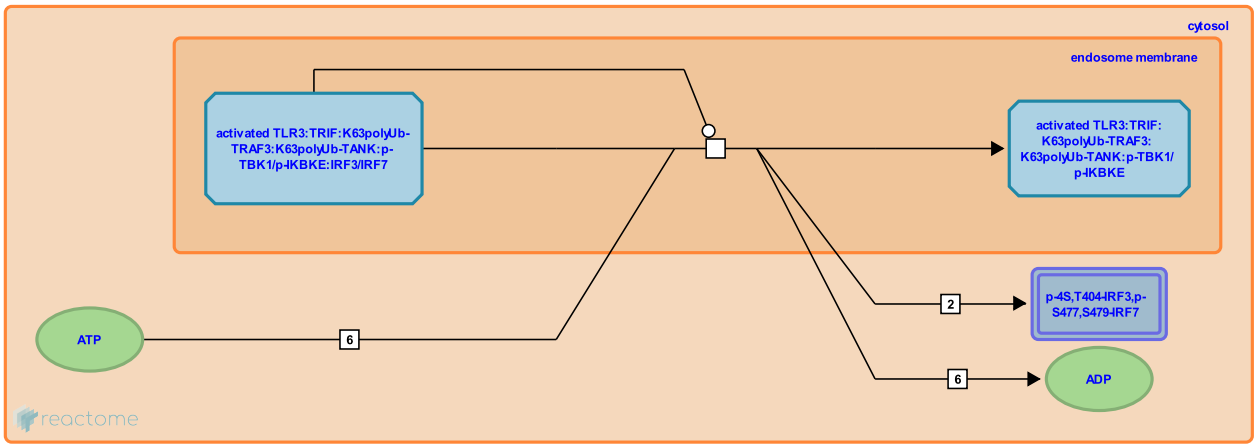
Phosphorylation of IRF-3/IRF7 and their release from the activated TLR3 complex ↗

Location: TICAM1-dependent activation of IRF3/IRF7

Stable identifier: R-HSA-9013978

Type: transition

Compartments: endosome membrane, cytosol



Human IRF3 is activated through a two step phosphorylation in the C-terminal domain mediated by TBK1 and/or IKKi. It requires Ser386 and/or Ser385 (site 1) and a cluster of serine/threonine residues between Ser396 and Ser405 (site 2) (Panne et al. 2007). Phosphorylated residues at site 2 alleviate autoinhibition to allow interaction with CBP (CREB-binding protein) and facilitate phosphorylation at site 1. Phosphorylation at site 1 is required for IRF3 dimerization.

IRF3 and IRF7 transcription factors possess distinct structural characteristics; IRF7 is phosphorylated on Ser477 and Ser479 residues (Lin R et al. 2000). TRAF6 mediated ubiquitination of IRF7 is also required and essential for IRF7 phosphorylation and activation. The K-63 linked ubiquitination occurs on the last three C-terminal lysine sites (positions 444, 446, and 452) of human IRF7 independently of its C-terminal functional phosphorylation sites.(Ning et al. 2008).

Preceded by: IRF3/IRF7 recruitment to p-TBK1/p-IKK epsilon bound to the activated TLR3

Literature references

Maniatis, T., Golenbock, DT., McWhirter, SM., Latz, E., Rowe, DC., Liao, SM. et al. (2003). IKKepsilon and TBK1 are essential components of the IRF3 signaling pathway. *Nat Immunol, 4*, 491-6. ↗

McWhirter, SM., Maniatis, T., Harrison, SC., Panne, D. (2007). Interferon regulatory factor 3 is regulated by a dual phosphorylation-dependent switch. *J Biol Chem, 282*, 22816-22. ↗

Fujita, T., Inagaki, F., Takahashi, K., Yoneyama, M., Mori, M., Ito, T. (2004). Identification of Ser-386 of interferon regulatory factor 3 as critical. *J Biol Chem, 279*, 9698-702. ↗

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2005-08-16	Authored	de Bono, B.
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2012-11-13	Reviewed	Fitzgerald, KA.
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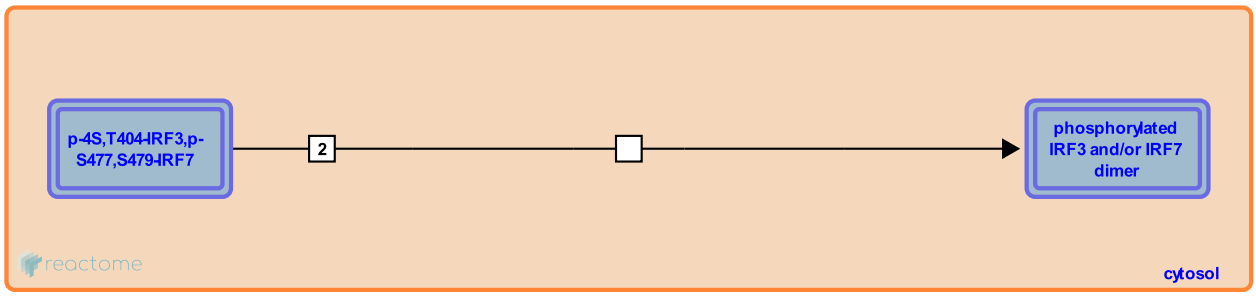
Dimerization of phosphorylated IRF3/IRF7

Location: TICAM1-dependent activation of IRF3/IRF7

Stable identifier: R-HSA-168933

Type: transition

Compartments: cytosol



Phosphorylation results in IRF-3 dimerization and removal of an autoinhibitory structure to allow interaction with the coactivators CBP/p300.

Followed by: Dimerized phospho-IRF3/IRF7 is transported to the nucleus

Literature references

Terasawa, H., Suhara, W., Fujita, T., Fukuhara, Y., Okabe, Y., Suzuki, NN. et al. (2003). X-ray crystal structure of IRF-3 and its functional implications. *Nat Struct Biol, 10*, 922-7.

Maniatis, T., Golenbock, DT., McWhirter, SM., Latz, E., Rowe, DC., Liao, SM. et al. (2003). IKKepsilon and TBK1 are essential components of the IRF3 signaling pathway. *Nat Immunol, 4*, 491-6.

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2006-04-24	Reviewed	Gay, NJ.
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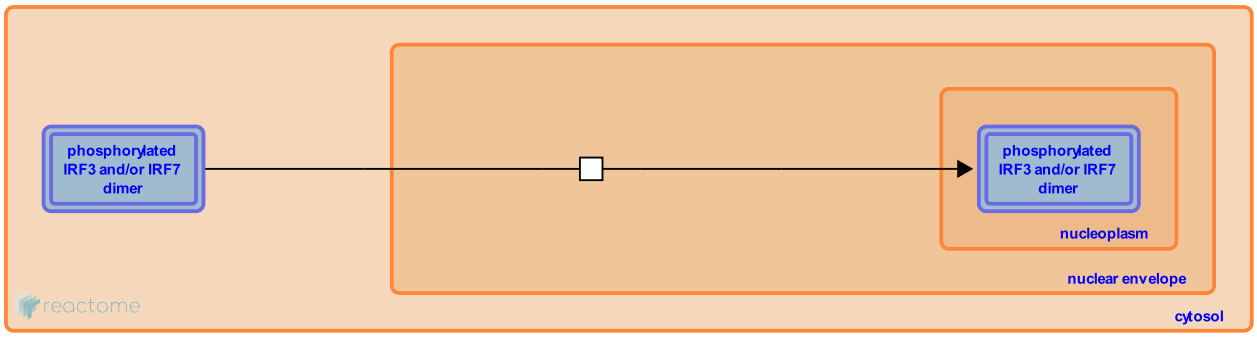
Dimerized phospho-IRF3/IRF7 is transported to the nucleus ↗

Location: TICAM1-dependent activation of IRF3/IRF7

Stable identifier: R-HSA-177671

Type: transition

Compartments: nuclear envelope, nucleoplasm, cytosol



IRF3-P:IRF3-P' is translocated from cytosol to nucleoplasm.

Preceded by: Dimerization of phosphorylated IRF3/IRF7

Literature references

Maniatis, T., Golenbock, DT., McWhirter, SM., Latz, E., Rowe, DC., Liao, SM. et al. (2003). IKKepsilon and TBK1 are essential components of the IRF3 signaling pathway. *Nat Immunol, 4*, 491-6. ↗

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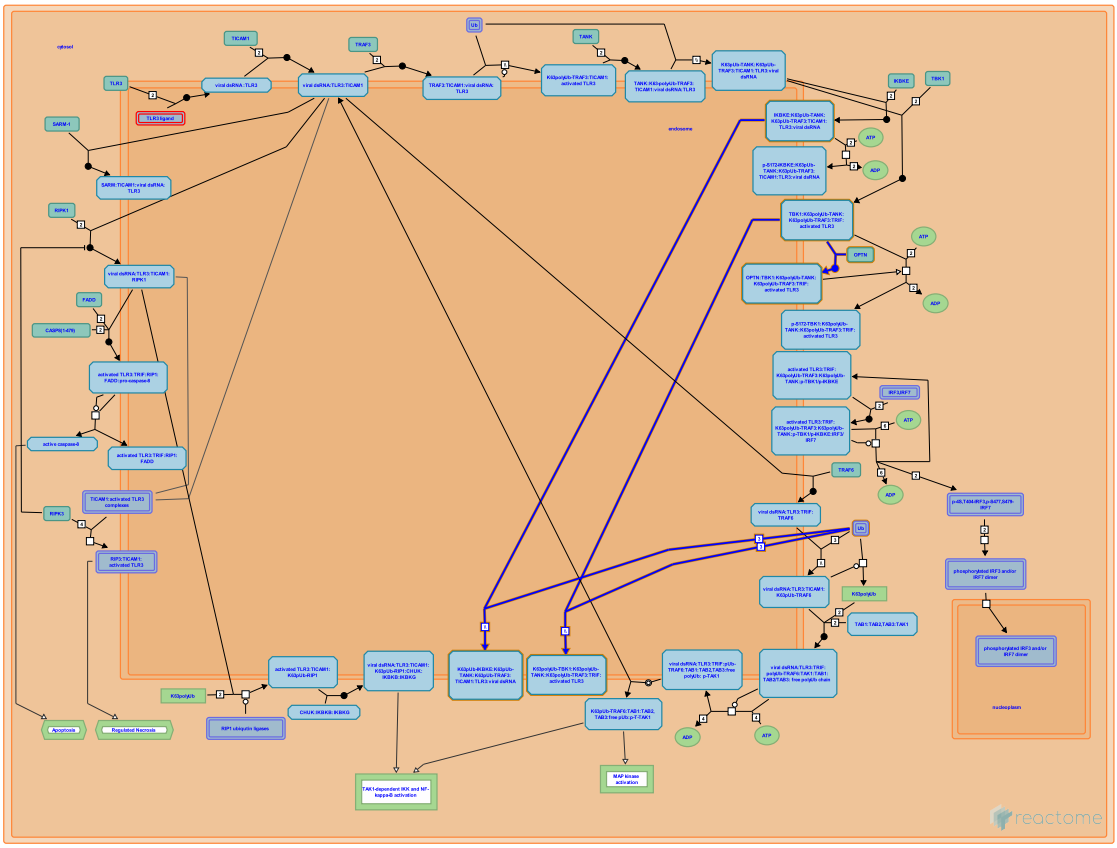
Regulation of TBK1, IKKε-mediated activation of IRF3, IRF7 upon TLR3 ligation ↗

Location: TICAM1-dependent activation of IRF3/IRF7

Stable identifier: R-HSA-9828211



Production of type I IFN genes in response to Toll-like receptor 3 (TLR3) and TLR4 ligands is mediated by TANK-binding kinase 1 (TBK1) or I-kappa-B kinase epsilon (IKKε, IKBKE), which phosphorylate IFN regulatory factor 3 (IRF3) and IRF7. The activity of TBK1 and/or IRF3, IRF7 is regulated by multiple mechanisms including post-translational modifications, protein-protein interactions, and protein degradation (Zhao W et al., 2013; Runde AP et al., 2022).

This Reactome module describes regulation of TBK1, IKKε activity by K63-linked ubiquitination of TBK1 and IKKε, and TBK1 interaction with OPTN.

Literature references

Zhao, W. (2013). Negative regulation of TBK1-mediated antiviral immunity. *FEBS Lett, 587*, 542-8. ↗

Zhang, J., Mack, R., S J, PB., Runde, AP. (2022). The role of TBK1 in cancer pathogenesis and anticancer immunity. *J Exp Clin Cancer Res, 41*, 135. ↗

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