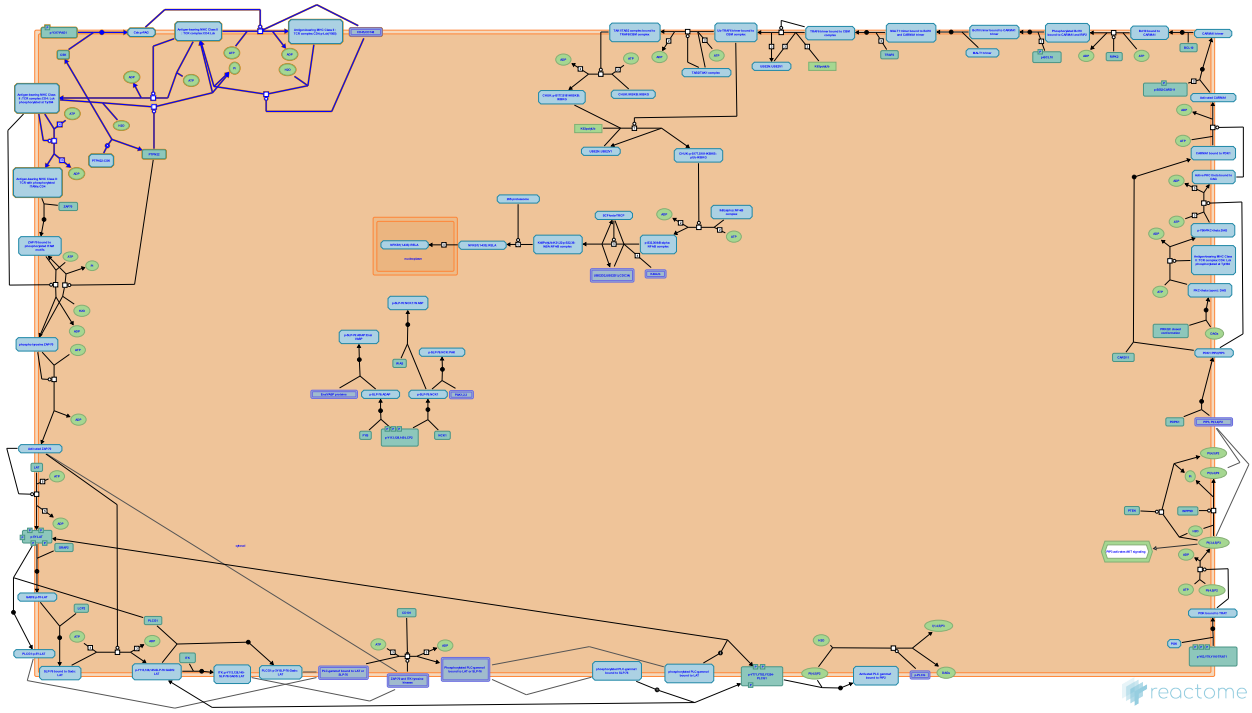
Phosphorylation of CD3 and TCR zeta chains



Bottini, N., Garapati, P V., Orlic-Milacic, M., Rudd, C.E.., Stanford, S., Trowsdale, J., de Bono, B.

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28/04/2024

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. ↗

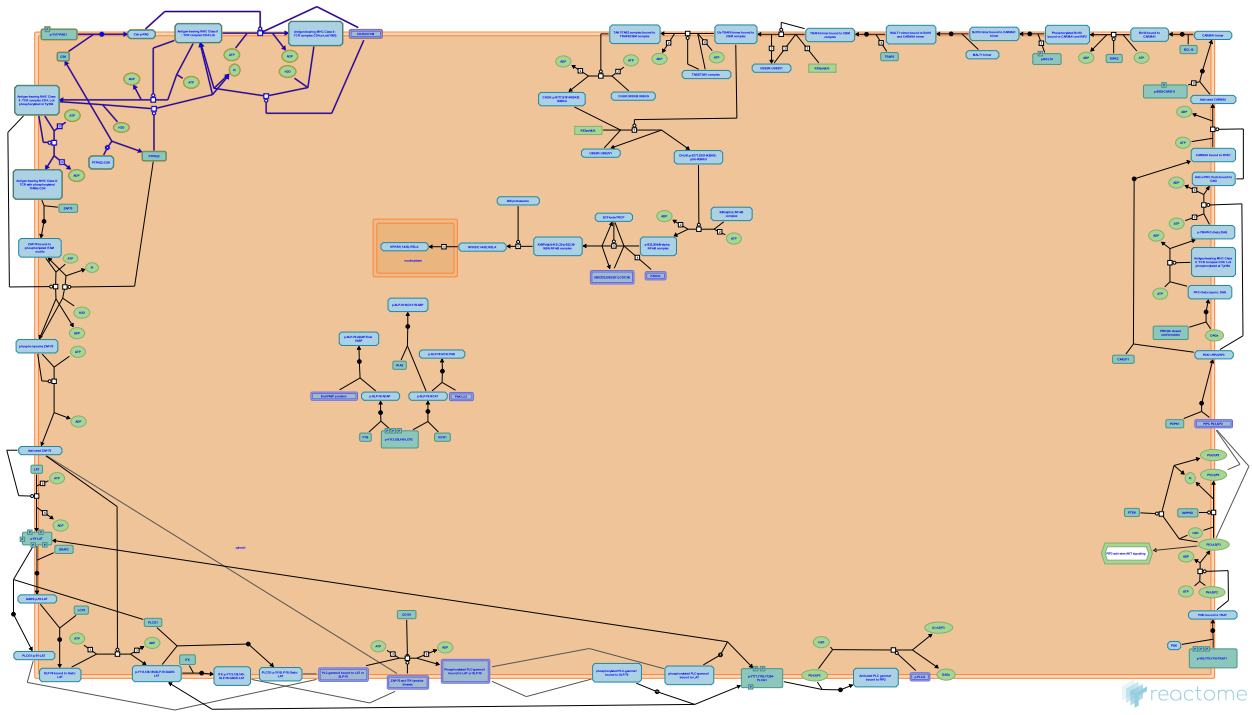
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

Phosphorylation of CD3 and TCR zeta chains ↗

Stable identifier: R-HSA-202427

Compartments: plasma membrane



Prior to T cell receptor (TCR) stimulation, CD4/CD8 associated LCK remains seperated from the TCR and is maintained in an inactive state by the action of CSK. PAG bound CSK phosphorylates the negative regulatory tyrosine of LCK and inactivates the LCK kinase domain (step 1). CSK also inhibits PTPN22 by sequestering it via binding (step 2). Upon TCR stimulation, CSK dissociates from PAG1 (step 3) and PTPN22 (step4) and is unable to inhibit LCK. Furthermore, LCK becomes activated via PTPRC-mediated dephosphorylation of negative regulatory tyrosine residues (step 5). CD4/CD8 binds MHCII receptor in APC and the associated LCK co-localizes with the TCR. LCK is further activated by trans-autophosphorylation on the tyrosine residue on its activation loop (step 6). Active LCK further phosphorylates the tyrosine residues on CD3 chains. The signal-transducing CD3 delta/epsilon/gamma and TCR zeta chains contain a critical signaling motif known as the immunoreceptor tyrosine-based activation motif (ITAM). The two critical tyrosines of each ITAM motif are phosphorylated by LCK (step 7).

Literature references

van Leeuwen, JE., Samelson, LE. (1999). T cell antigen-receptor signal transduction. *Curr Opin Immunol, 11*, 242-8. ↗

Editions

2008-01-24	Authored	de Bono, B., Garapati, P V., Rudd, C.E..
2008-02-26	Reviewed	Trowsdale, J.
2016-05-10	Revised	Stanford, S., Bottini, N.

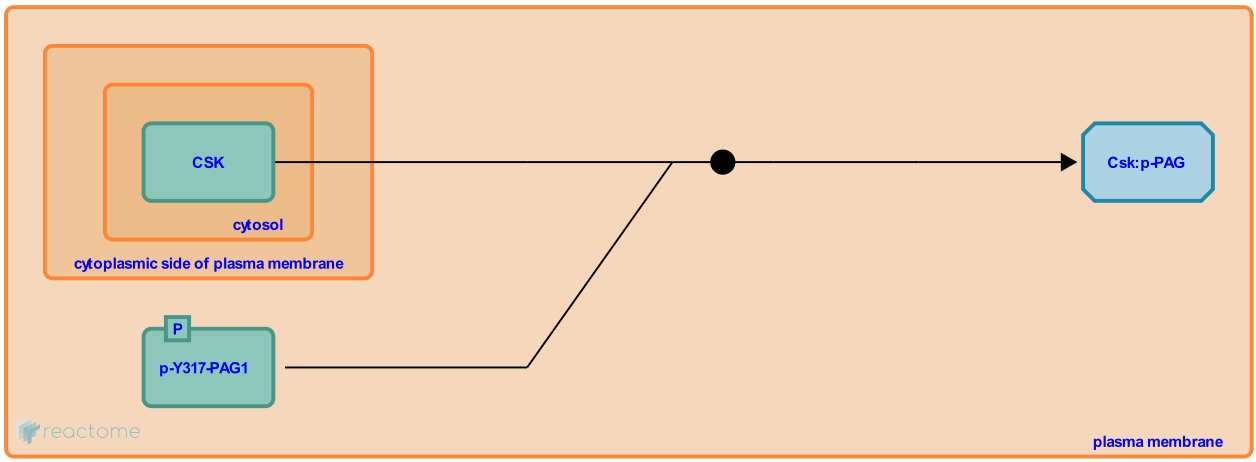
Interaction of Csk with PAG ↗

Location: Phosphorylation of CD3 and TCR zeta chains

Stable identifier: R-HSA-203774

Type: binding

Compartments: plasma membrane, cytosol



Csk is a tyrosine kinase that phosphorylates the negative regulatory C-terminal tyrosine residue Y505 of Lck to maintain Lck in an inactive state. In resting T cells, Csk is targeted to lipid rafts through engagement of its SH2 domain with phosphotyrosine residue pY317 of PAG. PAG is expressed as a tyrosine phosphorylated protein in nonstimulated T-cells. This interaction of Csk and PAG allows activation of Csk and inhibition of Lck. Given that PAG-1 T cell knock out show a weak phenotype, some other protein may substitute in activating Csk.

Followed by: Inactivation of Lck by Csk

Literature references

Tuosto, L., Marinari, B., Piccolella, E., Simeoni, L., Schraven, B. (2003). The activation of Csk by CD4 interferes with TCR-mediated activatory signaling. *Eur J Immunol, 33*, 2609-18. ↗

Shevchenko, A., Korinek, V., Bruyns, E., Scherer, J., Hilgert, I., Brdicka, T. et al. (2000). Phosphoprotein associated with glycosphingolipid-enriched microdomains (PAG), a novel ubiquitously expressed transmembrane adaptor protein, binds the protein tyrosine kinase csk and is involved in regulation of T cell activation. *J Exp Med, 191*, 1591-604. ↗

Editions

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

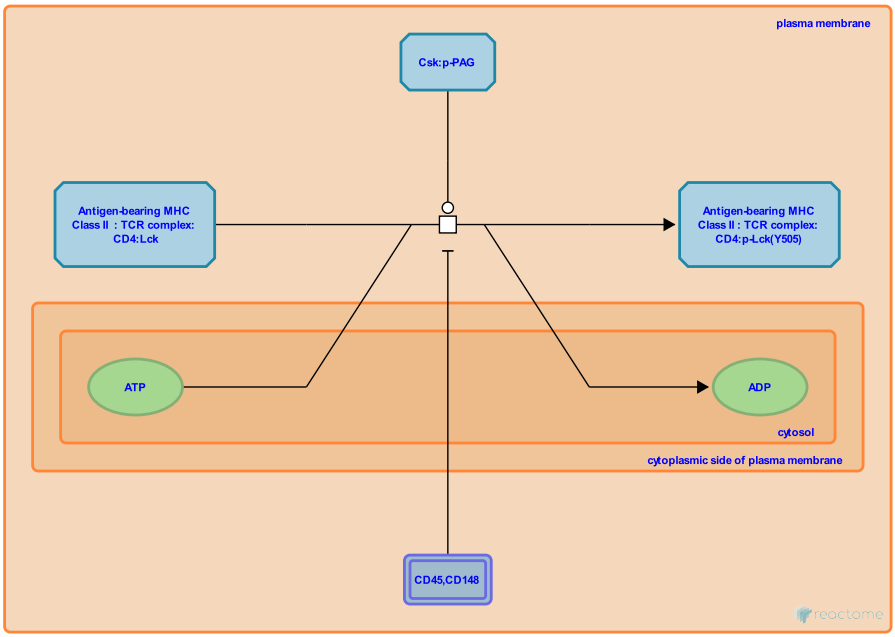
Inactivation of Lck by Csk ↗

Location: Phosphorylation of CD3 and TCR zeta chains

Stable identifier: R-HSA-202233

Type: transition

Compartments: plasma membrane, cytosol



Protein tyrosine phosphatase CD45 (PTPRC) and CD148 (PTPRJ) have dual function in TCR signaling. They act both in activation as well as inactivation of Src family kinases (SFKs) which are involved in the initiation of TCR signal transduction (Stepanek et al. 2011). The activator role is to dephosphorylate an inhibitory site tyrosine 505 (Y505) at the C-terminal end of Lck, which is needed to enable Lck to an open conformation and expose the activation loop (A-loop) containing the activating tyrosine 394 (Y394) (Xu et al. 1993. McNeill et al. 2007, Zikherman et al. 2010, Stepanek et al. 2011, Salmond et al. 2009).
Lck is a member of the Src family tyrosine kinases and these members have the following domains in common: N-terminal Myristoylation site for saturated fatty acid addition, a unique region, a Src-homology 3 (SH3) domain, an SH2 domain, a tyrosine kinase domain (SH1), and a C-terminal negative regulatory domain. Myristoylation engenders Lck with the ability to attach to cellular membranes. This interaction is mediated by both myristic acid and palmitic acid that are bound to the amino terminal glycine and Cys-3 and/or Cys-5.

The unique region of Lck is thought to be involved in the interaction with the cytoplasmic tails of coreceptors CD4 and CD8. The Lck/CD4 interaction require conserved cysteine motifs: a CxCP motif in CD4 and a CxxC motif in the Lck unique domain. The SH3 and SH2 domains of Lck are involved in intramolecular and intermolecular regulation by mediating protein-protein interactions via poly-proline and phosphotyrosine-specific interactions, respectively.

Lck adopts specific conformation that largely dictate its level of activity. The C-ter tail has an autoinhibitory phosphorylation site (tyr 505). When the Y505 is phosphorylated, Lck adopts a closed conformation, where the pY505 residue creates an intramolecular binding motif for the SH2 domain, effectively inactivating the kinase domain. The inactivating phosphorylation on Y505 is carried out by the Src-specific kinase Csk.

Preceded by: Interaction of Csk with PAG

Followed by: Dephosphorylation of Lck-pY505 by CD45

Literature references

Palacios, EH., Weiss, A. (2004). Function of the Src-family kinases, Lck and Fyn, in T-cell development and activation . *Oncogene, 23*, 7990-8000. ↗

Boggon, TJ., Eck, MJ. (2004). Structure and regulation of Src family kinases. *Oncogene, 23*, 7918-27. ↗

Editions

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

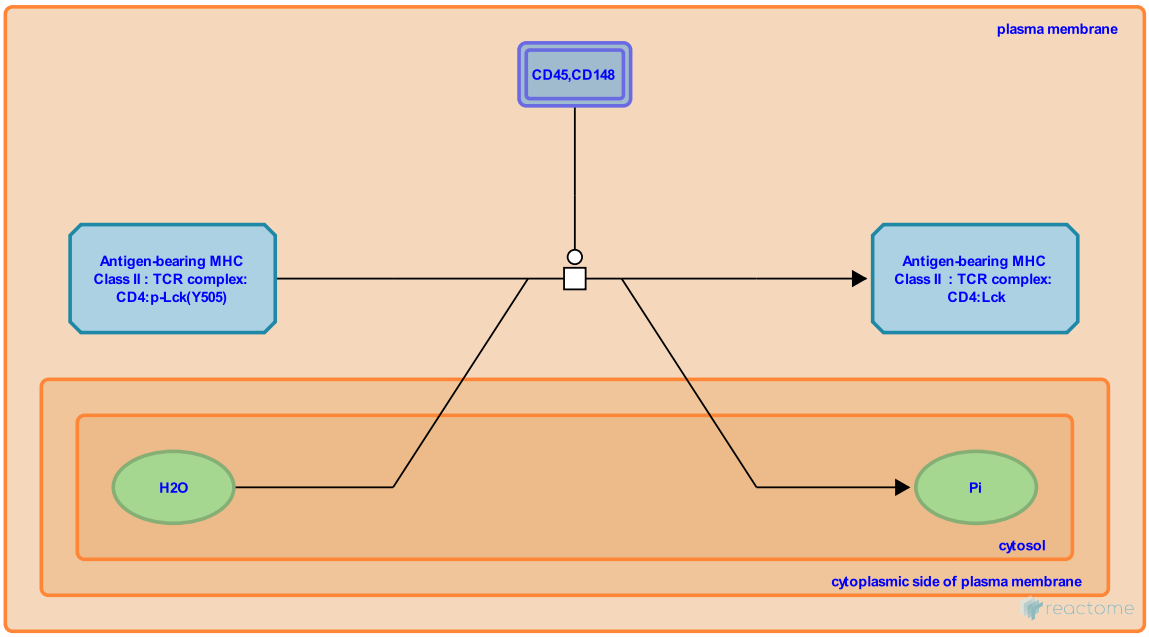
Dephosphorylation of Lck-pY505 by CD45 ↗

Location: Phosphorylation of CD3 and TCR zeta chains

Stable identifier: R-HSA-202214

Type: transition

Compartments: plasma membrane, cytosol



TCR stimulation induce the transient dephosphorylation of PAG thereby release the Csk from its plasma membrane anchor. The release of Csk from its proximity with Lck may serve to facilitate the activation of Lck.Protein tyrosine phosphtase CD45 (PTPRC) and CD148 (PTPRJ) have dual function in TCR signalling. They act both in activation as well as inactivation of Src family kinases (SFKs) which are involved in the initiation of TCR signal transduction (Stepanek et al. 2011). The activatory role is to dephosphorylate an inhibitory site tyrosine 505 (Y505) at the C-terminal end of Lck, which is needed to enable Lck to an open conformation and expose the activation loop (A-loop) containing the activating tyrosine 394 (Y394) (Xu et al. 1993. McNeill et al. 2007, Zikherman et al. 2010, Stepanek et al. 2011, Salmond et al. 2009).

Preceded by: Inactivation of Lck by Csk

Followed by: Activation of Lck

Literature references

Watson, S., Weiss, A., Goodnow, CC., Zikherman, J., Raschke, W., Jenne, C. et al. (2010). CD45-Csk phosphatase-kinase titration uncouples basal and inducible T cell receptor signaling during thymic development. *Immunity, 32*, 342-54. ↗

Draber, P., Stepanek, O., Brdicka, T., Weiss, A., Angelisová, P., Horejsí, V. et al. (2011). Regulation of Src family kinases involved in T cell receptor signaling by protein-tyrosine phosphatase CD148. *J. Biol. Chem., 286*, 22101-12. ↗

Horejsi, V., Wienands, J., Leo, A., Baier, G., Schraven, B. (2002). Adapters in lymphocyte signaling. *J Clin Invest, 109*, 301-9. ↗

Hurley, TR., Sefton, BM., Trowbridge, IS., Johnson, P., Ostergaard, HL., Hyman, R. et al. (1989). Expression of CD45 alters phosphorylation of the lck-encoded tyrosine protein kinase in murine lymphoma T-cell lines. *Proc. Natl. Acad. Sci. U.S.A., 86*, 8959-63. ↗

Bridge, M., van der Merwe, PA., Choudhuri, K., Basat, AB., Cordoba, SP., Zhang, H. et al. (2013). The large ectodomains of CD45 and CD148 regulate their segregation from and inhibition of ligated T-cell receptor. *Blood, 121*, 4295-302. ↗

Editions

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

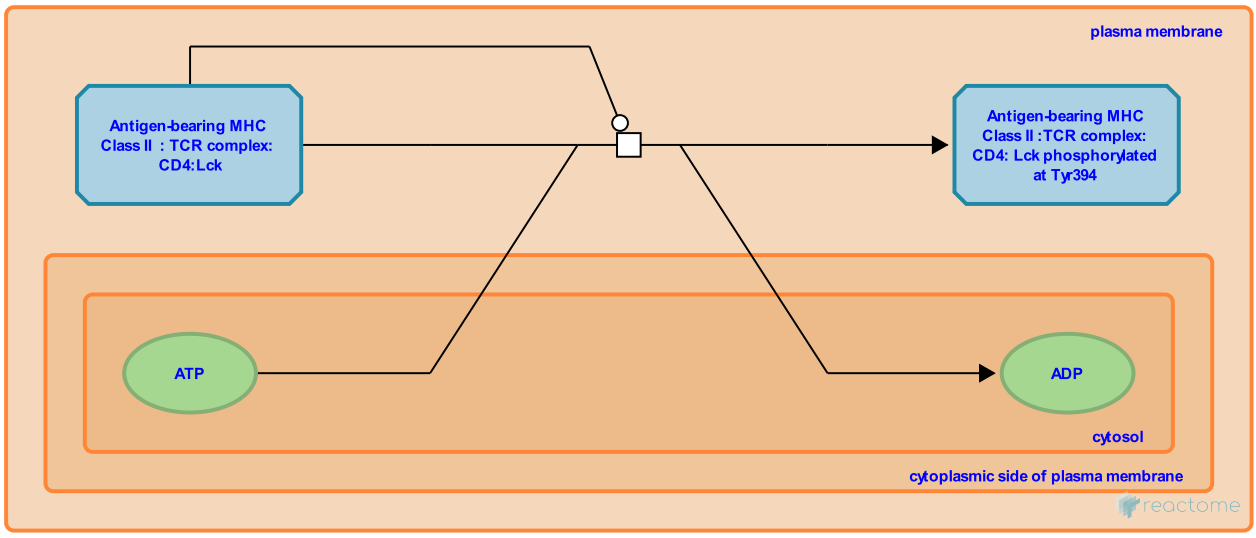
Activation of Lck ↗

Location: Phosphorylation of CD3 and TCR zeta chains

Stable identifier: R-HSA-202291

Type: transition

Compartments: plasma membrane, cytosol



The binding of CD4/CD8 to non-polymorphic regions of MHC brings Lck in to proximity with TCR subunits phosphorylation. Lck is further phosphorylated to promote the active conformation and to increase their catalytic activity. The C-term domain contain a regulatory activation loop, which is the site of activating Tyr 394 phosphorylation. This tyrosine is auto-phosphorylated to attain an active conformation on TCR stimulation. Now Lck through its kinase activity phosphorylates the ITAMs in TCR zeta and CD3 members.

Preceded by: Dephosphorylation of Lck-pY505 by CD45

Followed by: Inactivation of LCK by PTPN22, Phosphorylation of ITAM motifs in CD3 complexes

Literature references

Palacios, EH., Weiss, A. (2004). Function of the Src-family kinases, Lck and Fyn, in T-cell development and activation . *Oncogene, 23*, 7990-8000. ↗

Editions

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

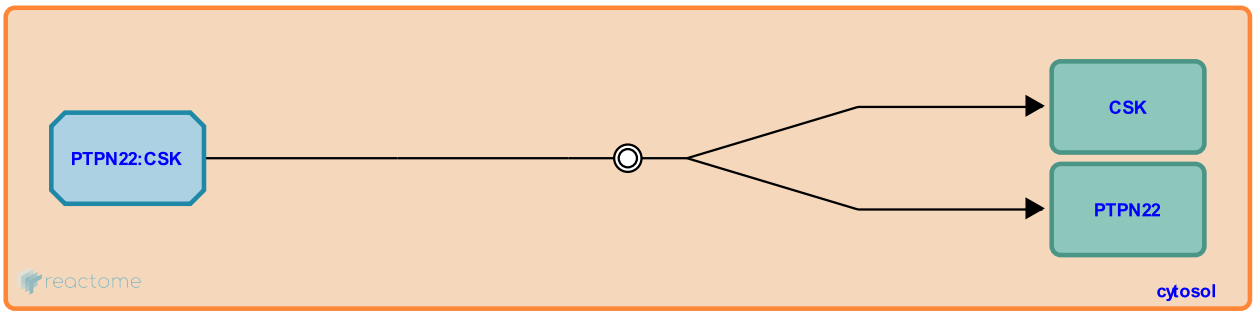
PTPN22 dissociates from CSK ↗

Location: Phosphorylation of CD3 and TCR zeta chains

Stable identifier: R-HSA-8855375

Type: dissociation

Compartments: cytosol



In unstimulated T-lymphocytes, protein tyrosine phosphatase PTPN22 (LYP, PEP) is associated with CSK, which inhibits the catalytic activity of PTPN22. In response to TCR-stimulation, the complex of CSK and PTPN22 dissociates through an unknown mechanism, which allows PTPN22 to be recruited to lipid rafts. The PTPN22 variant PTPN22 R620W, the result of a SNP associated with autoimmune diseases, does not bind to CSK and is constitutively active (Vang et al. 2012).

Followed by: Inactivation of LCK by PTPN22

Literature references

Liu, WH., Mustelin, T., Tautz, L., Tremblay, ML., Page, R., Tasken, K. et al. (2012). LYP inhibits T-cell activation when dissociated from CSK. *Nat. Chem. Biol., 8*, 437-46. ↗

Editions

2016-02-03	Authored, Edited	Orlic-Milacic, M.
2016-05-10	Reviewed	Stanford, S., Bottini, N.

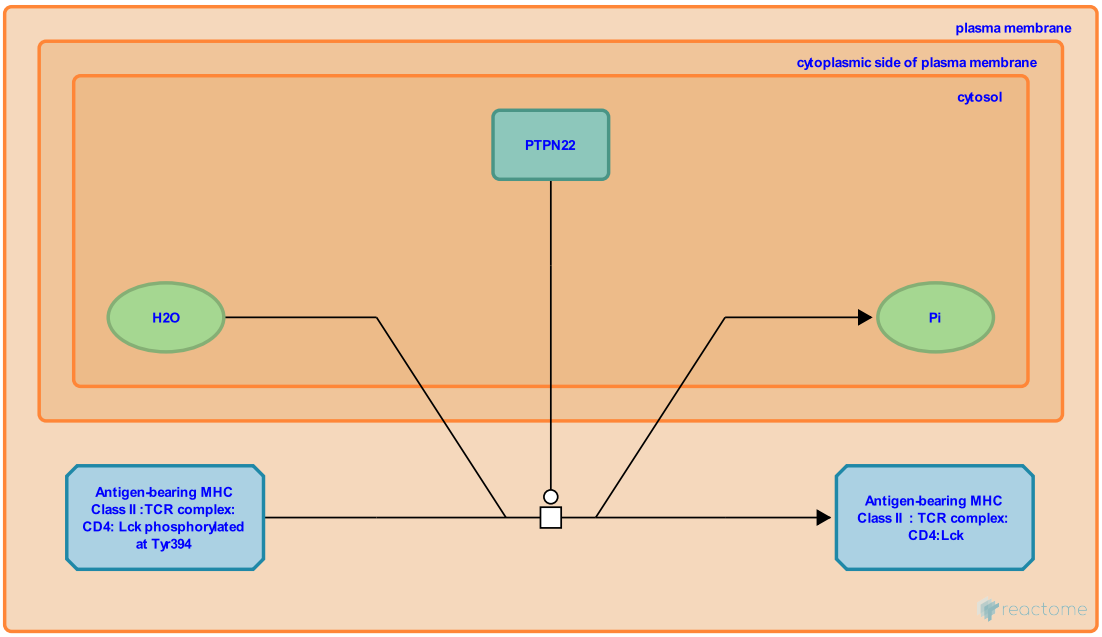
Inactivation of LCK by PTPN22 ↗

Location: Phosphorylation of CD3 and TCR zeta chains

Stable identifier: R-HSA-8852200

Type: transition

Compartments: plasma membrane, cytosol



Protein tyrosine phosphatase PTPN22 (LYP, PEP) (Cohen et al. 1999) dephosphorylates tyrosine residue Y394 of LCK, thus inactivating LCK and down-regulating TCR signaling (Wu et al. 2006, Vang et al. 2012).

Preceded by: PTPN22 dissociates from CSK, Activation of Lck

Literature references

Liu, WH., Mustelin, T., Tautz, L., Tremblay, ML., Page, R., Tasken, K. et al. (2012). LYP inhibits T-cell activation when dissociated from CSK. *Nat. Chem. Biol., 8*, 437-46. ↗

Sampang, J., Honigberg, LA., Smith, AM., Clark, JM., Jeffery, D., Buggy, J. et al. (2006). Identification of substrates of human protein-tyrosine phosphatase PTPN22. *J. Biol. Chem., 281*, 11002-10. ↗

Editions

2016-02-03	Authored, Edited	Orlic-Milacic, M.
2016-05-10	Reviewed	Stanford, S., Bottini, N.

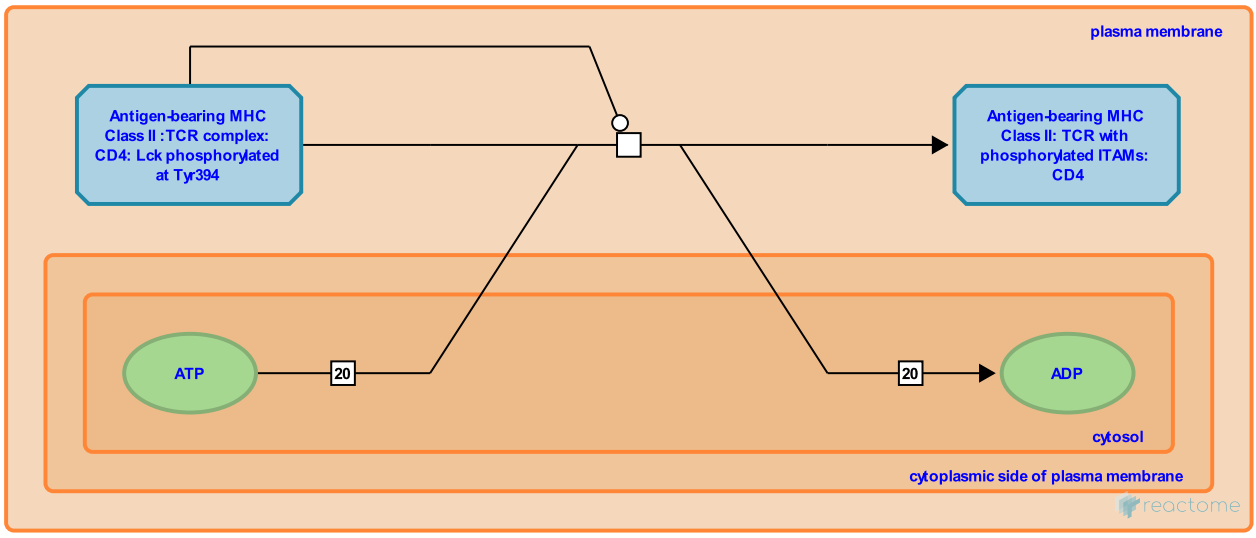
Phosphorylation of ITAM motifs in CD3 complexes ↗

Location: Phosphorylation of CD3 and TCR zeta chains

Stable identifier: R-HSA-202165

Type: transition

Compartments: plasma membrane, cytosol



The autophosphorylated, active Lck is now proximally positioned to phosphorylate specific tyrosine residues within ITAMs (immunoreceptor tyrosine-based activation motifs) located within the CD3 and the TCR zeta signaling chains of the TCR. ITAMs consist of evolutionarily conserved amino-acid sequence motifs of D/ExYxxLx(6-8)YxxL. Both the tyrosine residues in the motif are phosphorylated by Lck and the TCR complex include 10 ITAMs with one ITAM in each of the CD3 chains including the three tandem ITAMs in each zeta chains.

Preceded by: Activation of Lck

Literature references

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

Downey, JS., Rudd, CE., Wilkinson, B. (2005). T-cell signalling and immune system disorders. *Expert Rev Mol Med, 7*, 1-29. ↗

Editions

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

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