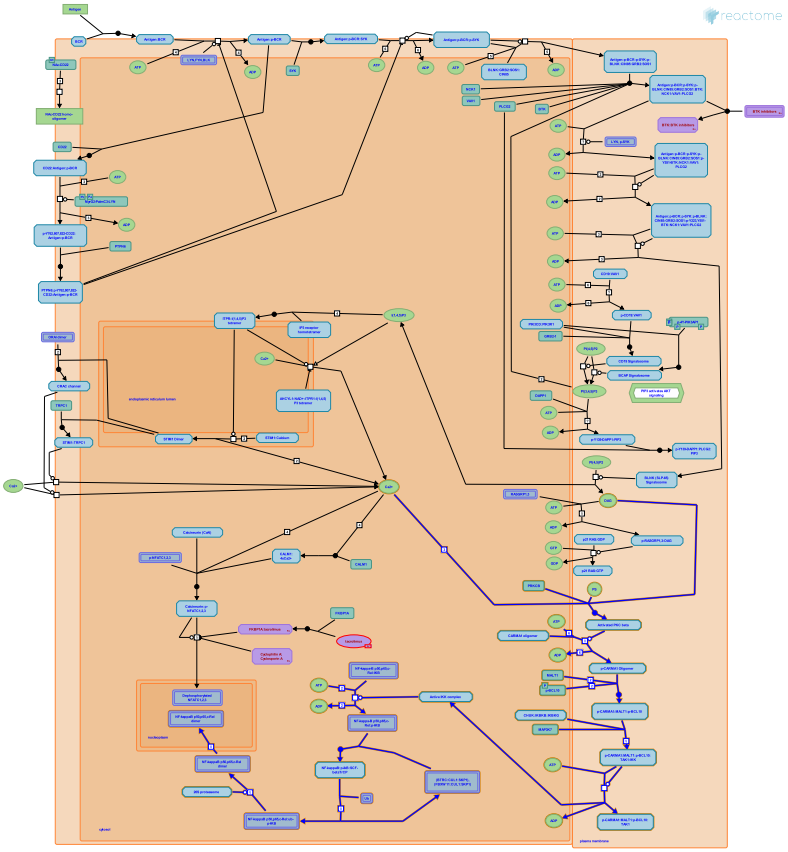
Activation of NF-kappaB in B cells



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

This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the Reactome Textbook.

04/05/2024

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. ↗

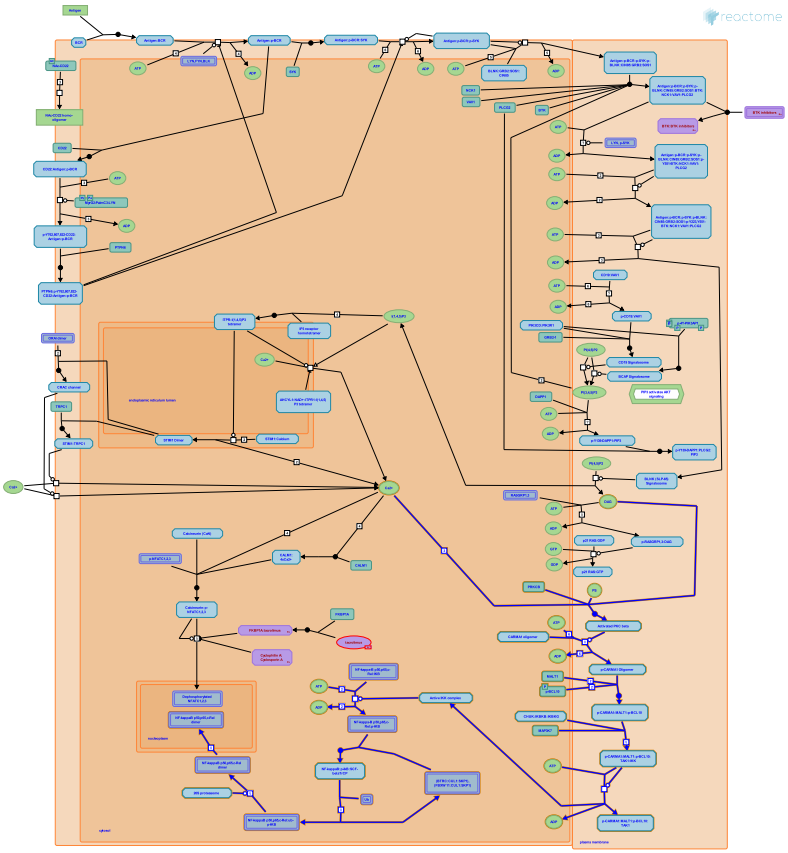
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

Activation of NF-kappaB in B cells ↗

Stable identifier: R-HSA-1169091

Compartments: cytosol, nucleoplasm, plasma membrane



DAG and calcium activate protein kinase C beta (PKC-beta, Kochs et al. 1991) which phosphorylates CARMA1 and other proteins (Sommer et al. 2005). Phosphorylated CARMA1 recruits BCL10 and MALT1 to form the CBM complex (Sommer et al. 2005, Tanner et al. 2007) which, in turn, recruits the kinase TAK1 and the IKK complex (Sommer et al. 2005, Shinohara et al. 2005 using chicken cells). TAK1 phosphorylates the IKK-beta subunit, activating it (Wang et al. 2001). The IKK complex then phosphorylates IkB complexed with NF-kappaB dimers in the cytosol (Zandi et al. 1998, Burke et al. 1999, Heilker et al. 1999), resulting in the degradation of IkB (Miyamoto et al. 1994, Traenckner et al. 1994, Alkalay et al. 1995, DiDonato et al. 1995, Li et al. 1995, Lin et al. 1995, Scherer et al. 1995, Chen et al. 1995). NF-kappaB dimers are thereby released and are translocated to the nucleus where they activate transcription (Baeuerle and Baltimore 1988, Blank et al. 1991, Ghosh et al. 2008, Fagerlund et al. 2008).

Literature references

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. ↗

Lin, YC., Siebenlist, U., Brown, K. (1995). Activation of NF-kappa B requires proteolysis of the inhibitor I kappa B-alpha: signal-induced phosphorylation of I kappa B-alpha alone does not release active NF-kappa B. *Proc Natl Acad Sci U S A, 92*, 552-6. ↗

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. ↗

Shinohara, H., Sakurai, H., Sanjo, H., Aiba, Y., Hamadate, M., Yasuda, T. et al. (2005). PKC beta regulates BCR-mediated IKK activation by facilitating the interaction between TAK1 and CARMA1. *J Exp Med, 202*, 1423-31. ↗

Cao, X., Melén, K., Fagerlund, R., Julkunen, I. (2008). NF-kappaB p52, RelB and c-Rel are transported into the nucleus via a subset of importin alpha molecules. *Cell Signal, 20*, 1442-51. ↗

Editions

2011-01-04	Authored, Edited	May, B.
2012-02-12	Reviewed	Wienands, J.

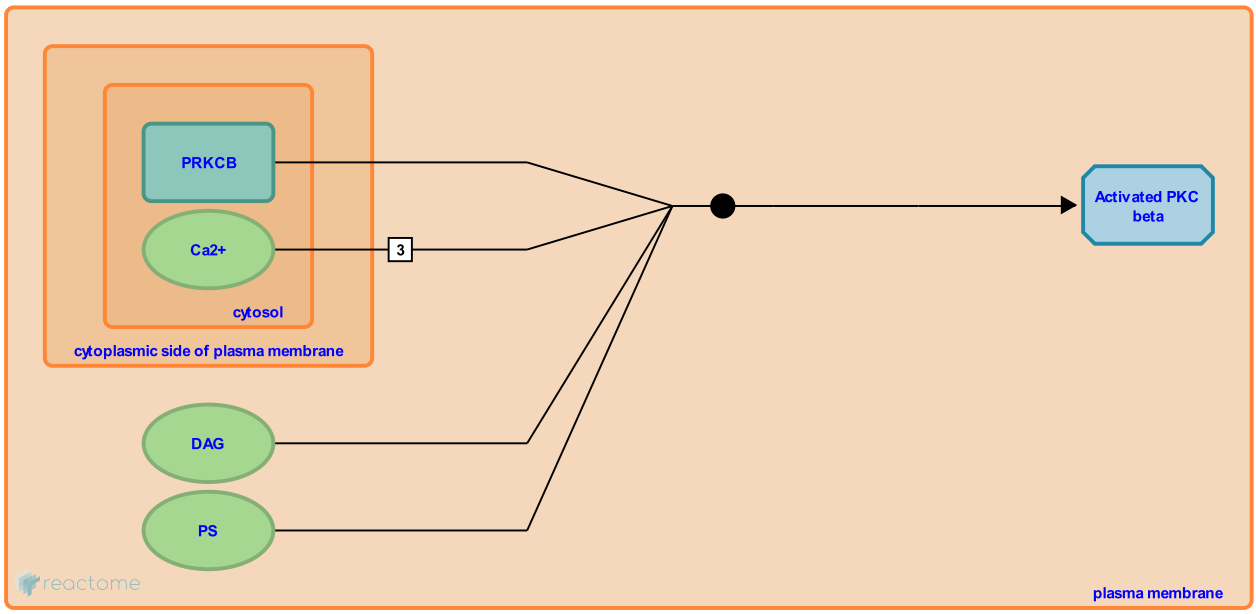
PRKCB (Protein kinase C beta, PKC-beta) binds diacylglycerol and phosphatidylserine ↗

Location: Activation of NF-kappaB in B cells

Stable identifier: R-HSA-1168373

Type: binding

Compartments: plasma membrane, cytosol



Human Protein kinase C beta (PKC-beta) is activated by calcium ions, diacylglycerol, and binds phosphatidylserine (Kochs et al. 1991). Experiments in mice have shown that knocking out PKC-beta causes severe defects in B cells, leading to the conclusion that PKC-beta is the predominant signaling PKC in these cells (Leitges et al. 1996, Su et al. 2002, Saijo et al. 2002).

Followed by: PRKCB (PKC-beta) phosphorylates CARMA1

Literature references

Hummel, R., Marmé, D., Sarre, TF., Fiebich, B., Hug, H., Kochs, G. (1993). Activation of purified human protein kinase C alpha and beta I isoenzymes in vitro by Ca2+, phosphatidylinositol and phosphatidylinositol 4,5-bisphosphate. *Biochem J, 291*, 627-33. ↗

Patrone, L., Teitell, M., Kang, S., Kawakami, Y., Kawakami, T., Kato, RM. et al. (2002). PKC-beta controls I kappa B kinase lipid raft recruitment and activation in response to BCR signaling. *Nat Immunol, 3*, 780-6. ↗

Mecklenbräuker, I., Saijo, K., Schmedt, C., Tarakhovsky, A., Leitger, M., Santana, A. (2002). Protein kinase C beta controls nuclear factor kappaB activation in B cells through selective regulation of the IkappaB kinase alpha. *J Exp Med, 195*, 1647-52. ↗

Stabel, S., Schmedt, C., Leitges, M., Tarakhovsky, A., Davoust, J., Guinamard, R. et al. (1996). Immunodeficiency in protein kinase cbeta-deficient mice. *Science, 273*, 788-91. ↗

Editions

2010-12-09	Authored, Edited	May, B.
2012-02-12	Reviewed	Wienands, J.

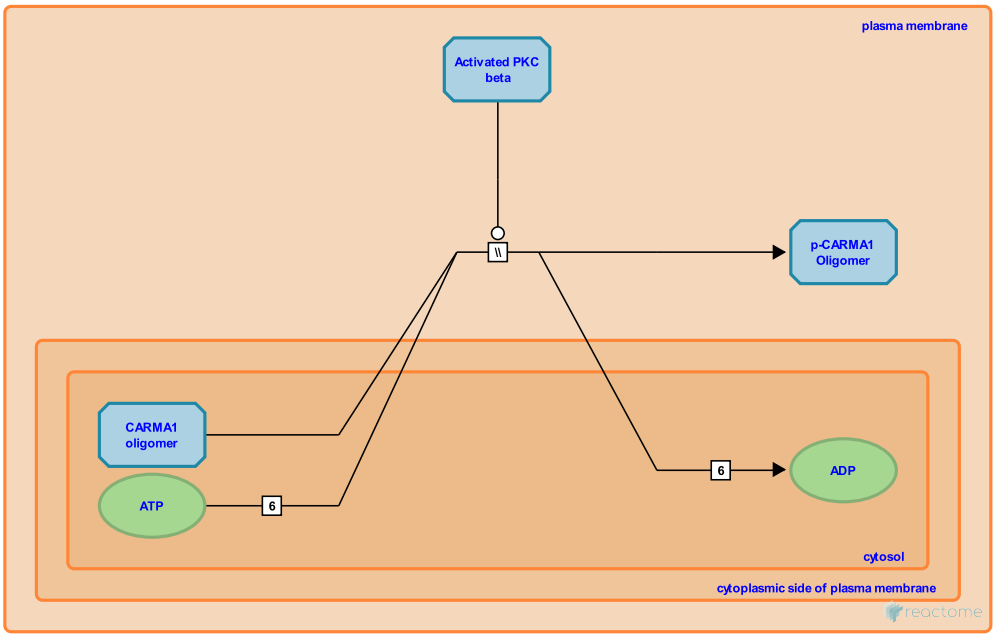
PRKCB (PKC-beta) phosphorylates CARMA1 ↗

Location: Activation of NF-kappaB in B cells

Stable identifier: R-HSA-1168635

Type: omitted

Compartments: plasma membrane, cytosol



CARMA1 is phosphorylated at serines 559, 644, and 652 by Protein Kinase C beta (PKC-beta) (Sommer et al. 2005). CARMA1 is constitutively oligomerized (Tanner et al. 2007) and most CARMA1 in unstimulated cells is cytosolic (Sommer et al. 2005, Tanner et al. 2007), though a portion is constitutively associated with the plasma membrane (Gaide et al. 2002, Sommer et al. 2005). After phosphorylation, CARMA1 is associated with lipid rafts in the plasma membrane (Sommer et al. 2005). Note that some publications refer to CARMA1 with a different N-terminal methionine that is 7 amino acids shorter. In this case the phosphorylated serines are 552, 537, and 645.

Preceded by: PRKCB (Protein kinase C beta, PKC-beta) binds diacylglycerol and phosphatidylserine

Followed by: CARMA1 recruits MALT1 and BCL10 forming CBM Complex

Literature references

Sommer, K., Pomerantz, JL., Rawlings, DJ., Guo, B., Bandaranayake, AD., Ovechkina, YL. et al. (2005). Phosphorylation of the CARMA1 linker controls NF-kappaB activation. *Immunity, 23*, 561-74. ↗

Editions

2010-12-19	Authored, Edited	May, B.
2012-02-12	Reviewed	Wienands, J.

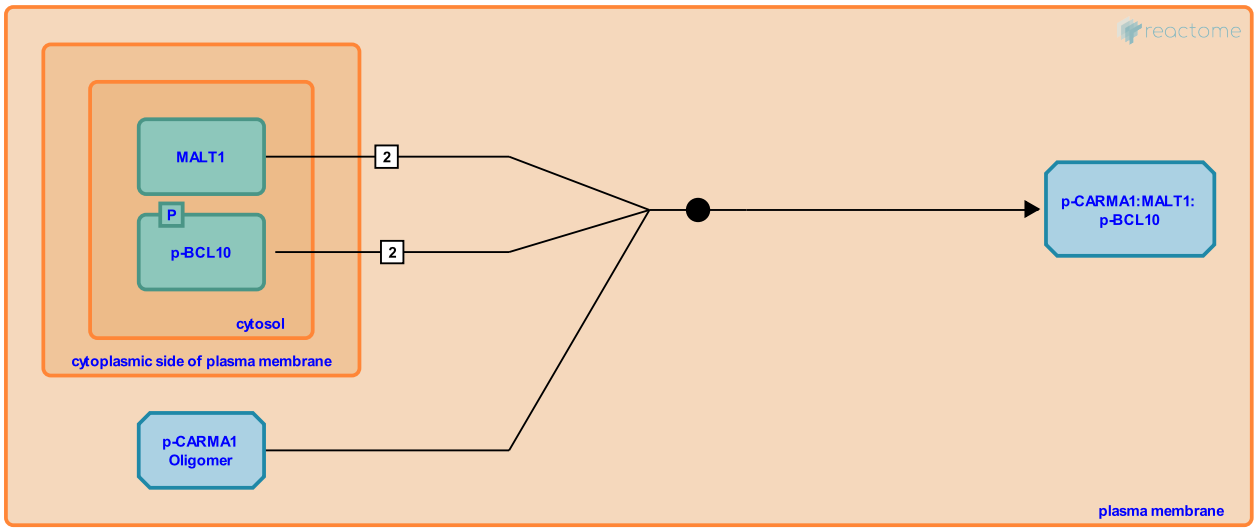
CARMA1 recruits MALT1 and BCL10 forming CBM Complex ↗

Location: Activation of NF-kappaB in B cells

Stable identifier: R-HSA-1168644

Type: binding

Compartments: plasma membrane, cytosol



CARMA1 is phosphorylated and recruits BCL10 and MALT1 to the plasma membrane to form the CBM complex (Sommer et al. 2005, Tanner et al. 2007). Evidence from T cells (Jurkat cells) indicates that MALT1 and BCL10 oligomerize to activate the IKK complex (Zhou 2004).

Preceded by: PRKCB (PKC-beta) phosphorylates CARMA1

Followed by: CARMA1:BCL10:MALT1 complex recruits TAK1 and IKK

Literature references

Tanner, MJ., Lin, X., Gaffen, SL., Hanel, W. (2007). CARMA1 coiled-coil domain is involved in the oligomerization and subcellular localization of CARMA1 and is required for T cell receptor-induced NF-kappaB activation. *J Biol Chem, 282*, 17141-7. ↗

Sommer, K., Pomerantz, JL., Rawlings, DJ., Guo, B., Bandaranayake, AD., Ovechkina, YL. et al. (2005). Phosphorylation of the CARMA1 linker controls NF-kappaB activation. *Immunity, 23*, 561-74. ↗

Dixit, VM., O'Rourke, K., Eby, M., Ultsch, M., Xiao, W., Wertz, I. et al. (2004). Bcl10 activates the NF-kappaB pathway through ubiquitination of NEMO. *Nature, 427*, 167-71. ↗

Editions

2010-12-19	Authored, Edited	May, B.
2012-02-12	Reviewed	Wienands, J.

CARMA1:BCL10:MALT1 complex recruits TAK1 and IKK ↗

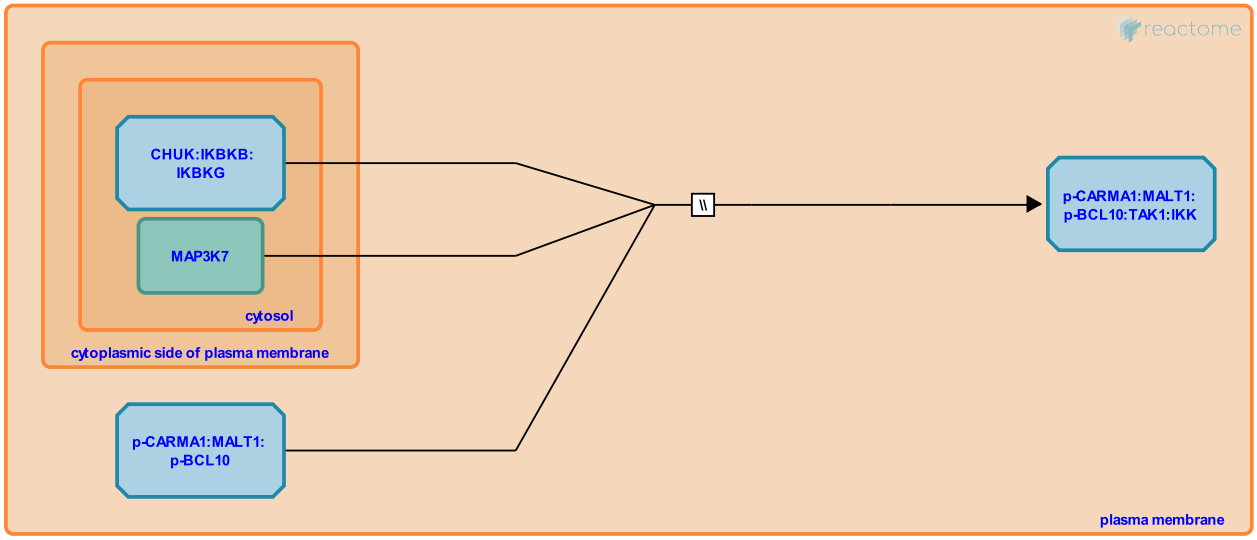
Location: Activation of NF-kappaB in B cells

Stable identifier: R-HSA-1168637

Type: omitted

Compartments: plasma membrane, cytosol

Inferred from: CARMA1 recruits TAK1 and the IKK complex (Gallus gallus)



TAK1 and the IKK complex are observed to migrate from the cytosol to lipid rafts containing the CARMA1:BCL10:MALT1 (CBM) complex (Sommer et al. 2005, Shinohara et al. 2005 using chicken cells). By analogy with activation of NF-KappaB signaling in T cells, TAK1 in B cells may also be bound to TAB1 and TAB2 or TAB3, which bind K63-conjugated polyubiquitin on a TRAF protein bound to the CBM complex (reviewed in Shinohara et al. 2009).

Preceded by: CARMA1 recruits MALT1 and BCL10 forming CBM Complex

Followed by: TAK1 associated with the CBM complex phosphorylates IKKbeta

Literature references

Sommer, K., Pomerantz, JL., Rawlings, DJ., Guo, B., Bandaranayake, AD., Ovechkina, YL. et al. (2005). Phosphorylation of the CARMA1 linker controls NF-kappaB activation. *Immunity, 23*, 561-74. ↗

Shinohara, H., Sakurai, H., Sanjo, H., Aiba, Y., Hamadate, M., Yasuda, T. et al. (2005). PKC beta regulates BCR-mediated IKK activation by facilitating the interaction between TAK1 and CARMA1. *J Exp Med, 202*, 1423-31. ↗

Shinohara, H., Kurosaki, T. (2009). Comprehending the complex connection between PKCbeta, TAK1, and IKK in BCR signaling. *Immunol Rev, 232*, 300-18. ↗

Editions

2010-12-19	Authored, Edited	May, B.
2012-02-12	Reviewed	Wienands, J.

TAK1 associated with the CBM complex phosphorylates IKKbeta ↗

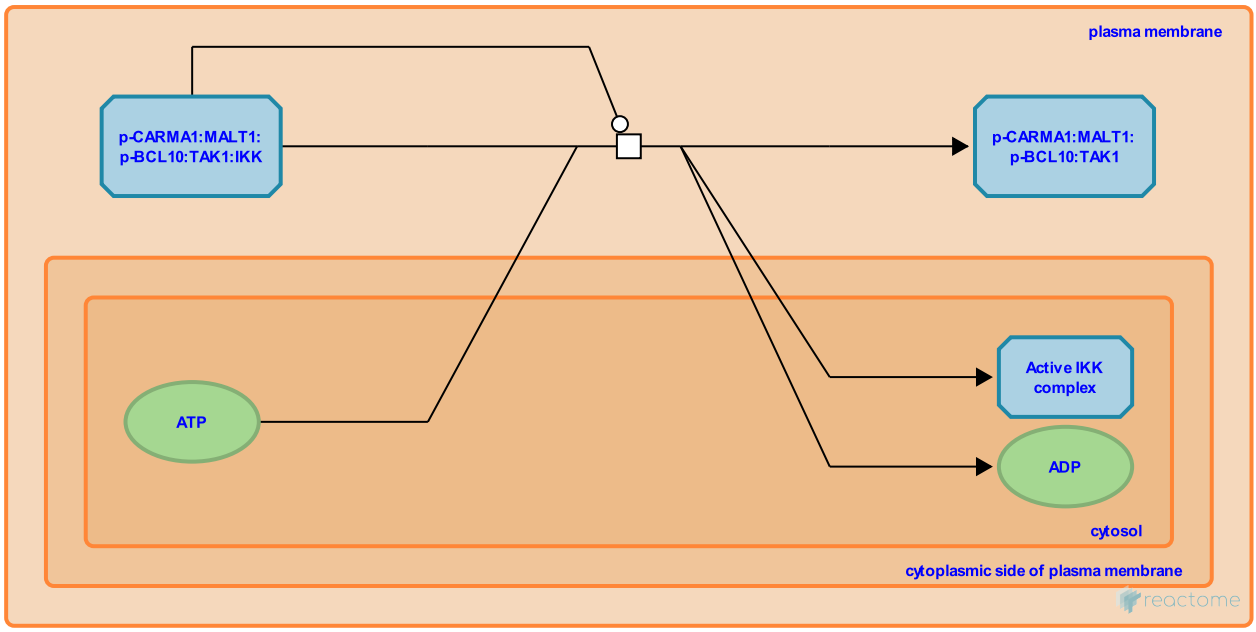
Location: Activation of NF-kappaB in B cells

Stable identifier: R-HSA-1168641

Type: transition

Compartments: plasma membrane, cytosol

Inferred from: Phosphorylation of IKKs complex by activated TAK1 (Gallus gallus), Activated TAK1 mediates phosphorylation of the IKK Complex (Homo sapiens)



TAK1 phosphorylates IKK-beta (Wang et al. 2001). As inferred from chicken B cells, the reaction in human B cells may occur when TAK1 and the IKK complex are associated with the CARMA1:BCL10:MALT1 (CBM) complex. During T cell activation TAK1 forms a complex with TAB1 and TAB2, which binds K-63 conjugated polyubiquitin attached to TRAF6 associated with the CBM complex (Sun et al. 2004, reviewed in Shinohara et al. 2009). TRAF6 also polyubiquitinates IKK-gamma in T cells (Zhou et al. 2004). B cells contain functional TRAF6 and TRAF2 (Zhang et al. 2010) so the same mechanism may occur during activation of B cells.

Preceded by: CARMA1:BCL10:MALT1 complex recruits TAK1 and IKK

Followed by: Activated IKK phosphorylates I-kappaB

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. ↗

Shinohara, H., Sakurai, H., Sanjo, H., Aiba, Y., Hamadate, M., Yasuda, T. et al. (2005). PKC beta regulates BCR-mediated IKK activation by facilitating the interaction between TAK1 and CARMA1. *J Exp Med, 202*, 1423-31. ↗

Zeng, XF., Wu, XL., Lipsky, PE., Zhang, W., Crammer, AC., He, LS. et al. (2010). Competition between TRAF2 and TRAF6 regulates NF-kappaB activation in human B lymphocytes. *Chin Med Sci J, 25*, 1-12. ↗

Shinohara, H., Kurosaki, T. (2009). Comprehending the complex connection between PKCbeta, TAK1, and IKK in BCR signaling. *Immunol Rev, 232*, 300-18. ↗

Dixit, VM., O'Rourke, K., Eby, M., Ultsch, M., Xiao, W., Wertz, I. et al. (2004). Bcl10 activates the NF-kappaB pathway through ubiquitination of NEMO. *Nature, 427*, 167-71. ↗

Editions

2010-12-19	Authored, Edited	May, B.
2012-02-12	Reviewed	Wienands, J.

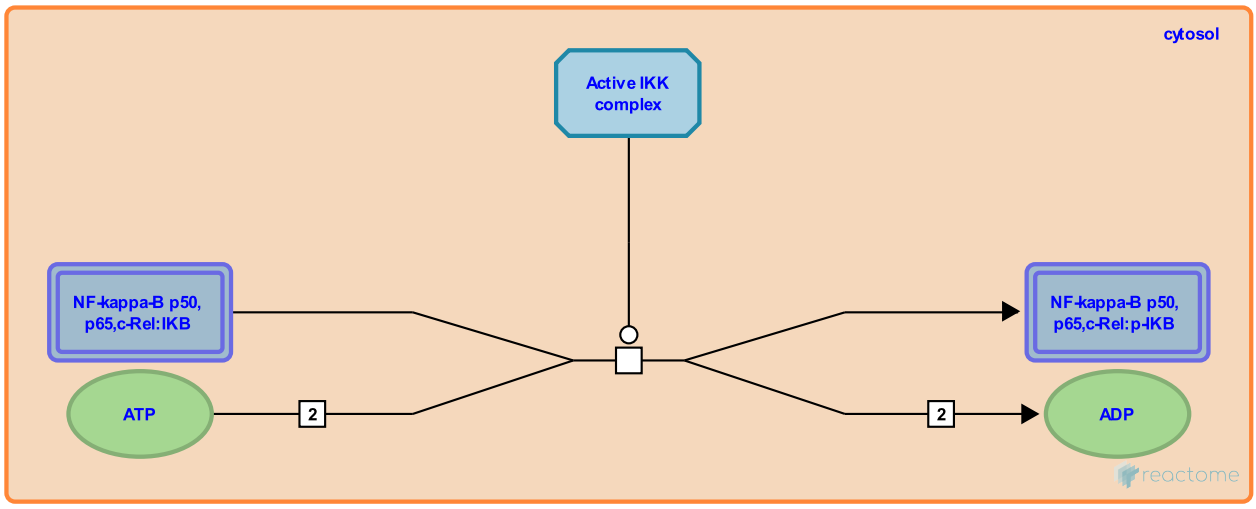
Activated IKK phosphorylates I-kappaB ↗

Location: Activation of NF-kappaB in B cells

Stable identifier: R-HSA-1168638

Type: transition

Compartments: cytosol



Activated IKK complex phosphorylates the I-kappaB component of the cytoplasmic NF-kappaB complex (Zandi et al. 1998, Burke et al. 1999, Heilker et al. 1999). B cells contain I-kappaB-alpha, I-kappaB-beta, and I-kappaB-epsilon (Whiteside et al. 1997, Li and Nabel 1997).

Preceded by: TAK1 associated with the CBM complex phosphorylates IKKbeta

Followed by: SCF with beta-TrCP1 or beta-TrCP2 binds NF-kappaB:phospho-IkB

Literature references

Nabel, GJ., Li, Z. (1997). A new member of the I kappaB protein family, I kappaB epsilon, inhibits RelA (p65)-mediated NF-kappaB transcription. *Mol Cell Biol, 17*, 6184-90. ↗

Epinat, JC., Israel, A., Whiteside, ST., Rice, NR. (1997). I kappa B epsilon, a novel member of the I kappa B family, controls RelA and cRel NF-kappa B activity. *EMBO J, 16*, 1413-26. ↗

Karin, M., Zandi, E., Chen, Y. (1998). Direct phosphorylation of IkappaB by IKKalpha and IKKbeta: discrimination between free and NF-kappaB-bound substrate. *Science, 281*, 1360-3. ↗

Pulfer, R., Eder, J., di Padova, F., Heilker, R., Freuler, F. (1999). All three IkappaB isoforms and most Rel family members are stably associated with the IkappaB kinase 1/2 complex. *Eur J Biochem, 259*, 253-61. ↗

Burke, JR., Wood, MK., Walther, S., Meyers, CA., Ryseck, RP. (1999). Peptides corresponding to the N and C termini of IkappaB-alpha, -beta, and -epsilon as probes of the two catalytic subunits of IkappaB kinase, IKK-1 and IKK-2. *J Biol Chem, 274*, 36146-52. ↗

Editions

2011-01-19	Authored, Edited	May, B.
2012-02-12	Reviewed	Wienands, J.

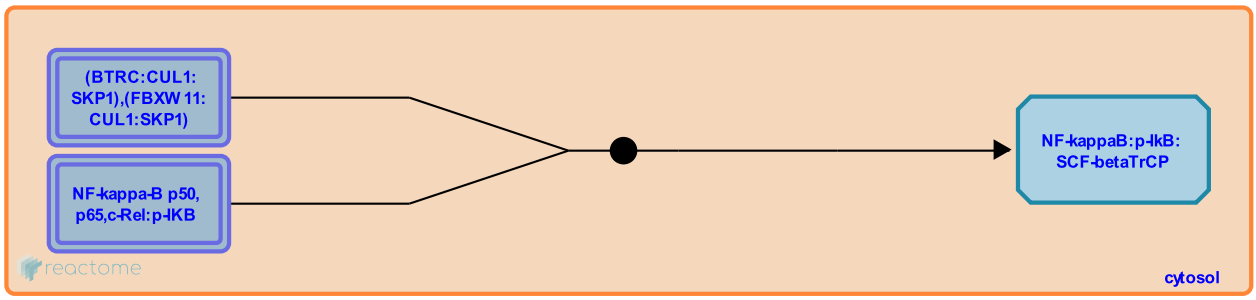
SCF with beta-TrCP1 or beta-TrCP2 binds NF-kappaB:phospho-IkB ↗

Location: Activation of NF-kappaB in B cells

Stable identifier: R-HSA-1168642

Type: binding

Compartments: cytosol



SKP:Cul:F-box (SCF) complexes containing F-box factors Beta-TrCP1 (BTRCP, E3RSIkappaB) or beta-TrCP2 (BTRCP2, FBXW11, HOS) bind IkappaB (Yaron et al. 1998, Fuchs et al. 1999, Suzuki et al. 1999, Tan et al. 1999, Winston et al. 1999, Wu and Ghosh 1999).

Preceded by: Activated IKK phosphorylates I-kappaB

Followed by: SCF-beta-TrCP ubiquitinylates IkB

Literature references

Wu, K., Fuchs, SY., Ronai, Z., Chen, A., Pan, ZQ., Tan, P. et al. (1999). Recruitment of a ROC1-CUL1 ubiquitin ligase by Skp1 and HOS to catalyze the ubiquitination of I kappa B alpha. *Mol Cell, 3*, 527-33. ↗

Wu, C., Ghosh, S. (1999). beta-TrCP mediates the signal-induced ubiquitination of IkappaBbeta. *J Biol Chem, 274*, 29591-4. ↗

Tanaka, K., Chiba, T., Ichiyama, A., Omata, M., Ikenoue, T., Suzuki, H. et al. (1999). IkappaBalpha ubiquitination is catalyzed by an SCF-like complex containing Skp1, cullin-1, and two F-box/WD40-repeat proteins, betaTrCP1 and betaTrCP2. *Biochem Biophys Res Commun, 256*, 127-32. ↗

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. ↗

Xiong, Y., Fuchs, SY., Ronai, Z., Chen, A., Pan, ZQ. (1999). HOS, a human homolog of Slimb, forms an SCF complex with Skp1 and Cullin1 and targets the phosphorylation-dependent degradation of IkappaB and beta-catenin. *Oncogene, 18*, 2039-46. ↗

Editions

2010-12-19	Authored, Edited	May, B.
2012-02-12	Reviewed	Wienands, J.

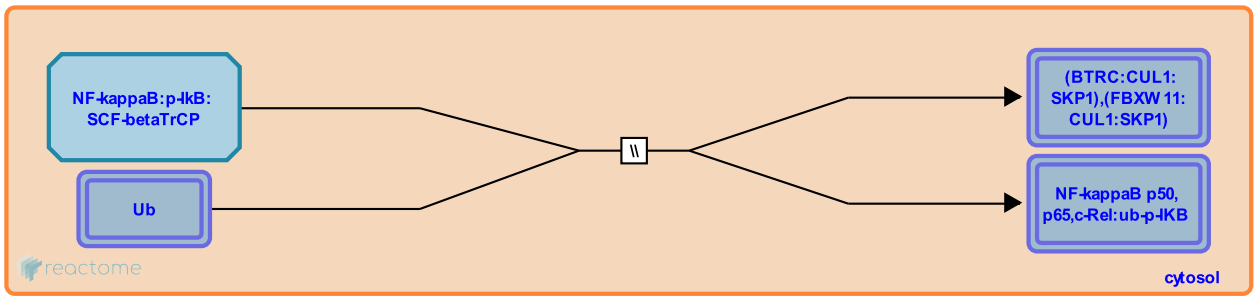
SCF-beta-TrCP ubiquitinylates IkB ↗

Location: Activation of NF-kappaB in B cells

Stable identifier: R-HSA-1168643

Type: omitted

Compartments: cytosol



SKP:Cul:F-box (SCF) complexes containing F-box factors Beta-TrCP1 (BTRCP, E3RSIkappaB) or beta-TrCP2 (BTRCP2, FBXW11, HOS) catalyze the polyubiquitination of IkappaB (Yaron et al. 1998, Fuchs et al. 1999, Suzuki et al. 1999, Tan et al. 1999, Winston et al. 1999, Wu and Ghosh 1999).

Preceded by: SCF with beta-TrCP1 or beta-TrCP2 binds NF-kappaB:phospho-IkB

Followed by: Ubiquitinated IkB is degraded

Literature references

Wu, C., Ghosh, S. (1999). beta-TrCP mediates the signal-induced ubiquitination of IkappaBbeta. *J Biol Chem, 274*, 29591-4. ↗

Wu, K., Fuchs, SY., Ronai, Z., Chen, A., Pan, ZQ., Tan, P. et al. (1999). Recruitment of a ROC1-CUL1 ubiquitin ligase by Skp1 and HOS to catalyze the ubiquitination of I kappa B alpha. *Mol Cell, 3*, 527-33. ↗

Tanaka, K., Chiba, T., Ichiyama, A., Omata, M., Ikenoue, T., Suzuki, H. et al. (1999). IkappaBalpha ubiquitination is catalyzed by an SCF-like complex containing Skp1, cullin-1, and two F-box/WD40-repeat proteins, betaTrCP1 and betaTrCP2. *Biochem Biophys Res Commun, 256*, 127-32. ↗

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. ↗

Xiong, Y., Fuchs, SY., Ronai, Z., Chen, A., Pan, ZQ. (1999). HOS, a human homolog of Slimb, forms an SCF complex with Skp1 and Cullin1 and targets the phosphorylation-dependent degradation of IkappaB and beta-catenin. *Oncogene, 18*, 2039-46. ↗

Editions

2010-12-19	Authored, Edited	May, B.
2012-02-12	Reviewed	Wienands, J.

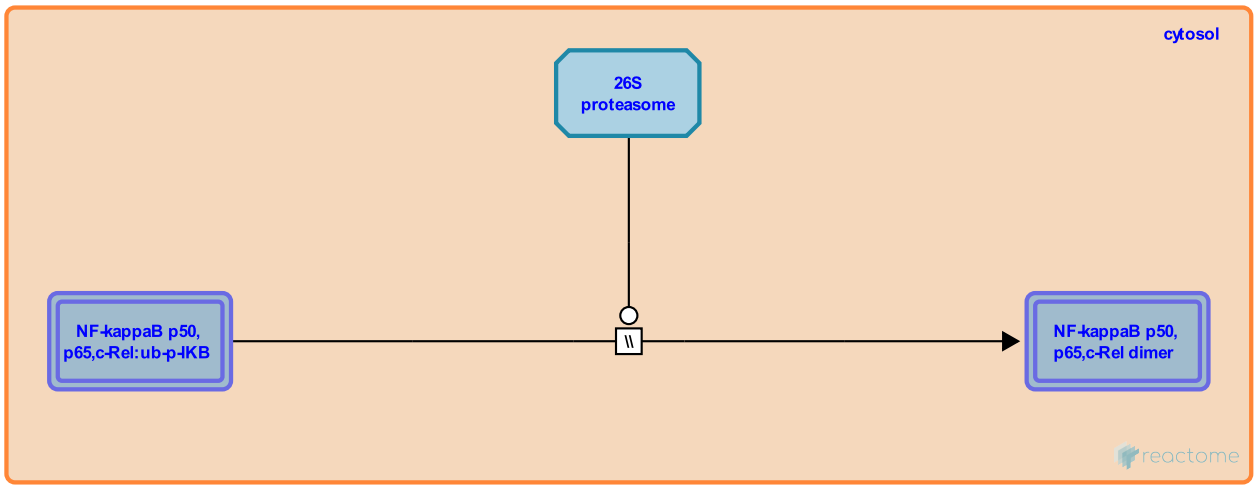
Ubiquitinated IkB is degraded ↗

Location: Activation of NF-kappaB in B cells

Stable identifier: R-HSA-1168640

Type: omitted

Compartments: cytosol



Phosphorylated, ubiquitinated IkB is degraded by the proteasome (Miyamoto et al. 1994, Traenckner et al. 1994, Alkalay et al. 1995, DiDonato et al. 1995, Li et al. 1995, Lin et al. 1995, Scherer et al. 1995, Chen et al. 1995). IkB does not dissociate from NF-kB before it is proteolyzed (Miyamoto et al. 1994, Traenckner et al. 1994, DiDonato et al. 1995, Lin et al. 1995).

Preceded by: SCF-beta-TrCP ubiquitinylates IkB

Followed by: NF-kappaB translocates from the cytosol to the nucleus

Literature references

Dai, RM., Li, CC., Longo, DL. (1995). Inactivation of NF-kappa B inhibitor I kappa B alpha: ubiquitin-dependent proteolysis and its degradation product. *Biochem Biophys Res Commun, 215*, 292-301. ↗

Wilk, S., Baeuerle, PA., Traenckner, EB. (1994). A proteasome inhibitor prevents activation of NF-kappa B and stabilizes a newly phosphorylated form of I kappa B-alpha that is still bound to NF-kappa B. *EMBO J, 13*, 5433-41. ↗

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. ↗

Hatanaka, M., Maki, M., Miyamoto, S., Verma, IM., Schmitt, MJ. (1994). Tumor necrosis factor alpha-induced phosphorylation of I kappa B alpha is a signal for its degradation but not dissociation from NF-kappa B. *Proc Natl Acad Sci U S A, 91*, 12740-4. ↗

Karin, M., DiDonato, JA., Mercurio, F. (1995). Phosphorylation of I kappa B alpha precedes but is not sufficient for its dissociation from NF-kappa B. *Mol Cell Biol, 15*, 1302-11. ↗

Editions

2010-12-19	Authored, Edited	May, B.
2012-02-12	Reviewed	Wienands, J.

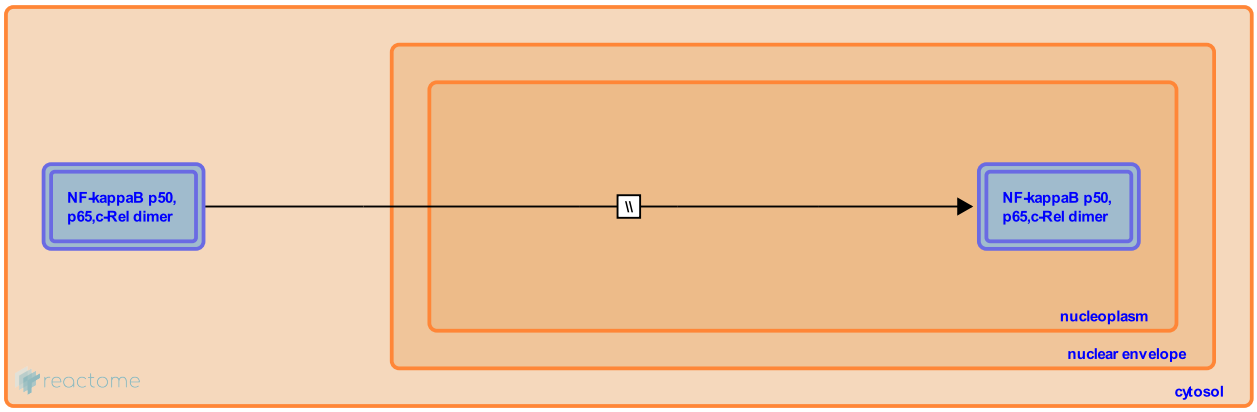
NF-kappaB translocates from the cytosol to the nucleus ↗

Location: Activation of NF-kappaB in B cells

Stable identifier: R-HSA-1168633

Type: omitted

Compartments: nucleoplasm, cytosol



Nf-kappaB subunits contain nuclear localization sequences and, in the absence of IkB, are translocated to the nucleus (Bauerle and Baltimore 1988, Blank et al. 1991, Ghosh et al. 2008, Fagerlund et al. 2008). c-Rel binds to importins alpha5, alpha6, and alpha7; RelB binds to importins alpha5 and alpha6; p52 binds importin alpha3, alpha4, alpha5, and alpha6 (Fagerlund et al. 2008)

Preceded by: Ubiquitinated IkB is degraded

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