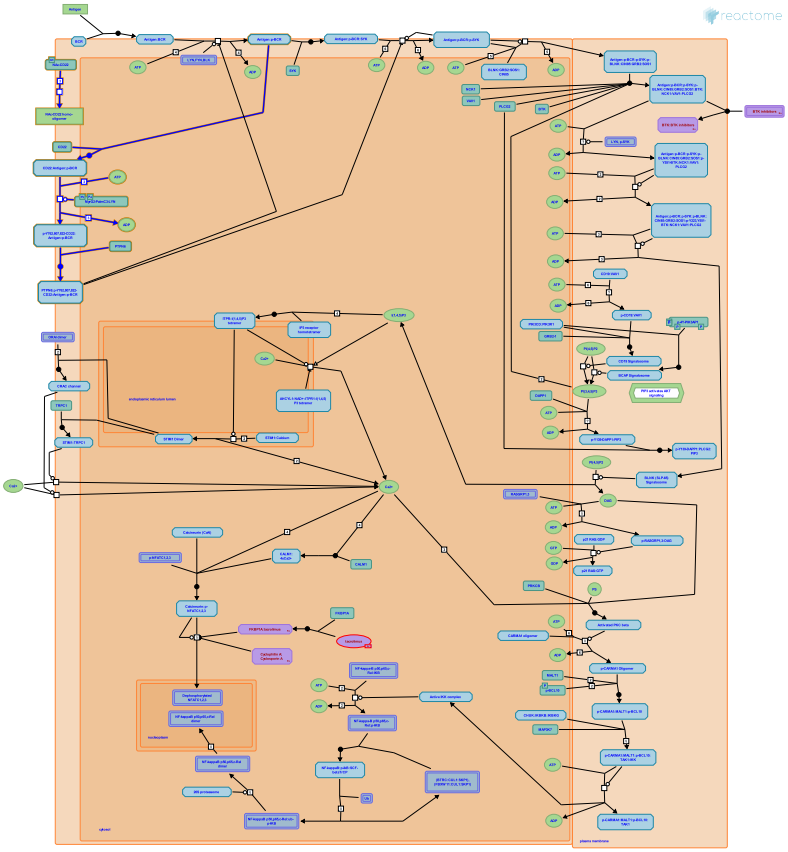
CD22 mediated BCR regulation



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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. ↗

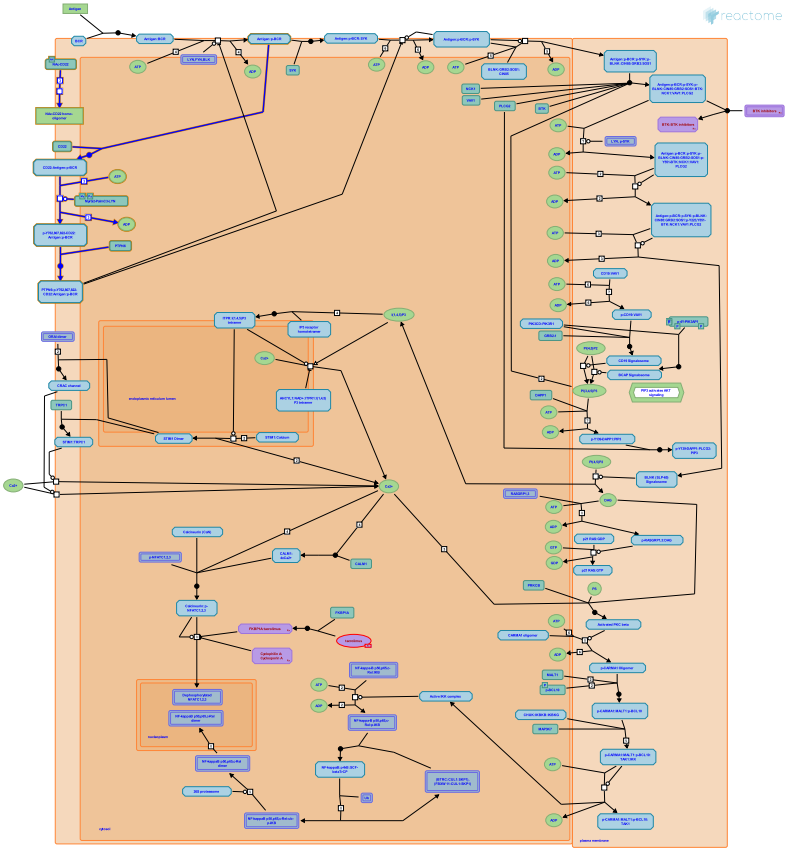
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

CD22 mediated BCR regulation ↗

Stable identifier: R-HSA-5690714



BCR activation is highly regulated and coreceptors like CD22 (SIGLEC2) set a signalling threshold to prevent aberrant immune response and autoimmune disease (Cyster et al. 1997, Han et al. 2005). CD22 is a glycoprotein found on the surface of B cells during restricted stages of development. CD22 is a member of the receptors of the sialic acid-binding Ig-like lectin (Siglec) family which binds specifically to the terminal sequence N-acetylneuraminic acid alpha(2-6) galactose (NeuAc-alpha(2-6)-Gal) present on many B-cell glycoproteins (Powell et al. 1993, Sgroi et al. 1993). CD22 has seven immunoglobulin (Ig)-like extracellular domains and a cytoplasmic tail containing six tyrosines, three of which belong to the inhibitory immunoreceptor tyrosine-based inhibition motifs (ITIMs) sequences. Upon BCR cross-linking CD22 is rapidly tyrosine phosphorylated by the tyrosine kinase Lyn, thereby recruiting and activating tyrosine phosphatase, SHP-1 and inhibiting calcium signalling.

Literature references

Tedder, TF., Haas, KM., Fujimoto, M., Miller, AS., Poe, JC., Sanford, IG. et al. (2004). CD22 regulates B lymphocyte function in vivo through both ligand-dependent and ligand-independent mechanisms. *Nat. Immunol., 5*, 1078-87. ↗

Jellusova, J., Nitschke, L. (2011). Regulation of B cell functions by the sialic acid-binding receptors siglec-G and CD22 . *Front Immunol, 2*, 96. ↗

Editions

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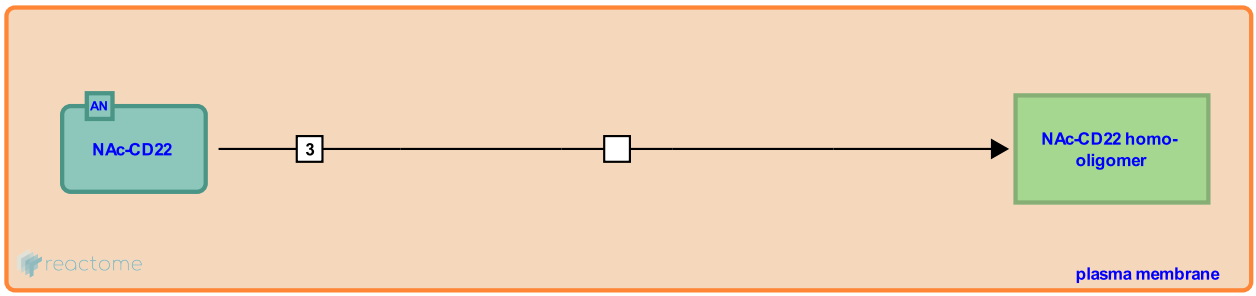
CD22 binds itself to form homo-oligomers ↗

Location: CD22 mediated BCR regulation

Stable identifier: R-HSA-5690669

Type: transition

Compartments: plasma membrane



In resting B cells, CD22 is a prominent cis ligand for itself, forming CD22 homo-oligomers. Cross-linking experiments showed that CD22 primarily recognizes alpha2,6-linked sialic acid (2,6Sia or N-acetylneuraminic acid (NAc)) on neighboring CD22 molecules present on the same B-cell (Han et al. 2005). NH2-terminal immuno globulin (Ig) domains, Ig1 and Ig2, mediate 2,6Sia binding (Law et al. 1998, Jin et al. 2002). Thus, CD22 recognizes self structures and triggers inhibitory signals, which may be relevant for suppression of autoimmune B-cell responses.

Literature references

Han, S., Collins, BE., Bengtson, P., Paulson, JC. (2005). Homomultimeric complexes of CD22 in B cells revealed by protein-glycan cross-linking. *Nat. Chem. Biol., 1*, 93-7. ↗

Editions

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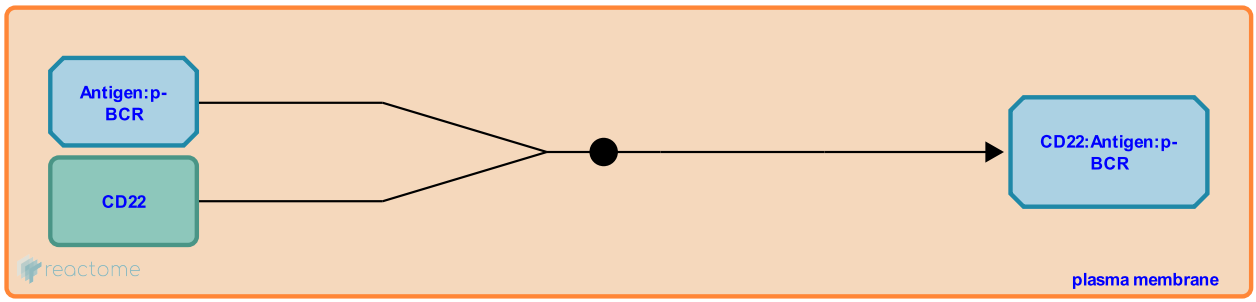
CD22 binds B-cell receptor ↗

Location: CD22 mediated BCR regulation

Stable identifier: R-HSA-5690740

Type: binding

Compartments: plasma membrane



Physical association of CD22 with the BCR seems to have direct involvement in the regulation of BCR signalling, as antibody-mediated clustering of CD22 with the BCR leads to dampened signaling (Smith et al. 1998), and evidence of their association has been obtained by confocal microscopy, coimmunoprecipitation and chemical crossing (Zhang et al. 2004, Phee et al. 2001, Peaker et al. 1993, Law et al. 1994, Leprince et al. 1993, Collins et al. 2006). Forced ligation of CD22 to the BCR dramatically increases CD22 phosphorylation and suppression of BCR signalling (Macauley, 2013). This is relevant to suppression of BCR signalling to membrane antigens on B cells that contain self sialic acids (Lanoue, 2002; Macauley 2013). CD22 ligand binding modulates its activity as a negative regulator of B cell signalling.

Followed by: LYN phosphorylates CD22

Literature references

Chandran, KA., Doty, RT., Clark, EA., Aruffo, A., Law, CL. (1995). Ig domains 1 and 2 of murine CD22 constitute the ligand-binding domain and bind multiple sialylated ligands expressed on B and T cells. *J. Immunol., 155*, 3368-76. ↗

Draves, KE., Clark, EA., Ledbetter, JA., Geahlen, RL., Leprince, C. (1993). CD22 associates with the human surface IgM-B-cell antigen receptor complex. *Proc. Natl. Acad. Sci. U.S.A., 90*, 3236-40. ↗

McLean, PA., Neel, BG., Wortis, HH., Jin, L. (2002). Sialic acid binding domains of CD22 are required for negative regulation of B cell receptor signaling. *J. Exp. Med., 195*, 1199-205. ↗

Varki, A., Hanasaki, K., Powell, LD. (1995). Binding of human plasma sialoglycoproteins by the B cell-specific lectin CD22. Selective recognition of immunoglobulin M and haptoglobin. *J. Biol. Chem., 270*, 7543-50. ↗

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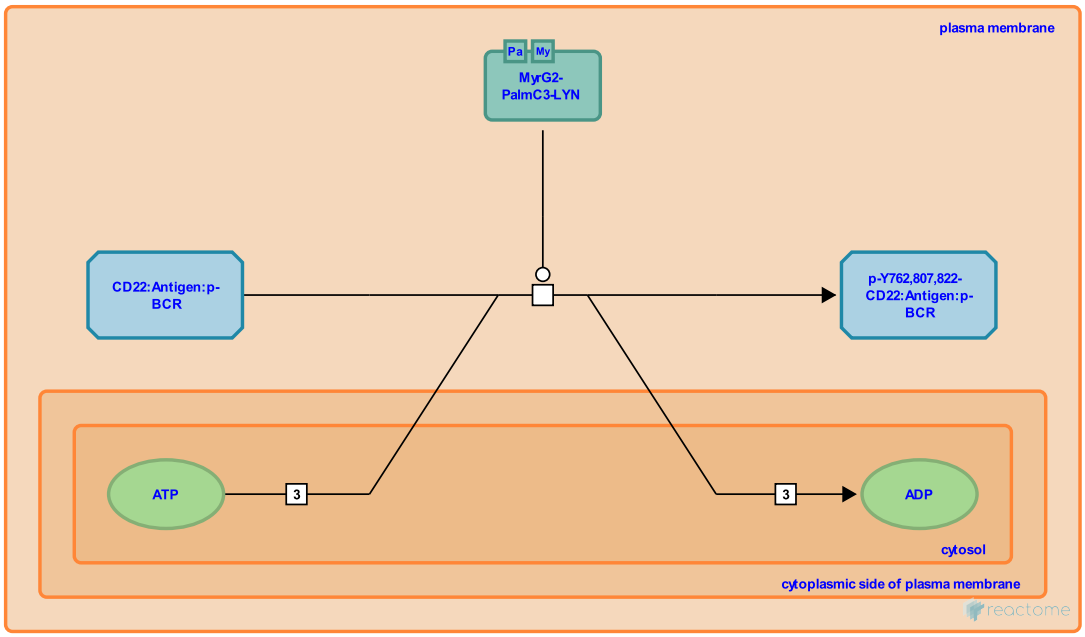
LYN phosphorylates CD22 ↗

Location: CD22 mediated BCR regulation

Stable identifier: R-HSA-5690702

Type: transition

Compartments: plasma membrane



After ligation of membrane-bound IgM, CD22 is quickly tyrosine phosphorylated on its cytoplasmic ITIM sequence (immunoreceptor tyrosine-based inhibition motif). The tyrosine kinase involved in CD22 phosphorylation is LYN, a member of the Src kinase family (Smith et al. 1998). The CD22 cytoplasmic tail contains six tyrosines, three of which belong to the ITIM sequence (Nitschke & Tsubata 2004).

Preceded by: CD22 binds B-cell receptor

Followed by: SHP1 binds p-CD22

Literature references

Yamamoto, T., Nishizumi, H., Mlinaric-Rascan, I., Horikawa, K. (1998). A double-edged kinase Lyn: a positive and negative regulator for antigen receptor-mediated signals. *J. Exp. Med., 187*, 1343-8. ↗

Chan, VW., DeFranco, AL., Lowell, CA. (1998). Defective negative regulation of antigen receptor signaling in Lyn-deficient B lymphocytes. *Curr. Biol., 8*, 545-53. ↗

Tarlinton, DM., Doody, GM., Hibbs, ML., Fearon, DT., Smith, KG. (1998). Inhibition of the B cell by CD22: a requirement for Lyn. *J. Exp. Med., 187*, 807-11. ↗

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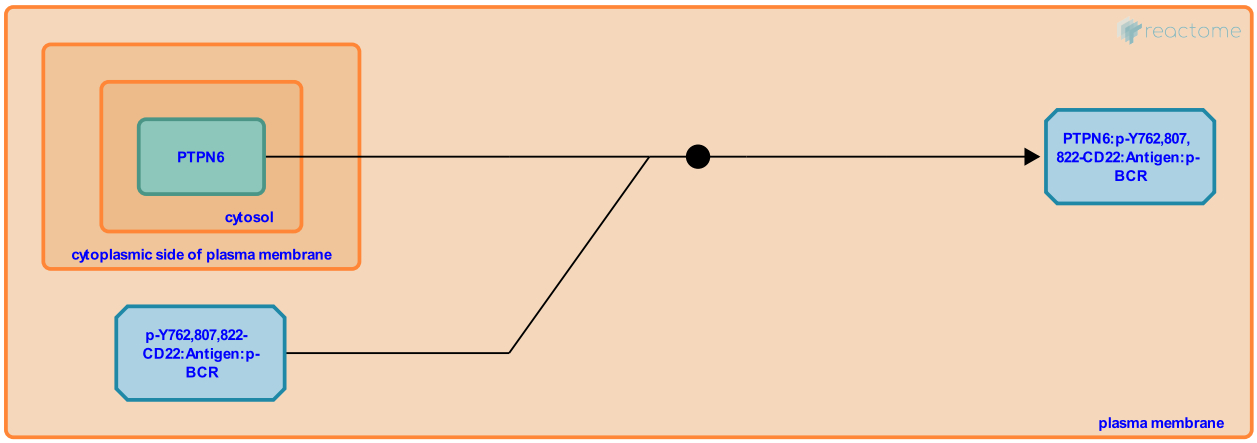
SHP1 binds p-CD22 ↗

Location: CD22 mediated BCR regulation

Stable identifier: R-HSA-5690701

Type: binding

Compartments: plasma membrane, cytosol



The phosphorylated ITIMs of CD22 facilitates recruitment of the tyrosine phosphatase SHP1 (Src homology region 2 domain-containing phosphatase-1 also referred as PTPN6/Tyrosine-protein phosphatase non-receptor type 6), which down modulates BCR signalling (Doody et al. 1995). Activation of SHP1 regulates the strength of the BCR-induced Ca+2 signal. Regulation of Ca+2 signalling occurs both by dephosphorylation of intracellular SHP1 substrates which are important for triggering of Ca+2 signals (Adachi et al. 2001, Stebbins et al. 2003), as well as by a SHP1 dependent activation of the Ca+2 plasma membrane pump PMCA4 which controls termination of the signal (Muller et al. 2013, Ghosh et al. 2006).

Preceded by: LYN phosphorylates CD22

Literature references

Thomas, ML., Doody, GM., Matthews, RJ., Justement, LB., Lin, J., Delibrias, CC. et al. (1995). A role in B cell activation for CD22 and the protein tyrosine phosphatase SHP. *Science, 269*, 242-4. ↗

Blasioli, J., Thomas, ML., Paust, S. (1999). Definition of the sites of interaction between the protein tyrosine phosphatase SHP-1 and CD22. *J. Biol. Chem., 274*, 2303-7. ↗

Angermüller, S., Brandl, C., Maity, PC., Müller, J., Obermeier, I., Nitschke, L. et al. (2013). CD22 ligand-binding and signaling domains reciprocally regulate B-cell Ca2+ signaling. *Proc. Natl. Acad. Sci. U.S.A., 110*, 12402-7. ↗

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