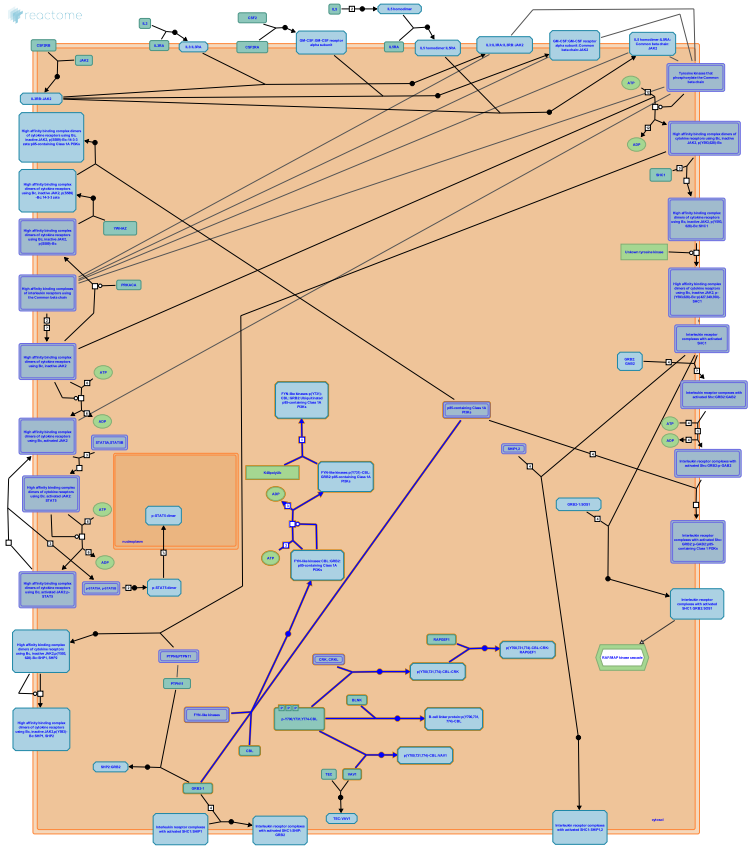
Regulation of signaling by CBL



Hercus, TR., Jupe, S., Lopez, AF., Ray, KP.

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

16/11/2019

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. ↗

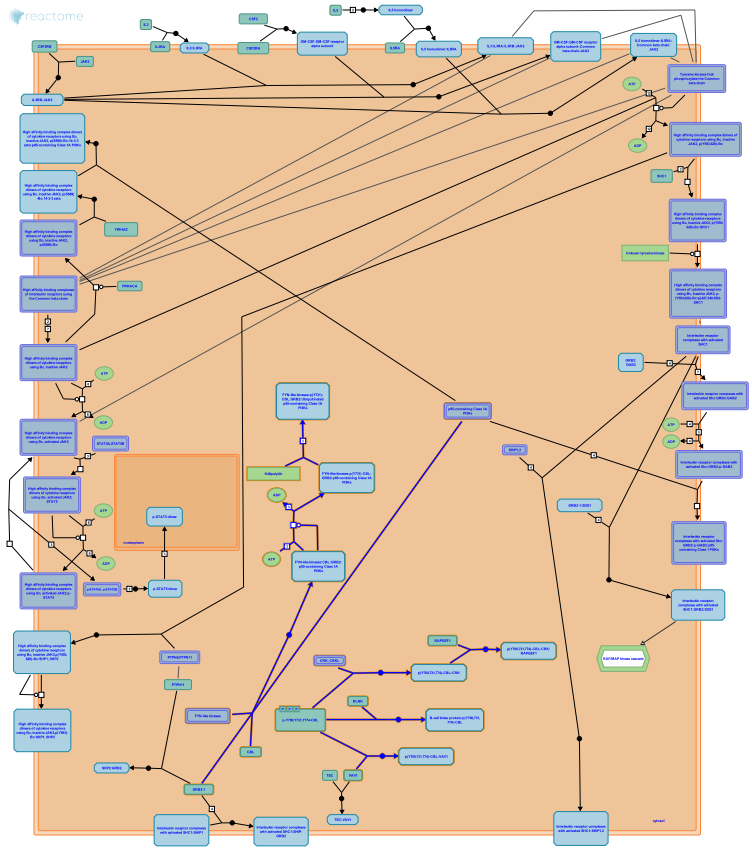
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

Regulation of signaling by CBL ↗

Stable identifier: R-HSA-912631

Compartments: cytosol



Cbl is an E3 ubiquitin-protein ligase that negatively regulates signaling pathways by targeting proteins for ubiquitination and proteasomal degradation (Rao et al. 2002). Cbl negatively regulates PI3K via this mechanism (Dufour et al. 2008). The binding of Cbl to the p85 subunit of PI3K is mediated at least in part by tyrosine phosphorylation at Y731 (Dufour et al. 2008). Fyn and the related kinases Hck and Lyn are known to be associated with Cbl (Anderson et al. 1997, Hunter et al. 1999). Fyn is proven capable of Cbl Y731 phosphorylation (Hunter et al. 1999).The association of Fyn and Cbl has been described as constitutive (Hunter et al. 1999). CBL further associates with the p85 subunit of PI3K (Hartley et al. 1995, Anderson et al. 1997, Hunter et al. 1997), this also described as constitutive and mediated by the SH3 domain of p85. Binding of the SH2 domain of p85 to a specific phosphorylation site in Cbl is postulated to explain the the increase in Cbl/p85 association seen in activated cells (Panchamoorthy et al 1996) which negatively regulates PI3K activity (Fang et al. 2001). The negative effect of increased Cbl-PI3K interaction is mediated by Y731 of Cbl. Cbl binding increases PI3K ubiquitination and proteasome degradation (Dufour et al. 2008).

Cbl is constitutively associated with Grb in resting hematopoietic cells (Anderson et al. 1997, Odai et al. 1995, Park et al. 1998, Panchamoorthy et al. 1996). Both the SH2 and SH3 domains of Grb2 are involved. Cbl has 2 distinct C-terminal domains, proximal and distal. The proximal domain binds Grb2 in resting and stimulated cells, and in stimulated cells also binds Shc. The distal domain binds the adaptor protein CRKL. Tyrosine phosphorylation of Cbl in response to IL-3 releases the SH3 domain of Grb2 which then is free to bind other molecules (Park et al. 1998). Cbl is tyrosine phosphorylated in response to many cytokines including IL-3, IL-2 (Gesbert et al. 1998) and IL-4 (Ueno et al. 1998).

Literature references

Park, RK., Kyono, WT., Liu, Y., Durden, DL. (1998). CBL-GRB2 interaction in myeloid immunoreceptor tyrosine activation motif signaling. *J Immunol, 160*, 5018-27. ↗

Editions

2010-05-17	Authored	Ray, KP.
2010-08-06	Edited	Jupe, S.
2010-09-06	Reviewed	Lopez, AF., Hercus, TR.

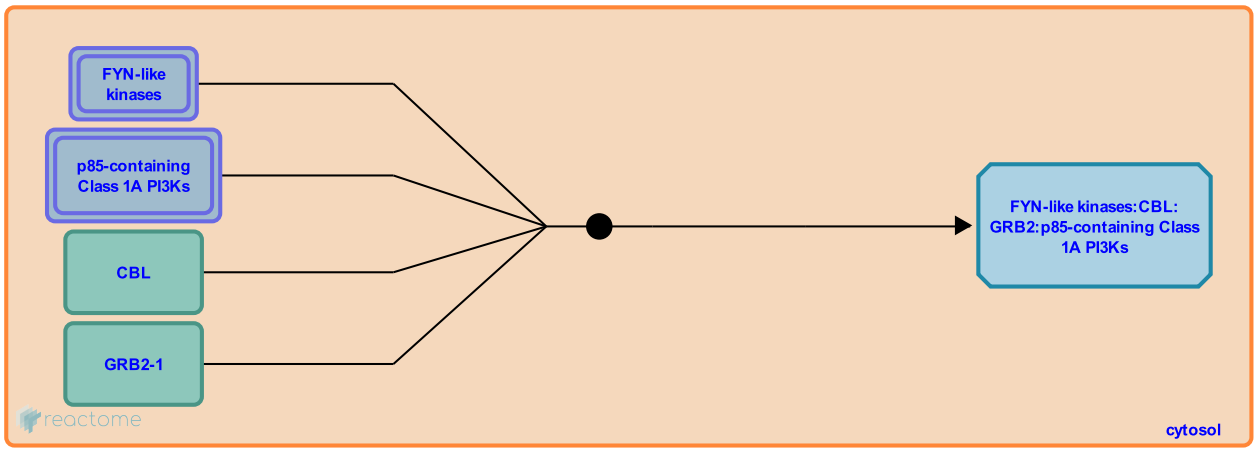
CBL, GRB2, FYN and PI3K p85 subunit are constitutively associated ↗

Location: Regulation of signaling by CBL

Stable identifier: R-HSA-879917

Type: binding

Compartments: cytosol



Cbl is constitutively associated with Grb2 in resting hematopoietic cells (Anderson et al. 1997, Odai et al. 1995, Park et al. 1998, Panchamoorthy et al. 1996). Both the SH2 and SH3 domains of Grb2 are involved. Cbl has 2 distinct C-terminal domains, proximal and distal. The proximal domain binds Grb2 in resting and stimulated cells, and in stimulated cells also binds Shc. The distal domain can bind the adaptor protein CRKL.

Tyrosine phosphorylation of Cbl in response to IL-3 releases the SH3 domain of Grb2 which then is free to bind other molecules (Park et al. 1998).

Cbl also associates with Fyn (Anderson et al. 1997) and the related kinases Hck and Lyn (Hunter et al. 1999). Binding studies indicate that this binding is independent of the phosphorylation state of Cbl; The association of Fyn with Cbl has been described as constitutive (Hunter et al. 1999).

Cbl further associates with the p85 subunit of PI3K (Hartley et al. 1995, Anderson et al. 1997, Hunter et al. 1997), this is also described as constitutive and is mediated by the SH3 domain of p85 (Hunter et al. 1997).

Followed by: CBL is tyrosine phosphorylated

Literature references

Park, RK., Kyono, WT., Liu, Y., Durden, DL. (1998). CBL-GRB2 interaction in myeloid immunoreceptor tyrosine activation motif signaling. *J Immunol, 160*, 5018-27. ↗

Odai, H., Sasaki, K., Iwamatsu, A., Hanazono, Y., Tanaka, T., Mitani, K. et al. (1995). The proto-oncogene product c-Cbl becomes tyrosine phosphorylated by stimulation with GM-CSF or Epo and constitutively binds to the SH3 domain of Grb2/Ash in human hematopoietic cells. *J Biol Chem, 270*, 10800-5. ↗

Anderson, SM., Burton, EA., Koch, BL. (1997). Phosphorylation of Cbl following stimulation with interleukin-3 and its association with Grb2, Fyn, and phosphatidylinositol 3-kinase. *J Biol Chem, 272*, 739-45. ↗

Hunter, S., Koch, BL., Anderson, SM. (1997). Phosphorylation of cbl after stimulation of Nb2 cells with prolactin and its association with phosphatidylinositol 3-kinase. *Mol Endocrinol, 11*, 1213-22. ↗

Editions

2010-05-17	Authored	Ray, KP.
2010-08-06	Edited	Jupe, S.
2010-09-06	Reviewed	Lopez, AF., Hercus, TR.

CBL is tyrosine phosphorylated ↗

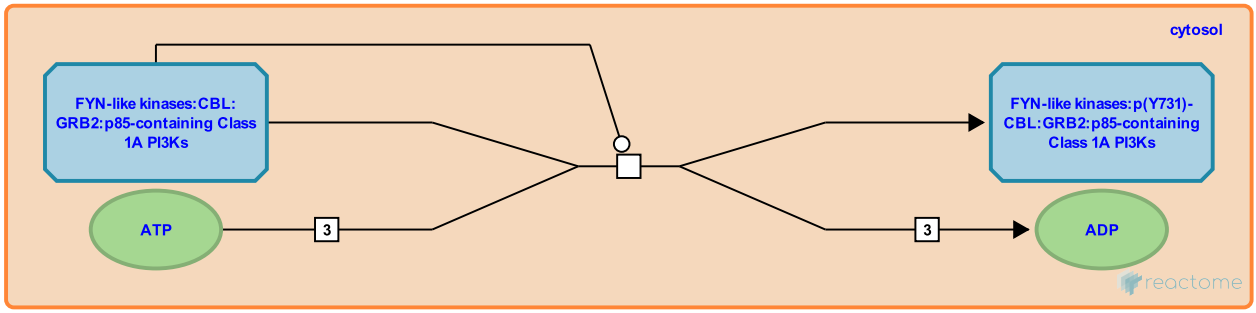
Location: Regulation of signaling by CBL

Stable identifier: R-HSA-912629

Type: transition

Compartments: cytosol

Inferred from: Cbl is tyrosine phosphorylated (Rattus norvegicus)



Cbl is tyrosine phosphorylated following stimulation with IL-3 (Anderson et al. 1997) and GM-CSF (Odai et al. 1995). Cbl may be phosphorylated prior to this IL-3 stimulated tyrosyl phosphorylation (Park et al. 1998). The kinase responsible for Cbl phosphorylation may be dependent on cell type; Fyn is demonstrated to have the ability to phosphorylate Cbl (Hunter et al. 1999), other candidates include Hck, Lyn (Hunter et al. 1999) and Syk (Park et al. 1998).

Tyrosines 700, 731 and 774 are the major sites of Cbl phosphorylation by non-receptor protein tyrosine kinases, with none showing any particular specificity for sites (Tsygankov et al. 2001). Fyn was observed to be constitutively associated with Cbl in lysates of several different cell types including the interleukin-3-dependent murine myeloid cell line 32Dcl3, and the prolactin-dependent rat thymoma cell line Nb2. Cbl phosphorylation at Y731 is postulated to provide an additional interaction between Cbl and the SH2 domain of p85-PI3K (Hunter et al. 1999). Cbl-p85 association increases in activated cells (Panchamoorthy et al. 1996). Expression of a Cbl Y731F mutant which abolishes binding of Cbl to p85 markedly increased levels of p85-PI3K (Dufour et al. 2008). Cbl-p85 binding negatively regulates PI3K activity (Fang et al. 2001); Cbl phosphorylation increased PI3K ubiquitination and proteasome degradation (Dufour et al. 2008). Cbl association with members of the Crk family is mediated by phosphorylation of Y700 and Y774 (Andoniou et al. 1996), binding with Vav is mediated by Y770 (Marengere et al 1997).

Preceded by: CBL, GRB2, FYN and PI3K p85 subunit are constitutively associated

Followed by: CBL binds B-cell linker protein, CBL binds VAV, CBL ubiquitinates PI3K, CBL binds CRK

Literature references

Odai, H., Sasaki, K., Iwamatsu, A., Hanazono, Y., Tanaka, T., Mitani, K. et al. (1995). The proto-oncogene product c-Cbl becomes tyrosine phosphorylated by stimulation with GM-CSF or Epo and constitutively binds to the SH3 domain of Grb2/Ash in human hematopoietic cells. *J Biol Chem, 270,* 10800-5. ↗

Feshchenko, EA., Langdon, WY., Tsygankov, AY. (1998). Fyn, Yes, and Syk phosphorylation sites in c-Cbl map to the same tyrosine residues that become phosphorylated in activated T cells. *J Biol Chem, 273,* 8323-31. ↗

Editions

2010-05-17	Authored	Ray, KP.
2010-08-06	Edited	Jupe, S.
2010-09-06	Reviewed	Lopez, AF., Hercus, TR.

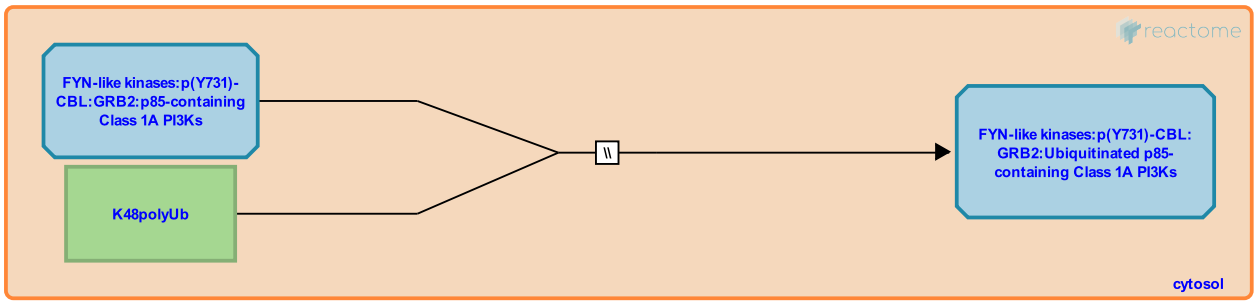
CBL ubiquitinates PI3K ↗

Location: Regulation of signaling by CBL

Stable identifier: R-HSA-912627

Type: omitted

Compartments: cytosol



Cbl is an E3 ubiquitin-protein ligase that negatively regulates signaling pathways by targeting proteins for ubiquitination and proteasomal degradation (Rao et al. 2002). Cbl-B targets PI3K for ubiquitination and degradation in T cells (Fang et al. 2000). Similarly, Cbl activation by tyrosine phosphorylation increases PI3K ubiquitination and proteasomal degradation (Dufour et al. 2008).

Preceded by: CBL is tyrosine phosphorylated

Literature references

Dufour, C., Guenou, H., Kaabeche, K., Bouvard, D., Sanjay, A., Marie, PJ. (2008). FGFR2-Cbl interaction in lipid rafts triggers attenuation of PI3K/Akt signaling and osteoblast survival. *Bone, 42*, 1032-9. ↗

Editions

2010-05-17	Authored	Ray, KP.
2010-08-06	Edited	Jupe, S.
2010-09-06	Reviewed	Lopez, AF., Hercus, TR.

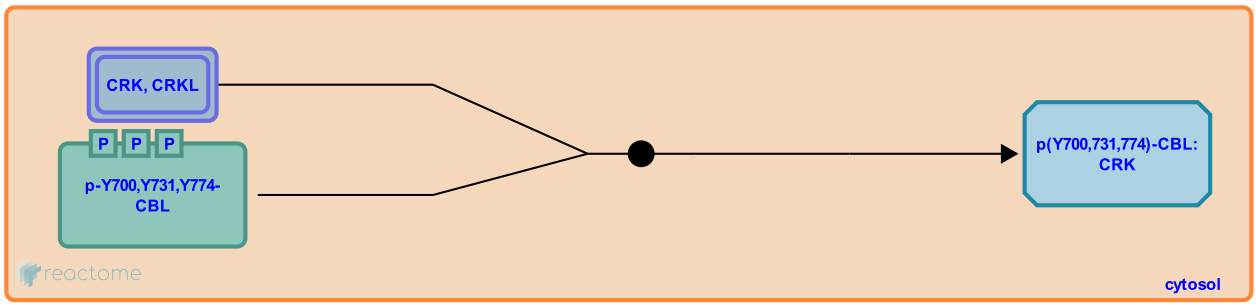
CBL binds CRK ↗

Location: Regulation of signaling by CBL

Stable identifier: R-HSA-912790

Type: binding

Compartments: cytosol



The Crk adapter protein family is comprised of Crk-I and Crk-II, alternatively spliced products of a single gene with differing biological functions, and Crk-L, a distinct Crk-like gene product. Cbl is the dominant phosphoprotein associated with Crk in activated lymphocytes. In vitro binding indicates that the Crk SH2 domain binds Y774 of Cbl (Reedquist et al. 1996), leaving the SH3 domain of Crk free to interact with other SH3 domain-associated proteins.

Preceded by: CBL is tyrosine phosphorylated

Followed by: CBL:CRKL binds RAPGEF1

Literature references

Andoniou, CE., Thien, CB., Langdon, WY. (1996). The two major sites of cbl tyrosine phosphorylation in abl-transformed cells select the crkL SH2 domain. *Oncogene, 12*, 1981-9. ↗

Reedquist, KA., Fukazawa, T., Panchamoorthy, G., Langdon, WY., Shoelson, SE., Druker, BJ. et al. (1996). Stimulation through the T cell receptor induces Cbl association with Crk proteins and the guanine nucleotide exchange protein C3G. *J Biol Chem, 271*, 8435-42. ↗

Editions

2010-05-17	Authored	Ray, KP.
2010-08-06	Edited	Jupe, S.
2010-09-06	Reviewed	Lopez, AF., Hercus, TR.

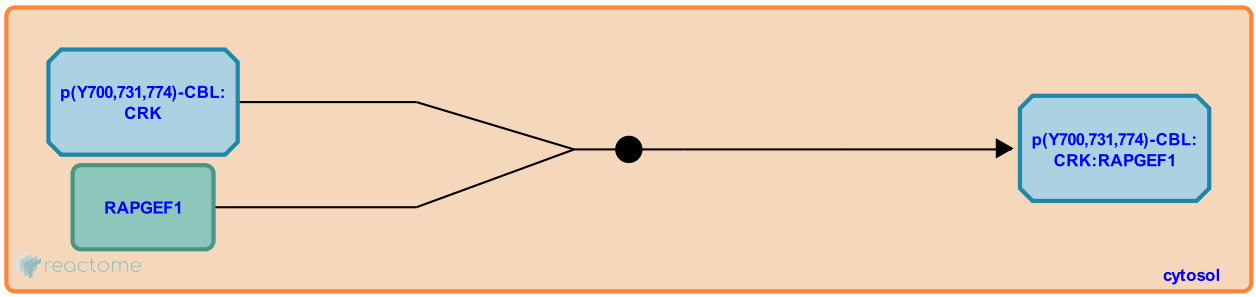
CBL:CRKL binds RAPGEF1 ↗

Location: Regulation of signaling by CBL

Stable identifier: R-HSA-912734

Type: binding

Compartments: cytosol



Cbl has been identified in ternary complexes with CRKL and C3G (RAPGEF1)(Reedquist et al. 1996) a Rap1 GEF, suggesting a role for Cbl in linking cytokine stimulation to Rap1 activation. Consistent with this, stimulation of NB-4 promyelocytic cells by IFN-gamma causes tyrosine phosphorylation and association of Cbl with CRKL followed by activation of Rap1 (Alsayed et al. 2000) and tyrosine phosphorylation of Cbl and its association with CRKL correlated with an increase in Rap 1 activity in anergic T cells (Boussiotis et al. 1997).

Preceded by: CBL binds CRK

Literature references

Reedquist, KA., Fukazawa, T., Panchamoorthy, G., Langdon, WY., Shoelson, SE., Druker, BJ. et al. (1996). Stimulation through the T cell receptor induces Cbl association with Crk proteins and the guanine nucleotide exchange protein C3G. *J Biol Chem, 271*, 8435-42. ↗

Editions

2010-05-17	Authored	Ray, KP.
2010-08-06	Edited	Jupe, S.
2010-09-06	Reviewed	Lopez, AF., Hercus, TR.

CBL binds B-cell linker protein ↗

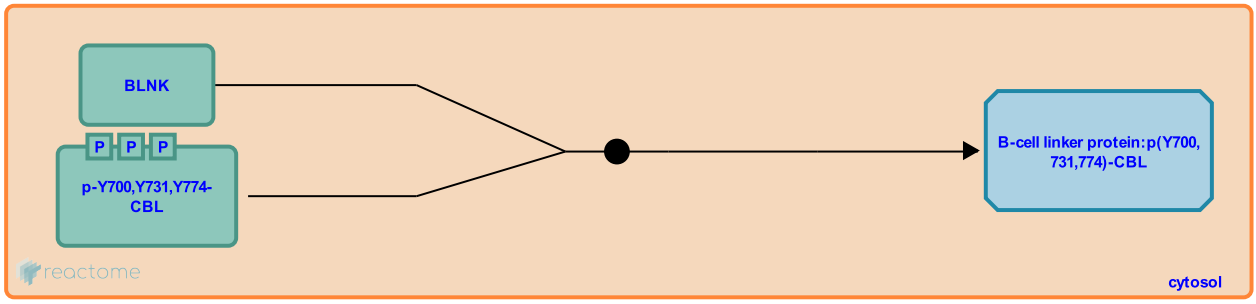
Location: Regulation of signaling by CBL

Stable identifier: R-HSA-912724

Type: binding

Compartments: cytosol

Inferred from: Cbl binds B-cell linker protein (Gallus gallus)



Cbl binds B-cell linker protein, a molecular scaffold bridging Syk to downstream signaling pathways by recruiting signaling molecules, such as Btk, phospholipase C gamma 2, Vav, and Grb2 to the cell membrane to form a signalosome complex. Cbl is believed to negatively regulate signaling from this complex. Consistent with this, Cbl inactivation reverses a number of critical defects in early B cell differentiation seen in BLNK-deficient mice (Song et al. 2007).

Preceded by: CBL is tyrosine phosphorylated

Literature references

Song, H., Zhang, J., Chiang, YJ., Siraganian, RP., Hodes, RJ. (2007). Redundancy in B cell developmental pathways: c-Cbl inactivation rescues early B cell development through a B cell linker protein-independent pathway. *J Immunol, 178*, 926-35. ↗

Editions

2010-05-17	Authored	Ray, KP.
2010-08-06	Edited	Jupe, S.
2010-09-06	Reviewed	Lopez, AF., Hercus, TR.

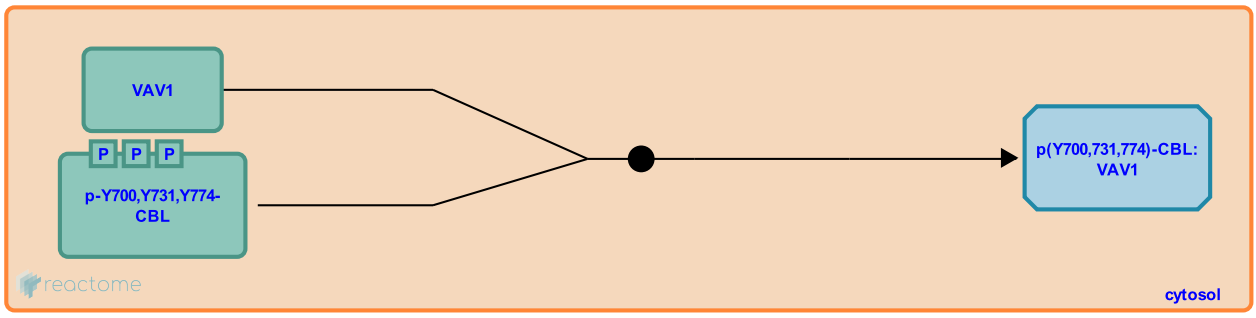
CBL binds VAV ↗

Location: Regulation of signaling by CBL

Stable identifier: R-HSA-912727

Type: binding

Compartments: cytosol



Cbl and Vav interact in thymocytes and peripheral T cells (Marengere et al. 1997). Cbl phosphorylated at Y700 binds Vav1 in 293T cells, leading to Vav ubiquitinylation and proteolytic degradation.

Preceded by: CBL is tyrosine phosphorylated

Literature references

Miura-Shimura, Y., Duan, L., Rao, NL., Reddi, AL., Shimura, H., Rottapel, R. et al. (2003). Cbl-mediated ubiquitinylation and negative regulation of Vav. *J Biol Chem, 278*, 38495-504. ↗

Marengère, LE., Mirtsos, C., Kozieradzki, I., Veillette, A., Mak, TW., Penninger, JM. (1997). Proto-oncoprotein Vav interacts with c-Cbl in activated thymocytes and peripheral T cells. *J Immunol, 159*, 70-6. ↗

Editions

2010-05-17	Authored	Ray, KP.
2010-08-06	Edited	Jupe, S.
2010-09-06	Reviewed	Lopez, AF., Hercus, TR.

Table of Contents