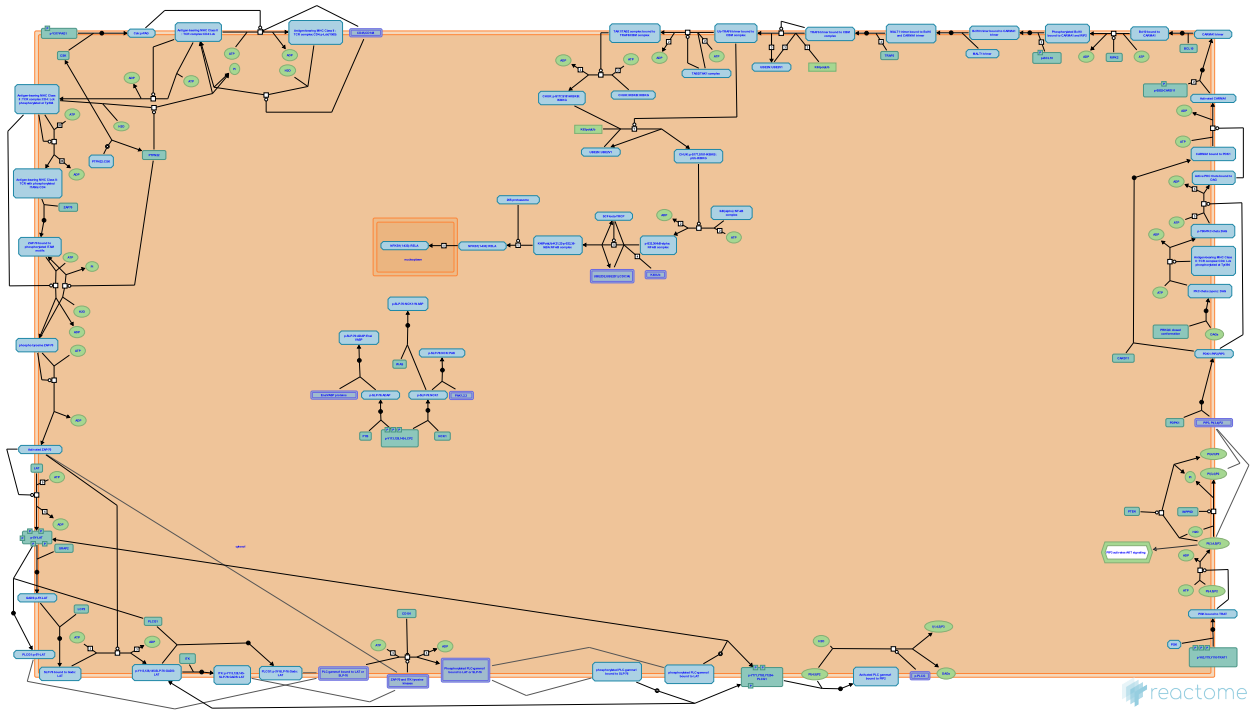
TCR signaling



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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.

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. ↗

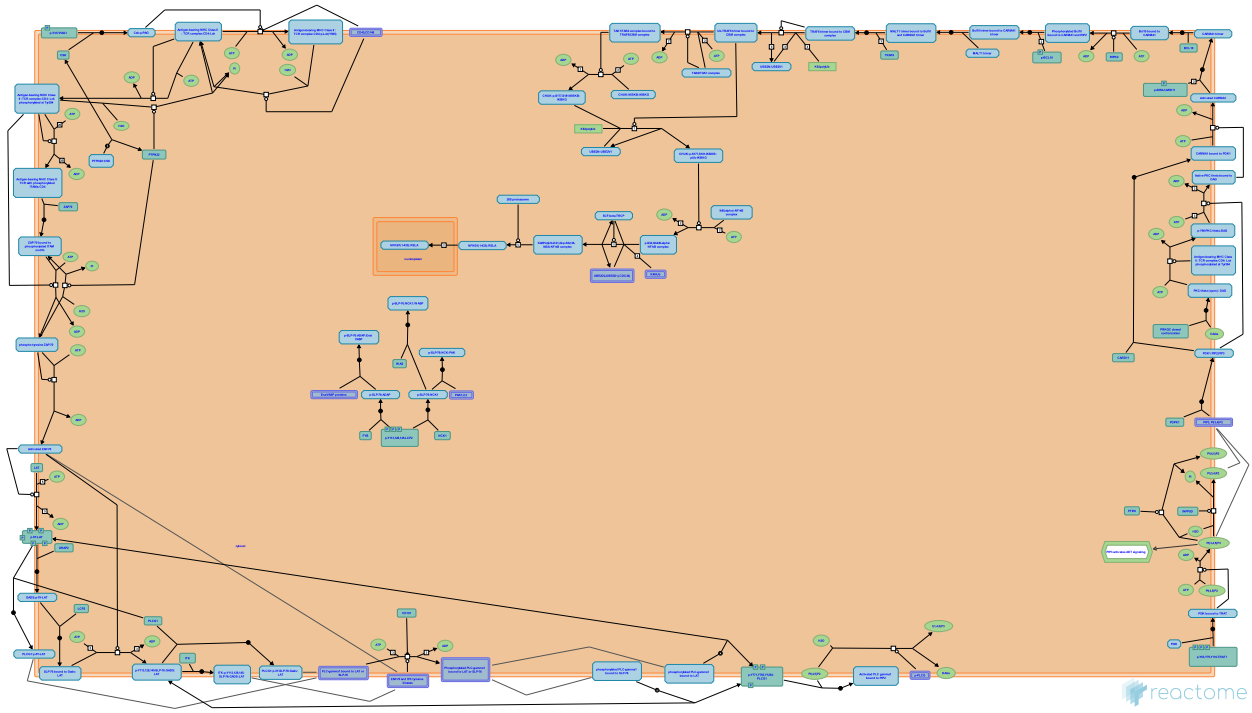
Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Reactome database release: 88

This document contains 5 pathways (see Table of Contents)

TCR signaling ↗

Stable identifier: R-HSA-202403



The TCR is a multisubunit complex that consists of clonotypic alpha/beta chains noncovalently associated with the invariant CD3 delta/epsilon/gamma and TCR zeta chains. T cell activation by antigen presenting cells (APCs) results in the activation of protein tyrosine kinases (PTKs) that associate with CD3 and TCR zeta subunits and the co-receptor CD4. Members of the Src kinases (Lck), Syk kinases (ZAP-70), Tec (Itk) and Csk families of nonreceptor PTKs play a crucial role in T cell activation. Activation of PTKs following TCR engagement results in the recruitment and tyrosine phosphorylation of enzymes such as phospholipase C gamma1 and Vav as well as critical adaptor proteins such as LAT, SLP-76 and Gads. These proximal activation leads to reorganization of the cytoskeleton as well as transcription activation of multiple genes leading to T lymphocyte proliferation, differentiation and/or effector function.

Literature references

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

Schneider, H., Rudd, CE. (2003). Unifying concepts in CD28, ICOS and CTLA4 co-receptor signalling. *Nat Rev Immunol, 3*, 544-56. ↗

Rudd, CE. (1999). Adaptors and molecular scaffolds in immune cell signaling. *Cell, 96*, 5-8. ↗

Editions

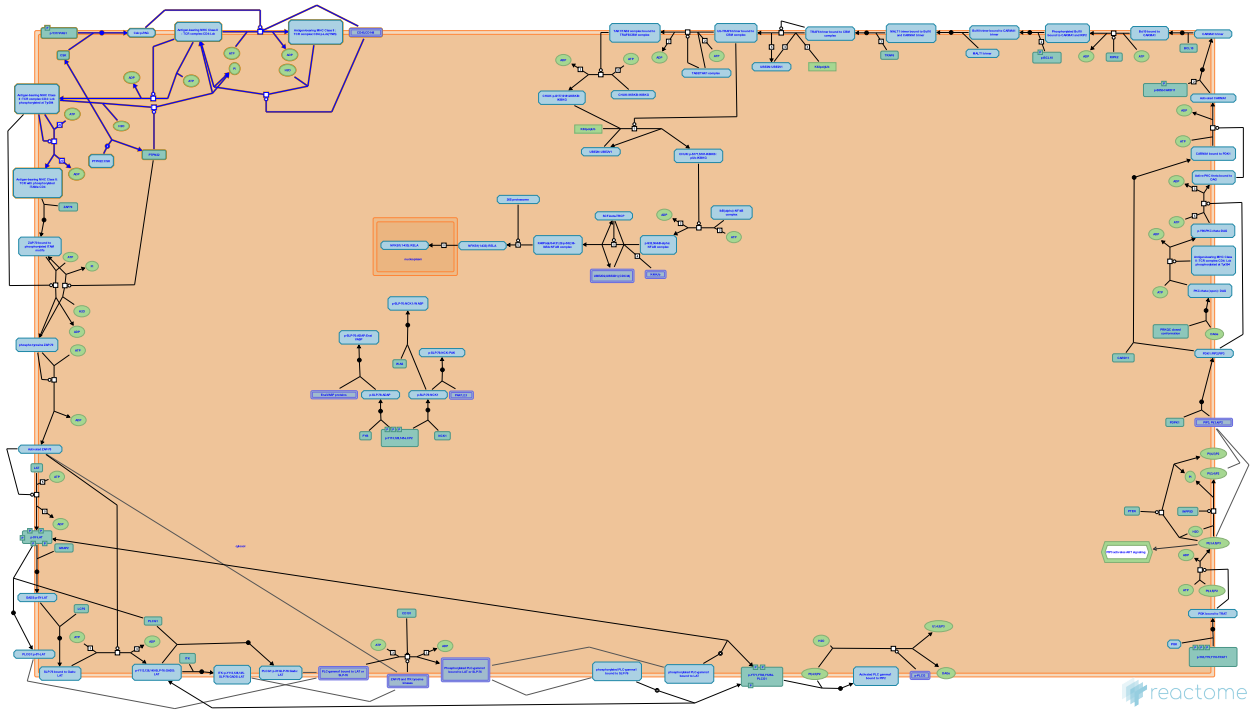
2008-01-24	Authored	de Bono, B., Garapati, P V., Rudd, C.E..
2008-02-26	Reviewed	Trowsdale, J.

Phosphorylation of CD3 and TCR zeta chains ↗

Location: TCR signaling

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

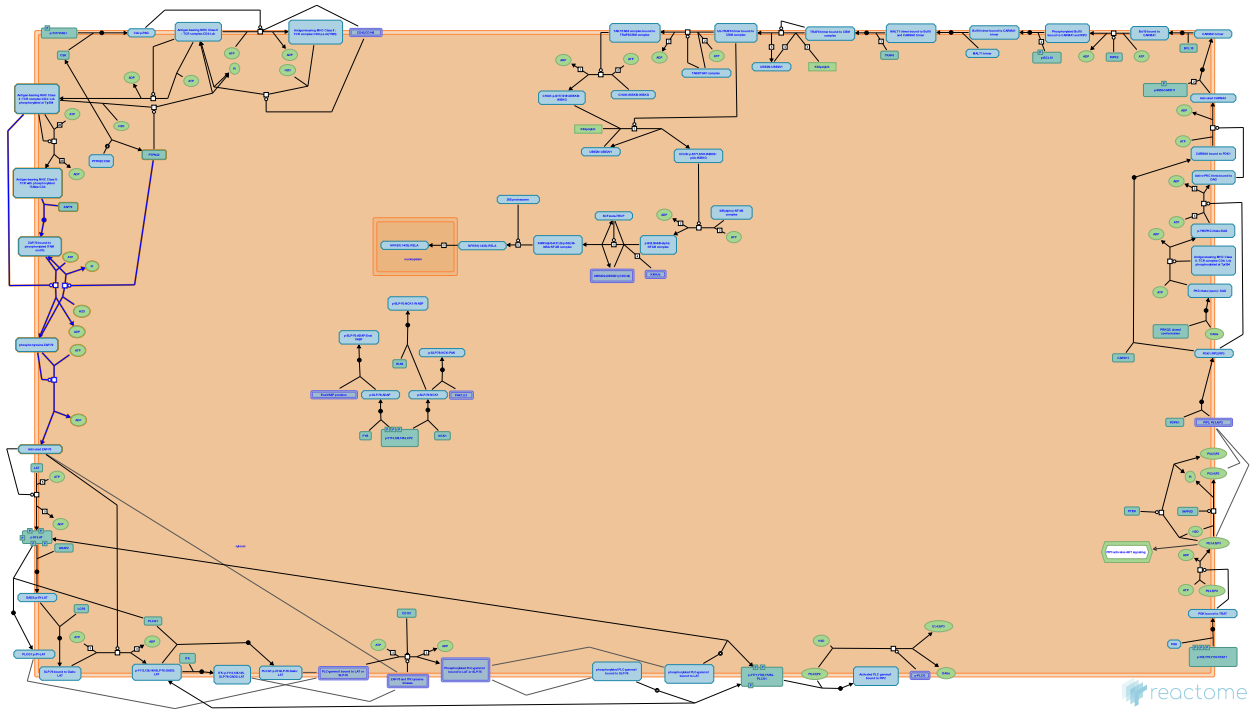
2008-01-24	Authored	de Bono, B., Garapati, P V., Rudd, C.E..
2008-02-26	Reviewed	Trowsdale, J.
2016-05-10	Revised	Stanford, S., Bottini, N.

Translocation of ZAP-70 to Immunological synapse ↗

Location: TCR signaling

Stable identifier: R-HSA-202430

Compartments: plasma membrane



The dual phosphorylated ITAMs recruit SYK kinase ZAP70 via their tandem SH2 domains (step 8). ZAP70 subsequently undergoes phosphorylation on multiple tyrosine residues for further activation. ZAP70 includes both positive and negative regulatory sites. Tyrosine 493 is a conserved regulatory site found within the activation loop of the kinase domain. This site has shown to be a positive regulatory site required for ZAP70 kinase activity and is phosphorylated by LCK (step 9). This phosphorylation contributes to the active conformation of the catalytic domain. Later ZAP70 undergoes trans-autophosphorylation at Y315 and Y319 (step 10). These sites appear to be positive regulatory sites. ZAP70 achieves its full activation after the trans-autophosphorylation. Activated ZAP70 along with LCK phosphorylates the multiple tyrosine residues in the adaptor protein LAT (step 11). PTPN22 can dephosphorylate and inhibit ZAP70 activity to downregulate TCR signaling (step 12).

Literature references

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

Editions

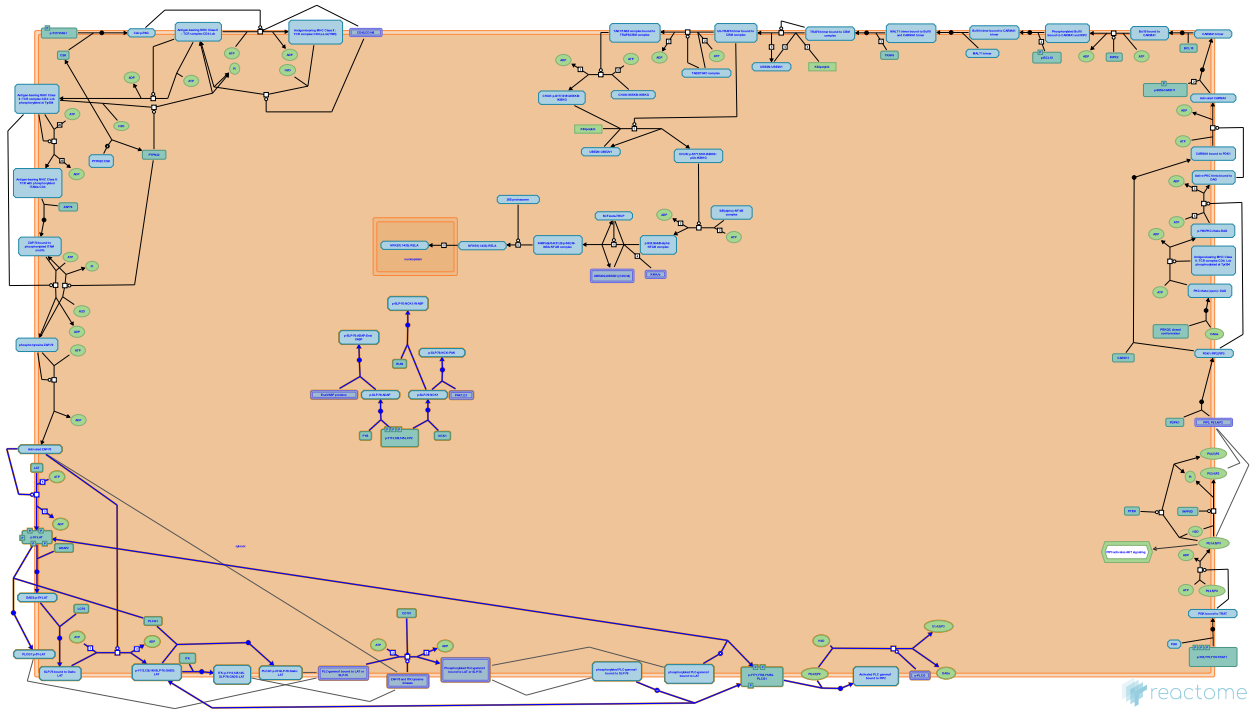
2008-01-24	Authored	de Bono, B., Garapati, P V., Rudd, C.E..
2008-02-26	Reviewed	Trowsdale, J.
2016-05-10	Revised	Stanford, S., Bottini, N.

Generation of second messenger molecules ↗

Location: TCR signaling

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. ↗

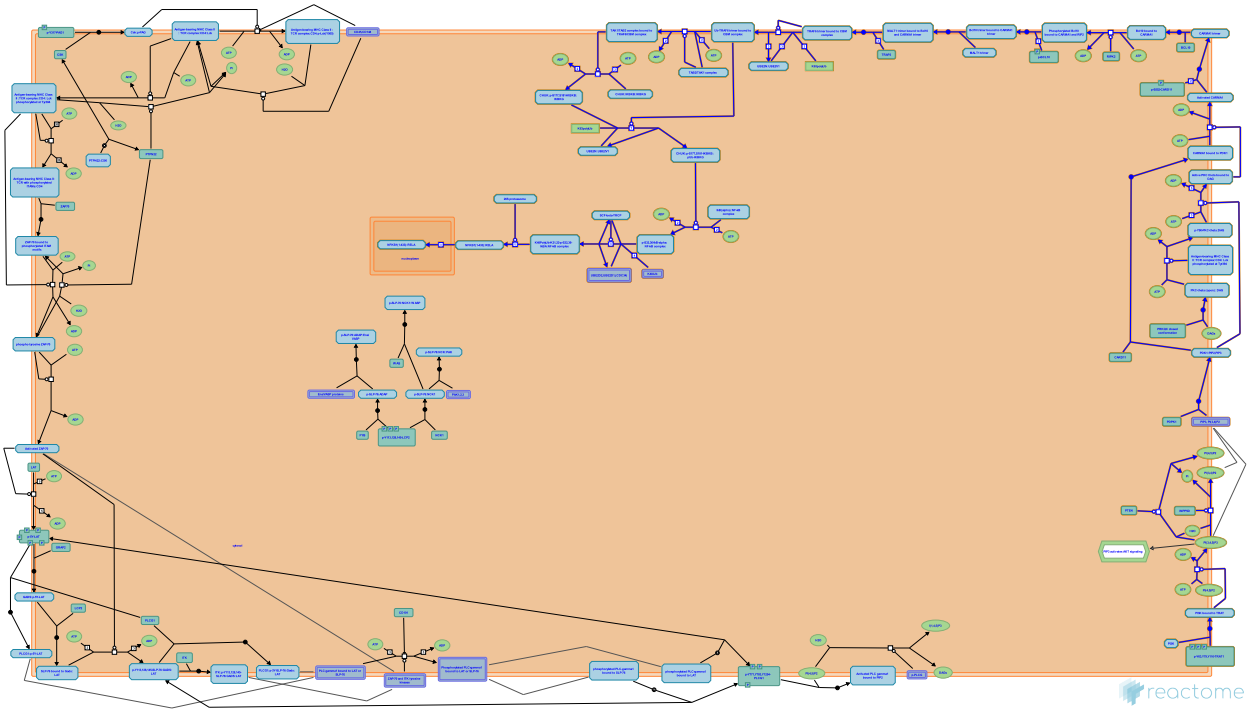
Editions

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

Downstream TCR signaling ↗

Location: TCR signaling

Stable identifier: R-HSA-202424



Changes in gene expression are required for the T cell to gain full proliferative competence and to produce effector cytokines. Three transcription factors in particular have been found to play a key role in TCR-stimulated changes in gene expression, namely NFkappaB, NFAT and AP-1. A key step in NFkappaB activation is the stimulation and translocation of PRKCQ. The critical element that effects PRKCQ activation is PI3K. PI3K translocates to the plasma membrane by interacting with phospho-tyrosines on CD28 via its two SH2 domains located in p85 subunit (step 24). The p110 subunit of PI3K phosphorylates the inositol ring of PIP2 to generate PIP3 (steps 25). The reverse dephosphorylation process from PIP3 to PIP2 is catalysed by PTEN (step 27). PIP3 may also be dephosphorylated by the phosphatase SHIP to generate PI-3,4-P2 (step 26). PIP3 and PI-3,4-P2 acts as binding sites to the PH domain of PDK1 (step 28) and AKT (step 29). PKB is activated in response to PI3K stimulation by PDK1 (step 30). PDK1 has an essential role in regulating the activation of PRKCQ and recruitment of CBM complex to the immune synapse. PRKCQ is a member of novel class (DAG dependent, Ca++ independent) of PKC and the only member known to translocate to this synapse. Prior to TCR stimulation PRKCQ exists in an inactive closed conformation. TCR signals stimulate PRKCQ (step 31) and release DAG molecules. Subsequently, DAG binds to PRKCQ via the C1 domain and undergoes phosphorylation on tyrosine 90 by LCK to attain an open conformation (step 32). PRKCQ is further phosphorylated by PDK1 on threonine 538 (step 33). This step is critical for PKC activity. CARMA1 translocates to the plasma membrane following the interaction of its SH3 domain with the 'PxxP' motif on PDK1 (step 34). CARMA1 is phosphorylated by PKC-theta on residue S552 (step 35), leading to the oligomerization of CARMA1. This complex acts as a scaffold, recruiting BCL10 to the synapse by interacting with their CARD domains (step 36). BCL10 undergoes phosphorylation mediated by the enzyme RIP2 (step 37). Activated BCL10 then mediates the ubiquitination of IKBKG by recruiting MALT1 and TRAF6. MALT1 binds to BCL10 with its Ig-like domains and undergoes oligomerization (step 38). TRAF6 binds to the oligomerized MALT1 and also undergoes oligomerization (step 39). Oligomerized TRAF6 acts as a ubiquitin-protein ligase, catalyzing auto-K63-linked polyubiquitination (step 40). This K-63 ubiquitinated TRAF6 activates MAP3K7 kinase bound to TAB2 (step 41) and also ubiquitinates IKBKG in the IKK complex (step 44). MAP3K7 undergoes autophosphorylation on residues T184 and T187 and gets activated (step 42). Activated MAP3K7 kinase phosphorylates IKBKB on residues S177 and S181 in the activation loop and activates the IKK kinase activity (step 43). IKBKB phosphorylates the NFKBIA bound to the NFkappaB heterodimer, on residues S19 and S23 (step 45) and directs NFKBIA to 26S proteasome degradation (step 47). The NFkappaB heterodimer with a free NTS sequence finally migrates to the nucleus to regulate gene transcription (step 46).

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..
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