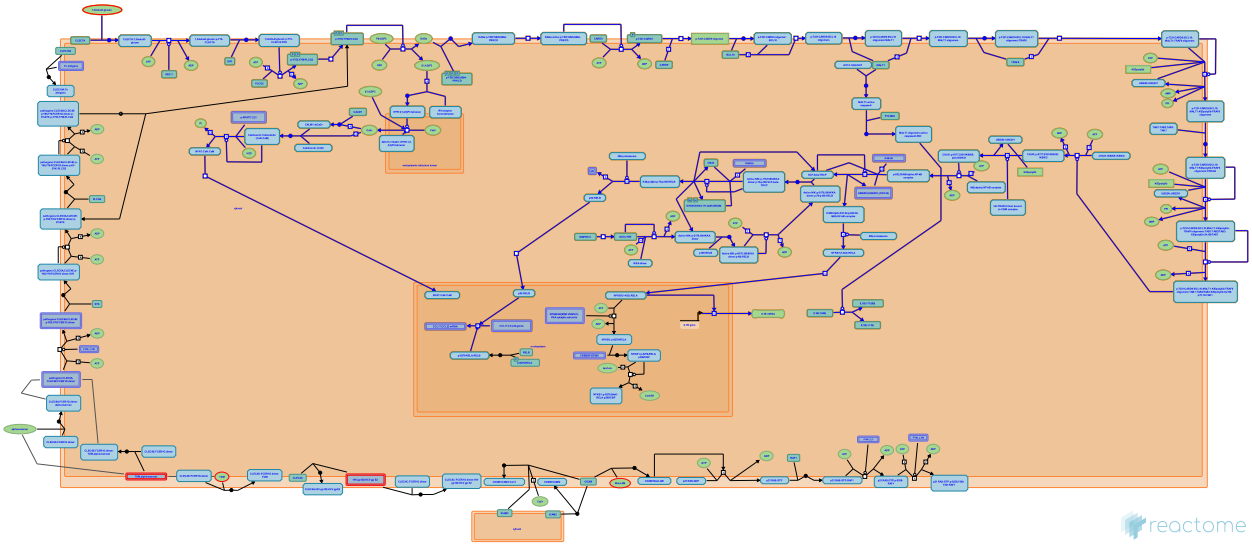
CLEC7A (Dectin-1) signaling



Garapati, P V., Geijtenbeek, TB., Niarakis, A., Roncagalli, R., Rudd, C.E.., Trowsdale, J., de Bono, B.

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

06/05/2024

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.
The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

Literature references

Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics, 18*, 142. ↗

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

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

Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

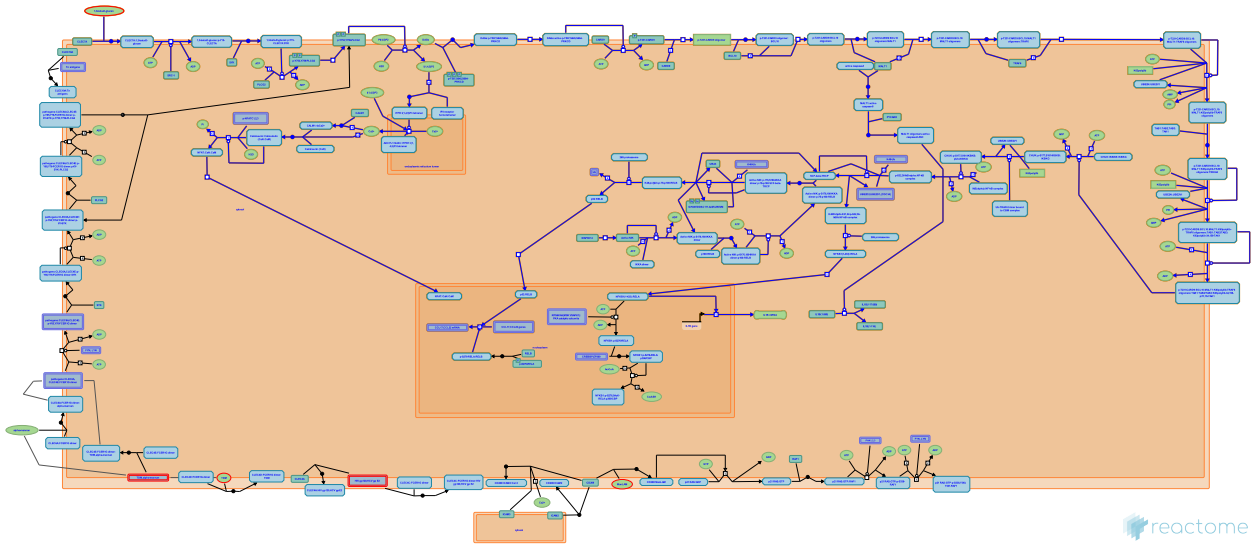
Reactome database release: 88

This document contains 4 pathways and 26 reactions (see Table of Contents)

CLEC7A (Dectin-1) signaling ↗

Stable identifier: R-HSA-5607764

Compartments: plasma membrane



CLEC7A (also known as Dectin-1) is a pattern-recognition receptor (PRR) expressed by myeloid cells (macrophages, dendritic cells and neutrophils) that detects pathogens by binding to beta-1,3-glucans in fungal cell walls and triggers direct innate immune responses to fungal and bacterial infections. CLEC7A belongs to thetype-II C-type lectin receptor (CLR) family that can mediate its own intracellular signaling. Upon binding particulate beta-1,3-glucans, CLEC7A mediates intracellular signalling through its cytoplasmic immunoreceptor tyrosine-based activation motif (ITAM)-like motif (Brown 2006). CLEC7A signaling can induce the production of various cytokines and chemokines, including tumour-necrosis factor (TNF), CXC-chemokine ligand 2 (CXCL2, also known as MIP2), interleukin-1beta (IL-1b), IL-2, IL-10 and IL-12 (Brown et al. 2003), it also triggers phagocytosis and stimulates the production of reactive oxygen species (ROS), thus contributing to microbial killing (Gantner et al. 2003, Herre et al. 2004, Underhill et al. 2005, Goodridge at al. 2011, Reid et al. 2009). These cellular responses mediated by CLEC7A rely on both Syk-dependent and Syk-independent signaling cascades. The pathways leading to the Syk-dependent activation of NF-kB can be categorised into both canonical and non-canonical routes (Gringhuis et al. 2009). Activation of the canonical NF-kB pathway is essential for innate immunity, whereas activation of the non-canonical pathway is involved in lymphoid organ development and adaptive immunity (Plato et al. 2013).

Literature references

Gordon, S., Williams, DL., Willment, JA., Marshall, AS., Brown, GD., Herre, J. (2003). Dectin-1 mediates the biological effects of beta-glucans. *J. Exp. Med., 197*, 1119-24. ↗

Brown, GD., Gow, NA., Reid, DM. (2009). Pattern recognition: recent insights from Dectin-1. *Curr. Opin. Immunol., 21* , 30-7. ↗

Editions

2014-07-14	Authored, Edited	Garapati, P V.
2014-09-02	Reviewed	Geijtenbeek, TB.

CLEC7A binds 1,3-beta-D-glucan ↗

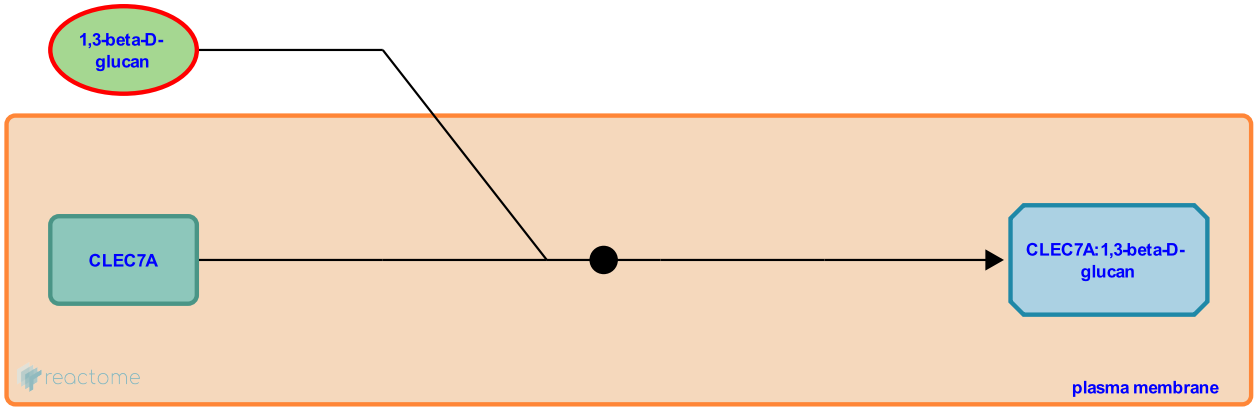
Location: CLEC7A (Dectin-1) signaling

Stable identifier: R-HSA-5607758

Type: binding

Compartments: plasma membrane, extracellular region

Inferred from: Clec7a binds 1,3-beta-D-glucan (Mus musculus)



CLEC7A (Dectin-1) was identified as a primary receptor for beta-glucans from fungi, bacteria, and plants and specifically recognises beta 1-3 linked glucans. Human CLEC7A has eight alternatively splice products of which only two are functional for beta-glucan binding (isoforms A and B) (Willment et al. 2001). CLEC7A possesses an extracellular C-type lectin-like domain (CTLD) that is connected by a stalk region to a transmembrane domain and cytoplasmic tail, which contains an immunoreceptor tyrosine-based activation (ITAM)-like motif. Two highly conserved amino acids (222W 224H in Human; 221W, 223H in Mouse) within the CTLD which have been identified as essential for beta-glucan binding (Brown et al. 2007, Adachi et al. 2004). Through the recognition of beta-glucans, CLEC7A binds several fungal species such as Aspergillus, Candida, Coccidioides, Pencillium, Pneumocystis and Saccharimyces.
Ferwerda et al. (2009) suggest that chronic mucocutaneous candidiasis may be caused by a genetic defect of CLEC7A. The mutation of nucleotide A-->C causes a change of amino acid 238 from tyrosine to a stop codon (Tyr238*), leading to the loss of the last nine amino acids of the carbohydrate-recognition domain (CRD). This mutated form of CLEC7A is poorly expressed and does not mediate beta-glucan binding, leading to defective production of cytokines after stimulation with beta-glucans or Candida albicans (Ferwerda et al. 2009).

Followed by: SRC kinase phosphorylates CLEC7A:1,3-beta-D-glucan

Editions

2014-07-14	Authored, Edited	Garapati, P V.
2014-09-02	Reviewed	Geijtenbeek, TB.

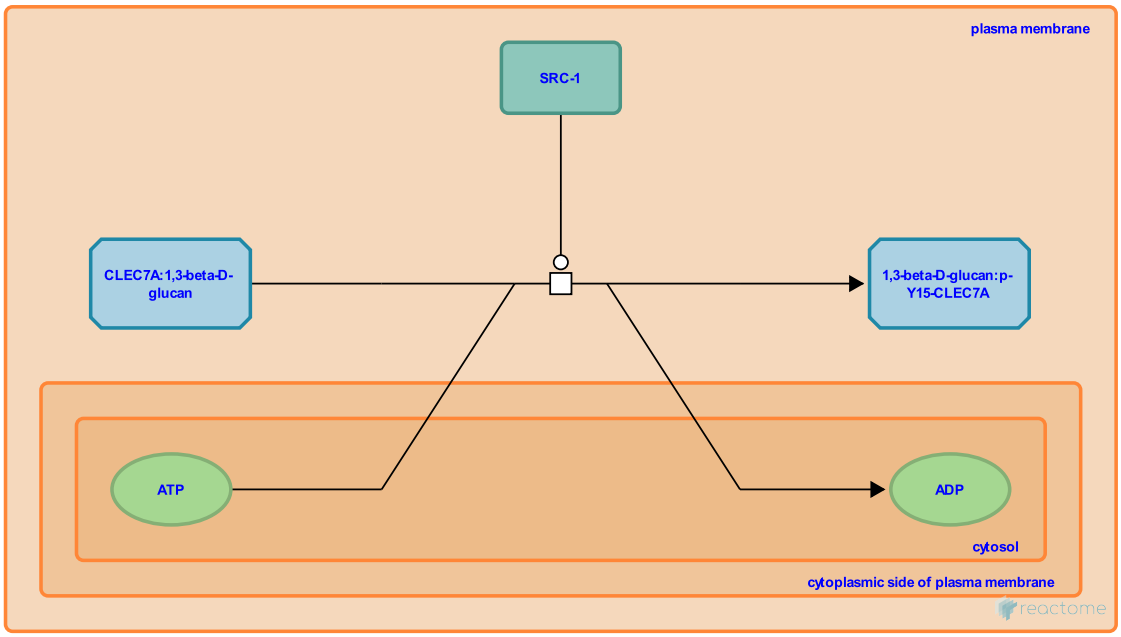
SRC kinase phosphorylates CLEC7A:1,3-beta-D-glucan ↗

Location: CLEC7A (Dectin-1) signaling

Stable identifier: R-HSA-5607750

Type: transition

Compartments: plasma membrane, cytosol



The signalling abilities of CLEC7A (Dectin-1) depend on its cytoplasmic (immunoreceptor tyrosine based activation motif) ITAM-like motif. In contrast to traditional ITAM sequences which consists of dual YXXL sequences, CLEC7A's ITAM (hemi-ITAM) has only a single YXXL motif (Ariizumi et al. 2000). Despite its unusual ITAM, CLEC7A upon ligation with beta-glucan containing particles undergoes tyrosine phoshorylation by SRC kinases (Kerrigan & Brown 2010).

Preceded by: CLEC7A binds 1,3-beta-D-glucan

Followed by: SYK binds p-Y15-CLEC7A:1,3-beta-D-glucan

Literature references

Gordon, S., Rogers, NC., Slack, EC., Williams, DL., Edwards, AD., Brown, GD. et al. (2005). Syk-dependent cytokine induction by Dectin-1 reveals a novel pattern recognition pathway for C type lectins. *Immunity, 22*, 507-17. ↗

Brown, GD. (2006). Dectin-1: a signalling non-TLR pattern-recognition receptor. *Nat. Rev. Immunol., 6*, 33-43. ↗

Magee, AS., Wolf, AJ., Weiss, A., Vasilakos, JP., Katsumoto, TR., Goodridge, HS. et al. (2011). Activation of the innate immune receptor Dectin-1 upon formation of a 'phagocytic synapse'. *Nature, 472*, 471-5. ↗

Edelbaum, D., Bergstresser, PR., Morita, A., Shikano, S., Ariizumi, K., Kumamoto, T. et al. (2000). Identification of a novel, dendritic cell-associated molecule, dectin-1, by subtractive cDNA cloning. *J. Biol. Chem., 275*, 20157-67. ↗

Kerrigan, AM., Brown, GD. (2010). Syk-coupled C-type lectin receptors that mediate cellular activation via single tyrosine based activation motifs. *Immunol. Rev., 234*, 335-52. ↗

Editions

2014-07-14	Authored, Edited	Garapati, P V.
2014-09-02	Reviewed	Geijtenbeek, TB.

SYK binds p-Y15-CLEC7A:1,3-beta-D-glucan ↗

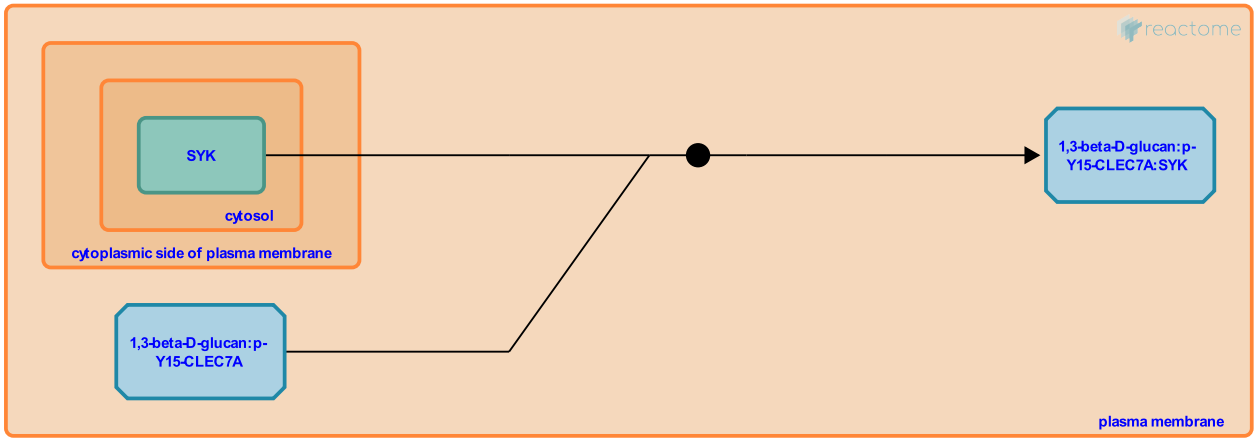
Location: CLEC7A (Dectin-1) signaling

Stable identifier: R-HSA-5607738

Type: binding

Compartments: plasma membrane, cytosol

Inferred from: SYK binds p-Y15-Clec7a:1,3-beta-D-glucan (Homo sapiens)



Spleen tyrosine kinase (SYK) is the key mediator of CLEC7A's (Dectin-1) downstream cellular responses, such as cytokine production and induction of the respiratory burst (Brown 2006). A phosphorylated tyrosine in CLEC7A provides the docking site for SYK. In contrast to usual ITAM receptors where dually phosphorylated tyrosines are necessary for SYK recruitment, phosphorylation of only the membrane proximal tyrosine is sufficient for SYK association with CLEC7A. Binding of SYK to the phosphorylated ITAM motif is sufficient to fully activate SYK (Tsang et al. 2008). SYK deficiency or SYK inhibitors inhibit CLEC7A-dependent cytokine production, MAPK activation and NF-kB activation, suggesting that SYK is essential for CLEC7A signalling (Rogers et al. 2005, Underhill et al. 2005, Fuller et al. 2007). Activation of NF-kB by SYK can be categorised into both canonical (c-Rel and p65) and NIK (NF-kB inhibitory kinase)-dependent non-canonical (RelB) routes (Gringhuis et al. 2009).

Preceded by: SRC kinase phosphorylates CLEC7A:1,3-beta-D-glucan

Followed by: 1,3-beta-D-glucan:p-Y15-CLEC7A:SYK phosphorylates PLCG

Editions

2014-07-14	Authored, Edited	Garapati, P V.
2014-09-02	Reviewed	Geijtenbeek, TB.

1,3-beta-D-glucan:p-Y15-CLEC7A:SYK phosphorylates PLCG ↗

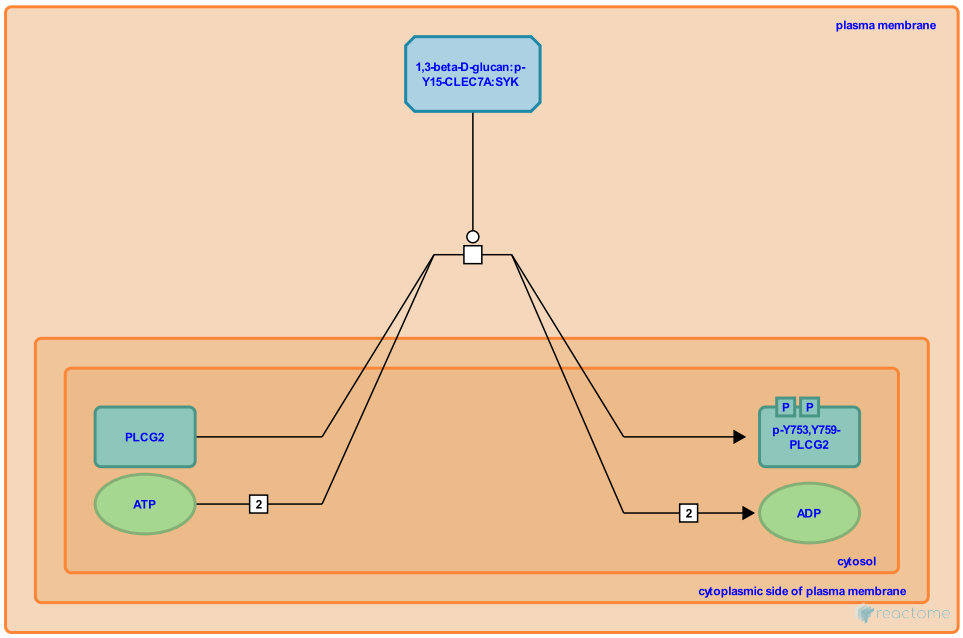
Location: CLEC7A (Dectin-1) signaling

Stable identifier: R-HSA-5607745

Type: transition

Compartments: plasma membrane, cytosol

Inferred from: 1,3-beta-D-glucan:p-15Y-Clec7a:Syk phosphorylates Plcg2 (Mus musculus)



Activation of SYK triggers multiple cascades, which induces NF-kB activation through a CARD9-dependent pathway. Phospholipase C-gamma 2 (PLCG2) is one of the key signaling components of the CLEC7A (Dectin-1) pathway that connects SYK activation to CARD9 recruitment. PLCG2 is activated upon CLEC7A engagement and triggers an intracellular Ca2+ flux. SYK and Src family kinases are upstream of PLCG2 (Xu et al. 2009, Tassi et al. 2009, Gorjestani et al. 2011). SYK phosphorylates PLCG2 on Y753 and Y759, enhancing the activity of PLCG2 (Suzuki-Inoue et al. 2004).

Preceded by: SYK binds p-Y15-CLEC7A:1,3-beta-D-glucan

Followed by: p-Y753,Y759-PLCG2 translocates from cytosol to plasma membrane

Editions

2014-07-14	Authored, Edited	Garapati, P V.
2014-09-02	Reviewed	Geijtenbeek, TB.

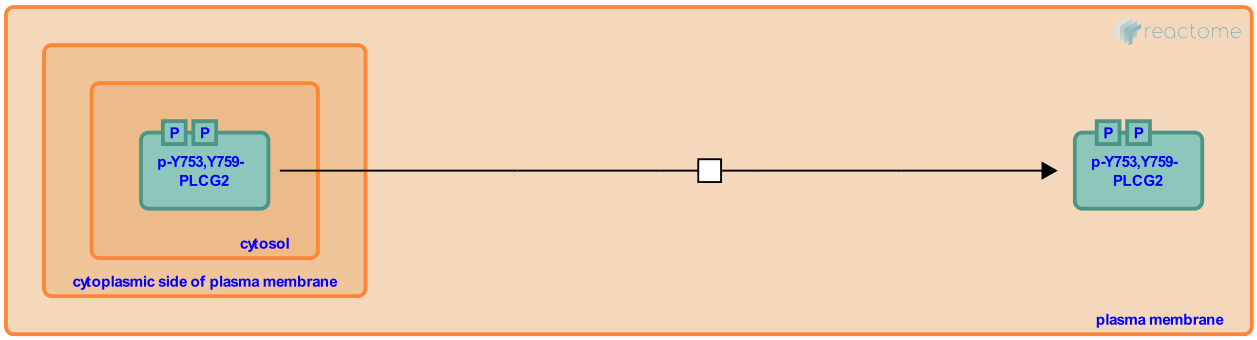
p-Y753,Y759-PLCG2 translocates from cytosol to plasma membrane ↗

Location: CLEC7A (Dectin-1) signaling

Stable identifier: R-HSA-5607755

Type: transition

Compartments: plasma membrane, cytosol



Tyrosine-phosphorylated Phospholipase C-gamma 2 (PLCG2) translocates from the cytosol to the plasma membrane. At the membrane PLCG2 is in close proximity to phosphatidylinositol 4,5-bisphosphate (PIP2) and its other substrates generating the second messengers IP3 and DAG (Rhee 2001). This leads to the activation of CARD9-BCL10-MALT1/NF-kB signaling and stimulates calcineurin/NFAT signaling.

Preceded by: 1,3-beta-D-glucan:p-Y15-CLEC7A:SYK phosphorylates PLCG

Followed by: p-Y753,Y759-PLCG2 hydrolyses PIP2

Literature references

Matsuda, M., Swann, K., Bravo, J., Katan, M., Jones, NP., Rodriguez, R. et al. (2001). Tyrosine residues in phospholipase Cgamma 2 essential for the enzyme function in B-cell signaling. *J Biol Chem, 276*, 47982-92. ↗

Hayakawa, T., Fujimoto, S., Kawakami, N., Sumida, Y., Shimohama, S. (1996). Tyrosine phosphorylation and translocation of phospholipase C-gamma 2 in polymorphonuclear leukocytes treated with pervanadate. *Biochim. Biophys. Acta, 1314*, 167-74. ↗

Editions

2014-07-14	Authored, Edited	Garapati, P V.
2014-09-02	Reviewed	Geijtenbeek, TB.

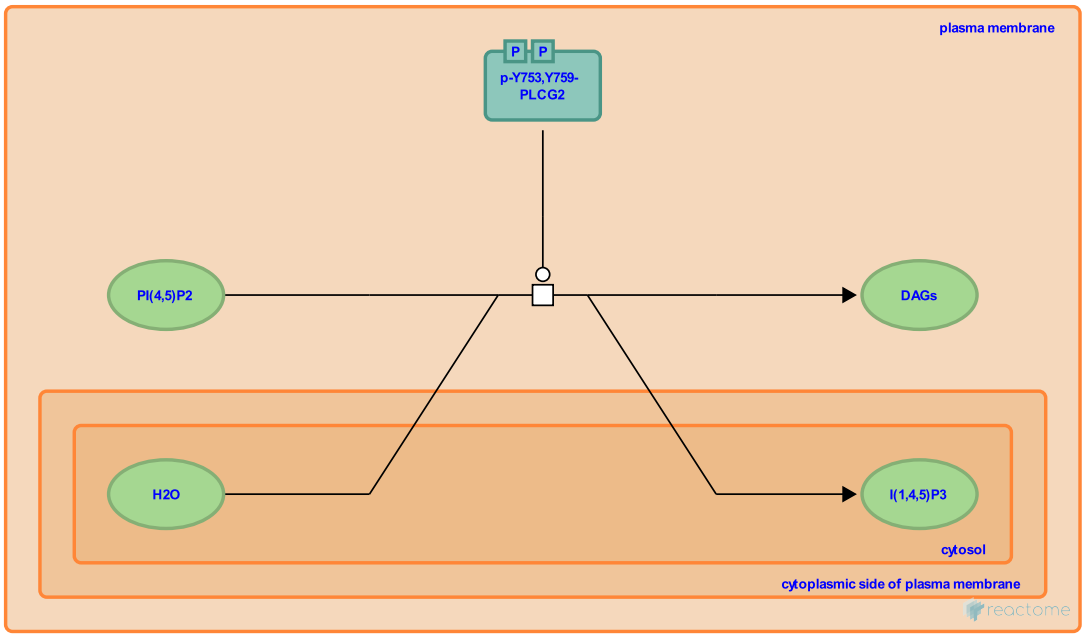
p-Y753,Y759-PLCG2 hydrolyses PIP2 ↗

Location: CLEC7A (Dectin-1) signaling

Stable identifier: R-HSA-5607735

Type: transition

Compartments: plasma membrane, cytosol



Following tyrosine phosphorylation, phospholipase C-gamma 2 (PLCG2) catalyzes the hydrolysis of phosphatidylinositol 4,5-bisphosphate [PtdIns(4,5)P2 or PIP2] to inositol 1,4,5-trisphosphate (IP3) and diacylglycerol (DAG).

Preceded by: p-Y753,Y759-PLCG2 translocates from cytosol to plasma membrane

Followed by: PKC-delta translocates to plasma membrane

Literature references

Lee, SB., Rhee, SG. (1995). Significance of PIP2 hydrolysis and regulation of phospholipase C isozymes. *Curr. Opin. Cell Biol., 7*, 183-9. ↗

Editions

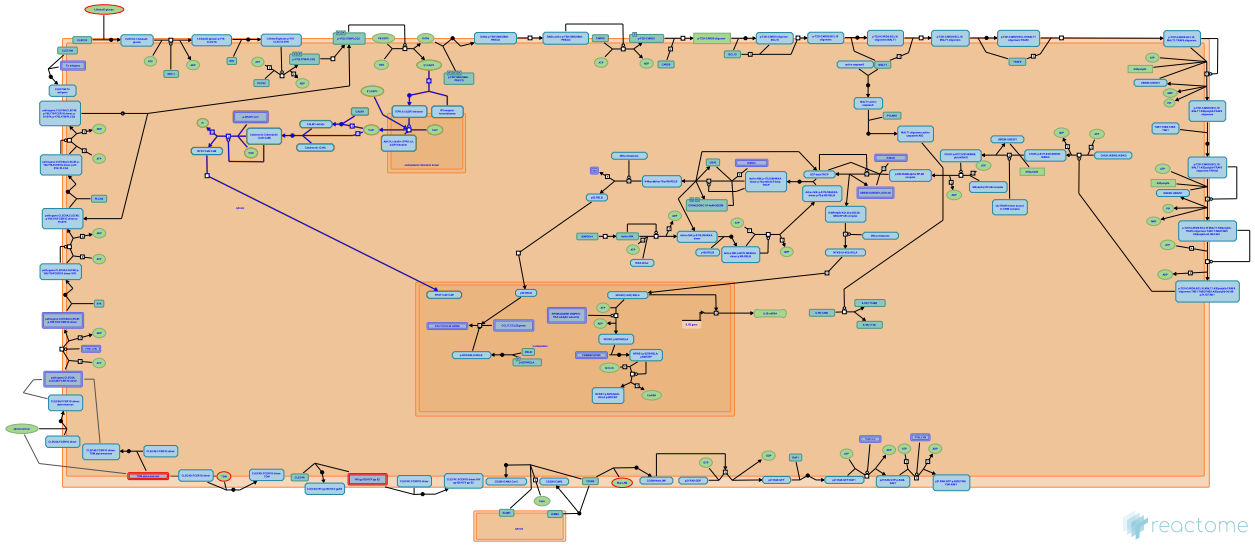
2014-07-14	Authored, Edited	Garapati, P V.
2014-09-02	Reviewed	Geijtenbeek, TB.

CLEC7A (Dectin-1) induces NFAT activation ↗

Location: CLEC7A (Dectin-1) signaling

Stable identifier: R-HSA-5607763

Compartments: plasma membrane, cytosol



CLEC7A (Dectin-1) signals through the classic calcineurin/NFAT pathway through Syk activation phospholipase C-gamma 2 (PLCG2) leading to increased soluble IP3 (inositol trisphosphate). IP3 is able to bind endoplasmic Ca2+ channels, resulting in an influx of Ca2+ into the cytoplasm. This increase in calcium concentration induces calcineurin activation and consequently, dephosphorylation of NFAT and its translocation into the nucleus, triggering gene transcription and extracellular release of Interleukin-2 (Plato et al. 2013, Goodridge et al. 2007, Mourao-Sa et al. 2011).

Literature references

Ricciardi-Castagnoli, P., Zelante, T., Mertes, A., Wong, AY., Yu, HB., Fric, J. (2012). NFAT control of innate immunity . *Blood, 120*, 1380-9. ↗

Simmons, RM., Underhill, DM., Goodridge, HS. (2007). Dectin-1 stimulation by Candida albicans yeast or zymosan triggers NFAT activation in macrophages and dendritic cells. *J. Immunol., 178*, 3107-15. ↗

Sancho, D., Chakravarty, P., Zelenay, S., Mourão-Sá, D., Reis e Sousa, C., Lambrecht, B. et al. (2011). CLEC-2 signaling via Syk in myeloid cells can regulate inflammatory responses. *Eur. J. Immunol., 41*, 3040-53. ↗

Editions

2014-07-14	Authored, Edited	Garapati, P V.
2014-09-02	Reviewed	Geijtenbeek, TB.

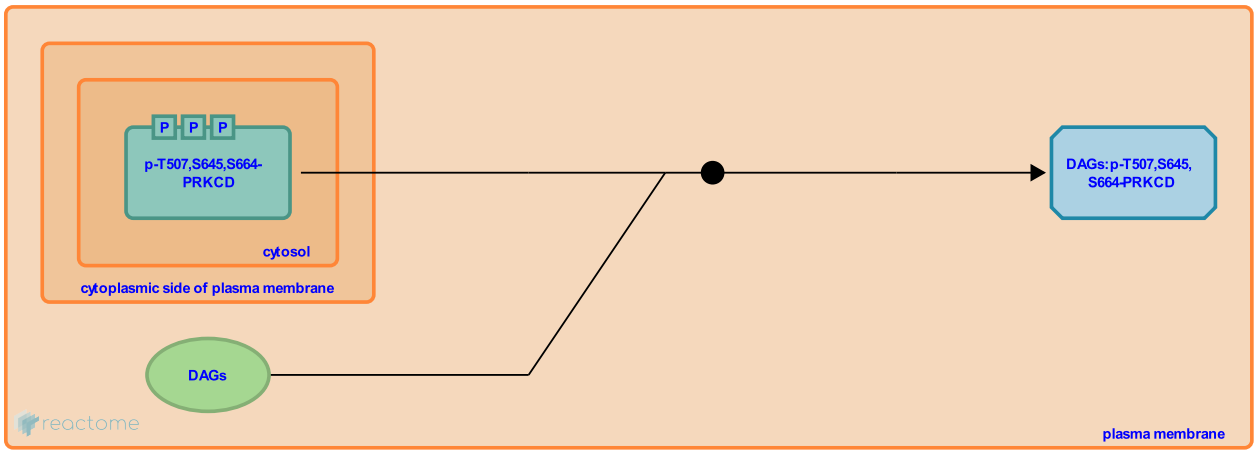
PKC-delta translocates to plasma membrane ↗

Location: CLEC7A (Dectin-1) signaling

Stable identifier: R-HSA-5607734

Type: binding

Compartments: plasma membrane, cytosol



Protein kinase C-delta (PRKCD), activated upon CLEC7A (Dectin-1)-SYK signaling, phosphorylates CARD9 leading to NF-kB activation (Strasser et al. 2012) and complex formation between CARD9 and BCL10. CLEC6A (Dectin-2) and CLEC4E (Mincle) also induces intracellular signaling through PRKCD and CARD9-BCL10-MALT1 pathway. Similar to the CLEC7A responses, both CLEC6A and CLEC4E-induced interleukin 10 (IL10) and tumour necrotic factor (TNF) production were severely impaired in the absence of PRKCD (Strasser et al. 2012). PRKCD is a member of the Ca2+ independent and diacylglycerol (DAG) dependent novel PKC subfamily. PKC family members exist in an immature inactive conformation that requires post-translational modifications to achieve catalytic maturity. The catalytic maturation of PRKCD involves the auto-phosphorylation of Ser645 and the phosphorylation of Thr507 and Ser664 (Li et al. 1997, Keranen et al. 1995). These phosphorylations of activation loop residues act as a priming step that allows the catalytic maturation of PRKCD (Dutil et al. 1998). Fully phosphorylated and primed PRKCD localises to the cytosol with its pseudosubstrate occupying the substrate-binding cavity. Signals that cause the lipid hydrolysis recruit PKC to membranes. The C1 domain in PRKCD is a cysteine-rich compact structure, identified as the interaction site for DAG and phorbol ester. PRKCD preferentially translocates to the plasma membrane (Stahelin et al. 2004, Newton 2010).

Preceded by: p-Y753,Y759-PLCG2 hydrolyses PIP2

Followed by: PKC-delta is activated

Literature references

Cho, W., Rafter, JD., Digman, MA., Medkova, M., Stahelin, RV., Melowic, HR. et al. (2004). Mechanism of diacylglycerol-induced membrane targeting and activation of protein kinase Cdelta. *J. Biol. Chem., 279*, 29501-12. ↗

Newton, AC. (1995). Protein kinase C: structure, function, and regulation. *J. Biol. Chem., 270*, 28495-8. ↗

Matsuzaki, H., Yamamoto, T., Kikkawa, U. (2002). Protein kinase C delta (PKC delta): activation mechanisms and functions. *J. Biochem., 132*, 831-9. ↗

Editions

2014-07-14	Authored, Edited	Garapati, P V.
2014-09-02	Reviewed	Geijtenbeek, TB.

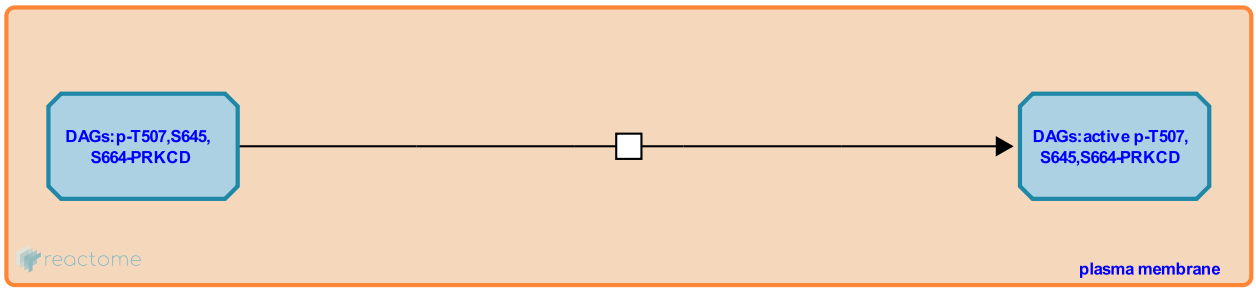
PKC-delta is activated ↗

Location: CLEC7A (Dectin-1) signaling

Stable identifier: R-HSA-5607746

Type: transition

Compartments: plasma membrane



Membrane-bound PKC adopts an open conformation, in which the pseudosubstrate is released from the kinase domain, allowing downstream signaling (Newton 2010).

Preceded by: PKC-delta translocates to plasma membrane

Followed by: PKC-delta phosphorylates CARD9

Literature references

Newton, AC. (2010). Protein kinase C: poised to signal. *Am. J. Physiol. Endocrinol. Metab., 298*, E395-402. ↗

Cho, W., Rafter, JD., Digman, MA., Medkova, M., Stahelin, RV., Melowic, HR. et al. (2004). Mechanism of diacylglycerol-induced membrane targeting and activation of protein kinase Cdelta. *J. Biol. Chem., 279*, 29501-12. ↗

Editions

2014-07-14	Authored, Edited	Garapati, P V.
2014-09-02	Reviewed	Geijtenbeek, TB.

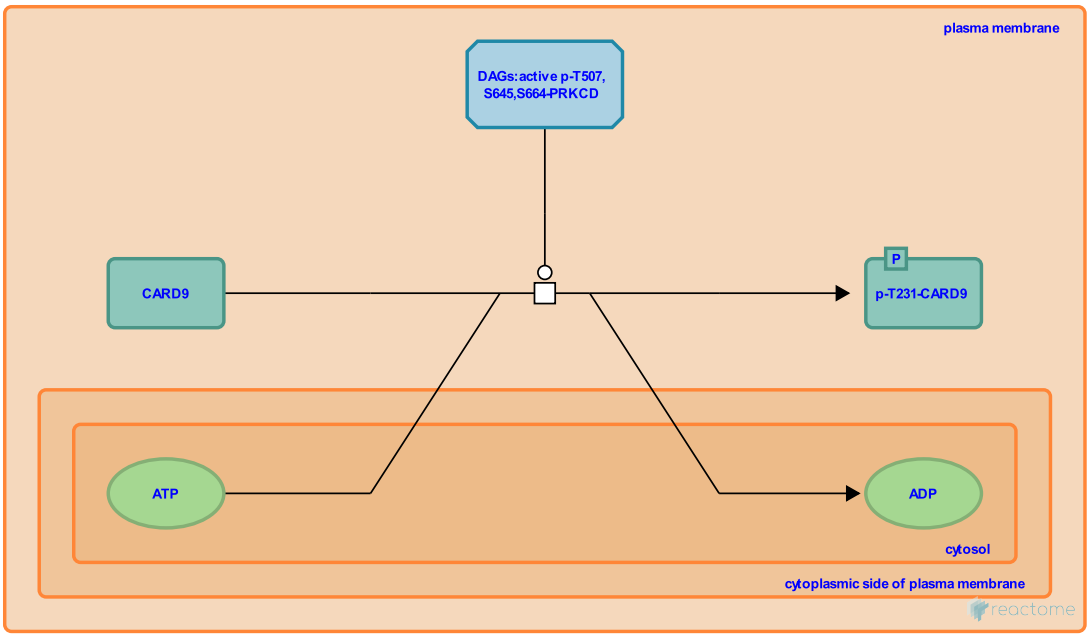
PKC-delta phosphorylates CARD9 ↗

Location: CLEC7A (Dectin-1) signaling

Stable identifier: R-HSA-5607740

Type: transition

Compartments: plasma membrane, cytosol



Activation of NF-kB signaling is a critical event downstream of CLEC7A (Dectin-1), CLEC6A (Dectin-2) (Bi et al. 2010) and CLEC4E (Mincle) (Yamasaki et al. 2008), requiring the adapter protein Caspase recruitment domain (CARD)-containing protein 9 (CARD9) in dendritic cells and in macrophages (Gross et al. 2006, Hara et al. 2007). CARD9 is analogous to CARD-containing MAGUK protein 1 (CARMA1), which mediates T-cell receptor (TCR) activation of NF-kB in lymphocytes. CARD9 is downstream of SYK and becomes phosphorylated by PRKCD (Protein kinase C-delta) phosphorylates CARD9 on Thr-231 (T231), which is required for the signal-induced association of CARD9 with B-cell lymphoma 10 (BCL10) and Mucosa-associated lymphoid tissue 1 (MALT1) and the subsequent recruitment of MAP3K transforming growth factor beta activated kinase 1 (TAK1), leading to activation of the NF-kB pathway (Strasser et al. 2012). A homozygous loss-of-function mutation in human CARD9 results in a premature termination codon (Gln295*). Patients with this mutation are highly susceptible to fungal infections (Glocker et al. 2009).

Preceded by: PKC-delta is activated

Followed by: CARD9 oligomerizes

Literature references

Baier, G., Rojowska, A., Ruland, J., Leitges, M., Neumann, K., Urlaub, H. et al. (2012). Syk kinase-coupled C-type lectin receptors engage protein kinase C-? to elicit Card9 adaptor-mediated innate immunity. *Immunity, 36*, 32-42. ↗

Editions

2014-07-14	Authored, Edited	Garapati, P V.
2014-09-02	Reviewed	Geijtenbeek, TB.

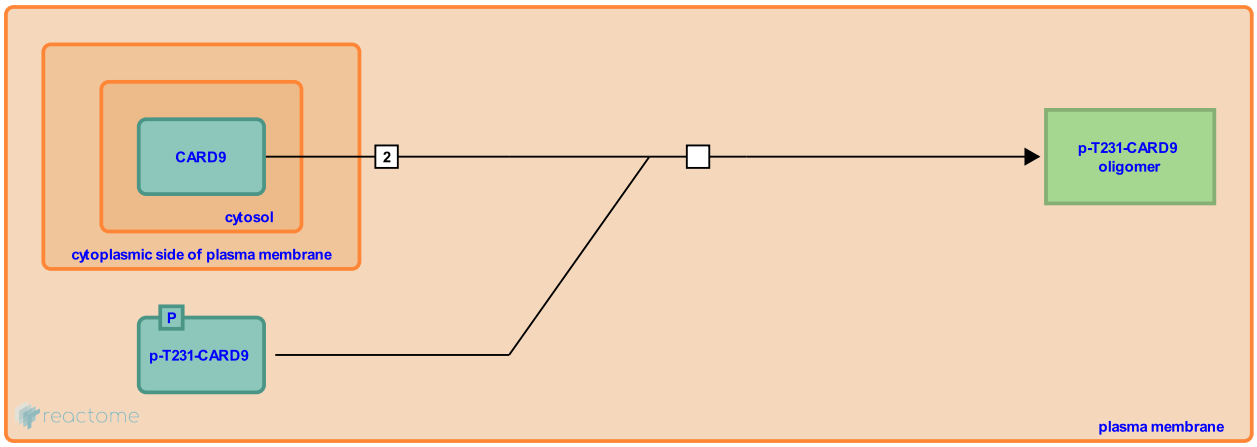
CARD9 oligomerizes ↗

Location: CLEC7A (Dectin-1) signaling

Stable identifier: R-HSA-5607753

Type: transition

Compartments: plasma membrane, cytosol



Activated CARD9 localised in lipid rafts may self-associate with other CARD9 molecules (oligomerization). Residues 140-420 of CARD9 contain heptad repeats characteristic of coiled-coil structures that function in protein oligomerization (Bertin et al. 2000).

Preceded by: PKC-delta phosphorylates CARD9

Followed by: BCL10 binds CARD9

Literature references

Alnemri, ES., Du, MQ., Robison, KE., Srinivasula, SM., DiStefano, PS., Dyer, MJ. et al. (2000). CARD9 is a novel caspase recruitment domain-containing protein that interacts with BCL10/CLAP and activates NF-kappa B. *J. Biol. Chem., 275*, 41082-6. ↗

Hara, H., Saito, T. (2009). CARD9 versus CARMA1 in innate and adaptive immunity. *Trends Immunol., 30*, 234-42. ↗

Editions

2014-07-14	Authored, Edited	Garapati, P V.
2014-09-02	Reviewed	Geijtenbeek, TB.

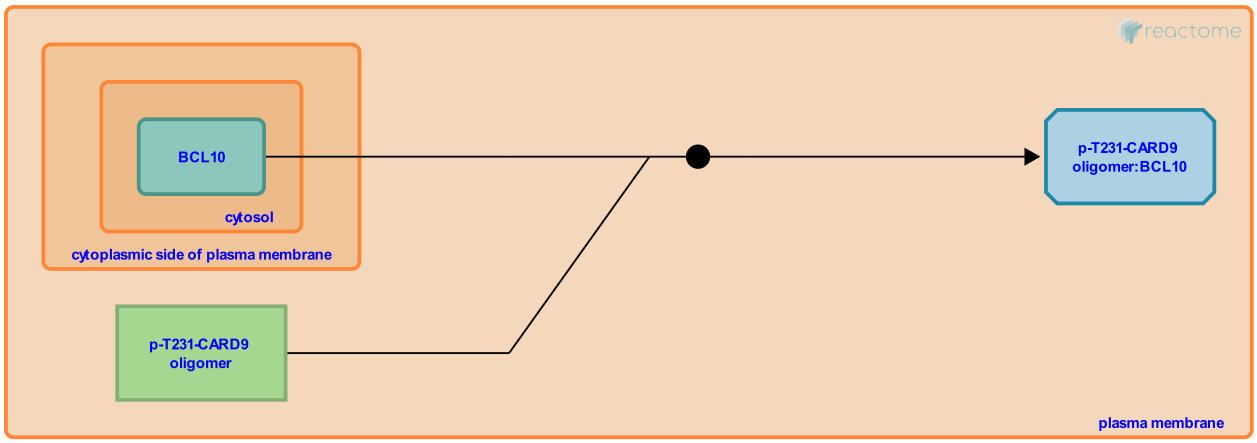
BCL10 binds CARD9 ↗

Location: CLEC7A (Dectin-1) signaling

Stable identifier: R-HSA-5607733

Type: binding

Compartments: plasma membrane, cytosol



B-cell lymphoma/leukemia 10 (BCL10) is the downstream signaling partner of CARD9 and it interacts selectively with the CARD activation domain of CARD9. BCL10 functions as an adaptor between the effector IKK complex and the proximal signaling complexes that interact with CARD9 (Bertin et al. 2000).

Preceded by: CARD9 oligomerizes

Followed by: BCL10 oligomerizes

Literature references

Alnemri, ES., Du, MQ., Robison, KE., Srinivasula, SM., DiStefano, PS., Dyer, MJ. et al. (2000). CARD9 is a novel caspase recruitment domain-containing protein that interacts with BCL10/CLAP and activates NF-kappa B. *J. Biol. Chem., 275*, 41082-6. ↗

Editions

2014-07-14	Authored, Edited	Garapati, P V.
2014-09-02	Reviewed	Geijtenbeek, TB.

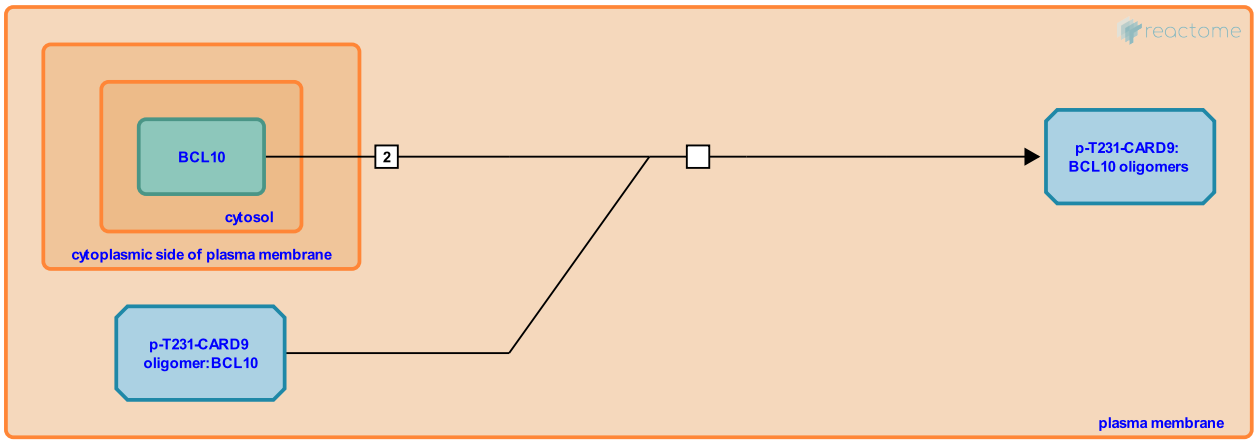
BCL10 oligomerizes ↗

Location: CLEC7A (Dectin-1) signaling

Stable identifier: R-HSA-5607737

Type: transition

Compartments: plasma membrane, cytosol



CARD interactions between CARD9 and BCL10 induce BCL10 oligomerization (through its CARD domain), required for oligomerization and activation of MALT1.

Preceded by: BCL10 binds CARD9

Followed by: MALT1 binds BCL10

Literature references

Nunez, G., Merino, J., Inohara, N., Hottiger, MO., Carrio, R., Chen, S. et al. (1999). CIPER, a novel NF kappaB-activating protein containing a caspase recruitment domain with homology to Herpesvirus-2 protein E10. *J. Biol. Chem., 274*, 9955-61. ↗

Editions

2014-07-14	Authored, Edited	Garapati, P V.
2014-09-02	Reviewed	Geijtenbeek, TB.

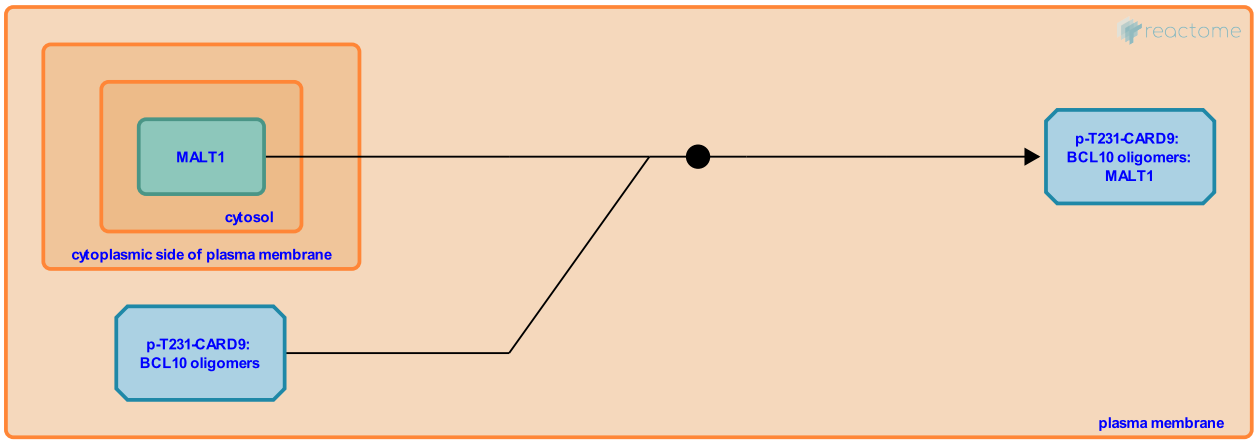
MALT1 binds BCL10 ↗

Location: CLEC7A (Dectin-1) signaling

Stable identifier: R-HSA-5607744

Type: binding

Compartments: plasma membrane, cytosol



Mucosa-associated lymphoid tissue lymphoma translocation protein 1 (MALT1) is the main downstream target of BCL10. MALT1 interacts directly with BCL10 and this interaction involves a short stretch of amino acids that follow the BCL10 CARD motif (amino acids 107–119 of human BCL10) and the two immunoglobulin-like domains of MALT1 (Uren et al. 2000, Lucas et al. 2001).

Preceded by: BCL10 oligomerizes

Followed by: MALT1 oligomerizes

Literature references

Nunez, G., Inohara, N., Lucas, PC., Abazeed, ME., Chen, FF., Seto, M. et al. (2001). Bcl10 and MALT1, independent targets of chromosomal translocation in malt lymphoma, cooperate in a novel NF-kappa B signaling pathway. *J. Biol. Chem., 276*, 19012-9. ↗

Koonin, EV., Seshagiri, S., Pisabarro, MT., O'Rourke, K., Uren, AG., Dixit, VM. et al. (2000). Identification of paracaspases and metacaspases: two ancient families of caspase-like proteins, one of which plays a key role in MALT lymphoma. *Mol. Cell, 6*, 961-7. ↗

Editions

2014-07-14	Authored, Edited	Garapati, P V.
2014-09-02	Reviewed	Geijtenbeek, TB.

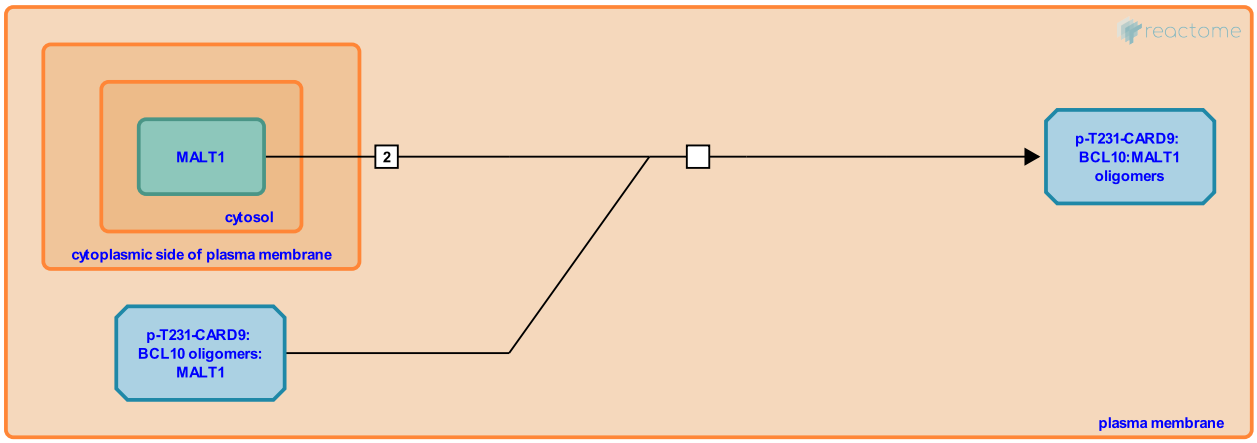
MALT1 oligomerizes ↗

Location: CLEC7A (Dectin-1) signaling

Stable identifier: R-HSA-5607736

Type: transition

Compartments: plasma membrane, cytosol



After binding BCL10, MALT1 also undergoes oligomerization. Like traditional caspases, MALT1 also becomes activated through the formation of oligomers. Once the CARD9-BCL10-MALT1 (CBM) signalosome is assembled, MALT1 functions as the effector protein and mediates activation of the IKK complex (McAllister-Lucas & Lucas 2008).

Preceded by: MALT1 binds BCL10

Followed by: TRAF6 binds MALT1 oligomers

Literature references

Qiu, L., Dhe-Paganon, S. (2011). Oligomeric structure of the MALT1 tandem Ig-like domains. *PLoS ONE, 6*, e23220. ↗

David, L., Qiao, Q., Yang, C., Fontán, L., Wu, H., Melnick, A. et al. (2013). Structural architecture of the CARMA1/Bcl10/MALT1 signalosome: nucleation-induced filamentous assembly. *Mol. Cell, 51*, 766-79. ↗

Nunez, G., Inohara, N., Lucas, PC., Abazeed, ME., Chen, FF., Seto, M. et al. (2001). Bcl10 and MALT1, independent targets of chromosomal translocation in malt lymphoma, cooperate in a novel NF-kappa B signaling pathway. *J. Biol. Chem., 276*, 19012-9. ↗

Editions

2014-07-14	Authored, Edited	Garapati, P V.
2014-09-02	Reviewed	Geijtenbeek, TB.

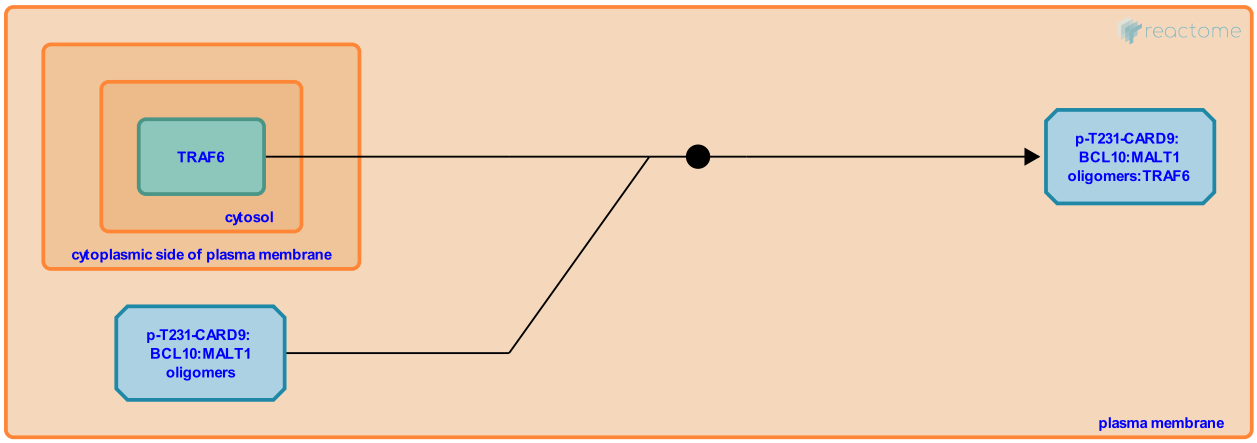
TRAF6 binds MALT1 oligomers ↗

Location: CLEC7A (Dectin-1) signaling

Stable identifier: R-HSA-5607747

Type: binding

Compartments: plasma membrane, cytosol



TRAF6 (tumor necrosis factor receptor-associated factor 6) is a RING (really interesting new gene) domain ubiquitin (Ub) ligase that mediates NF-kB activation by regulating the ubiquitination of transforming growth factor beta-activated kinase (TAK1) and IkB kinase (IKK). TRAF6 has been implicated as downstream effector of MALT1. MALT1 binds to TRAF6 through two putative C-terminal TRAF6-binding motifs (Sun et al. 2004). Gorjestani et al. demonstrate that TRAF6 and TAK1 are required for C-type lectin receptor-induced NF-kB activation and play critical roles in anti-fungal innate immune responses (Gorjestani et al. 2012).

Preceded by: MALT1 oligomerizes

Followed by: TRAF6 oligomerizes

Literature references

Deng, L., Chen, ZJ., Sun, L., Xia, ZP., Ea, CK. (2004). The TRAF6 ubiquitin ligase and TAK1 kinase mediate IKK activation by BCL10 and MALT1 in T lymphocytes. *Mol Cell, 14*, 289-301. ↗

Editions

2014-07-14	Authored, Edited	Garapati, P V.
2014-09-02	Reviewed	Geijtenbeek, TB.

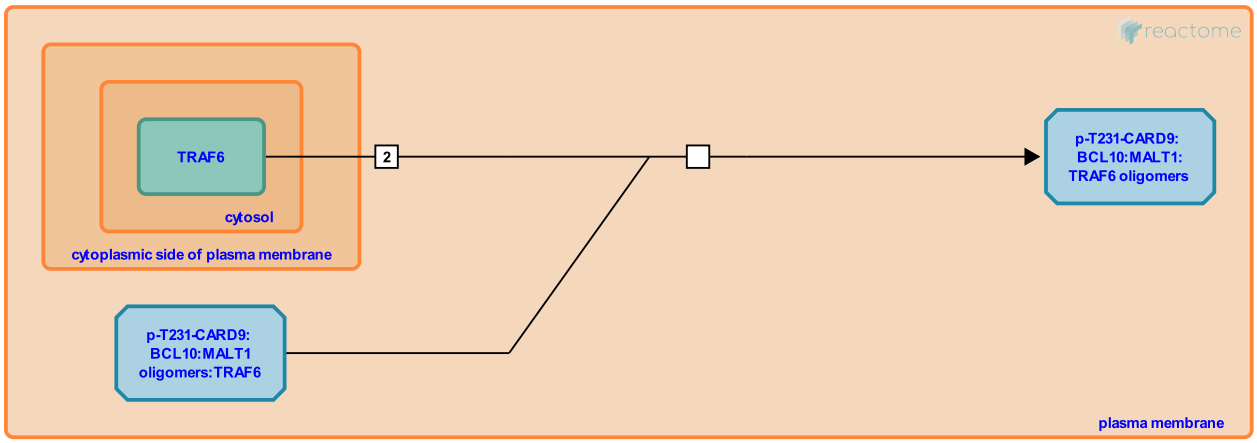
TRAF6 oligomerizes ↗

Location: CLEC7A (Dectin-1) signaling

Stable identifier: R-HSA-5607751

Type: transition

Compartments: plasma membrane, cytosol



The MALT1 oligomers bound to TRAF6 induce TRAF6 oligomerization and activate TRAF6 E3 ubiquitin ligase activity (Sun et al. 2004).

Preceded by: TRAF6 binds MALT1 oligomers

Followed by: TRAF6 oligomer autoubiquitinates

Literature references

Deng, L., Chen, ZJ., Sun, L., Xia, ZP., Ea, CK. (2004). The TRAF6 ubiquitin ligase and TAK1 kinase mediate IKK activation by BCL10 and MALT1 in T lymphocytes. *Mol Cell, 14*, 289-301. ↗

Editions

2014-07-14	Authored, Edited	Garapati, P V.
2014-09-02	Reviewed	Geijtenbeek, TB.

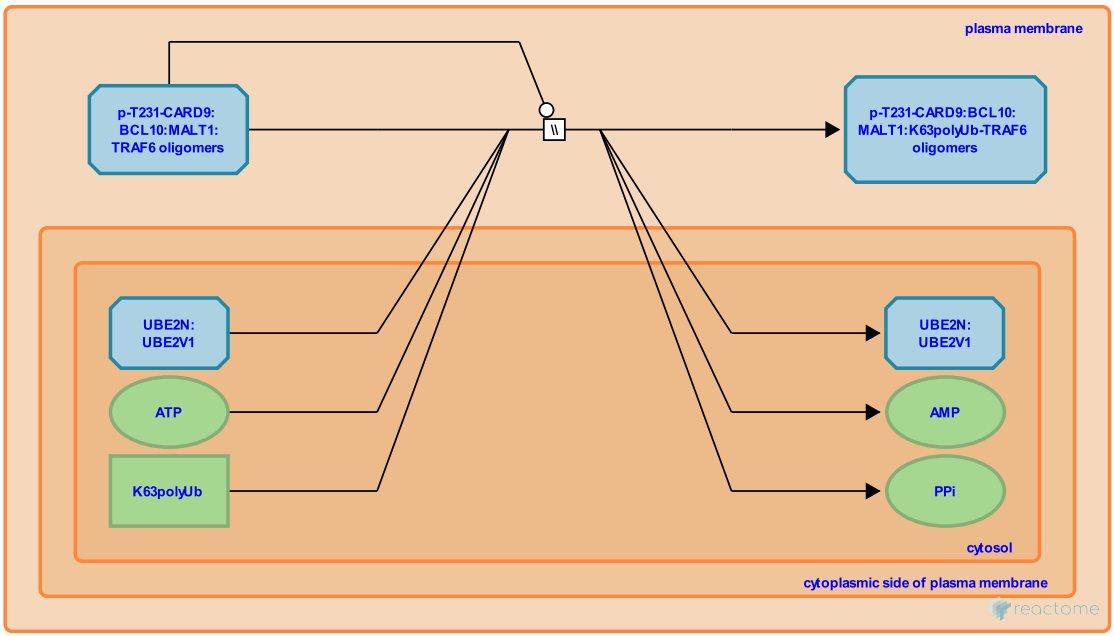
TRAF6 oligomer autoubiquitinates ↗

Location: CLEC7A (Dectin-1) signaling

Stable identifier: R-HSA-5607756

Type: omitted

Compartments: plasma membrane, cytosol



TRAF6 possesses ubiquitin ligase activity and undergoes K-63-linked auto-ubiquitination after its oligomerization. In the first step, ubiquitin is activated by an E1 ubiquitin activating enzyme. The activated ubiquitin is transferred to a E2 conjugating enzyme (a heterodimer of proteins Ubc13 and Uev1A also known as TRIKA1 (TRAF6-regulated IKK activator 1)) 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 (Deng et al. 2000, Lamothe et al. 2007). In contrast to K-48-linked ubiquitination that leads to the proteosomal degradation of the target protein, K-63-linked polyubiquitin chains act as a scaffold to assemble protein kinase complexes and mediate their activation through proteosome-independent mechanisms. This K63 polyubiquitinated TRAF6 activates the TAK1 kinase complex.

Preceded by: TRAF6 oligomerizes

Followed by: TRIKA2 binds K63polyUb-TRAF6 oligomer

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. ↗

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

Editions

2014-07-14	Authored, Edited	Garapati, P V.
2014-09-02	Reviewed	Geijtenbeek, TB.

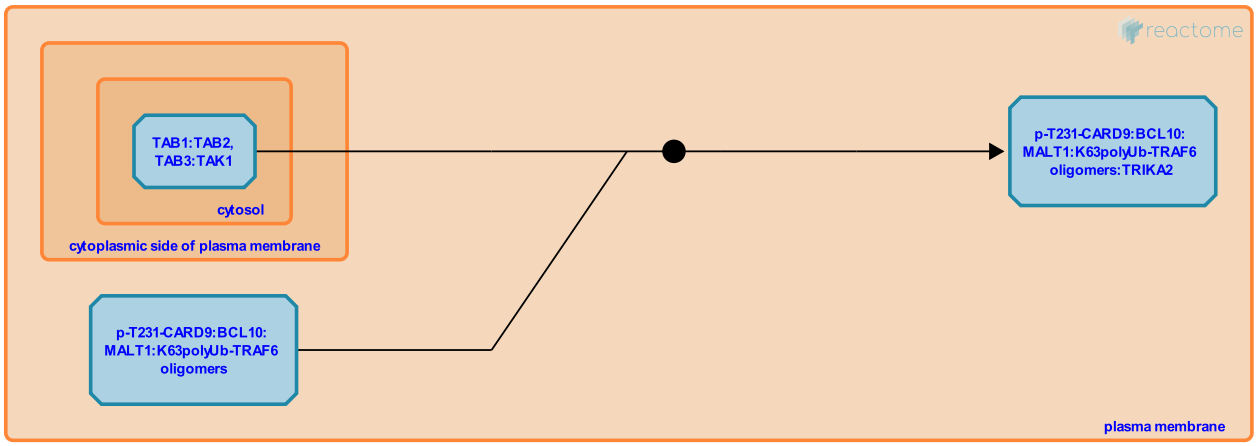
TRIKA2 binds K63polyUb-TRAF6 oligomer ↗

Location: CLEC7A (Dectin-1) signaling

Stable identifier: R-HSA-5607759

Type: binding

Compartments: plasma membrane, cytosol



K-63 linked polyubiquitin (pUb) chain on TRAF6 provides a scaffold to recruit downstream effector molecules to activate NF-kB. Transforming growth factor beta-associated kinase 1 (TAK1) is a member of the mitogen-activated protein kinase (MAPK) kinase kinase family that is shown to be an essential intermediate that transmits the upstream signals from the receptor complex to the downstream MAPKs and to the NF-kB pathway (Broglie et al. 2009). As a member of the MAP3K family, TAK1 is unique in that its activity requires its binding proteins TAK1-binding protein 1 (TAB1), TAB2 and TAB3. TAB1 acts as the kinase subunit of the TAK1 complex, aiding in the autophosphorylation of TAK1, whereas TAB2 and its homologue TAB3, acts as an adaptor of TAK1 that facilitate the assembly of TAK1 complex to TRAF6 (Takaesu et al. 2000, Ishitani et al. 2003). This protein kinase complex containing the kinase subunit TAK1 and the regulatory subunits TAB1 and TAB2/TAB3 is also known as TRIKA2 (TRAF6-regulated IKK activator 2) (Adhikari et al. 2007).

Preceded by: TRAF6 oligomer autoubiquitinates

Followed by: K63polyUb-TRAF6 ubiquitinates TAK1

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. ↗

Maddineni, U., Wu, H., Darnay, BG., Lin, SC., Besse, A., Lamothe, B. et al. (2007). TAK1-dependent signaling requires functional interaction with TAB2/TAB3. *J Biol Chem, 282*, 3918-28. ↗

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

Editions

2014-07-14	Authored, Edited	Garapati, P V.
2014-09-02	Reviewed	Geijtenbeek, TB.

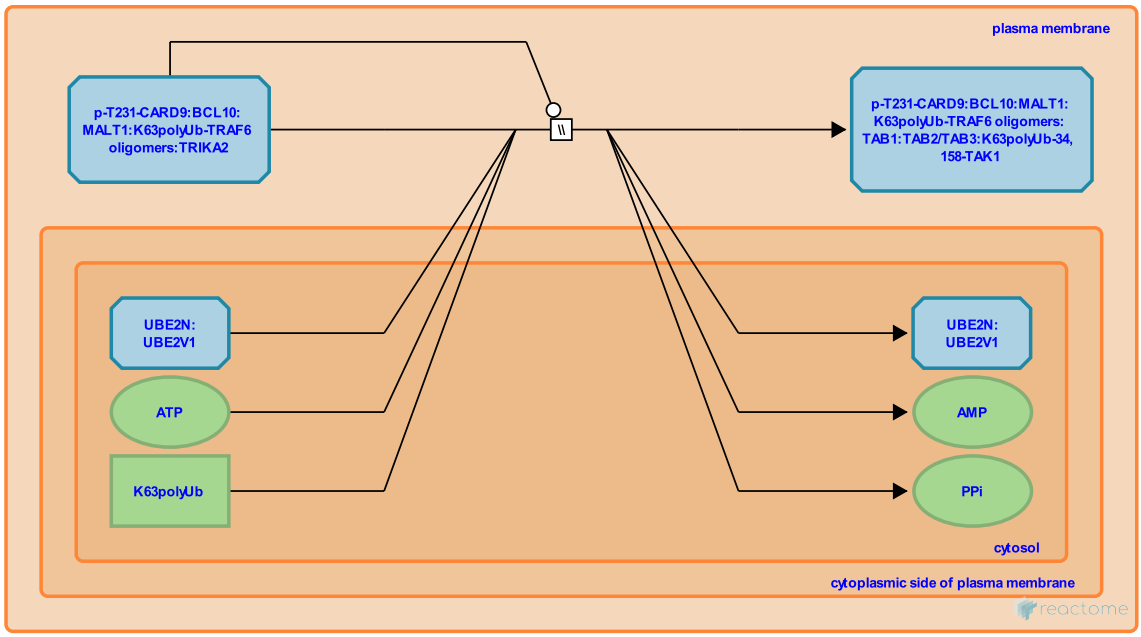
K63polyUb-TRAF6 ubiquitinates TAK1 ↗

Location: CLEC7A (Dectin-1) signaling

Stable identifier: R-HSA-5607757

Type: omitted

Compartments: plasma membrane, cytosol



TAK1-binding protein 2 (TAB2), or its homologue TAB3, binds preferentially to K63-linked polyubiquitin chains in TRAF6 and links TRAF6 (TNF receptor-associated factor 6) to TAK1 (Transforming growth factor beta-associated kinase 1). TRAF6 ubiquitinates TAK1 on K34 and K158 and this triggers conformational changes in TAK1 that lead to autophosphorylation and activation (Fan et al. 2010, Hamidi et al. 2011).

Preceded by: TRIKA2 binds K63polyUb-TRAF6 oligomer

Followed by: K63polyUb-TAK1 autophosphorylates

Literature references

Landström, M., Barluenga, S., von Bulow, V., Winssinger, N., Hamidi, R., Heldin, CH. et al. (2012). Polyubiquitination of transforming growth factor ? (TGF?)-associated kinase 1 mediates nuclear factor-?B activation in response to different inflammatory stimuli. *J. Biol. Chem., 287*, 123-33. ↗

Xie, M., Fan, Y., Fu, S., Zhang, H., Shi, Y., Mao, R. et al. (2010). Lysine 63-linked polyubiquitination of TAK1 at lysine 158 is required for tumor necrosis factor alpha- and interleukin-1beta-induced IKK/NF-kappaB and JNK/AP-1 activation. *J. Biol. Chem., 285*, 5347-60. ↗

Editions

2014-07-14	Authored, Edited	Garapati, P V.
2014-09-02	Reviewed	Geijtenbeek, TB.

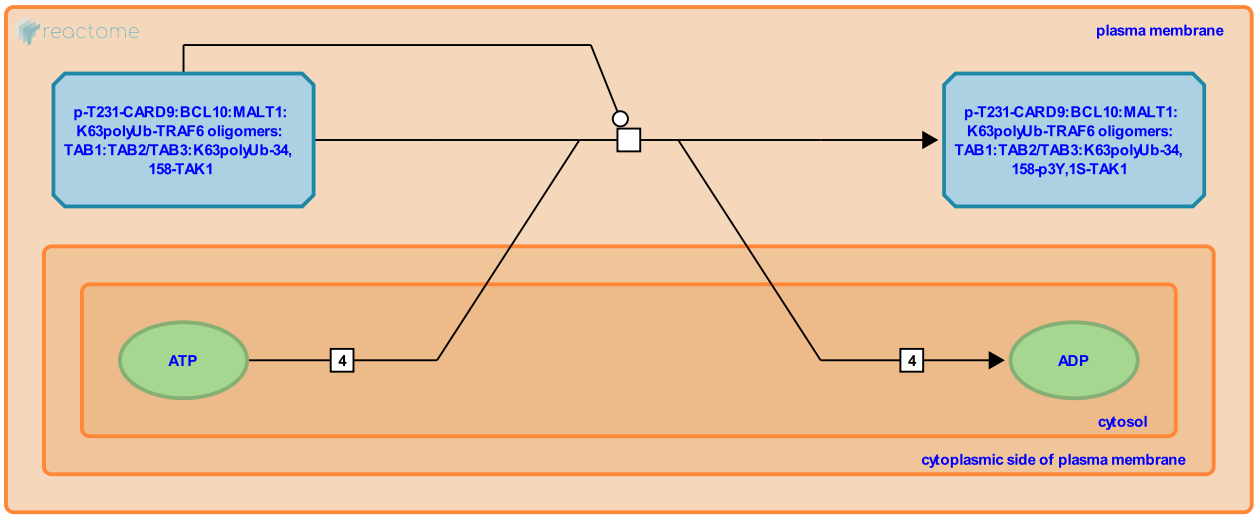
K63polyUb-TAK1 autophosphorylates ↗

Location: CLEC7A (Dectin-1) signaling

Stable identifier: R-HSA-5607732

Type: transition

Compartments: plasma membrane, cytosol



TAK1-binding protein 1 (TAB1) is a TAK1-interacting protein and induces TAK1 (Transforming growth factor beta-associated kinase 1) kinase activity through promoting autophosphorylation of key serine/threonine sites of the kinase activation loop. There are four phosphorylation sites in the activation loop and analysis of these site mutants indicate that autophosphorylation of S192, is followed by sequential phosphorylation of T178, T187, and finally T184 (Scholz et al. 2010).

Preceded by: K63polyUb-TRAF6 ubiquitinates TAK1

Followed by: K63polyUb-p-3T,1S-TAK1 phosphorylates IKK-beta

Literature references

Thali, RF., Scholz, R., Neumann, D., Sidler, CL., Winssinger, N., Cheung, PC. (2010). Autoactivation of transforming growth factor beta-activated kinase 1 is a sequential bimolecular process. *J. Biol. Chem., 285*, 25753-66. ↗

Editions

2014-07-14	Authored, Edited	Garapati, P V.
2014-09-02	Reviewed	Geijtenbeek, TB.

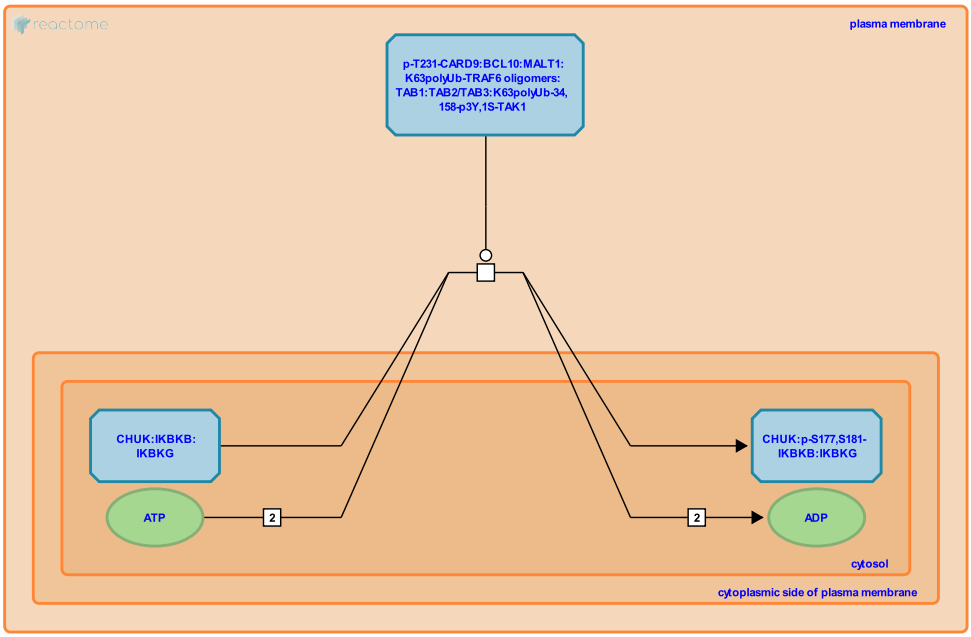
K63polyUb-p-3T,1S-TAK1 phosphorylates IKK-beta ↗

Location: CLEC7A (Dectin-1) signaling

Stable identifier: R-HSA-5607742

Type: transition

Compartments: plasma membrane, cytosol



In humans, the IkB kinase (IKK) complex serves as the master regulator for the activation of NF-kB by various stimuli. It contains two catalytic subunits, IKK alpha and IKK beta, and a regulatory subunit, IKKgamma/NEMO. The activation of IKK complex is dependent on the phosphorylation of IKK alpha/beta at its activation loop and the K63-linked ubiquitination of NEMO. This basic trimolecular complex is referred to as the IKK complex.
IKK subunits have a N-term kinase domain a leucine zipper (LZ) motifs, a helix-loop-helix (HLH) and a C-ter NEMO binding domain (NBD). IKK catalytic subunits are dimerized through their LZ motifs. IKK beta is the major IKK catalytic subunit for NF-kB activation. Activated TAK1 phosphorylate IKK beta on S177 and S181 (S176 and S180 in IKK alpha) in the activation loop and thus activate the IKK kinase activity, leading to the IkB alpha phosphorylation and NF-kB activation.

Preceded by: K63polyUb-TAK1 autophosphorylates

Followed by: Ubiquitination of NEMO by TRAF6

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. ↗

Pennington, KN., Carter, RS., Ballard, DW., Arrate, P., Ungurait, BJ. (2003). Signal-induced ubiquitination of I kappaB Kinase-beta. *J. Biol. Chem., 278*, 48903-6. ↗

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

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

Ballard, DW., Acevedo-Suárez, CA., Geyer, BC., Carter, RS., Xie, M. (2001). Persistent activation of NF-kappa B by the tax transforming protein involves chronic phosphorylation of IkappaB kinase subunits IKKbeta and IKKgamma. *J. Biol. Chem., 276*, 24445-8. ↗

Editions

2014-07-14	Authored, Edited	Garapati, P V.
2014-09-02	Reviewed	Geijtenbeek, TB.

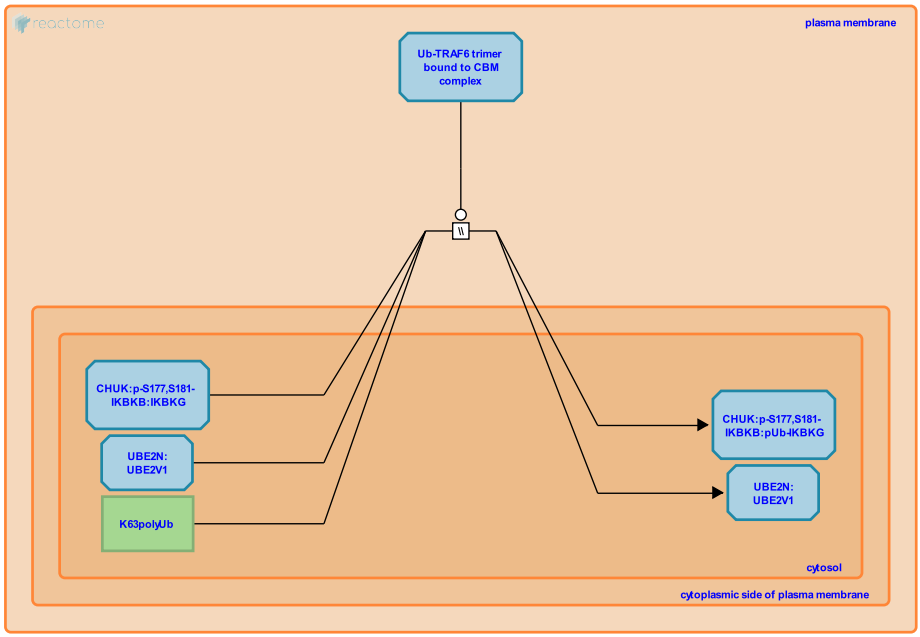
Ubiquitination of NEMO by TRAF6 ↗

Location: CLEC7A (Dectin-1) signaling

Stable identifier: R-HSA-202534

Type: omitted

Compartments: plasma membrane



During the phosphorylation of the IKK beta, the regulatory subunit NEMO undergoes K-63-linked polyubiquitination. Ubiquitinated TRAF6 trimer, acts as a E3 ligase and induces this ubiquitination. The ubiquitin target sites in NEMO are not yet clearly identified. Studies of different NF-kB signaling pathways revealed several potential ubiquitination sites on NEMO (e.g., K285, K277, K309 and K399) (Fuminori et al. 2009).

Preceded by: K63polyUb-p-3T,1S-TAK1 phosphorylates IKK-beta

Followed by: p-S177,S181-IKKB:IKKA:pUb-NEMO phosphorylates IkB-alpha:NF-kB

Literature references

Sebban-Benin, H., Pescatore, A., Courtois, G., Fusco, F., Ursini, MV., Yamaoka, S. et al. (2007). Identification of TRAF6-dependent NEMO polyubiquitination sites through analysis of a new NEMO mutation causing incontinentia pigmenti. *Hum Mol Genet, 127*. ↗

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

Editions

2008-01-24	Authored	de Bono, B., Garapati, P V., Rudd, C.E..
2008-02-26	Reviewed	Trowsdale, J.

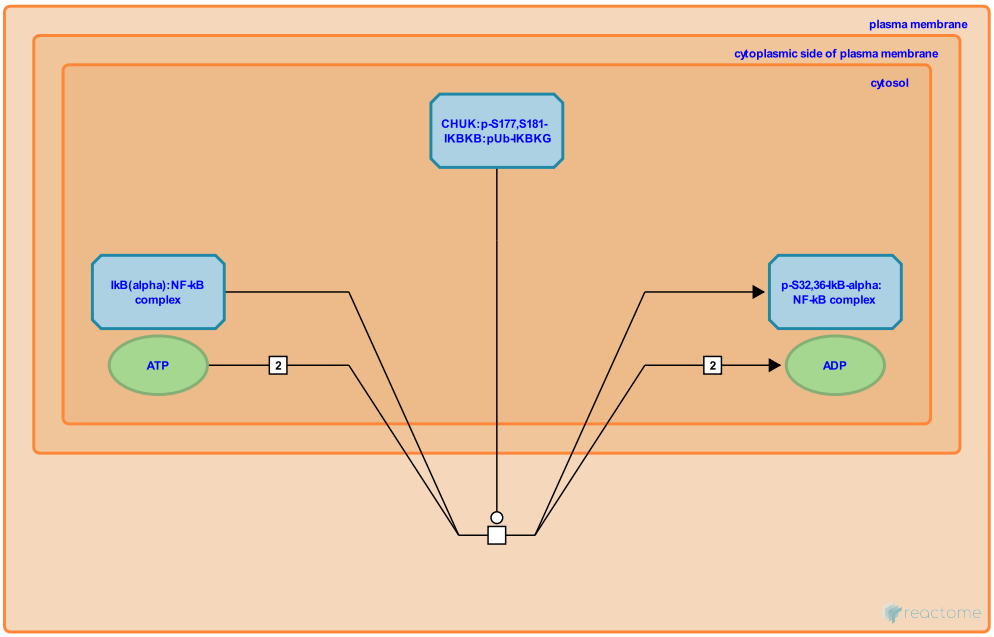
p-S177,S181-IKKB:IKKA:pUb-NEMO phosphorylates IkB-alpha:NF-kB ↗

Location: CLEC7A (Dectin-1) signaling

Stable identifier: R-HSA-202541

Type: transition

Compartments: plasma membrane



NF-kB is sequestered in the cytosol of unstimulated cells through the interactions with a class of inhibitor proteins, called IkBs, which mask the nuclear localization signal (NLS) of NF-kB and prevent its nuclear translocation. A key event in NF-kB activation involves phosphorylation of IkB (at sites equivalent to Ser32 and Ser36 of IkB-alpha or Ser19 and Ser22 of IkB-beta) by IKK. The phosphorylated IkB-alpha is recognized by the E3 ligase complex and targeted for ubiquitin-mediated proteasomal degradation, releasing the NF-kB dimer p50/p65 into the nucleus to turn on target genes. (Karin & Ben-Neriah 2000)

Preceded by: Ubiquitination of NEMO by TRAF6

Followed by: beta-TRCP ubiquitinates IkB-alpha in p-S32,33-IkB-alpha:NF-kB complex

Literature references

Rothwarf, DM., Karin, M., Zandi, E., DiDonato, JA., Hayakawa, M. (1997). A cytokine-responsive IkappaB kinase that activates the transcription factor NF-kappaB. *Nature, 388*, 548-54. ↗

Sakurai, H., Pappu, BP., Hara, H., Li, H., Lin, X., Darnay, BG. et al. (2007). Phosphorylation and ubiquitination of the IkappaB kinase complex by two distinct signaling pathways. *EMBO J, 26*, 1794-805. ↗

Karin, M., Bonizzi, G. (2004). The two NF-kappaB activation pathways and their role in innate and adaptive immunity . *Trends Immunol, 25*, 280-8. ↗

Hayden, MS., Ghosh, S. (2004). Signaling to NF-kappaB. *Genes Dev, 18*, 2195-224. ↗

Parent, L., Chen, ZJ., Maniatis, T. (1996). Site-specific phosphorylation of IkappaBalpha by a novel ubiquitination-dependent protein kinase activity. *Cell, 84*, 853-62. ↗

Editions

2008-01-24	Authored	de Bono, B., Garapati, P V., Rudd, C.E..
2008-02-26	Reviewed	Trowsdale, J.

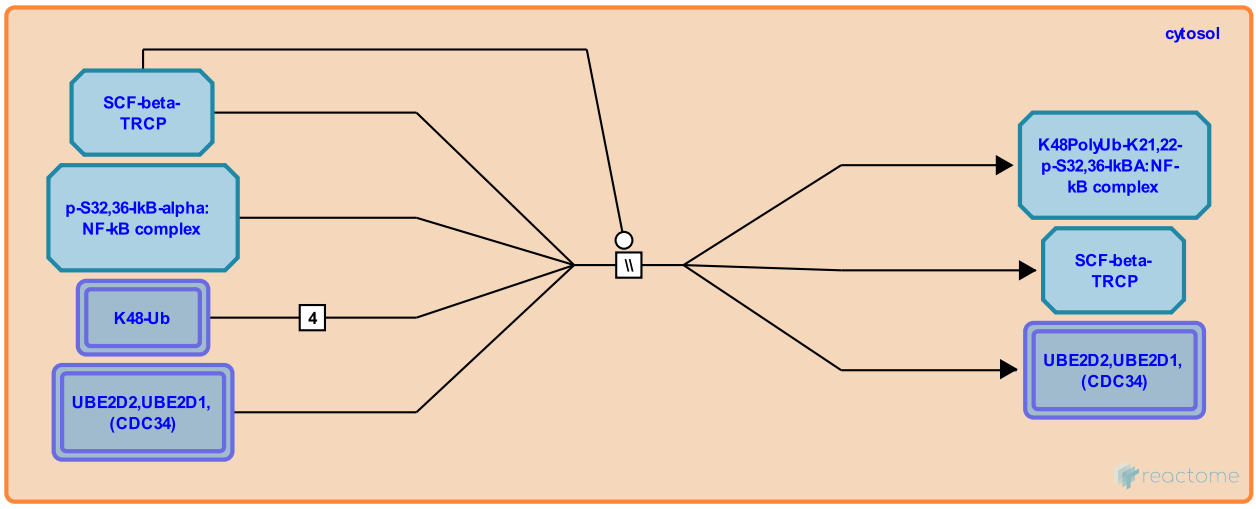
beta-TRCP ubiquitinates IkB-alpha in p-S32,33-IkB-alpha:NF-kB complex ↗

Location: CLEC7A (Dectin-1) signaling

Stable identifier: R-HSA-5607728

Type: omitted

Compartments: cytosol



Two major signaling steps are required for the removal of IkappaB (IkB) alpha an inhibitor of NF-kB: activation of the IkB kinase (IKK) and degradation of the phosphorylated IkB alpha. IKK activation and IkB degradation involve different ubiquitination modes; the former is mediated by K63-ubiquitination and the later by K48-ubiquitination. Mutational analysis of IkB alpha has indicated that K21 and K22 are the primary sites for addition of multiubiquitination chains while K38 and K47 are the secondary sites. In a transesterification reaction the ubiquitin is transferred from the ubiquitin-activating enzyme (E1) to an E2 ubiquitin-conjugating enzyme, which may, in turn, transfer the ubiquitin to an E3 ubiquitin protein ligase. UBE2D2 (UBC4) or UBE2D1 (UBCH5) or CDC34 (UBC3) acts as the E2 and SCF (SKP1-CUL1-F-box)-beta-TRCP complex acts as the E3 ubiquitin ligase (Strack et al. 2000, Wu et al. 2010). beta-TRCP (beta-transducin repeats-containing protein) is the substrate recognition subunit for the SCF-beta-TRCP E3 ubiquitin ligase. beta-TRCP binds specifically to phosphorylated IkB alpha and recruits it to the SCF complex, allowing the associated E2, such as UBC4 and or UBCH5 to ubiquitinate Ikappa B alpha (Baldi et al. 1996, Rodriguez et al. 1996, Scherer et al. 1995, Alkalay et al. 1995).

Preceded by: p-S177,S181-IKKB:IKKA:pUb-NEMO phosphorylates IkB-alpha:NF-kB

Followed by: 26S proteasome processes K48PolyUb-K21,22-p-S32,36-IkBA:NF-kB complex to form NF-kB complex

Literature references

Baldi, L., Franzoso, G., Siebenlist, U., Brown, K. (1996). Critical role for lysines 21 and 22 in signal-induced, ubiquitin-mediated proteolysis of I kappa B-alpha. *J. Biol. Chem., 271*, 376-9. ↗

Pennington, KN., Carter, RS., Ballard, DW., Arrate, P., Ungurait, BJ. (2003). Signal-induced ubiquitination of I kappaB Kinase-beta. *J. Biol. Chem., 278*, 48903-6. ↗

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. ↗

Ciechanover, A., Hatzubai, A., Alkalay, I., Yaron, A., Orian, A., Ben-Neriah, Y. (1995). Stimulation-dependent I kappa B alpha phosphorylation marks the NF-kappa B inhibitor for degradation via the ubiquitin-proteasome pathway. *Proc Natl Acad Sci U S A, 92*, 10599-603. ↗

Editions

2014-07-14	Authored, Edited	Garapati, P V.
2014-09-02	Reviewed	Geijtenbeek, TB.

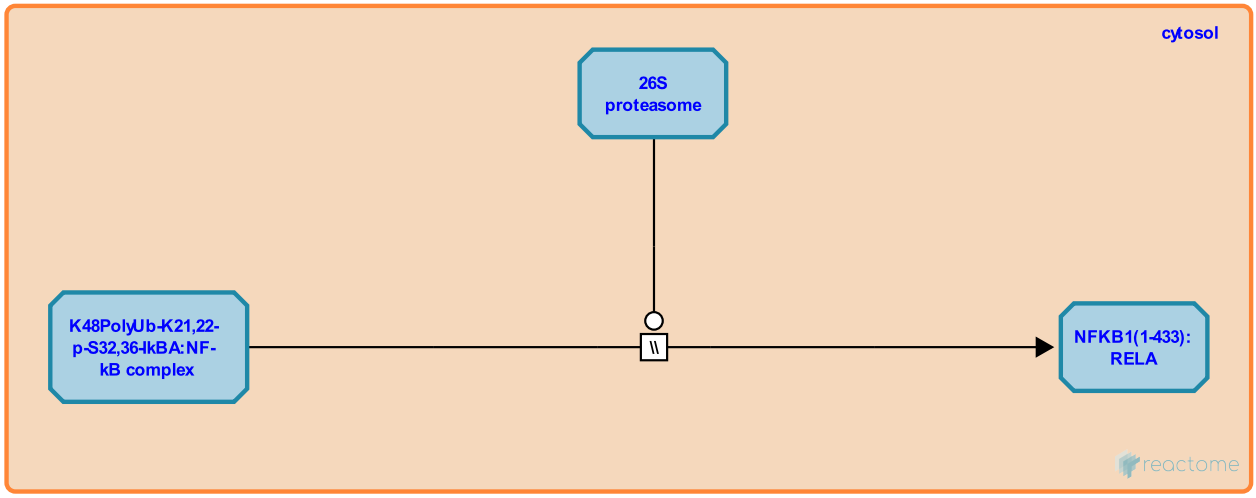
26S proteasome processes K48PolyUb-K21,22-p-S32,36-IkBA:NF-kB complex to form NF-kB complex ↗

Location: CLEC7A (Dectin-1) signaling

Stable identifier: R-HSA-5607724

Type: omitted

Compartments: cytosol



Following ubiquitination NF-kappa-B inhibitor alpha (NFKBIA or IκBα) is rapidly degraded by 26S-proteasome, allowing NF-kB to translocate into the nucleus where it activates gene transcription (Spencer et al. 1999).

Severe acute respiratory syndrome coronavirus (SARS-CoV) 1a-encoded papain-like protease (PLPro or nsp3) was found to cleave Lys48-linked polyUb chains of NFKBIA (IκBα) (Békés M et al. 2016;Ratia K et al. 2014) suggesting an inhibitory effect of SARS-CoV-1 nsp3 on 26S proteasome-dependent degradation of NFKBIA.

Preceded by: beta-TRCP ubiquitinates IkB-alpha in p-S32,33-IkB-alpha:NF-kB complex

Followed by: NFKB1:RELA translocates from the cytosol to the nucleus

Literature references

Desterro, MJ., Kroll, M., Arenzana-Seisdedos, F., Marin, A., Thomas, D., Virelizier, JL. et al. (1997). The carboxy-terminus of I kappaB alpha determines susceptibility to degradation by the catalytic core of the proteasome. *Oncogene, 15*, 1841-50. ↗

Editions

2014-07-14	Authored, Edited	Garapati, P V.
2014-09-02	Reviewed	Geijtenbeek, TB.

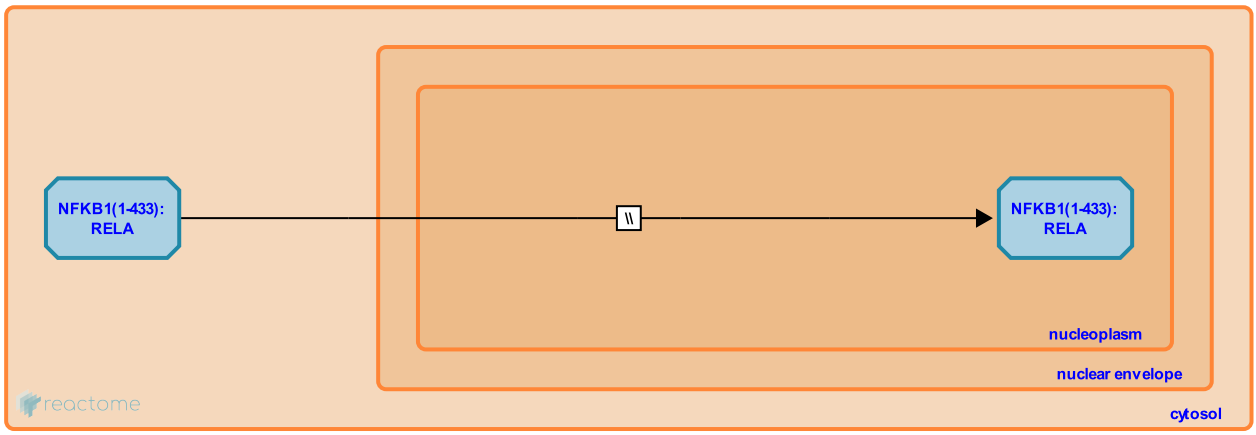
NFKB1:RELA translocates from the cytosol to the nucleus ↗

Location: CLEC7A (Dectin-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.

Preceded by: 26S proteasome processes K48PolyUb-K21,22-p-S32,36-IkBA:NF-kB complex to form NF-kB complex

Literature references

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

Editions

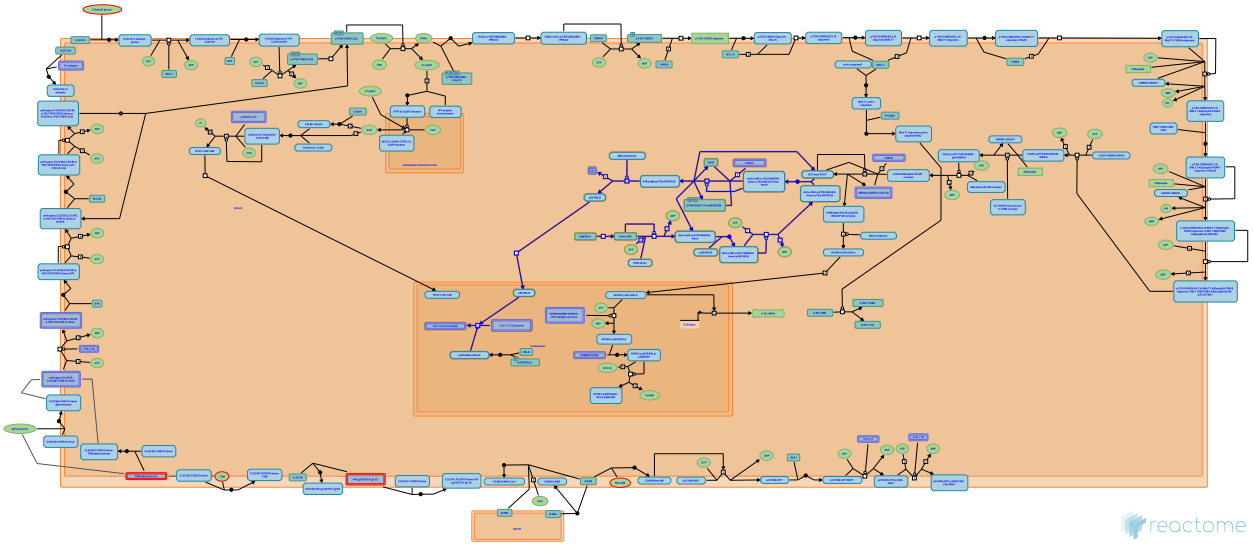
2012-08-22	Edited	Garapati, P V.
2012-12-21	Authored	Niarakis, A.
2013-02-13	Reviewed	Roncagalli, R.

Dectin-1 mediated noncanonical NF-kB signaling ↗

Location: CLEC7A (Dectin-1) signaling

Stable identifier: R-HSA-5607761

Compartments: nucleoplasm, cytosol



In addition to the activation of canonical NF-kB subunits, activation of SYK pathway by Dectin-1 leads to the induction of the non-canonical NF-kB pathway, which mediates the nuclear translocation of RELB-p52 dimers through the successive activation of NF-kB-inducing kinase (NIK) and IkB kinase-alpha (IKKa) (Geijtenbeek & Gringhuis 2009, Gringhuis et al. 2009). Noncanonical activity tends to build more slowly and remain sustained several hours longer than does the activation of canonical NF-kB. The noncanonical NF-kB pathway is characterized by the post-translational processing of NFKB2 (Nuclear factor NF-kappa-B) p100 subunit to the mature p52 subunit. This subsequently leads to nuclear translocation of p52:RELB (Transcription factor RelB) complexes to induce cytokine expression of some genes (C-C motif chemokine 17 (CCL17) and CCL22) and transcriptional repression of others (IL12B) (Gringhuis et al. 2009, Geijtenbeek & Gringhuis 2009, Plato et al. 2013).

Literature references

Willment, JA., Brown, GD., Plato, A. (2013). C-type lectin-like receptors of the dectin-1 cluster: ligands and signaling pathways. *Int. Rev. Immunol., 32*, 134-56. ↗

Karin, M., Vallabhapurapu, S. (2009). Regulation and function of NF-kappaB transcription factors in the immune system. *Annu. Rev. Immunol., 27*, 693-733. ↗

Geijtenbeek, TB., Gringhuis, SI. (2009). Signalling through C-type lectin receptors: shaping immune responses. *Nat. Rev. Immunol., 9*, 465-79. ↗

Editions

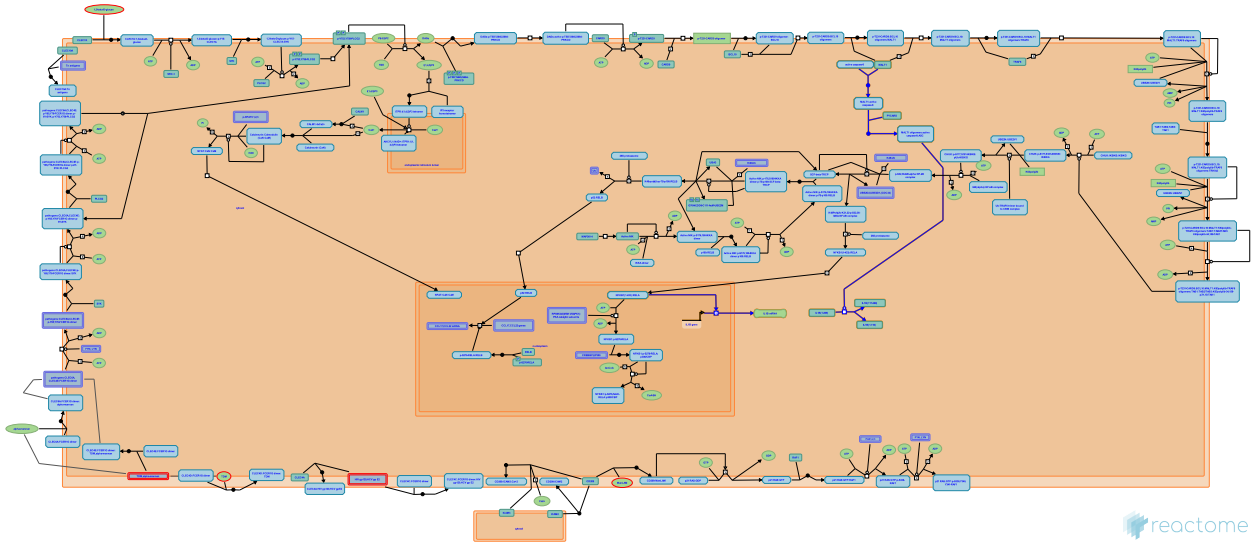
2014-07-14	Authored, Edited	Garapati, P V.
2014-09-02	Reviewed	Geijtenbeek, TB.

CLEC7A/inflammasome pathway ↗

Location: CLEC7A (Dectin-1) signaling

Stable identifier: R-HSA-5660668

Compartments: plasma membrane, cytosol



Antifungal immunity through the induction of T-helper 17 cells (TH17) responses requires the production of mature, active interleukin-1beta (IL1B). CLEC7A (dectin-1) through the SYK route induces activation of NF-kB and transcription of the gene encoding pro-IL1B via the CARD9-BCL10-MALT1 complex as well as the formation and activation of a MALT1-caspase-8-ASC complex that mediated the processing of pro-IL1B. The inactive precursor pro-IL1B has to be processed into mature bioactive form of IL1B and is usually mediated by inflammatory cysteine protease caspase-1. Gringhuis et al. showed that CLEC7A mediated processing of IL1B occurs through two distinct mechanisms: CLEC7A triggering induced a primary noncanonical caspase-8 inflammasome for pro-IL1B processing that was independent of caspase-1 activity, whereas some fungi triggered a second additional mechanism that required activation of the NLRP3/caspase 1 inflammasome. Unlike the canonical caspase-1 inflammasome, CLEC7A mediated noncanonical caspase-8-dependent inflammasome is independent of pathogen internalization. CLEC7A/inflammasome pathway enables the host immune system to mount a protective TH17 response against fungi and bacterial infection (Gringhuis et al. 2012, Cheng et al. 2011).

Literature references

Cavalieri, D., Stoffels, M., Netea, MG., Preechasuth, K., van de Veerdonk, FL., Kanneganti, TD. et al. (2011). The dectin-1/inflammasome pathway is responsible for the induction of protective T-helper 17 responses that discriminate between yeasts and hyphae of Candida albicans. *J. Leukoc. Biol., 90*, 357-66. ↗

Geijtenbeek, TB., Gringhuis, SI., Boekhout, T., Theelen, B., Wevers, BA., van der Vlist, M. et al. (2012). Dectin-1 is an extracellular pathogen sensor for the induction and processing of IL-1? via a noncanonical caspase-8 inflammasome. *Nat. Immunol., 13*, 246-54. ↗

Editions

2014-09-02	Reviewed	Geijtenbeek, TB.
2015-01-05	Authored, Edited	Garapati, P V.

Table of Contents