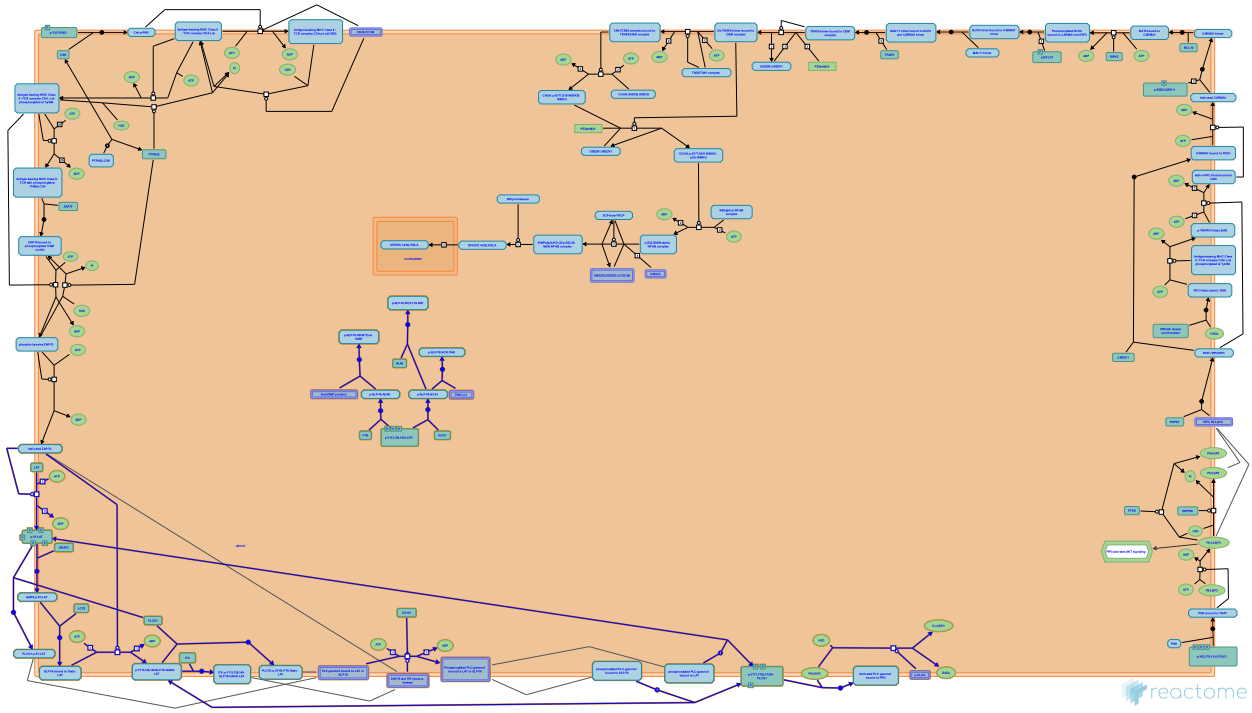
Generation of second messenger molecules



Akkerman, JW., Garapati, P V., Harper, MT., Jones, ML., Jupe, S., Murillo, JI., Poole, AW., 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.

29/04/2024

Introduction

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

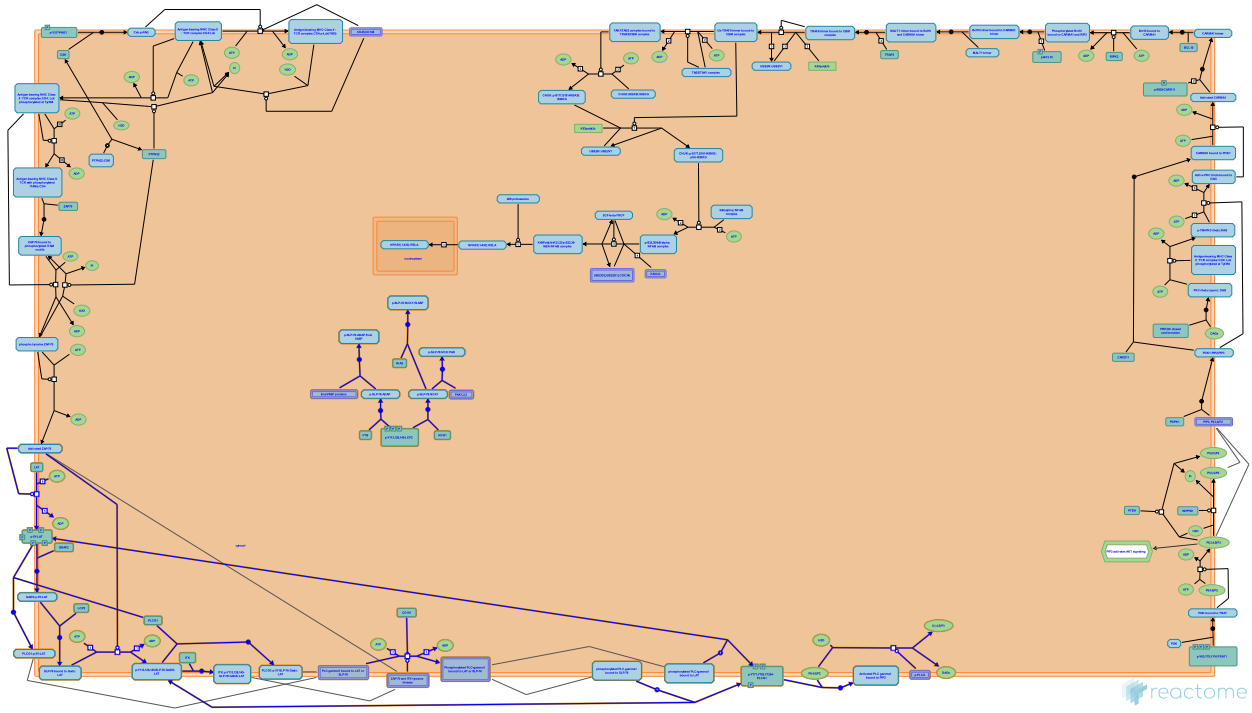
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

Generation of second messenger molecules ↗

Stable identifier: R-HSA-202433

Compartments: plasma membrane



In addition to serving as a scaffold via auto-phosphorylation, ZAP70 also phosphorylates a restricted set of substrates following TCR stimulation - including LAT (step 13) and LCP2. These substrates have been recognized to play pivotal role in TCR signaling by releasing second messengers. When phosphorylated, LAT and SLP-76 act as adaptor proteins which serve as nucleation points for the construction of a higher order signalosome: PLC-gamma1 (step 14) and GRAP2 (step 15) bind to the LAT on the phosphorylated tyrosine residues. LCP2 is then moved to the signalosome by interacting with the SH3 domains of GRAP2 using their proline rich sequences (step 16). Once LCP2 binds to GRAP2, three LCP2 acidic domain N-term tyrosine residues are phosphorylated by ZAP70 (step 17). These phospho-tyrosine residues act as binding sites to the SH2 domains of ITK (steps 18) and PLC-gamma1 (step 19). PLC-gamma1 is activated by dual phosphorylation on the tyrosine residues at positions 771, 783 and 1254 by ITK (step 20) and ZAP70 (step 21). Phosphorylated PLC-gamma1 subsequently detaches from LAT and LCP2 and translocates to the plasma membrane by binding to phosphatidylinositol-4,5-bisphosphate (PIP2) via its PH domain (step 22). PLC-gamma1 goes on to hydrolyse PIP2 to second messengers DAG and IP3 (step 23). These second messengers are involved in PKC and NF-kB activation and calcium mobilization.

Literature references

Huang, Y., Wange, RL. (2004). T cell receptor signaling: beyond complex complexes. *J Biol Chem, 279*, 28827-30. ↗

Editions

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

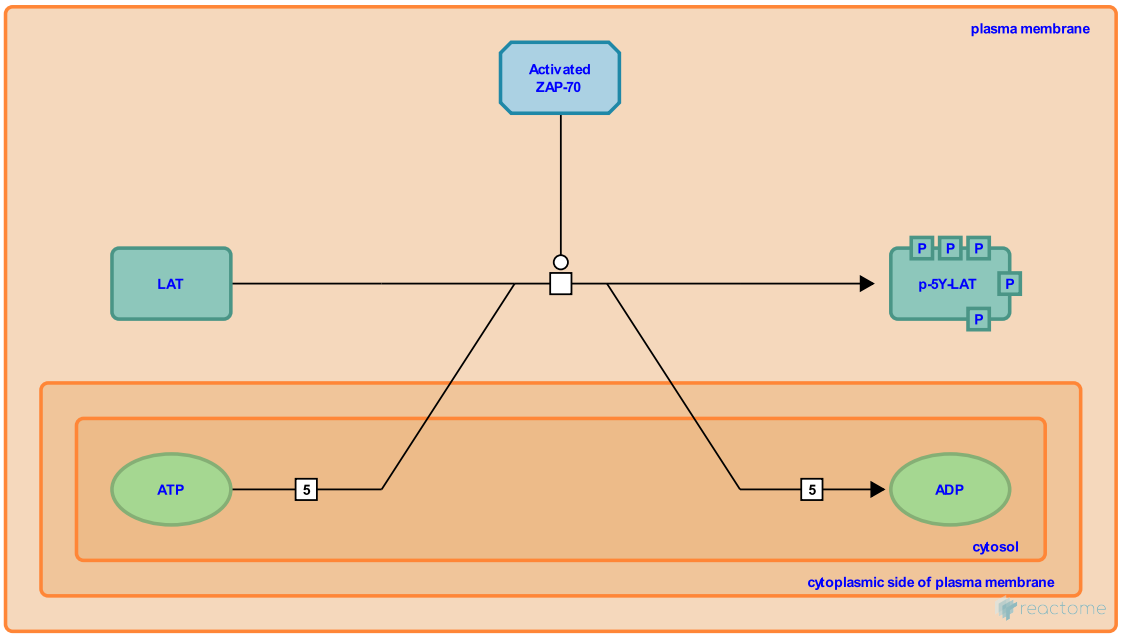
Phosphorylation of TBSMs in LAT ↗

Location: Generation of second messenger molecules

Stable identifier: R-HSA-202245

Type: transition

Compartments: plasma membrane, cytosol



The adaptor molecule LAT (Linker for the Activation of T cells) is a membrane protein that links the TCR signal to the cell activation. It has a total 10 (Y36, Y45, Y64, Y110, Y156, Y161, Y200, Y220, and Y255) conserved TBSMs (tyrosine based signaling motifs) in its cytoplasmic region. These tyrosine residues are phosphorylated by the activated ZAP-70 upon TCR/CD3 complex engagement. Phosphorylation of LAT creates binding sites for the Src homology 2 (SH2) domains of other proteins, including PLC-gamma1, Grb2 and Gads, and indirectly binds SOS, Vav, SLP-76, and Itk. The residues Y200, Y220 and Y255 are responsible for Grb2 binding, Y200 and Y220 but not Y255, are necessary for Gads binding and Y161 for the PLC-gamma1 binding (numbering based on Uniprot isoform 1).

Followed by: Recruitment of PLC-gamma1 to LAT, Recruitment of Gads to LAT

Literature references

Liu, SK., Samelson, LE., Zhang, W., Zhu, M., McGlade, CJ., Trible, RP. (2000). Association of Grb2, Gads, and phospholipase C-gamma 1 with phosphorylated LAT tyrosine residues. Effect of LAT tyrosine mutations on T cell angigen receptor-mediated signaling. *J Biol Chem, 275*, 23355-61. ↗

Wange, RL. (2000). LAT, the linker for activation of T cells: a bridge between T cell-specific and general signaling pathways. *Sci STKE, 2000*, RE1. ↗

Wang, H., Rudd, CE. (2003). Hematopoietic adaptors in T-cell signaling: potential applications to transplantation. *Am J Transplant, 3*, 1204-10. ↗

Editions

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

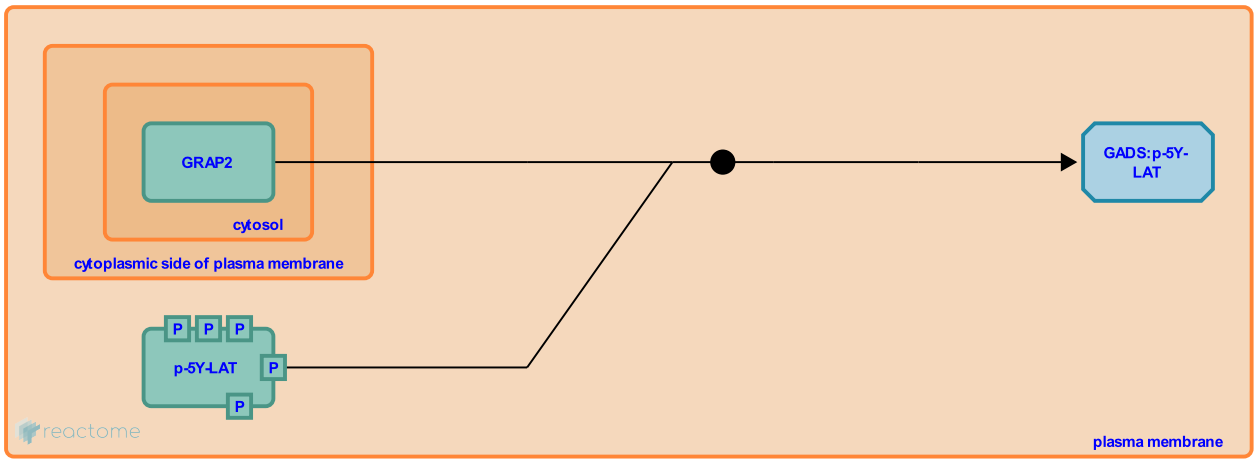
Recruitment of Gads to LAT ↗

Location: Generation of second messenger molecules

Stable identifier: R-HSA-202325

Type: binding

Compartments: plasma membrane, cytosol



Gads is a member of the Grb2 family containing SH2 and SH3 domains with the arrangement SH3-SH2-SH3. Gads binds to the tyrosine phosphorylated residues Y171 and Y191 of LAT through its SH2 domain. It plays a critical role in signaling from the T cell receptor by promoting the formation of a complex between SLP-76 and LAT.

Preceded by: Phosphorylation of TBSMs in LAT

Followed by: Recruitment of SLP-76 to Gads

Literature references

Liu, SK., McGlade, CJ., Berry, DM. (2001). The role of Gads in hematopoietic cell signalling. *Oncogene, 20*, 6284-90. ↗

Editions

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

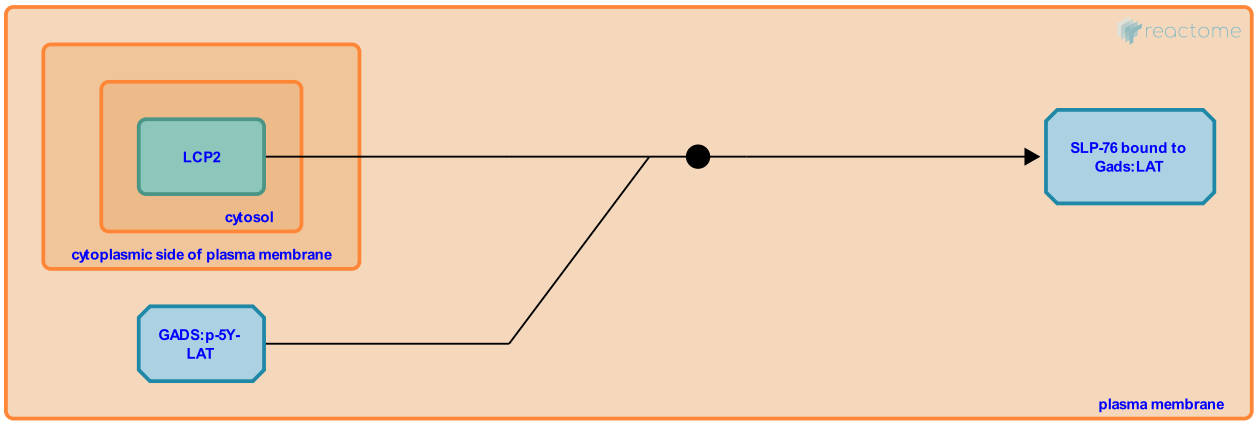
Recruitment of SLP-76 to Gads ↗

Location: Generation of second messenger molecules

Stable identifier: R-HSA-202241

Type: binding

Compartments: plasma membrane, cytosol



SLP-76 is an adaptor protein that links proximal and distal T cell receptor signaling events through its function as a molecular scaffold in the assembly of multi molecular signaling complexes. SLP-76 consists of three domains that mediate interactions with many different signaling proteins: an N-terminal acidic domain containing three tyrosine phosphorylation sites, a large central proline-rich region, and a C-terminal SH2 domain. The function of SLP-76 is dependent on its association with Gads. SLP-76 constitutively binds through its 'RxxK' motif in the proline rich region to the SH3 domain of Gads upon TCR activation.

Preceded by: Recruitment of Gads to LAT

Followed by: Phosphorylation of SLP-76

Literature references

Liu, SK., McGlade, CJ., Berry, DM. (2001). The role of Gads in hematopoietic cell signalling. *Oncogene, 20*, 6284-90. ↗

Editions

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

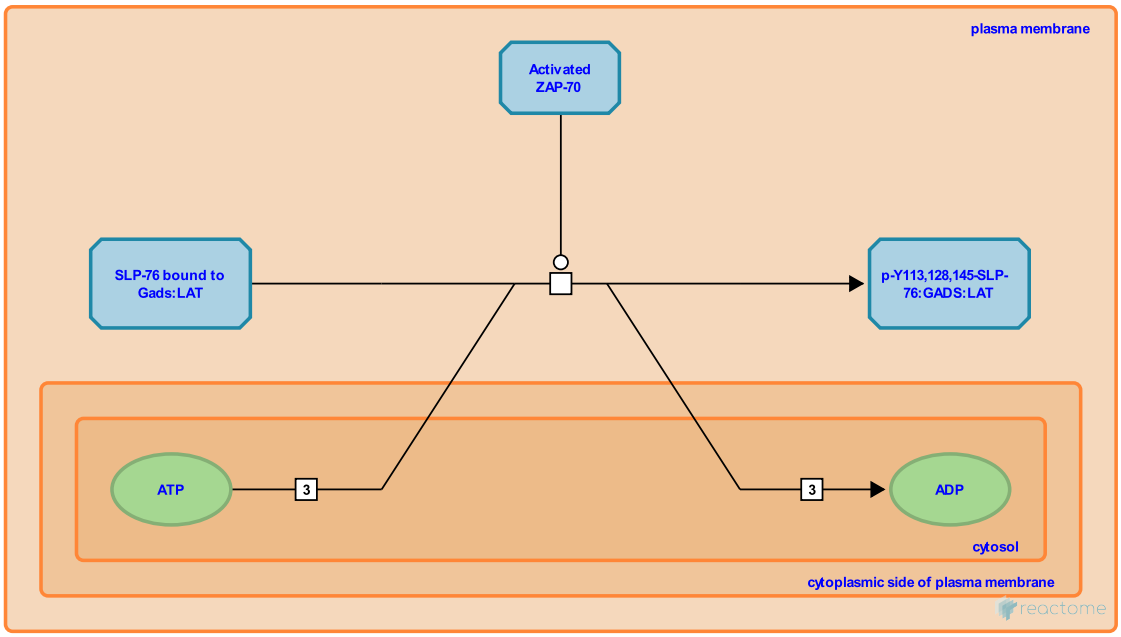
Phosphorylation of SLP-76 ↗

Location: Generation of second messenger molecules

Stable identifier: R-HSA-202216

Type: transition

Compartments: plasma membrane, cytosol



Once SLP-76 is recruited to Gads its rapidly phosphorylated on the tyrosine residues in the N-terminal acidic domain. This domain contains three tyrosine phosphorylation sites, Y113, Y128 and Y145. These tyrosine residues are phosphorylated by tyrosine kinase ZAP-70 and these phosphorylated tyrosine residues provide the binding site for the SH2 domains of the incoming signaling proteins like Vav, Itk and PLC-gamma1.

Preceded by: Recruitment of SLP-76 to Gads

Followed by: p-SLP-76 binds ADAP, Recruitment of PLC-gamma1 to SLP-76, Recruitment of ITK to SLP-76

Literature references

August, A., Qi, Q. (2007). Keeping the (kinase) party going: SLP-76 and ITK dance to the beat. *Sci STKE, 2007*, pe39. ↗

Editions

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

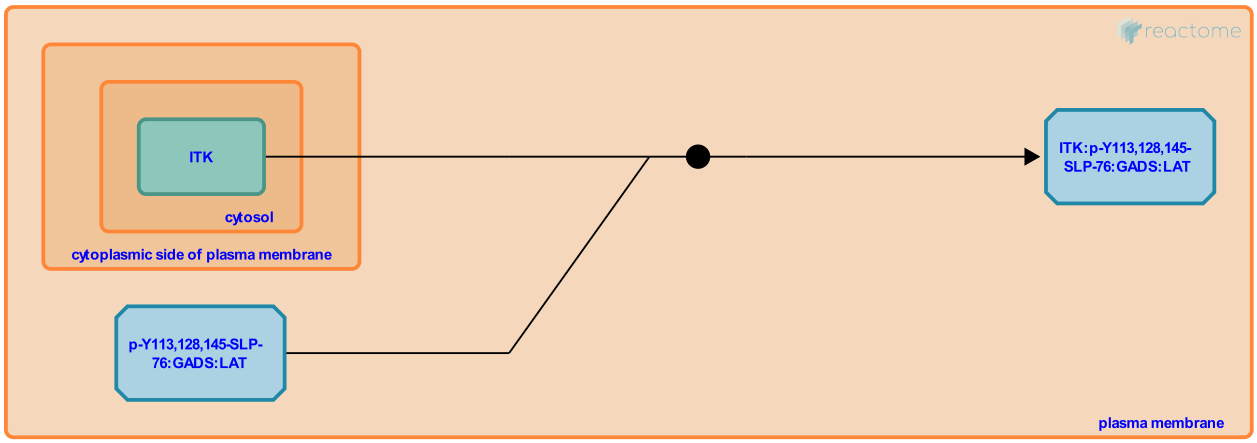
Recruitment of ITK to SLP-76 ↗

Location: Generation of second messenger molecules

Stable identifier: R-HSA-202375

Type: binding

Compartments: plasma membrane, cytosol



ITK is a member of the Tec protein tyrosine kinase family which forms a complex with SLP-76 after TCR activation. ITK has N-terminal pleckstrin homology (PH) domain, a Tec homology (TH) domain, a proline rich domain, a SH3 domain, an SH2 domain and a C-term kinase domain. The SH2 domain of ITK may interact with Y145 within the N-ter acidic domain of SLP-76 and the SH3 domain of the ITK binds the proline rich region of SLP-76. ITK plays an important role in phosphorylating and activating PLC-gamma-1, leading to the development of second-messenger molecules.

Preceded by: Phosphorylation of SLP-76

Followed by: Phosphorylation of PLC-gamma1

Literature references

August, A., Qi, Q. (2007). Keeping the (kinase) party going: SLP-76 and ITK dance to the beat. *Sci STKE, 2007*, pe39. ↗

Editions

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

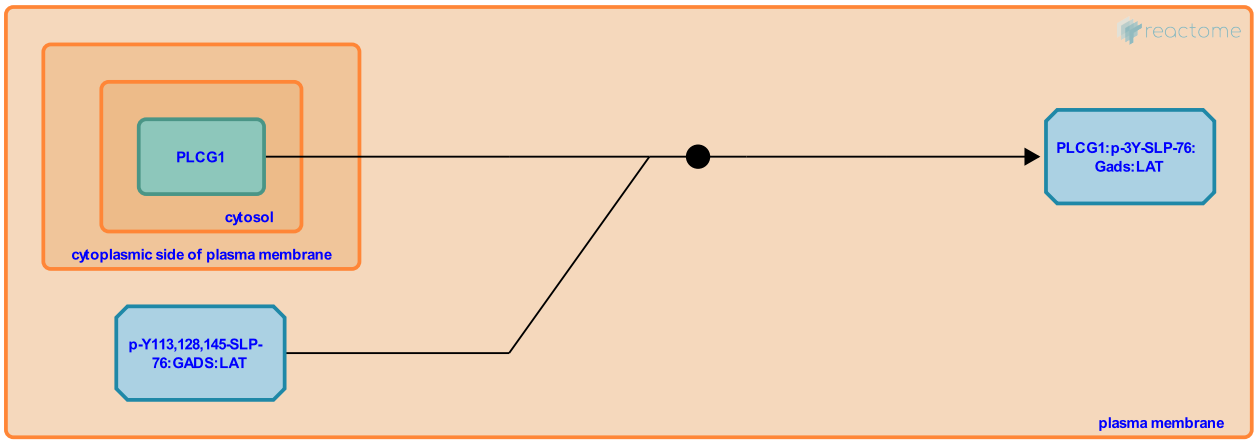
Recruitment of PLC-gamma1 to SLP-76 ↗

Location: Generation of second messenger molecules

Stable identifier: R-HSA-202331

Type: binding

Compartments: plasma membrane, cytosol



PLC-gamma1 plays an important role in transducing the external signal in to second messengers by hydrolysing PIP2. PLC-gamma1 contains an N-term PH domain, a catalytic domain 'X' followed by two SH2 domains and an SH3 domain, a C-term catalytic domain 'Y' and a C2 domain (Ca++ binding). PLC-gamma1 interacts with both SLP-76 aswell as LAT. It interacts with its SH3 domain to the proline rich sequence of SLP-76. This interaction aids in localizing PLC-gamma1 to the membrane. This recruitment of PLC-gamma1 to LAT and SLP-76 is essential for its TCR induced tyrosine phosphorylation and activation.

Preceded by: Phosphorylation of SLP-76

Followed by: Phosphorylation of PLC-gamma1

Literature references

Suh, PG., Kim, MJ., Kim, E., Ryu, SH. (2000). The mechanism of phospholipase C-gamma1 regulation. *Exp Mol Med, 32*, 101-9. ↗

Kadlecek, T., Yablonski, D., Weiss, A. (2001). Identification of a phospholipase C-gamma1 (PLC-gamma1) SH3 domain-binding site in SLP-76 required for T-cell receptor-mediated activation of PLC-gamma1 and NFAT. *Mol Cell Biol, 21*, 4208-18. ↗

Editions

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

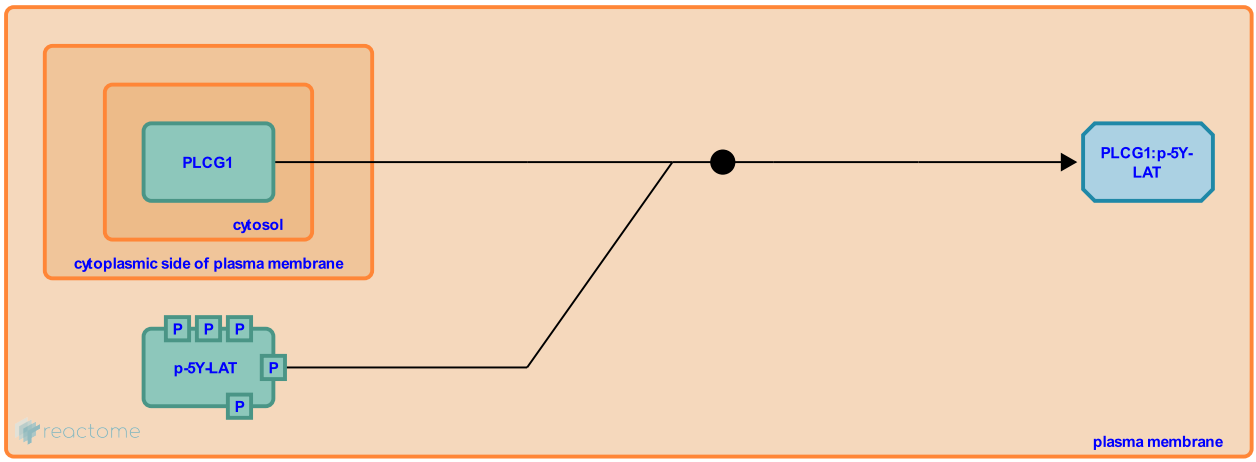
Recruitment of PLC-gamma1 to LAT ↗

Location: Generation of second messenger molecules

Stable identifier: R-HSA-202212

Type: binding

Compartments: plasma membrane, cytosol



PLC-gamma1 interacts with its SH2 domain to the pY132 residue of LAT.

Preceded by: Phosphorylation of TBSMs in LAT

Followed by: Phosphorylation of PLC-gamma1

Literature references

Suh, PG., Kim, MJ., Kim, E., Ryu, SH. (2000). The mechanism of phospholipase C-gamma1 regulation. *Exp Mol Med, 32*, 101-9. ↗

Editions

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

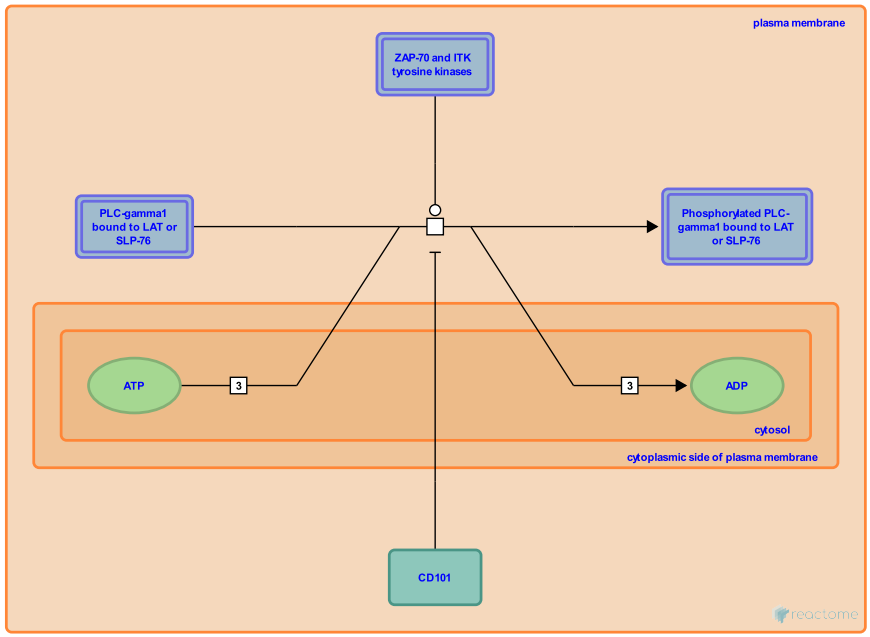
Phosphorylation of PLC-gamma1 ↗

Location: Generation of second messenger molecules

Stable identifier: R-HSA-202248

Type: transition

Compartments: plasma membrane, cytosol



Three tyrosine residues at positions 771, 783 and 1254 in PLC-gamma1 have been identified as the sites of receptor tyrosine kinase phosphorylation. Of these Y783 and Y1254 are required for activation of PLC-gamma1. The phosphorylation of the tyrosine residues and the activation of PLC-gamma1 is mediated by both Syk tyrosine kinase ZAP-70 and Tec kinase ITK.
Immunoglobulin superfamily member 2 (IgSF2 or cell surface glycoprotein V7)ligation interferes with T cell activation and IL-2 secretion through a Ca2+ and tyrosine kinase-dependent pathway that inhibits PLC-gamma1 phosphorylation and prevents NF-AT translocation to the nucleus (Soares et al. 1998, 1997).

Preceded by: Recruitment of PLC-gamma1 to SLP-76, Recruitment of PLC-gamma1 to LAT, Recruitment of ITK to SLP-76

Followed by: Disassociation of PLC-gamma1 from LAT, Disassociation of PLC-gamma1 from SLP-76, Translocation of PLC-gamma1 to PIP2

Literature references

Suh, PG., Kim, MJ., Kim, E., Ryu, SH. (2000). The mechanism of phospholipase C-gamma1 regulation. *Exp Mol Med, 32*, 101-9. ↗

Editions

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

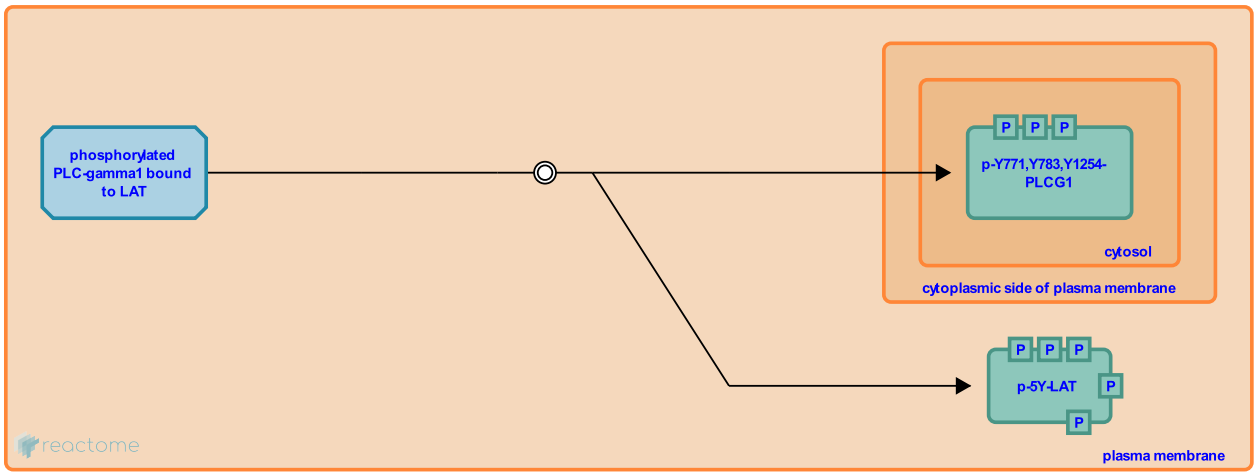
Disassociation of PLC-gamma1 from LAT ↗

Location: Generation of second messenger molecules

Stable identifier: R-HSA-213406

Type: dissociation

Compartments: plasma membrane, cytosol



The activated PLC-gamma1 detaches from its substrate LAT and translocates to the membrane.

Preceded by: Phosphorylation of PLC-gamma1

Followed by: Translocation of PLC-gamma1 to PIP2

Literature references

Suh, PG., Kim, MJ., Kim, E., Ryu, SH. (2000). The mechanism of phospholipase C-gamma1 regulation. *Exp Mol Med, 32*, 101-9. ↗

Editions

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

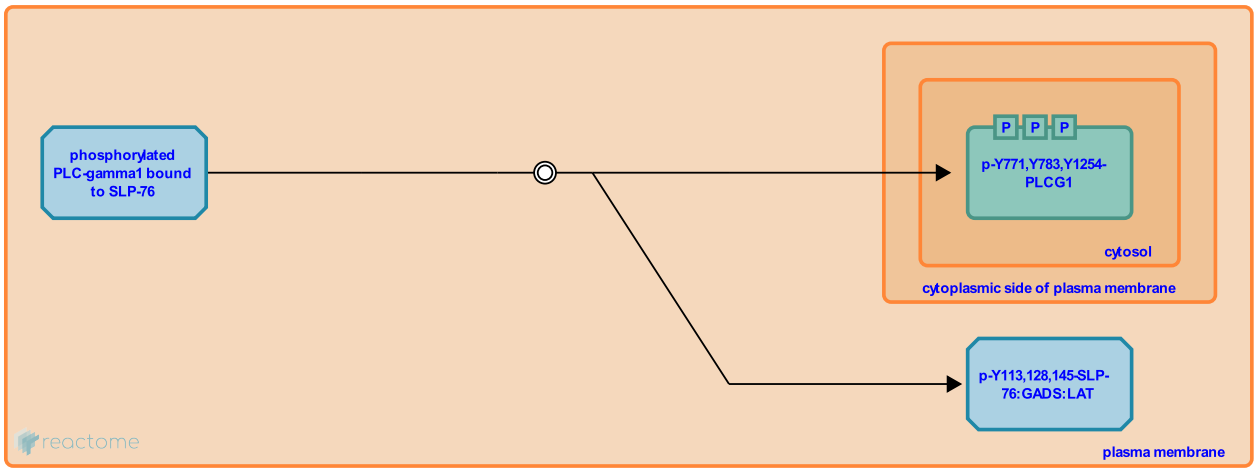
Disassociation of PLC-gamma1 from SLP-76 ↗

Location: Generation of second messenger molecules

Stable identifier: R-HSA-213407

Type: dissociation

Compartments: plasma membrane, cytosol



The activated PLC-gamma1 detaches from its substrate SLP-76 and translocates to the membrane.

Preceded by: Phosphorylation of PLC-gamma1

Followed by: Translocation of PLC-gamma1 to PIP2

Literature references

Suh, PG., Kim, MJ., Kim, E., Ryu, SH. (2000). The mechanism of phospholipase C-gamma1 regulation. *Exp Mol Med, 32*, 101-9. ↗

Editions

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

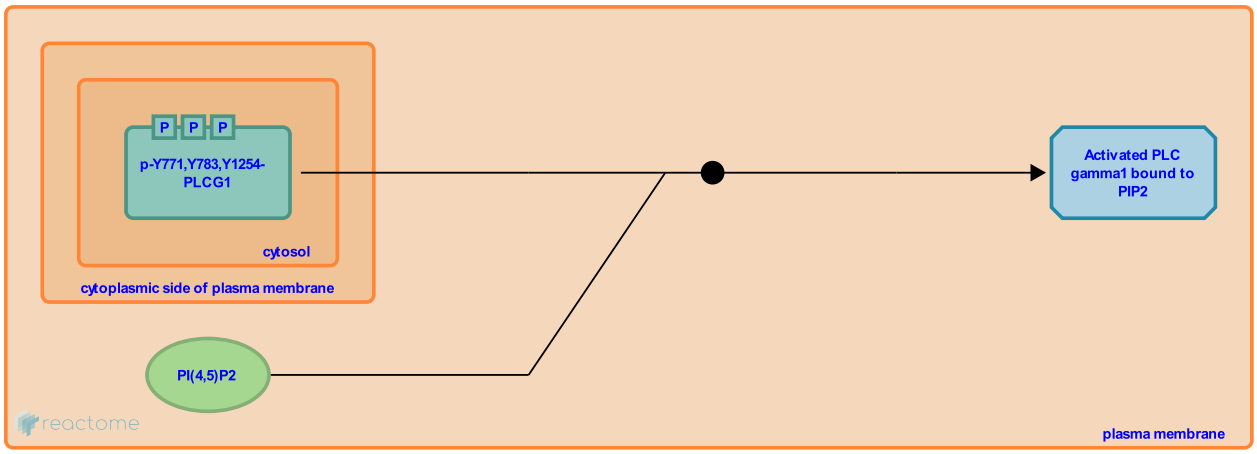
Translocation of PLC-gamma1 to PIP2 ↗

Location: Generation of second messenger molecules

Stable identifier: R-HSA-202354

Type: binding

Compartments: plasma membrane, cytosol



Activated PLA-gamma1 translocates to the plasmamembrane and interacts with the inositol ring of the membrane bound phosphatidylinositol 4,5-bisphosphate (PIP2) with its PH domain.

Preceded by: Disassociation of PLC-gamma1 from LAT, Disassociation of PLC-gamma1 from SLP-76, Phosphorylation of PLC-gamma1

Followed by: PLC-gamma1 hydrolyses PIP2

Literature references

Suh, PG., Kim, MJ., Kim, E., Ryu, SH. (2000). The mechanism of phospholipase C-gamma1 regulation. *Exp Mol Med, 32*, 101-9. ↗

Editions

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

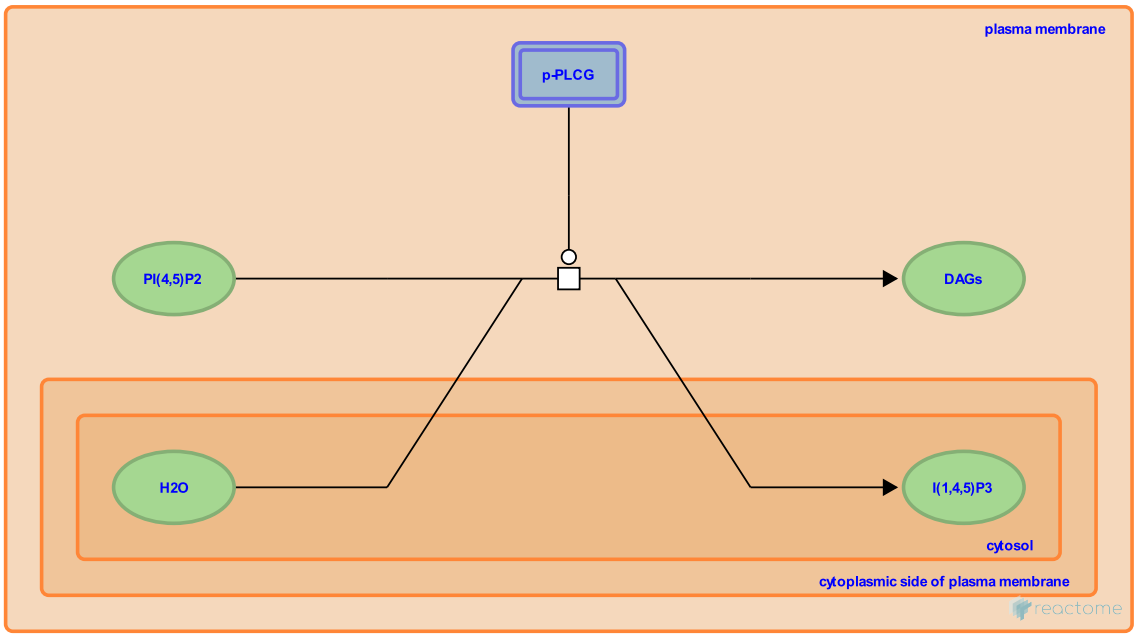
PLC-gamma1 hydrolyses PIP2 ↗

Location: Generation of second messenger molecules

Stable identifier: R-HSA-202407

Type: transition

Compartments: plasma membrane, cytosol



On recruitment to plasma membrane PLC-gamma1 then hydrolyses PIP2 producing two second messengers, diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP3). IP3 induces a transient increase in intracellular free Ca++, while DAG is a direct activator of protein kinase C (PKC theta). These process have been implicated in many cellular physiological functions like cell proliferation, cell growth and differentiation.

Preceded by: Translocation of PLC-gamma1 to PIP2

Literature references

Suh, PG., Kim, MJ., Kim, E., Ryu, SH. (2000). The mechanism of phospholipase C-gamma1 regulation. *Exp Mol Med, 32*, 101-9. ↗

Editions

2008-01-24	Authored	de Bono, B., Garapati, P V., Rudd, C.E..
2008-02-26	Reviewed	Trowsdale, J.
2020-02-05	Edited	Murillo, JI.

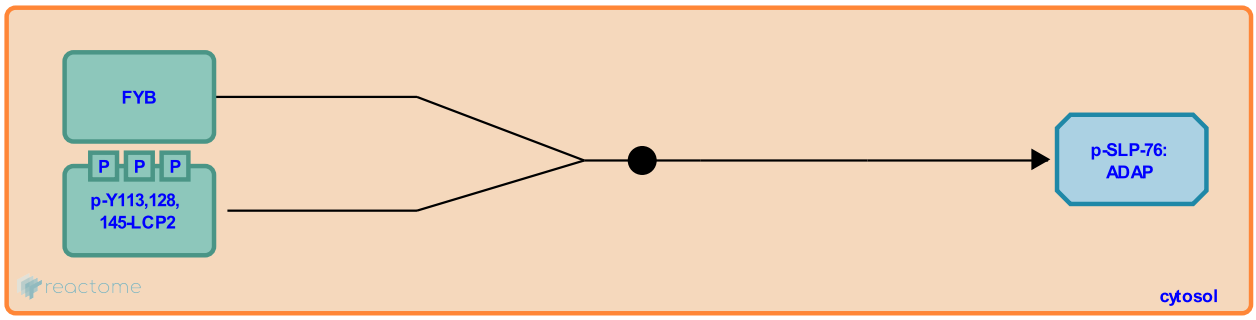
p-SLP-76 binds ADAP ↗

Location: Generation of second messenger molecules

Stable identifier: R-HSA-430135

Type: binding

Compartments: cytosol



SLP-76 inducibly-associates with ADAP (also known as FYN-binding protein or SLAP-130) a hematopoietic-specific adapter protein. ADAP has been implicated in T cell migration and rearrangement of the actin cytoskeleton. In platelets, adhesion to fibrinogen stimulates the association of SLP-76 with ADAP and VASP (Obergfell et al. 2001). ADAP knockout mice exhibit mild thrombocytopenia (Kasirer-Friede et al. 2007).

Preceded by: Phosphorylation of SLP-76

Literature references

Hendricks-Taylor, LR., Musci, MA., Paskind, M., Turck, CW., Kamens, J., Motto, DG. et al. (1997). Molecular cloning of SLAP-130, an SLP-76-associated substrate of the T cell antigen receptor-stimulated protein tyrosine kinases. *J Biol Chem, 272*, 11674-7. ↗

Boerth, NJ., Koretzky, GA., Judd, BA. (2000). Functional association between SLAP-130 and SLP-76 in Jurkat T cells. *J Biol Chem, 275*, 5143-52. ↗

Editions

2009-06-03	Authored	Akkerman, JW.
2009-11-02	Reviewed	Poole, AW., Jones, ML., Harper, MT.
2009-11-03	Edited	Jupe, S.

p-SLP-76:ADAP binds Ena/VASP ↗

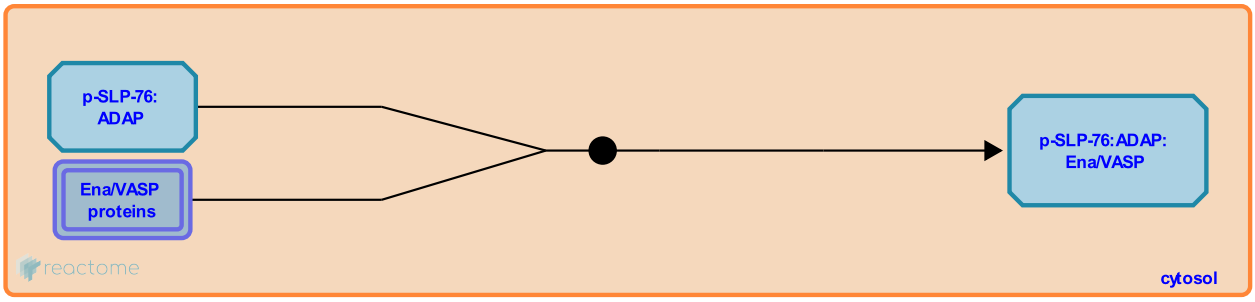
Location: Generation of second messenger molecules

Stable identifier: R-HSA-430201

Type: binding

Compartments: cytosol

Inferred from: p-SLP-76:ADAP binds Ena/VASP (Mus musculus)



ADAP (FYB) is an adaptor protein containing multiple binding motifs including an enabled protein vasodilator-stimulated phosphoprotein homology domain 1 (EVH1)-binding domain. This domain binds Ena-VASP family proteins that regulate actin dynamics. The Ena-VASP family member EVL is found in regions of dynamic actin polymerization, such as F-actin rich patches and the distal tips of microspikes.

Literature references

Konradt, M., Krause, M., Wehland, J., Gertler, FB., Sechi, AS., Monner, D. (2000). Fyn-binding protein (Fyb)/SLP-76-associated protein (SLAP), Ena/vasodilator-stimulated phosphoprotein (VASP) proteins and the Arp2/3 complex link T cell receptor (TCR) signaling to the actin cytoskeleton. *J Cell Biol, 149*, 181-94. ↗

Editions

2009-06-03	Authored	Akkerman, JW.
2009-11-02	Reviewed	Poole, AW., Jones, ML., Harper, MT.
2009-11-03	Edited	Jupe, S.

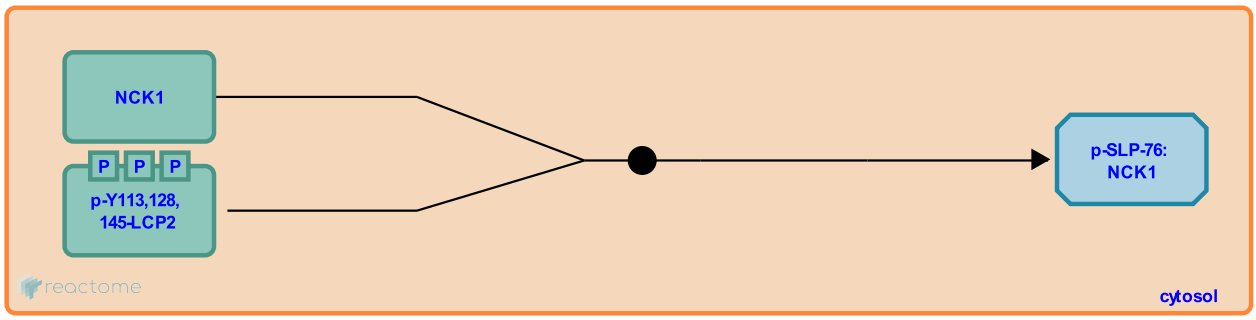
p-SLP-76 binds NCK ↗

Location: Generation of second messenger molecules

Stable identifier: R-HSA-430190

Type: binding

Compartments: cytosol



SLP-76 interacts with the adaptor protein NCK1. This interaction involved the SH2 domain of NCK1, leaving 3 three SH3 domains free to interact with other proteins, notably PAK1, N-WASP and Sos.

Literature references

Pappu, R., Bubeck Wardenburg, J., Straus, D., Mayer, B., Bu, JY., Chan, AC. et al. (1998). Regulation of PAK activation and the T cell cytoskeleton by the linker protein SLP-76. *Immunity, 9*, 607-16. ↗

Editions

2009-06-03	Authored	Akkerman, JW.
2009-11-02	Reviewed	Poole, AW., Jones, ML., Harper, MT.
2009-11-03	Edited	Jupe, S.

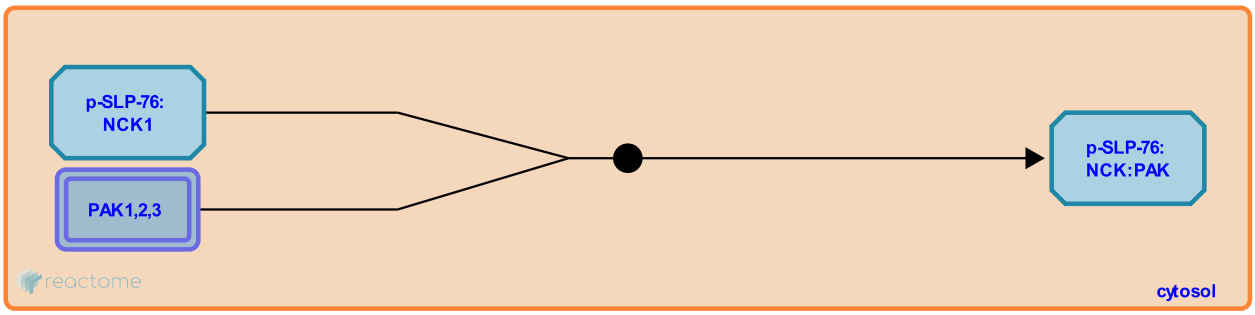
NCK binds PAK ↗

Location: Generation of second messenger molecules

Stable identifier: R-HSA-430183

Type: binding

Compartments: cytosol



NCK binds to PAK through its second SH3 domain. PAK interacts with NCK via the amino terminal SH3 binding domain. This interaction leads to the phosphorylation of NCK at multiple sites.

Literature references

Schlessinger, J., Galisteo, ML., Skolnik, EY., Chernoff, J., Su, YC. (1996). The adaptor protein Nck links receptor tyrosine kinases with the serine-threonine kinase Pak1. *J Biol Chem, 271*, 20997-1000. ↗

Knaus, UG., Wang, Y., Bokoch, GM., Quilliam, LA., Bohl, BP., Sells, MA. (1996). Interaction of the Nck adapter protein with p21-activated kinase (PAK1). *J Biol Chem, 271*, 25746-9. ↗

Editions

2009-06-03	Authored	Akkerman, JW.
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2009-11-03	Edited	Jupe, S.

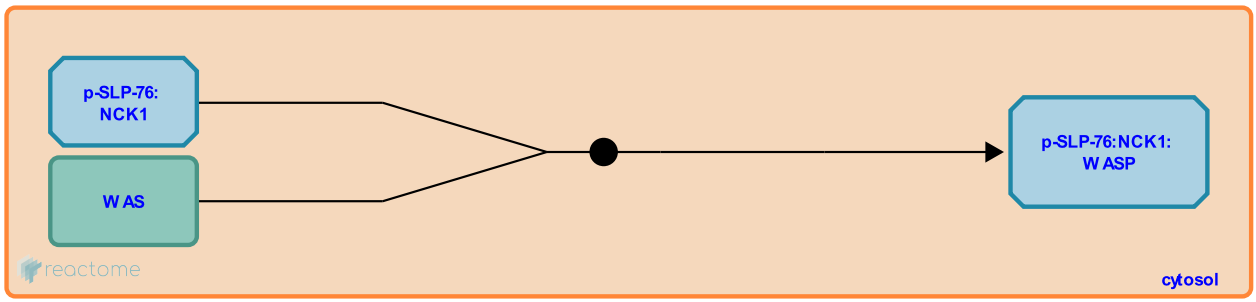
NCK recruits WASP ↗

Location: Generation of second messenger molecules

Stable identifier: R-HSA-430180

Type: binding

Compartments: cytosol



The second SH3 domain of NCK interacts with the carboxy-terminal SH3 domain of WASP. WASP family proteins bind the Arp2/3 complex, stimulating its ability to nucleate actin filaments and induce filament branching.

Literature references

Robbins, KC., Rivero-Lezcano, OM., Marcilla, A., Sameshima, JH. (1995). Wiskott-Aldrich syndrome protein physically associates with Nck through Src homology 3 domains. *Mol Cell Biol, 15*, 5725-31. ↗

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