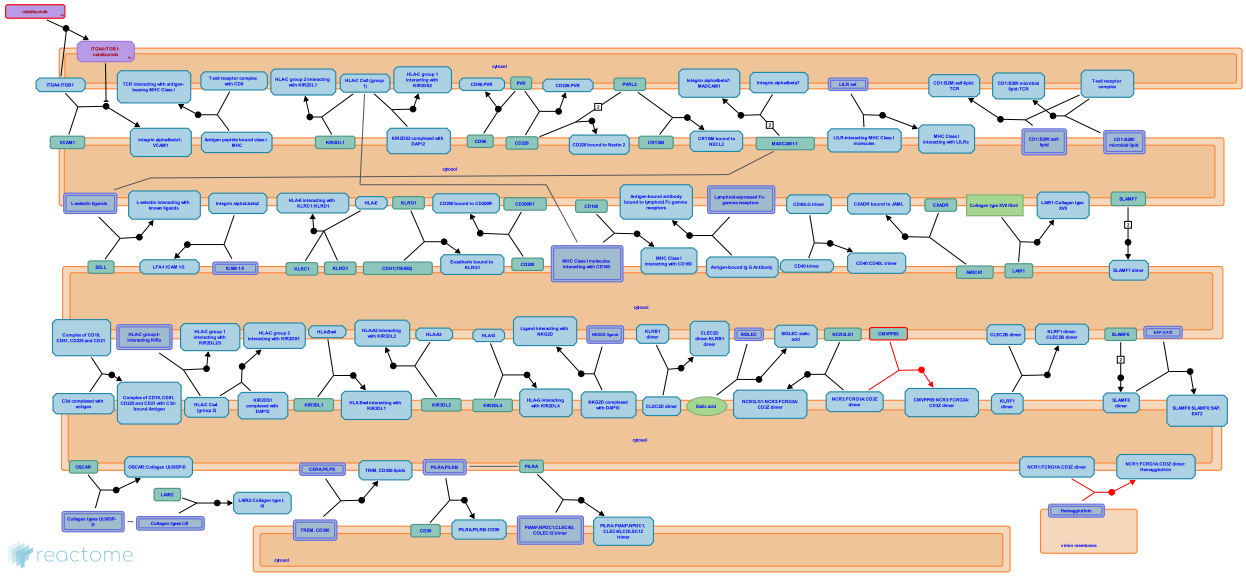
Immunoregulatory interactions between a Lymphoid and a non-Lymphoid cell



Adams, EJ., Barrow, AD., Garapati, P V., Jassal, B., Jupe, S., Luoma, AM., Ouwehand, WH., Shamovsky, V., Shoichet, BK., Trowsdale, J., Zajonc, DM., Zarrin, AA., Zwaginga, JJ., de Bono, B.

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

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. ↗

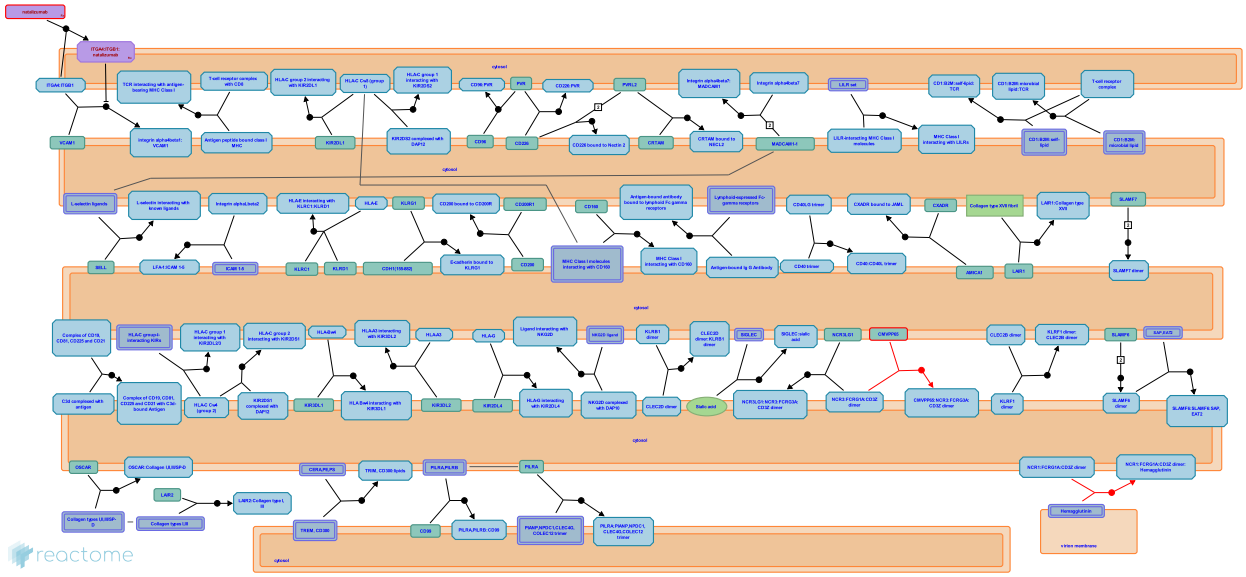
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

Immunoregulatory interactions between a Lymphoid and a non-Lymphoid cell ↗

Stable identifier: R-HSA-198933



A number of receptors and cell adhesion molecules play a key role in modifying the response of cells of lymphoid origin (such as B-, T- and NK cells) to self and tumor antigens, as well as to pathogenic organisms.

Molecules such as KIRs and LILRs form part of a crucial surveillance system that looks out for any derangement, usually caused by cancer or viral infection, in MHC Class I presentation. Somatic cells are also able to report internal functional impairment by displaying surface stress markers such as MICA. The presence of these molecules on somatic cells is picked up by C-lectin NK immune receptors.

Lymphoid cells are able to regulate their location and movement in accordance to their state of activation, and home in on tissues expressing the appropriate complementary ligands. For example, lymphoid cells may fine tune the presence and concentration of adhesion molecules belonging to the IgSF, Selectin and Integrin class that interact with a number of vascular markers of inflammation.

Furthermore, there are a number of avenues through which lymphoid cells may interact with antigen. This may be presented directly to a specific T-cell receptor in the context of an MHC molecule. Antigen-antibody complexes may anchor to the cell via a small number of lymphoid-specific Fc receptors that may, in turn, influence cell function further. Activated complement factor C3d binds to both antigen and to cell surface receptor CD21. In such cases, the far-reaching influence of CD19 on B-lymphocyte function is tempered by its interaction with CD21.

Literature references

Kelley, J., Trowsdale, J., Walter, L. (2005). Comparative genomics of natural killer cell receptor gene clusters. *PLoS Genet., 1*, 129-39. ↗

Tomasello, E., Walzer, T., Vivier, E., Baratin, M., Ugolini, S. (2008). Functions of natural killer cells. *Nat. Immunol., 9*, 503-10. ↗

Vivier, E., Harris, J., Trowsdale, J., Vely, F., Nedvetzki, S., Davis, DM. et al. (2007). Reciprocal regulation of human natural killer cells and macrophages associated with distinct immune synapses. *Blood, 109*, 3776-85. ↗

Batista, FD., Carrasco, YR. (2006). B cell recognition of membrane-bound antigen: an exquisite way of sensing ligands. *Curr Opin Immunol, 18*, 286-91. ↗

Shaw, A., Cemerski, S. (2006). Immune synapses in T-cell activation. *Curr Opin Immunol, 18*, 298-304. ↗

Editions

2007-07-08	Authored	de Bono, B.
2007-08-06	Reviewed	Trowsdale, J.
2015-03-27	Authored	Garapati, P V.
2015-05-13	Reviewed	Barrow, AD.

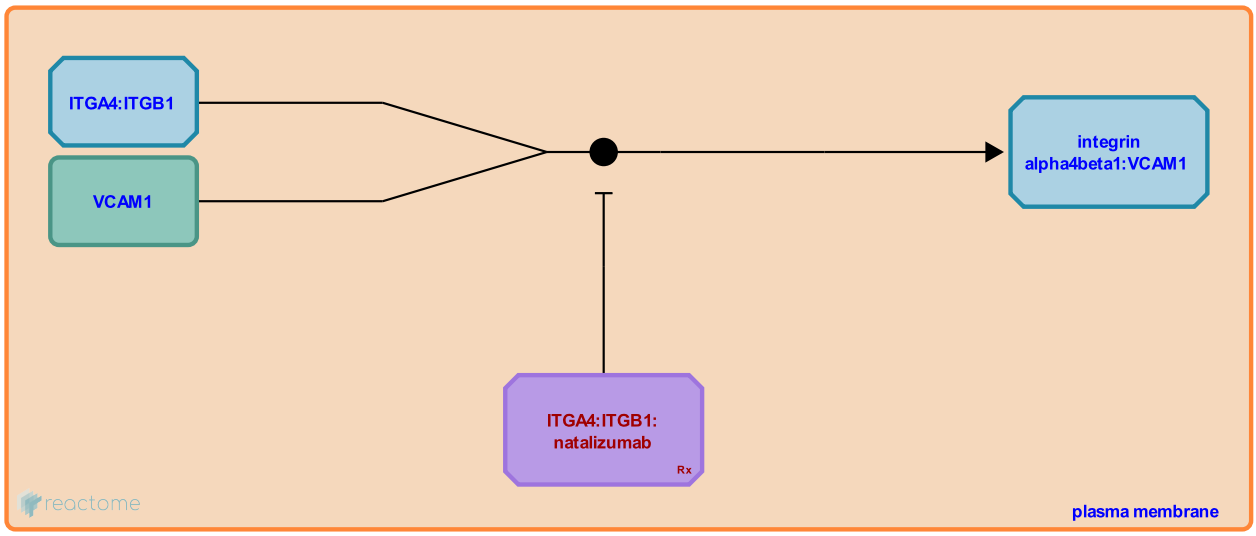
VCAM1 binds Integrin alpha4beta1 ↗

Location: Immunoregulatory interactions between a Lymphoid and a non-Lymphoid cell

Stable identifier: R-HSA-198941

Type: binding

Compartments: plasma membrane



Integrins play a central role in mediating lymphocyte adhesion to a number of surfaces. Integrin alphaLbeta2 (LFA-1) interacts with Intercellular adhesion molecule (ICAM)1-5, which are typically expressed on other immune system cells. ICAM4 and 5 are known to be expressed on telencepahlic neurons. VCAM-1 regulates lymphocyte adhesion to activated endothelial cells via Very Late Antigen-4 (VLA-4). To function in a circulating mode, leukocytes express LFA-1 and VLA-4 in a low ligand binding capacity. When leukocytes reach sites of imflammation, these integrins are switched to a higher binding state to guide the complex process of transmigration, tethering, rolling, arrest, adhesion and shape change. Signal cascades between LFA-1 and VLA-4 may cross-talk affecting binding affinities in a reciprocal fashion.

Literature references

Clements, JM., Harlos, K., Jones, EY., Dudgeon, TJ., Bottomley, MJ., Edwards, RM. et al. (1995). Crystal structure of an integrin-binding fragment of vascular cell adhesion molecule-1 at 1.8 A resolution. *Nature, 373*, 539-44. ↗

Yusuf-Makagiansar, H., Murray, JS., Siahaan, TJ., Anderson, ME., Yakovleva, TV. (2002). Inhibition of LFA-1/ICAM-1 and VLA-4/VCAM-1 as a therapeutic approach to inflammation and autoimmune diseases. *Med Res Rev, 22*, 146-67 . ↗

Editions

2007-07-08	Authored	de Bono, B.
2007-08-06	Reviewed	Trowsdale, J.
2015-05-13	Reviewed	Barrow, AD.

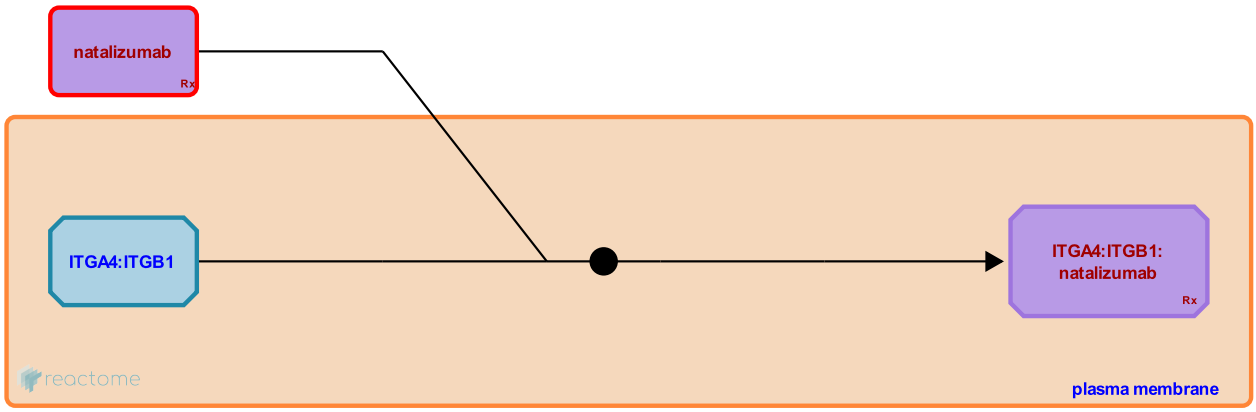
ITGA4:ITGB1 binds natalizumab ↗

Location: Immunoregulatory interactions between a Lymphoid and a non-Lymphoid cell

Stable identifier: R-HSA-9679740

Type: binding

Compartments: plasma membrane, extracellular region



Integrins are the receptors that mediate cell adhesion to the extracellular matrix (ECM). They are involved in cell adhesion and recognition in a variety of processes including embryogenesis, hemostasis, tissue repair, immune response and metastatic diffusion of tumor cells. Integrin alpha-4 (ITGA4) is a receptor for fibronectin. ITGA4 functions as a heterodimer of an alpha subunit and the beta subunit of either the beta-1 chain or the beta-7 chain (ITGA4:ITGB1 shown here).

Natalizumab (Tysabri) is a humanised monoclonal antibody against the cell adhesion molecule α4-integrin. It is a medication used to treat multiple sclerosis and Crohn's disease (No authors 2004). It binds to the α4-subunit of α4b1 and α4b7 integrins expressed on the surface of all leukocytes except neutrophils, and inhibits the α4-mediated adhesion of leukocytes to their counter-receptors. This is thought to reduce the ability of inflammatory immune cells to attach to and pass through the cell layers lining the intestines and blood–brain barrier (Rice et al. 2005).

Literature references

Hartung, HP., Calabresi, PA., Rice, GP. (2005). Anti-alpha4 integrin therapy for multiple sclerosis: mechanisms and rationale. *Neurology, 64*, 1336-42. ↗

Editions

2020-03-25	Authored, Edited	Jassal, B.
2020-05-14	Reviewed	Shoichet, BK.

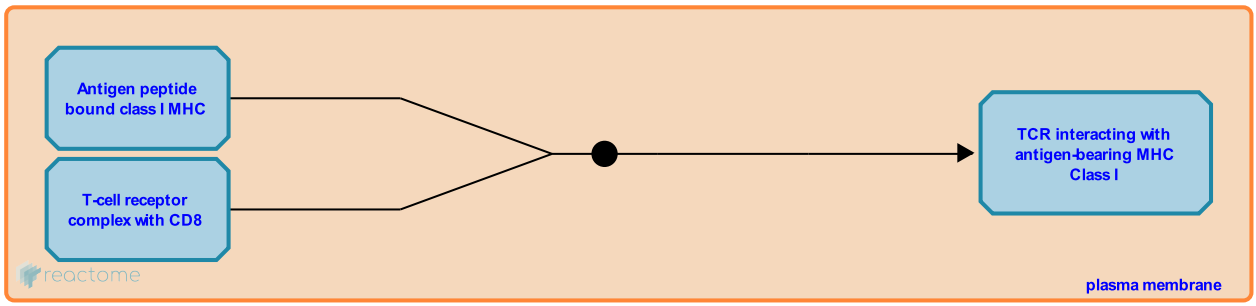
TCR complex interacts with peptide antigen-presenting MHC Class I ↗

Location: Immunoregulatory interactions between a Lymphoid and a non-Lymphoid cell

Stable identifier: R-HSA-198955

Type: binding

Compartments: plasma membrane



T cells distinguish foreign material from self through presentation of fragments of the antigen by the MHC cell surface receptors. Only if an MHC molecule presents an appropriate antigenic peptide will a cellular immune response be triggered. The orchestration of recognition and signaling events, from the initial recognition of antigenic peptides to the lysis of the target cell, is performed in a localized environment on the T cell, called the immunological synapse, and requires the coordinated activities of several T-Cell Receptor (TCR)-associated molecules. This particular reaction depicts the interaction of the TCR with MHC Class I molecules on somatic cell, requiring the support of CD3 and CD8 proteins.

Literature references

Beddoe, T., Purcell, AW., Dunstone, MA., McCluskey, J., Ely, LK., Mifsud, NA. et al. (2004). Crystal structure of the human T cell receptor CD3 epsilon gamma heterodimer complexed to the therapeutic mAb OKT3. *Proc Natl Acad Sci U S A, 101*, 7675-80. ↗

Stanfield, RL., Rudolph, MG., Wilson, IA. (2006). How TCRs bind MHCs, peptides, and coreceptors. *Annu Rev Immunol, 24*, 419-66. ↗

Arnett, KL., Wiley, DC., Harrison, SC. (2004). Crystal structure of a human CD3-epsilon/delta dimer in complex with a UCHT1 single-chain antibody fragment. *Proc Natl Acad Sci U S A, 101*, 16268-73. ↗

Editions

2007-07-08	Authored	de Bono, B.
2007-08-06	Reviewed	Trowsdale, J.
2015-05-13	Reviewed	Barrow, AD.

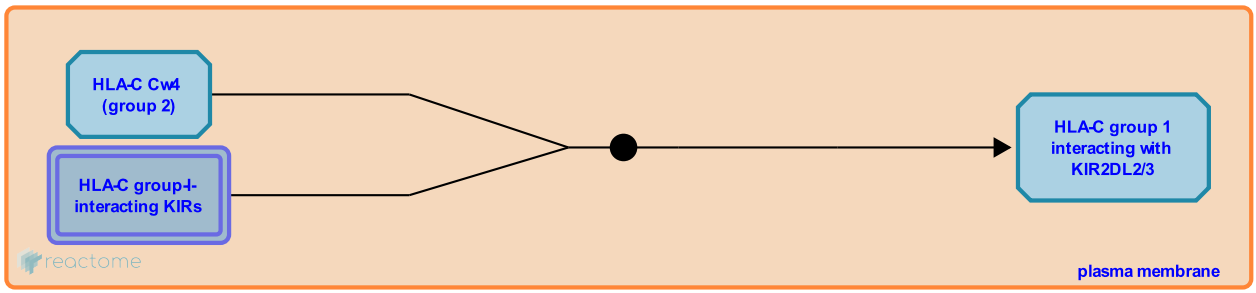
KIR2DL2/3 interacting with HLA-C group 1 (Cw4) ↗

Location: Immunoregulatory interactions between a Lymphoid and a non-Lymphoid cell

Stable identifier: R-HSA-198958

Type: binding

Compartments: plasma membrane



A hallmark of human NK cells is the expression of HLA class I-specific killer-cell immunoglobulin-like receptors (KIR). KIRs are not only variably expressed on the level of single NK cells but they are also highly polymorphic and polygenic (i.e. the gene content of the KIR cluster varies from individual to individual).

There are 15 functional KIR genes known to date, 11 encoding receptors with two immunoglobulin domains (KIR2D genes) and 4 with three domains (KIR3D genes). Inhibitory KIR genes are characterized by long cytoplasmic tails featuring immunoreceptor tyrosine-based inhibitory motifs (ITIM), which upon engagement transmit inhibitory signals leading to the general shutdown of NK cell effector functions. There are six inhibitory KIRs with clearly defined specificities, all of the inhibitory kind and all for HLA class I allotypes: KIR2DL2 and KIR2DL3 for HLA-C group 1, KIR2DL1 for HLA-C group 2, KIR3DL1 for HLA-B (Bw4 epitope), KIR3DL2 with HLA-A3 and KIR2DL4 with HLA-G.

In contrast, stimulatory KIR have short cytoplasmic tails lacking ITIM, but have a charged amino acid in the transmembrane region that provides a docking site for the activating adapter molecule DAP12. KIR2DS1 is known to bind HLA-C group 2 and KIR2DS2 binds HLA-C group 1.

Literature references

Uhrberg, M. (2005). The KIR gene family: life in the fast lane of evolution. *Eur J Immunol, 35*, 10-5. ↗

Boyington, JC., Sun, PD. (2002). A structural perspective on MHC class I recognition by killer cell immunoglobulin-like receptors. *Mol Immunol, 38*, 1007-21. ↗

Parham, P., Vilches, C. (2002). KIR: diverse, rapidly evolving receptors of innate and adaptive immunity. *Annu Rev Immunol, 20*, 217-51. ↗

Editions

2007-07-08	Authored	de Bono, B.
2007-08-06	Reviewed	Trowsdale, J.
2015-05-13	Reviewed	Barrow, AD.

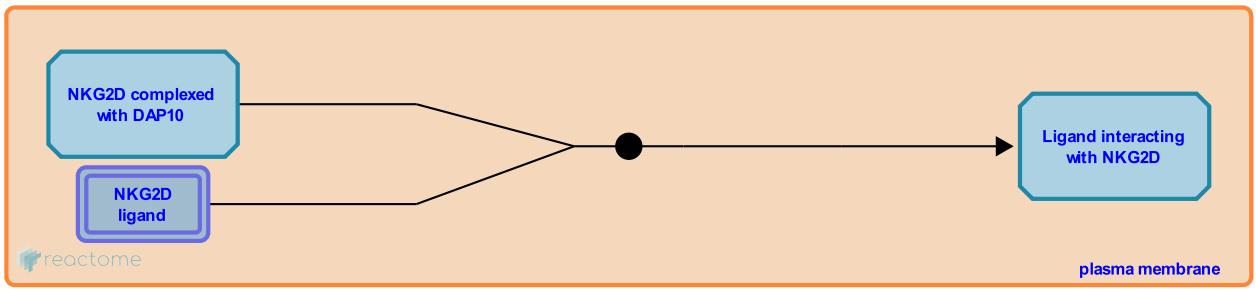
NKG2D homodimer interacting with ligands ↗

Location: Immunoregulatory interactions between a Lymphoid and a non-Lymphoid cell

Stable identifier: R-HSA-198983

Type: binding

Compartments: plasma membrane



NKG2D is an activating immunoreceptor. By engaging NKG2D, HlA Class I-like molecules such as MICA, MICB, ULBP1-4 and RAE-1 provide powerful costimulation for NK cells and T-cells and can determine the magnitude and outcome of certain effector functions. NKG2D ligands are upregulated on the surfaces of cells under conditions of stress, for example infection or tumorigenesis, and therefore act as molecular flags to the immune system that something is wrong.

Literature references

Deng, L., Mariuzza, RA. (2006). Structural basis for recognition of MHC and MHC-like ligands by natural killer cell receptors. *Semin Immunol, 18*, 159-66. ↗

Strong, RK. (2002). Asymmetric ligand recognition by the activating natural killer cell receptor NKG2D, a symmetric homodimer. *Mol Immunol, 38*, 1029-37. ↗

Coligan, JE., Kim, DK., Pena, J., Solana, R., Maasho, K., Lieto, L. et al. (2002). Structure and function of major histocompatibility complex (MHC) class I specific receptors expressed on human natural killer (NK) cells. *Mol Immunol, 38*, 637-60. ↗

Editions

2007-07-08	Authored	de Bono, B.
2007-08-06	Reviewed	Trowsdale, J.
2015-05-13	Reviewed	Barrow, AD.

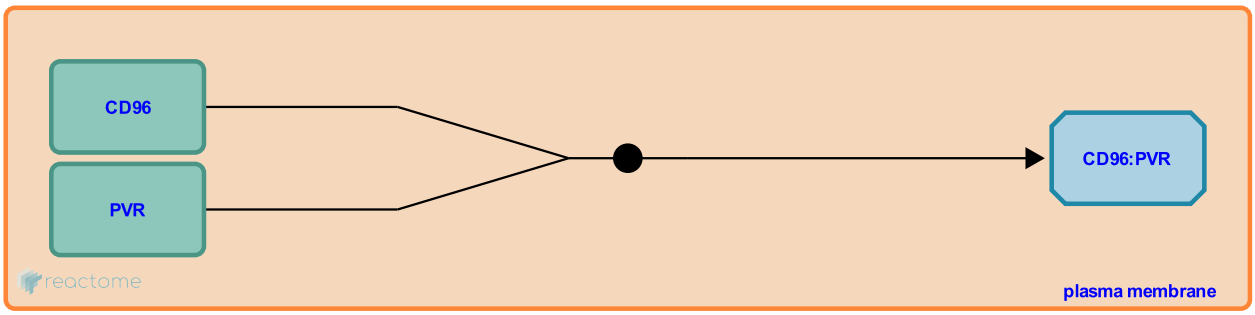
CD96 binds PVR ↗

Location: Immunoregulatory interactions between a Lymphoid and a non-Lymphoid cell

Stable identifier: R-HSA-199014

Type: binding

Compartments: plasma membrane



NK cells express adhesion molecules that allow interaction with their tumour targets, promoting their lysis.

For instance, the activating receptor CD226 is known to be involved in cytotoxic lymphocyte formation, as well as platelet adhesion to the endothelium. The cytoplasmic domain of CD226 contains binding motifs for members of the band 4.1 family of proteins, and for members of the membrane-associated guanylate kinase homolog (MAGUK) family. These proteins connect the CD226 receptor to the cytoskeleton and may promote clustering with LFA-1 integrin (also discussed in this pathway), which is known to participate in CD226's signaling cascade. CD226 plays a role in transendothelial migration, where it facilitates adherence to endothelial cells and migration between cell junctions.

Nectin-2 binds CD226. It is ubiquitously expressed in cells of various tissues, especially in epithelial cells, neurons and fibroblasts. Like many other nectin and Necl proteins, nectin-2 serves as a viral entry receptor for alpha-herpesviruses including herpes simplex virus (HSV-1 and HSV-2). The other CD226 ligand, Necl-5, was initially identified as a receptor for poliovirus.

CD96, another ligand for Necl-5, is strongly upregulated in activated NK cells.

CRTAM is similarly up-regulated, and has been shown to to bind Necl-2, promoting NK cell cytotoxicity towards otherwise poorly immunogenic targets.

Literature references

Shaw, AS., Colonna, M., Giurisato, E., Cella, M., Fuchs, A. (2004). Cutting edge: CD96 (tactile) promotes NK cell-target cell adhesion by interacting with the poliovirus receptor (CD155). *J Immunol, 172*, 3994-8. ↗

Editions

2007-07-08	Authored	de Bono, B.
2007-08-06	Reviewed	Trowsdale, J.
2015-05-13	Reviewed	Barrow, AD.

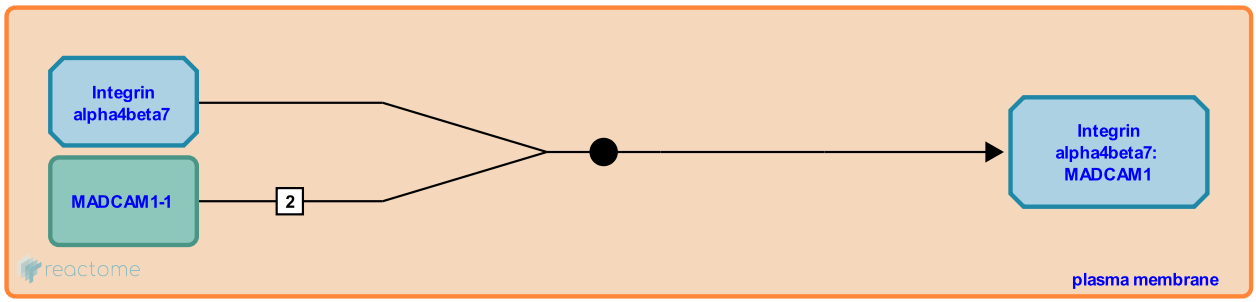
MADCAM1-1 binds Integrin alpha4beta7 ↗

Location: Immunoregulatory interactions between a Lymphoid and a non-Lymphoid cell

Stable identifier: R-HSA-199032

Type: binding

Compartments: plasma membrane



Mucosal addressin cell adhesion molecule (MADCAM1) is present in the endothelium of mucosa, and binds alpha-4 beta-7 integrin and L-selectin, regulating both the passage and retention of leukocytes in mucosal tissues. MADCAM1 has been shown to be present as a homodimer.

Literature references

Springer, TA., Wang, J. (1998). Structural specializations of immunoglobulin superfamily members for adhesion to integrins and viruses. *Immunol Rev, 163*, 197-215. ↗

King, DJ., Brady, RL., Dando, J., Ortlepp, S., Wilkinson, KW. (2002). A reassessment of the MAdCAM-1 structure and its role in integrin recognition. *Acta Crystallogr D Biol Crystallogr, 58*, 233-41. ↗

Editions

2007-07-08	Authored	de Bono, B.
2007-08-06	Reviewed	Trowsdale, J.
2015-05-13	Reviewed	Barrow, AD.

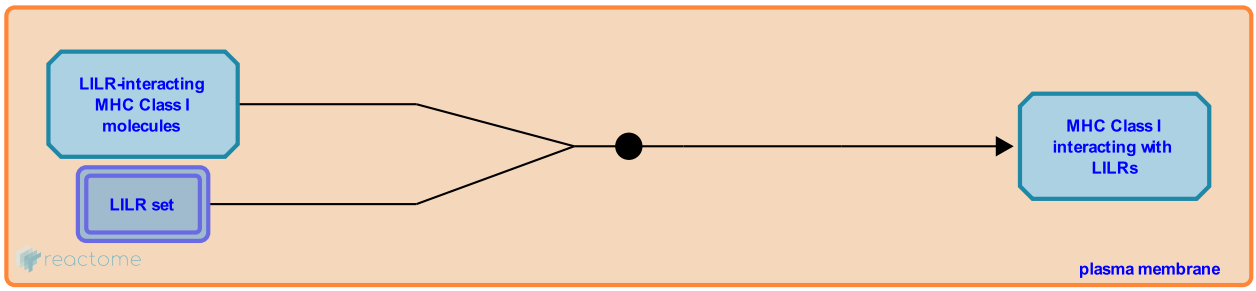
LILRs interact with MHC Class I ↗

Location: Immunoregulatory interactions between a Lymphoid and a non-Lymphoid cell

Stable identifier: R-HSA-199043

Type: binding

Compartments: plasma membrane



Leukocyte immunoglobulin (Ig)-like receptors [LILRs, also known as Ig-like transcripts (ILTs)] are a family of inhibitory and stimulatory receptors encoded within the leukocyte receptor complex and are expressed by immune cell types of both myeloid and lymphoid lineage. Several members of the LILR family recognize major histocompatibility complex class I. The immunomodulatory role of LILR receptors indicates that they may exert an influence on signaling pathways of both innate and adaptive immune systems.

Signaling mechanisms are employed that are similar to the ones adopted by the closely related killer cell inhibitory receptors (KIRs). ITIMs recruit inhibitory phosphatases that dephosphorylate ITIM and ITAM domains in order to influence intracellular signaling cascades. In contrast, activating LILRs, which lack any signaling domains of their own, rely on association with an adaptor protein such as FceRI-gamma to transmit their signal through its intracellular ITAMs.

Literature references

Trowsdale, J., Allen, R., Brown, D. (2004). The LILR family: modulators of innate and adaptive immune pathways in health and disease. *Tissue Antigens, 64*, 215-25. ↗

Editions

2007-07-08	Authored	de Bono, B.
2007-08-06	Reviewed	Trowsdale, J.
2015-05-13	Reviewed	Barrow, AD.

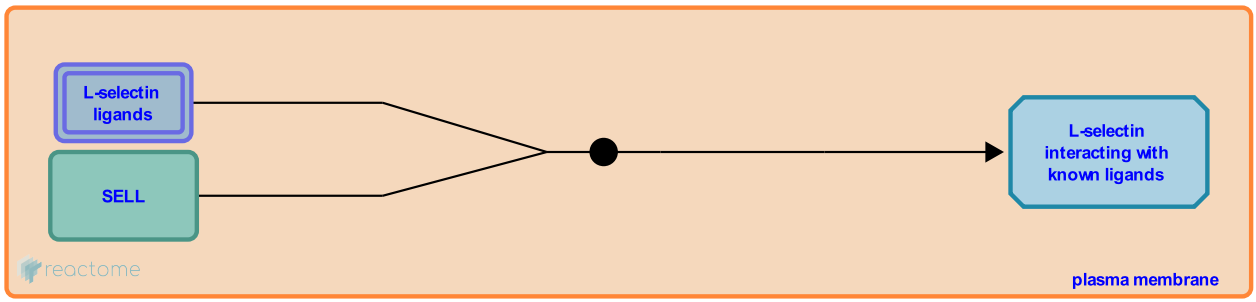
Ligands bind L-selectin ↗

Location: Immunoregulatory interactions between a Lymphoid and a non-Lymphoid cell

Stable identifier: R-HSA-199046

Type: binding

Compartments: plasma membrane



L-selectin plays a major role in leukocyte traffic through lymph node high endothelial venules.

Both MAdCAM and GlyCAM-1 are major L-selectin ligands produced by these venules and mediate leukocyte rolling, particularly in lymphocytes. They are also expressed in mammary tissue and play an important role in the transfer of immune cells into milk secretions.

The adhesive properties of CD34 and its potential role in homing lymphocytes to lymphoid tissues mimics the mechanims leukocytes adopt to travel to inflammatory sites.

Literature references

Nishimura, T. (2003). Expression of potential lymphocyte trafficking mediator molecules in the mammary gland. *Vet Res, 34*, 3-10. ↗

Editions

2007-07-08	Authored	de Bono, B.
2007-08-06	Reviewed	Trowsdale, J.
2015-05-13	Reviewed	Barrow, AD.

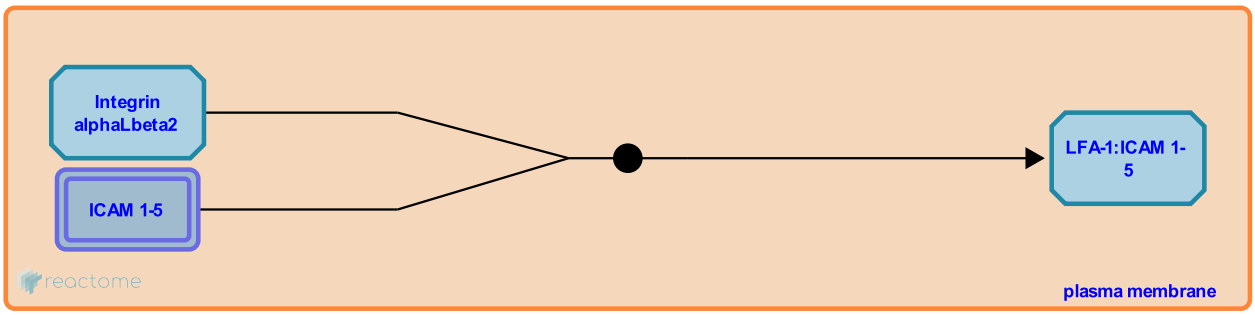
ICAM1-5 bind Integrin alphaLbeta2 (LFA-1) ↗

Location: Immunoregulatory interactions between a Lymphoid and a non-Lymphoid cell

Stable identifier: R-HSA-199050

Type: binding

Compartments: plasma membrane



Integrins play a central role in mediating lymphocyte adhesion to a number of surfaces. Integrin alphaLbeta2 (LFA-1) interacts with Intercellular adhesion molecule (ICAM)1-5, which are typically expressed on other immune system cells. ICAM4 and 5 are known to be expressed on telencepahlic neurons. VCAM-1 regulates lymphocyte adhesion to activated endothelial cells via Very Late Antigen-4 (VLA-4). To function in a circulating mode, leukocytes express LFA-1 and VLA-4 in a low ligand binding capacity. When leukocytes reach sites of imflammation, these integrins are switched to a higher binding state to guide the complex process of transmigration, tethering, rolling, arrest, adhesion and shape change. Signal cascades between LFA-1 and VLA-4 may cross-talk affecting binding affinities in a reciprocal fashion.

Literature references

Mori, K., Kagamiyama, H., Yoshihara, Y., Inazawa, J., Mizuno, T. (1997). cDNA cloning and chromosomal localization of the human telencephalin and its distinctive interaction with lymphocyte function-associated antigen-1. *J. Biol. Chem., 272*, 1156-63. ↗

Yusuf-Makagiansar, H., Murray, JS., Siahaan, TJ., Anderson, ME., Yakovleva, TV. (2002). Inhibition of LFA-1/ICAM-1 and VLA-4/VCAM-1 as a therapeutic approach to inflammation and autoimmune diseases. *Med Res Rev, 22*, 146-67 . ↗

Editions

2007-07-08	Authored	de Bono, B.
2007-08-06	Reviewed	Trowsdale, J.
2015-05-13	Reviewed	Barrow, AD.

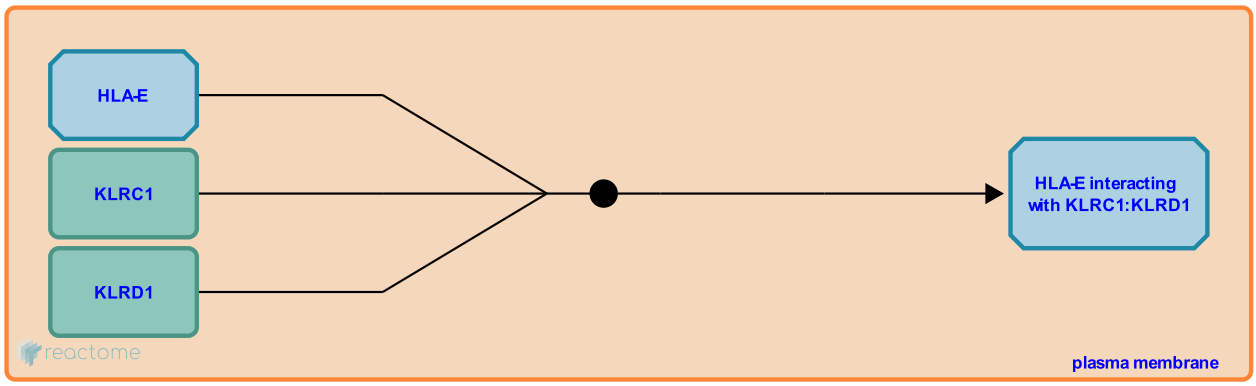
KLRC1:KLRD1 heterodimer interacts with HLA-E ↗

Location: Immunoregulatory interactions between a Lymphoid and a non-Lymphoid cell

Stable identifier: R-HSA-199062

Type: binding

Compartments: plasma membrane



After interaction with its ligand HLA-E, which is expressed on normal cells, the C-type lectin inhibitory receptor CD94/NKG2A suppresses activation signaling processes. CD94/NKG2A receptors continuously recycle from the cell surface through endosomal compartments and back again in a process that requires energy and the cytoskeleton. This steady state process appears to be largely unaffected by exposure to ligand.

Literature references

Wang, J., Sawicki, MW., Mariuzza, RA., Natarajan, K., Margulies, DH., Dimasi, N. (2001). Structural basis of MHC class I recognition by natural killer cell receptors. *Immunol Rev, 181*, 52-65. ↗

Editions

2007-07-08	Authored	de Bono, B.
2007-08-06	Reviewed	Trowsdale, J.
2015-05-13	Reviewed	Barrow, AD.

Epithelial cadherin binds to KLRG1 ↗

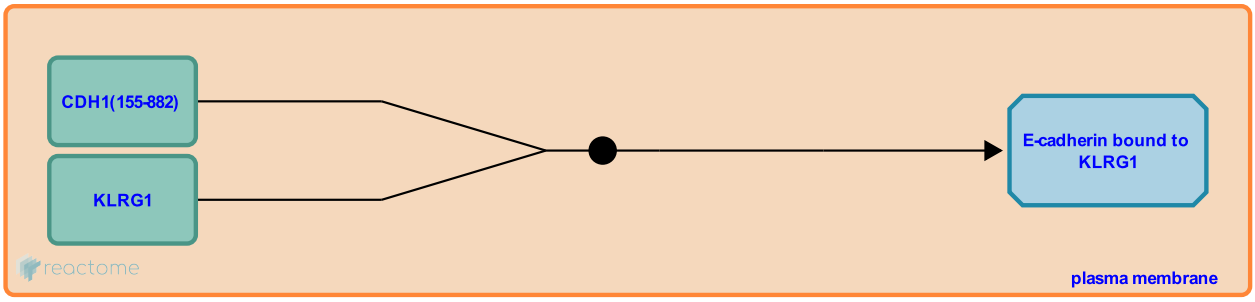
Location: Immunoregulatory interactions between a Lymphoid and a non-Lymphoid cell

Stable identifier: R-HSA-199079

Type: binding

Compartments: plasma membrane

Inferred from: Epithelial cadherin binds to KLRG1 in mice (Mus musculus)



The lectin-like NK cell receptor KLRG1 binds to cadherins on epithelial cells and transmits inhibitory signals to the leukocyte.

Editions

2007-07-08	Authored	de Bono, B.
2007-08-06	Reviewed	Trowsdale, J.
2015-05-13	Reviewed	Barrow, AD.

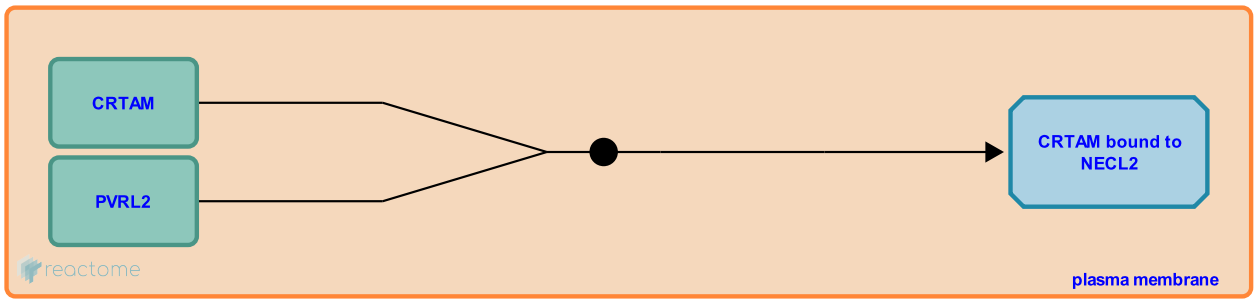
CRTAM binds to NECL2 ↗

Location: Immunoregulatory interactions between a Lymphoid and a non-Lymphoid cell

Stable identifier: R-HSA-199112

Type: binding

Compartments: plasma membrane



NK cells express adhesion molecules that allow interaction with their tumour targets, promoting their lysis.

For instance, the activating receptor CD226 is known to be involved in cytotoxic lymphocyte formation, as well as platelet adhesion to the endothelium. The cytoplasmic domain of CD226 contains binding motifs for members of the band 4.1 family of proteins, and for members of the membrane-associated guanylate kinase homolog (MAGUK) family. These proteins connect the CD226 receptor to the cytoskeleton and may promote clustering with LFA-1 integrin (also discussed in this pathway), which is known to participate in CD226's signaling cascade. CD226 plays a role in transendothelial migration, where it facilitates adherence to endothelial cells and migration between cell junctions.

Nectin-2 binds CD226. It is ubiquitously expressed in cells of various tissues, especially in epithelial cells, neurons and fibroblasts. Like many other nectin and Necl proteins, nectin-2 serves as a viral entry receptor for alpha-herpesviruses including herpes simplex virus (HSV-1 and HSV-2). The other CD226 ligand, Necl-5, was initially identified as a receptor for poliovirus.

CD96, another ligand for Necl-5, is strongly upregulated in activated NK cells.

CRTAM is similarly up-regulated, and has been shown to to bind Necl-2, promoting NK cell cytotoxicity towards otherwise poorly immunogenic targets.

Literature references

Scholler, J., Walzer, T., Van der Vuurst de Vries, AR., Derry, JM., Baum, PR., Johnson, RS. et al. (2005). Nectin-like protein 2 defines a subset of T-cell zone dendritic cells and is a ligand for class-I-restricted T-cell-associated molecule. *J Biol Chem, 280*, 21955-64. ↗

Yokosuka, T., Hirano, S., Takeuchi, A., Arase, N., Saito, T., Arase, H. et al. (2005). Heterotypic interaction of CRTAM with Necl2 induces cell adhesion on activated NK cells and CD8+ T cells. *Int Immunol, 17*, 1227-37. ↗

Editions

2007-07-08	Authored	de Bono, B.
2007-08-06	Reviewed	Trowsdale, J.
2015-05-13	Reviewed	Barrow, AD.

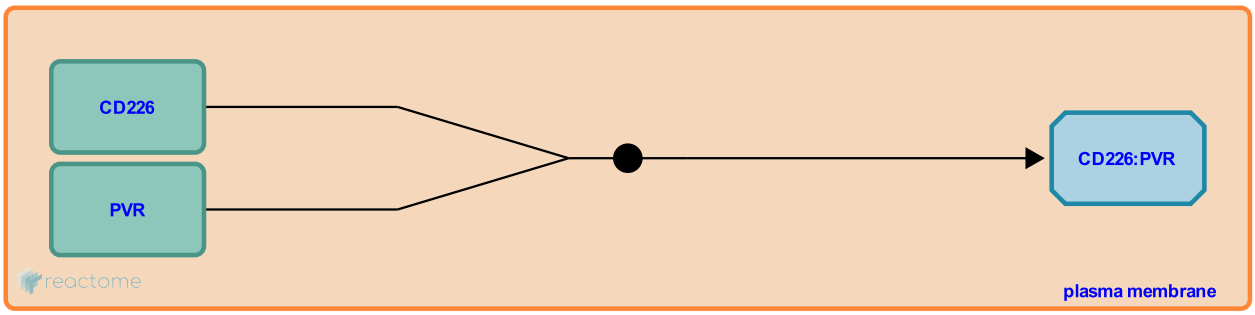
PVR binds CD226 ↗

Location: Immunoregulatory interactions between a Lymphoid and a non-Lymphoid cell

Stable identifier: R-HSA-199131

Type: binding

Compartments: plasma membrane



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Reymond, N., Carnemolla, B., Rivera, P., Cantoni, C., Bottino, C., Spaggiari, GM. et al. (2005). PVR (CD155) and Nectin-2 (CD112) as ligands of the human DNAM-1 (CD226) activating receptor: involvement in tumor cell lysis. *Mol Immunol, 42*, 463-9. ↗

Colonna, M., Fuchs, A. (2006). The role of NK cell recognition of nectin and nectin-like proteins in tumor immunosurveillance. *Semin Cancer Biol, 16*, 359-66. ↗

Editions

2007-07-08	Authored	de Bono, B.
2007-08-06	Reviewed	Trowsdale, J.
2015-05-13	Reviewed	Barrow, AD.

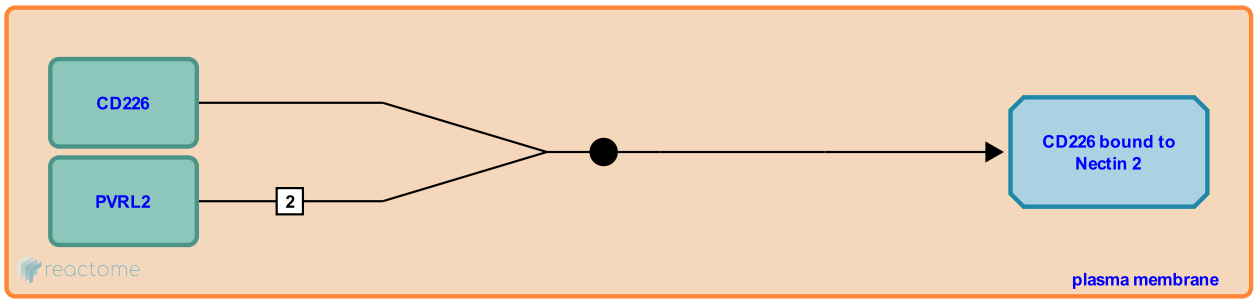
Nectin 2 binds CD226 ↗

Location: Immunoregulatory interactions between a Lymphoid and a non-Lymphoid cell

Stable identifier: R-HSA-199144

Type: binding

Compartments: plasma membrane



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Editions

2007-07-08	Authored	de Bono, B.
2007-08-06	Reviewed	Trowsdale, J.
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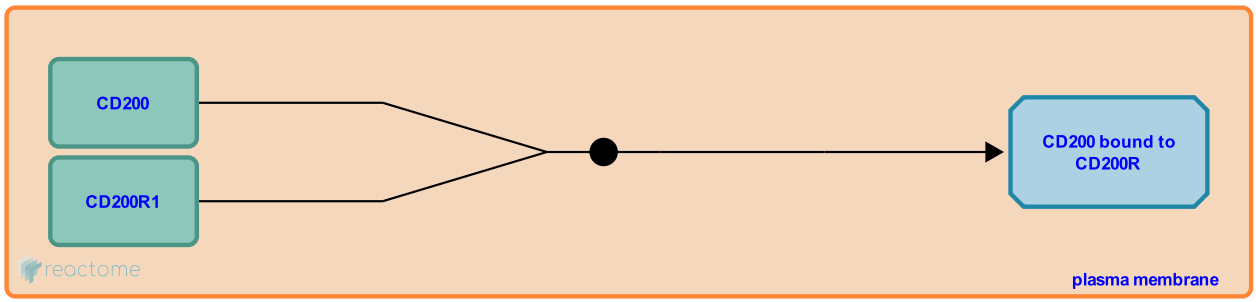
CD200 binds to CD200R ↗

Location: Immunoregulatory interactions between a Lymphoid and a non-Lymphoid cell

Stable identifier: R-HSA-199154

Type: binding

Compartments: plasma membrane



While not ubiquitously distributed, CD200 is expressed on a wide range of cell types including thymocytes, B-cells, activated T-cells, follicular dendritic cells, endothelium, CNS neurons in the central nervous system, cells in reproductive organs, keratinocytes and renal glomeruli. CD200R is a myeloid-inhibitory receptor, despite the absence of classical ITIMs in the cytoplasmic portion of the protein. Interestingly, CD200 is also expressed on neurons within the CNS and would be predicted to modulate activation of microglia through CD200R.

Literature references

Gorczynski, R., Chen, Z., Kai, Y., Lee, L., Wong, S., Marsden, PA. (2004). CD200 is a ligand for all members of the CD200R family of immunoregulatory molecules. *J Immunol, 172*, 7744-9. ↗

Minas, K., Liversidge, J. (2006). Is the CD200/CD200 receptor interaction more than just a myeloid cell inhibitory signal?. *Crit Rev Immunol, 26*, 213-30. ↗

Editions

2007-07-08	Authored	de Bono, B.
2007-08-06	Reviewed	Trowsdale, J.
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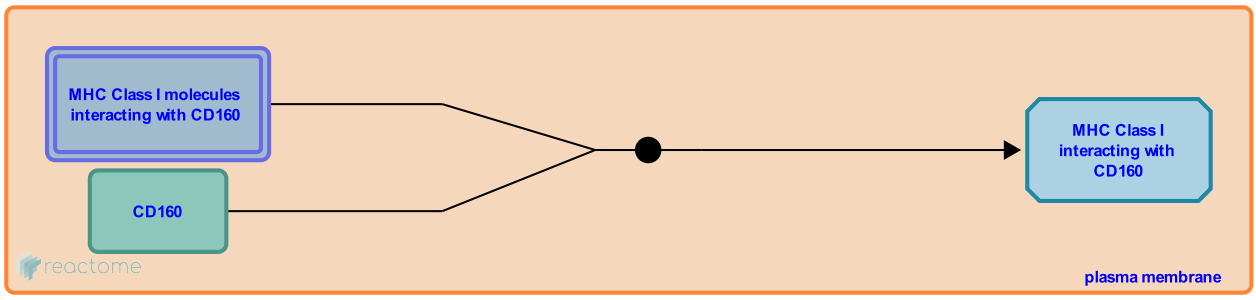
MHC Class I interacts with CD160 ↗

Location: Immunoregulatory interactions between a Lymphoid and a non-Lymphoid cell

Stable identifier: R-HSA-199169

Type: binding

Compartments: plasma membrane



CD160 is a GPI-anchored lymphocyte surface receptor in which expression is mostly restricted to the highly cytotoxic NK cells. MHC class I molecules bind to CD160 receptors on circulating NK lymphocytes and this triggers their cytotoxic activity and cytokine production. NK cells stimulated by IL-15 secrete soluble CD160 protein that binds to MHC-I molecules, resulting in the inhibition of the cytotoxic CD8+ T lymphocyte activity and of the CD160-mediated NK cell cytotoxicity.

Literature references

Bensussan, A., Marie-Cardine, A., Giustiniani, J. (2007). A soluble form of the MHC class I-specific CD160 receptor is released from human activated NK lymphocytes and inhibits cell-mediated cytotoxicity. *J Immunol, 178*, 1293-300 . ↗

Strbo, N., Polgar, B., Berrebi, A., Bensussan, A., Tabiasco, J., Rukavina, D. et al. (2005). HLA class I/NK cell receptor interaction in early human decidua basalis: possible functional consequences. *Chem Immunol Allergy, 89*, 72-83. ↗

Editions

2007-07-08	Authored	de Bono, B.
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2015-05-13	Reviewed	Barrow, AD.

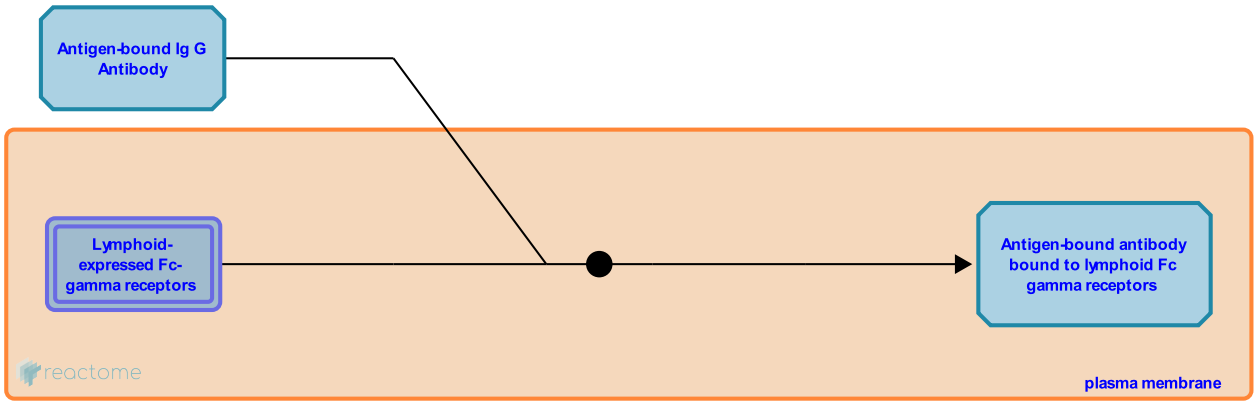
Fc gamma receptors interact with antigen-bound IgG ↗

Location: Immunoregulatory interactions between a Lymphoid and a non-Lymphoid cell

Stable identifier: R-HSA-199161

Type: binding

Compartments: plasma membrane, extracellular region



Most cells of the immune system express receptors for the Fc region of IgG. This heterogeneous family of molecules plays a critical role in immunity, by linking the humoral to the cellular responses. NK cells and B cells have been shown to express exclusively Fc-gamma RIIIa and RIIb respectively.

Literature references

Radaev, S., Sun, P. (2002). Recognition of immunoglobulins by Fcgamma receptors. *Mol Immunol, 38*, 1073-83. ↗

Editions

2007-07-08	Authored	de Bono, B.
2007-08-06	Reviewed	Trowsdale, J.
2015-05-13	Reviewed	Barrow, AD.

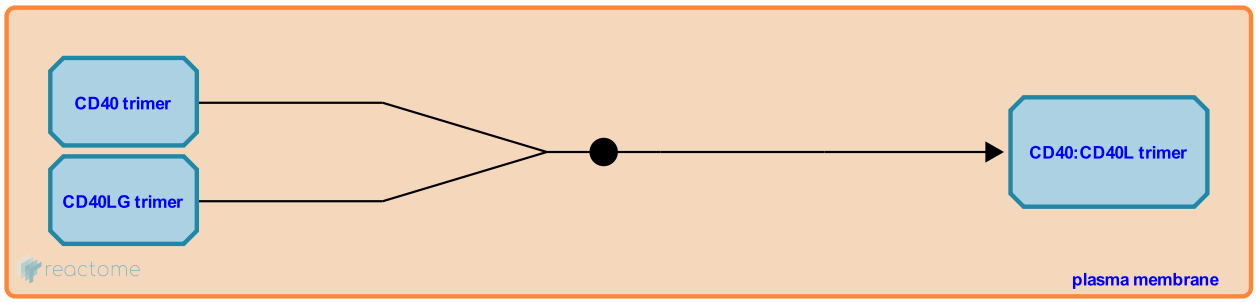
CD40L binds CD40 ↗

Location: Immunoregulatory interactions between a Lymphoid and a non-Lymphoid cell

Stable identifier: R-HSA-199404

Type: binding

Compartments: plasma membrane



CD40 is a member of the Tumour Necrosis Factor receptor family and its ligand CD40L is a type II transmembrane protein of the TNF superfamily. The latter is expressed preferentially on T-cells and platelets. In the immune system, CD40-CD40L interaction affects some key processes such as immune cell activation, differentiation, proliferation, and apoptosis. CD40-CD40L interaction also upregulates costimulatory molecules (ICAM-1, VCAM-1, E-selectin, LFA-3, B7.1, B7.2, class II MHC, and CD40 itself).

Literature references

Wang, JM., Chen, K., Zhang, L., Yu, P., Huang, J., Gong, W. (2006). CD40/CD40L dyad in the inflammatory and immune responses in the central nervous system. *Cell Mol Immunol, 3*, 163-9. ↗

Editions

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2007-08-06	Reviewed	Trowsdale, J.
2015-05-13	Reviewed	Barrow, AD.

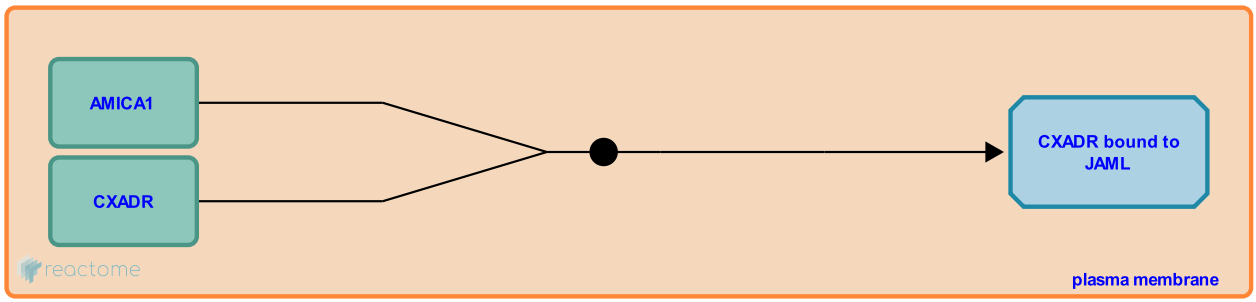
CXADR binds to AMICA1 ↗

Location: Immunoregulatory interactions between a Lymphoid and a non-Lymphoid cell

Stable identifier: R-HSA-199093

Type: binding

Compartments: plasma membrane



JAM members, such as JAML, bind coxsackie and adenovirus receptor (CXADR) on epithelial and endothelial cells.

Literature references

Nusrat, A., Babbin, BA., Parkos, CA., Liu, Y., Zen, K., McCall, IC. et al. (2005). Neutrophil migration across tight junctions is mediated by adhesive interactions between epithelial coxsackie and adenovirus receptor and a junctional adhesion molecule-like protein on neutrophils. *Mol Biol Cell, 16*, 2694-703. ↗

Editions

2007-11-12	Authored	Ouwehand, WH.
2007-11-12	Reviewed	Zwaginga, JJ.

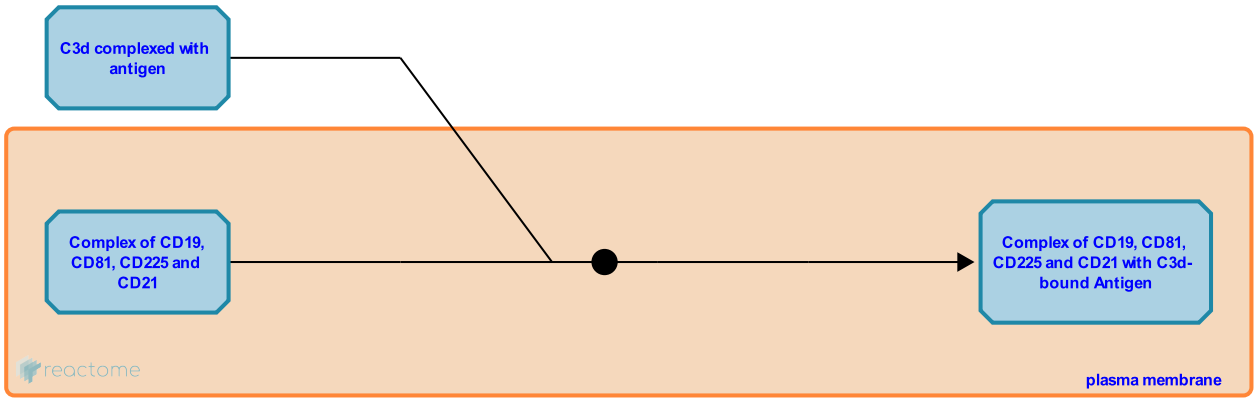
C3d-complexed antigen binds to complement receptor ↗

Location: Immunoregulatory interactions between a Lymphoid and a non-Lymphoid cell

Stable identifier: R-HSA-199518

Type: binding

Compartments: plasma membrane, extracellular region



CD19 is a lymphocyte cell surface molecule that functions as a general response regulator or rheostat, which defnes signalling thresholds. These responses are infuenced by signals transduced through a CD19-CD21 cell surface receptor complex, where the binding of complement C3d to CD21 links humoral immune responses with the innate immune system. The CD19-CD21 complex is composed of at least four non-covalently associated proteins: CD19, CD21(complement receptor 2),CD81 and CD225.

Literature references

Ross, TM., Toapanta, FR. (2006). Complement-mediated activation of the adaptive immune responses: role of C3d in linking the innate and adaptive immunity. *Immunol Res, 36*, 197-210. ↗

Rickert, RC., Kolla, RV., Del Nagro, CJ., Anzelon, AN., Otero, DC., Omori, SA. (2005). CD19 function in central and peripheral B-cell development. *Immunol Res, 31*, 119-31. ↗

Barrington, RA., Carter, RH. (2004). Signaling by the CD19/CD21 complex on B cells. *Curr Dir Autoimmun, 7*, 4-32. ↗

Editions

2007-07-08	Authored	de Bono, B.
2007-08-06	Reviewed	Trowsdale, J.
2015-05-13	Reviewed	Barrow, AD.

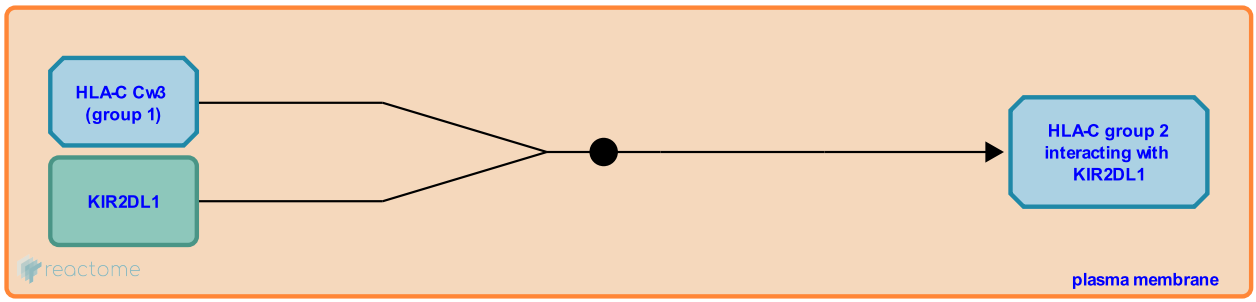
KIR2DL1 interacting with HLA-C group 2 (Cw3) ↗

Location: Immunoregulatory interactions between a Lymphoid and a non-Lymphoid cell

Stable identifier: R-HSA-199558

Type: binding

Compartments: plasma membrane



A hallmark of human NK cells is the expression of HLA class I-specific killer-cell immunoglobulin-like receptors (KIR). KIRs are not only variably expressed on the level of single NK cells but they are also highly polymorphic and polygenic (i.e. the gene content of the KIR cluster varies from individual to individual).

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In contrast, stimulatory KIR have short cytoplasmic tails lacking ITIM, but have a charged amino acid in the transmembrane region that provides a docking site for the activating adapter molecule DAP12. KIR2DS1 is known to bind HLA-C group 2 and KIR2DS2 binds HLA-C group 1.

Literature references

Uhrberg, M. (2005). The KIR gene family: life in the fast lane of evolution. *Eur J Immunol, 35*, 10-5. ↗

Boyington, JC., Sun, PD. (2002). A structural perspective on MHC class I recognition by killer cell immunoglobulin-like receptors. *Mol Immunol, 38*, 1007-21. ↗

Parham, P., Vilches, C. (2002). KIR: diverse, rapidly evolving receptors of innate and adaptive immunity. *Annu Rev Immunol, 20*, 217-51. ↗

Editions

2007-07-08	Authored	de Bono, B.
2007-08-06	Reviewed	Trowsdale, J.
2015-05-13	Reviewed	Barrow, AD.

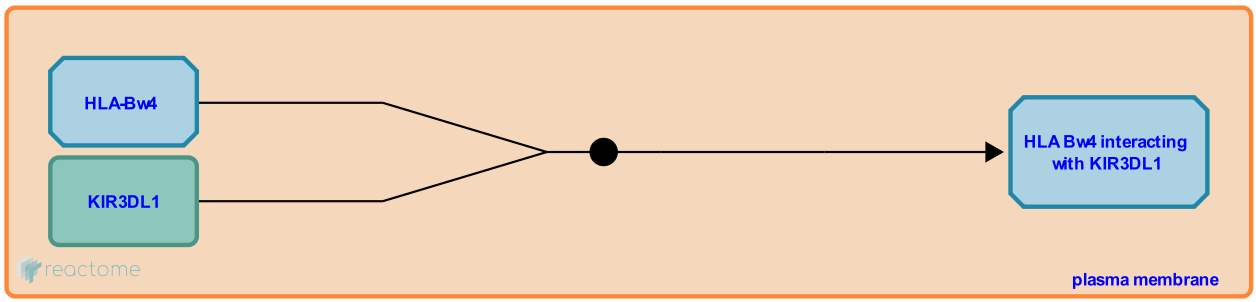
KIR3DL1 interacting with HLA Bw4 ↗

Location: Immunoregulatory interactions between a Lymphoid and a non-Lymphoid cell

Stable identifier: R-HSA-199566

Type: binding

Compartments: plasma membrane



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Editions

2007-07-08	Authored	de Bono, B.
2007-08-06	Reviewed	Trowsdale, J.
2015-05-13	Reviewed	Barrow, AD.

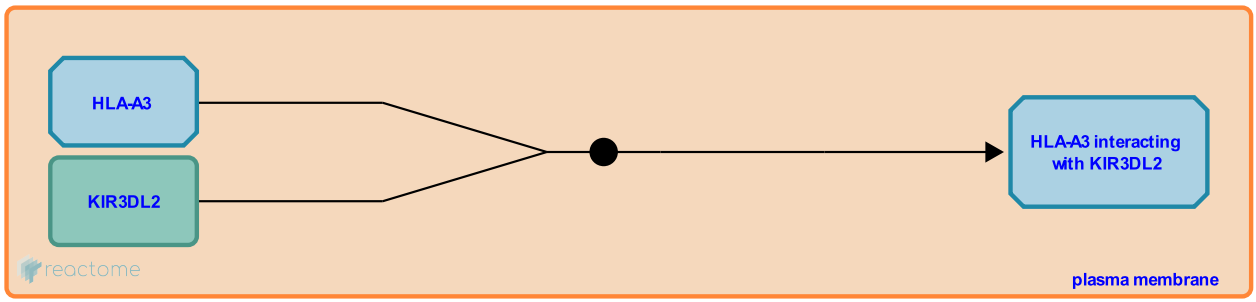
KIR3DL2 interacting with HLA-A3 ↗

Location: Immunoregulatory interactions between a Lymphoid and a non-Lymphoid cell

Stable identifier: R-HSA-199576

Type: binding

Compartments: plasma membrane



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Parham, P., Vilches, C. (2002). KIR: diverse, rapidly evolving receptors of innate and adaptive immunity. *Annu Rev Immunol, 20*, 217-51. ↗

Editions

2007-07-08	Authored	de Bono, B.
2007-08-06	Reviewed	Trowsdale, J.
2015-05-13	Reviewed	Barrow, AD.

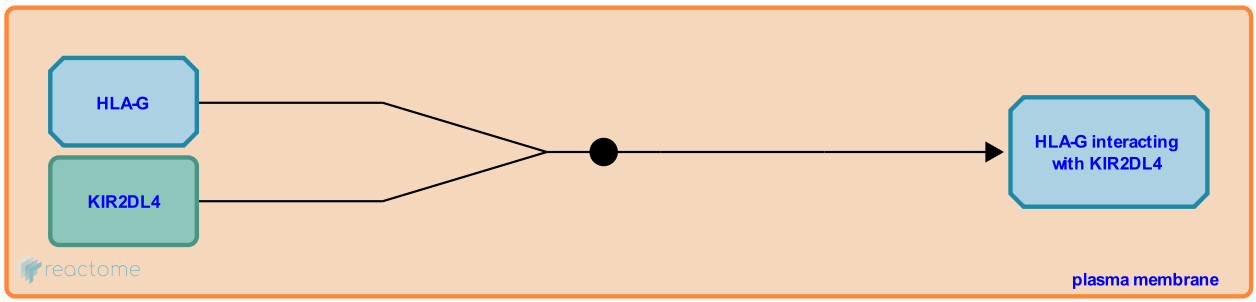
KIR2DL4 interacting with HLA-G ↗

Location: Immunoregulatory interactions between a Lymphoid and a non-Lymphoid cell

Stable identifier: R-HSA-199579

Type: binding

Compartments: plasma membrane



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Parham, P., Vilches, C. (2002). KIR: diverse, rapidly evolving receptors of innate and adaptive immunity. *Annu Rev Immunol, 20*, 217-51. ↗

Editions

2007-07-08	Authored	de Bono, B.
2007-08-06	Reviewed	Trowsdale, J.
2015-05-13	Reviewed	Barrow, AD.

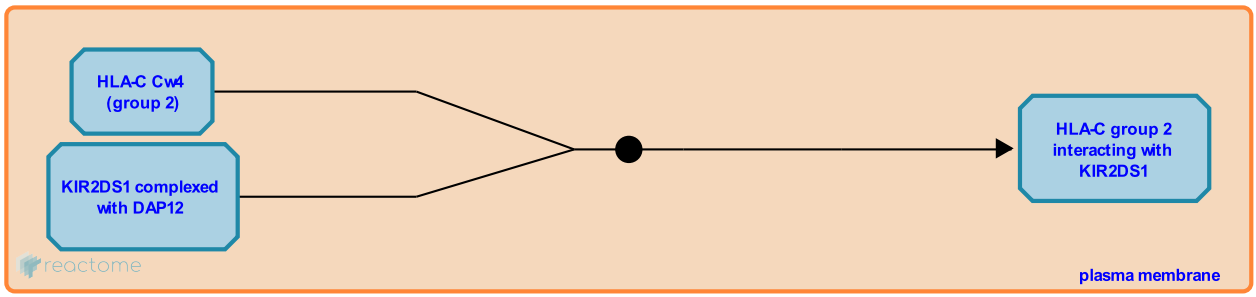
KIR2DS1 interacting with HLA-C group 2 (Cw4) ↗

Location: Immunoregulatory interactions between a Lymphoid and a non-Lymphoid cell

Stable identifier: R-HSA-199587

Type: binding

Compartments: plasma membrane



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Boyington, JC., Sun, PD. (2002). A structural perspective on MHC class I recognition by killer cell immunoglobulin-like receptors. *Mol Immunol, 38*, 1007-21. ↗

Parham, P., Vilches, C. (2002). KIR: diverse, rapidly evolving receptors of innate and adaptive immunity. *Annu Rev Immunol, 20*, 217-51. ↗

Editions

2007-07-08	Authored	de Bono, B.
2007-08-06	Reviewed	Trowsdale, J.
2015-05-13	Reviewed	Barrow, AD.

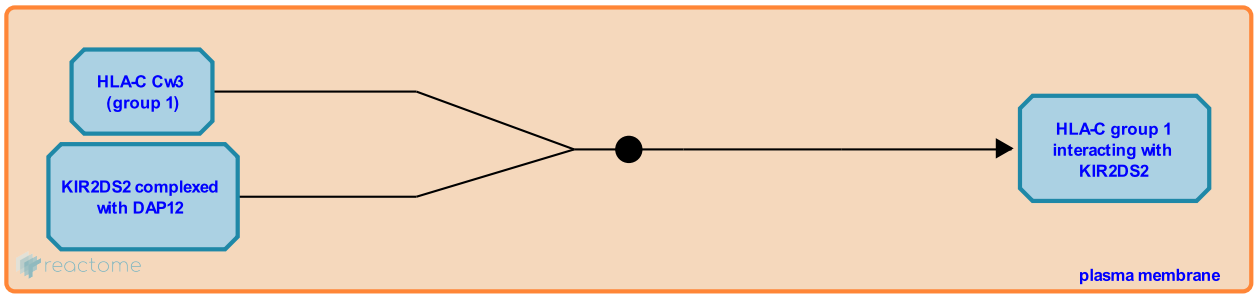
KIR2DS2 interacting with HLA-C group 1 (Cw3) ↗

Location: Immunoregulatory interactions between a Lymphoid and a non-Lymphoid cell

Stable identifier: R-HSA-199583

Type: binding

Compartments: plasma membrane



A hallmark of human NK cells is the expression of HLA class I-specific killer-cell immunoglobulin-like receptors (KIR). KIRs are not only variably expressed on the level of single NK cells but they are also highly polymorphic and polygenic (i.e. the gene content of the KIR cluster varies from individual to individual).

There are 15 functional KIR genes known to date, 11 encoding receptors with two immunoglobulin domains (KIR2D genes) and 4 with three domains (KIR3D genes). Inhibitory KIR genes are characterized by long cytoplasmic tails featuring immunoreceptor tyrosine-based inhibitory motifs (ITIM), which upon engagement transmit inhibitory signals leading to the general shutdown of NK cell effector functions. There are six inhibitory KIRs with clearly defined specificities, all of the inhibitory kind and all for HLA class I allotypes: KIR2DL2 and KIR2DL3 for HLA-C group 1, KIR2DL1 for HLA-C group 2, KIR3DL1 for HLA-B (Bw4 epitope), KIR3DL2 with HLA-A3 and KIR2DL4 with HLA-G.

In contrast, stimulatory KIR have short cytoplasmic tails lacking ITIM, but have a charged amino acid in the transmembrane region that provides a docking site for the activating adapter molecule DAP12. KIR2DS1 is known to bind HLA-C group 2 and KIR2DS2 binds HLA-C group 1.

Literature references

Uhrberg, M. (2005). The KIR gene family: life in the fast lane of evolution. *Eur J Immunol, 35*, 10-5. ↗

Boyington, JC., Sun, PD. (2002). A structural perspective on MHC class I recognition by killer cell immunoglobulin-like receptors. *Mol Immunol, 38*, 1007-21. ↗

Parham, P., Vilches, C. (2002). KIR: diverse, rapidly evolving receptors of innate and adaptive immunity. *Annu Rev Immunol, 20*, 217-51. ↗

Editions

2007-07-08	Authored	de Bono, B.
2007-08-06	Reviewed	Trowsdale, J.
2015-05-13	Reviewed	Barrow, AD.

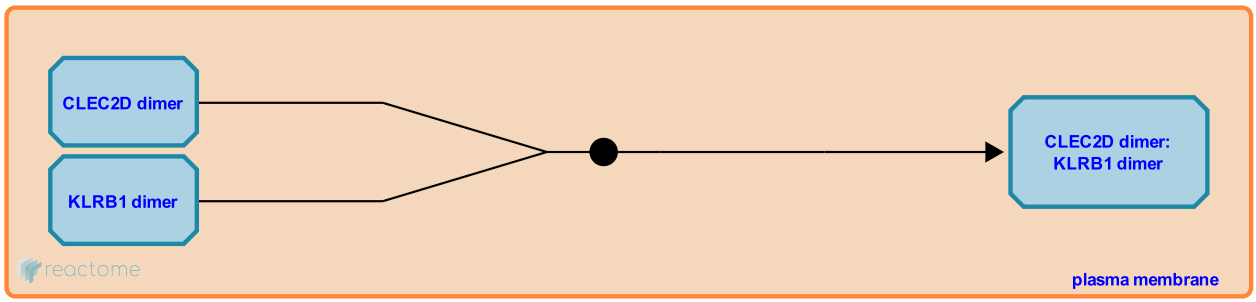
CLEC2D binds KLRB1 ↗

Location: Immunoregulatory interactions between a Lymphoid and a non-Lymphoid cell

Stable identifier: R-HSA-5685606

Type: binding

Compartments: plasma membrane



Natural killer cell surface protein P1A (NKRP1A or KLRB1 or CD161) receptor is a lectin like surface molecule expressed as a type II disulphide-linked homodimer on natural killer (NK) cells and subsets of T cells (Lknair et al. 1994, Mesci et al. 2006). Its expression is upregulated on mature NK cells by interleukin-12 (Poggi et al. 2007). It is thought to be involved in the regulation of NK and NKT cell function. Lectin-like transcript-1 molecule (LLT1) (also referred to as CLEC2D) a member of the KLR (killer cell lectin-like receptor) family has been identified as a ligand for the human NKRP1A (Aldemir et al. 2005, Rosen et al. 2005).

Literature references

Rosen, DB., Mathew, PA., Warren, HS., Lanier, LL., Alsharifi, M., Bettadapura, J. (2005). Cutting edge: lectin-like transcript-1 is a ligand for the inhibitory human NKR-P1A receptor. *J. Immunol., 175*, 7796-9. ↗

Editions

2015-03-27	Authored, Edited	Garapati, P V.
2015-05-13	Reviewed	Barrow, AD.

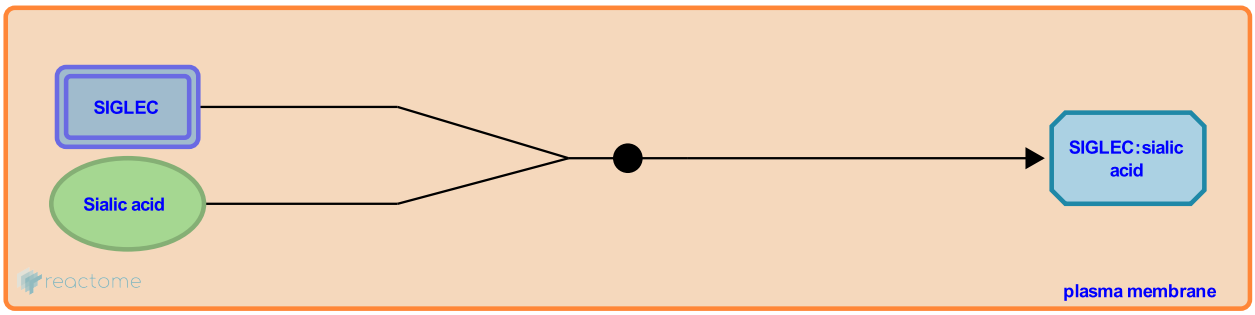
Sialic acid binds SIGLEC ↗

Location: Immunoregulatory interactions between a Lymphoid and a non-Lymphoid cell

Stable identifier: R-HSA-5685607

Type: binding

Compartments: plasma membrane



Sialic acid binding immunoglobulins (Ig)-like lectins (SIGLECs) belong to I-type lectin with a selective expression on the haematopoetic cell lineages. These have amazing structural diversity each recognizing differently linked terminal sialic acid on glycoproteins and glycolipids expressed on host cells as well as pathogen (Powell & Varki 1995, Crocker 2002). Fifteen human SIGLECs have been identified so far. Interaction with various sialylated glycoconjugates, SIGLECs undertake various functions such as internalization of sialylated pathogens, attenuation of inflammation, restraining cellular activation, attenuation of damage-associated molecular pattern-mediated in?ammation along with inhibition of NK cell activation (von Gunten & Bochner 2008, Pillai et al. 2012, Matthew et al. 2014). The sialic acid-binding Ig-like lectins CD33 (SIGLEC3), SIGLEC7 and -9 are inhibitory receptors expressed on human NK cells and subsets of peripheral T cells that recognise sialic acid-containing carbohydrates (Hernández-Caselles et al. 2006, Falco et al. 1999).

Literature references

García-Alonso, A., García-Peñarrubia, P., Martínez-Esparza, M., Alvarez-López, DM., Quintanilla-Cecconi, AM., Hernández-Caselles, T. et al. (2006). A study of CD33 (SIGLEC-3) antigen expression and function on activated human T and NK cells: two isoforms of CD33 are generated by alternative splicing. *J. Leukoc. Biol., 79*, 46-58. ↗

Angata, T., Varki, A. (2006). Siglecs--the major subfamily of I-type lectins. *Glycobiology, 16*, 1R-27R. ↗

Bottino, C., Sivori, S., Moretta, A., Moretta, L., Biassoni, R., Falco, M. et al. (1999). Identification and molecular cloning of p75/AIRM1, a novel member of the sialoadhesin family that functions as an inhibitory receptor in human natural killer cells. *J. Exp. Med., 190*, 793-802. ↗

Editions

2015-03-27	Authored, Edited	Garapati, P V.
2015-05-13	Reviewed	Barrow, AD.

viral HA binds NCRI ↗

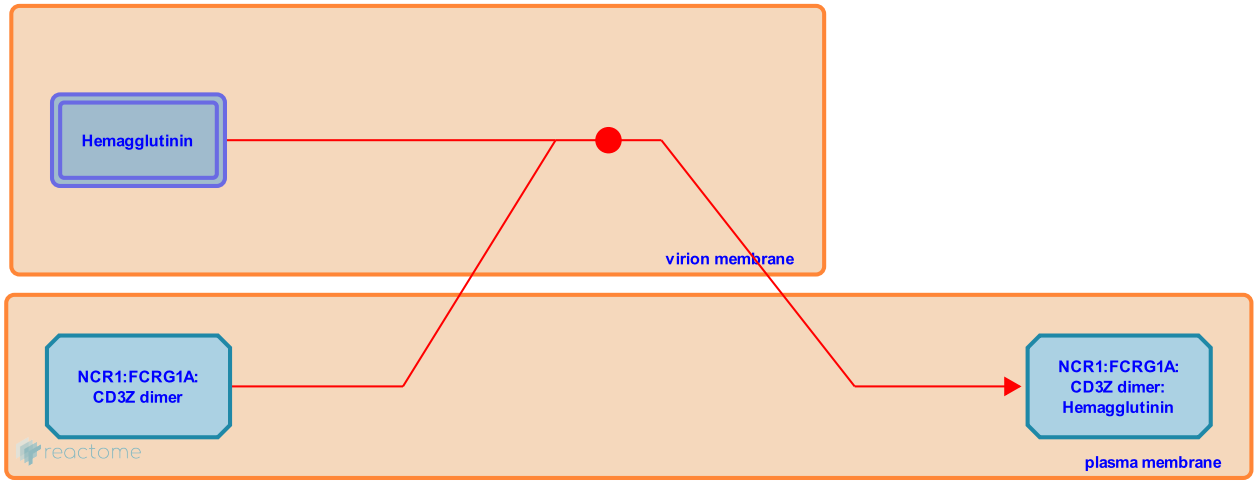
Location: Immunoregulatory interactions between a Lymphoid and a non-Lymphoid cell

Stable identifier: R-HSA-5685600

Type: binding

Compartments: virion membrane, plasma membrane

Diseases: influenza



Natural killer (NK) cells express a multitude of activating and inactivating cell surface receptors through which they recognise tumors and infected cells. Among the activating receptors, the family of Ig-like molecules is termed natural cytotoxicity receptors (NCRs). These NCRs include Natural cytotoxicity triggering receptor 1 (NCR1 also referred as NKp46 or LY94), Natural cytotoxicity triggering receptor 2 (NCR2 also referred as NKp44) and Natural cytotoxicity triggering receptor 3 (NCR3 also referred as NKp30) (Hecht et al. 2009). All three NCRs are involved in the elimination of both tumor and virus infected cells. NCRs are coupled to different signal transducing adaptor proteins, including CD3zeta, FCER1G, and KARAP/DAP12.
NCR1 (NKp46) is selectively expressed by all resting and activated human NK cells (Sivori et al. 1997). NCRI recognises and targets the direct killing of virus-infected cells. The antiviral activity is initiated by the interaction of NCR1 with hemagglutinin of influenza virus or Sendai virus (Mandelboim et al. 2001). Biochemical analysis revealed that NCR1 molecules are coupled with associated adaptor proteins CD3z and FCERIG that contain immune tyrosine-based activating motifs (ITAM) (Moretta et al. 2001).

Literature references

Bottino, C., Sivori, S., Moretta, A., Moretta, L., Morelli, L., Sanseverino, L. et al. (1997). p46, a novel natural killer cell-specific surface molecule that mediates cell activation. *J. Exp. Med., 186*, 1129-36. ↗

Bottino, C., Sivori, S., Moretta, A., Moretta, L., Morelli, L., Biassoni, R. et al. (1998). Molecular cloning of NKp46: a novel member of the immunoglobulin superfamily involved in triggering of natural cytotoxicity. *J. Exp. Med., 188* , 953-60. ↗

Editions

2015-03-27	Authored, Edited	Garapati, P V.
2015-05-13	Reviewed	Barrow, AD.

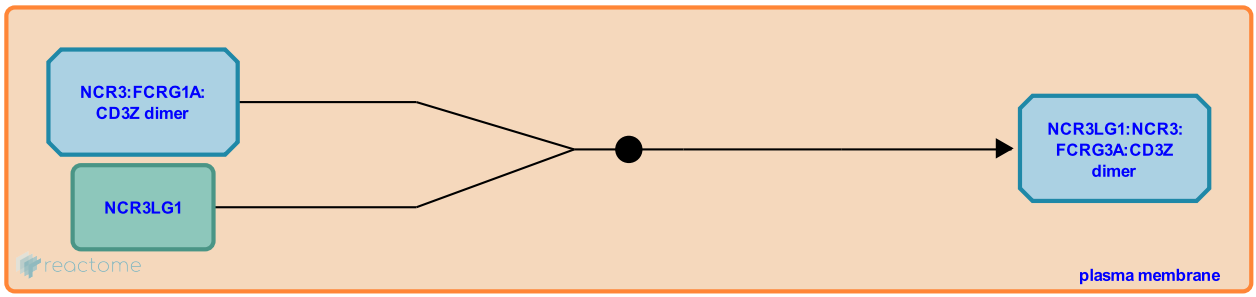
NCR3LG1 binds NCR3 ↗

Location: Immunoregulatory interactions between a Lymphoid and a non-Lymphoid cell

Stable identifier: R-HSA-5685602

Type: binding

Compartments: plasma membrane



NCR3 (NKp30) is one of the natural cytotoxicity receptors (NCRs) expressed mainly on the surface of the natural killer (NK) cells. NKp30 is a major receptor targeting virus-infected cells, malignantly transformed cells, and immature dendritic cells. NCR3 (NKp30) recognizes tumor antigens B7H6, a member of the B7 family (Kaifu et al. 2011, Brandt et al. 2009). B7H6 is not expressed normally, and is found on tumor cells, and sensitizes targets to NCR3-dependent cytotoxicity by NK cells.

Literature references

Binici, J., Koch, J. (2014). BAG-6, a jack of all trades in health and disease. *Cell. Mol. Life Sci., 71*, 1829-37. ↗

Kaifu, T., Gastinel, LN., Vivier, E., Baratin, M., Escalière, B. (2011). B7-H6/NKp30 interaction: a mechanism of alerting NK cells against tumors. *Cell. Mol. Life Sci., 68*, 3531-9. ↗

Böll, B., McKinnon, PJ., Pogge von Strandmann, E., Simhadri, VR., Hansen, HP., Hallek, M. et al. (2007). Human leukocyte antigen-B-associated transcript 3 is released from tumor cells and engages the NKp30 receptor on natural killer cells. *Immunity, 27*, 965-74. ↗

Editions

2015-03-27	Authored, Edited	Garapati, P V.
2015-05-13	Reviewed	Barrow, AD.

CMVPP65 binds NCR3

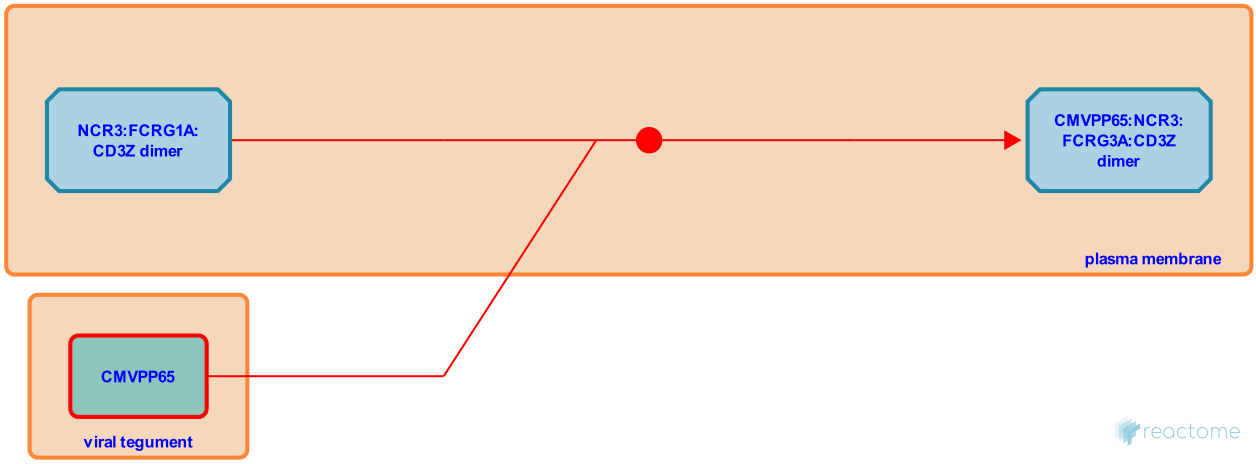
Location: Immunoregulatory interactions between a Lymphoid and a non-Lymphoid cell

Stable identifier: R-HSA-6793275

Type: binding

Compartments: plasma membrane, viral tegument

Diseases: viral infectious disease



Other potential NCR3 ligands include human cytomegalovirus (HCMV) tegument protein pp65 (CMVPP65). Interaction between NCR3 and pp65 resulted in NK cell inhibition (Arnon et al.2005).

Literature references

Binici, J., Koch, J. (2014). BAG-6, a jack of all trades in health and disease. *Cell. Mol. Life Sci., 71*, 1829-37.

Kaifu, T., Gastinel, LN., Vivier, E., Baratin, M., Escalière, B. (2011). B7-H6/NKp30 interaction: a mechanism of alerting NK cells against tumors. *Cell. Mol. Life Sci., 68*, 3531-9.

Böll, B., McKinnon, PJ., Pogge von Strandmann, E., Simhadri, VR., Hansen, HP., Hallek, M. et al. (2007). Human leukocyte antigen-B-associated transcript 3 is released from tumor cells and engages the NKp30 receptor on natural killer cells. *Immunity, 27*, 965-74.

Editions

2015-03-27	Authored, Edited	Garapati, P V.
2015-05-13	Reviewed	Barrow, AD.

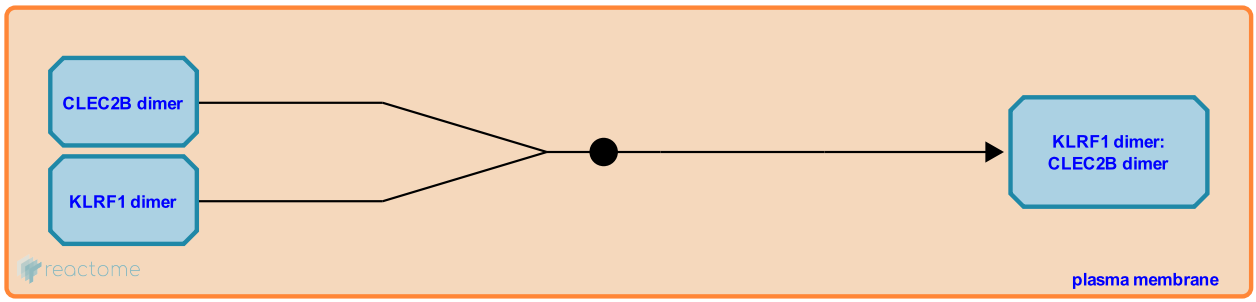
CLEC2B binds KLRF1 dimer ↗

Location: Immunoregulatory interactions between a Lymphoid and a non-Lymphoid cell

Stable identifier: R-HSA-5685608

Type: binding

Compartments: plasma membrane



Killer cell lectin-like receptor subfamily F member 1 (KLRF1 also referred as NKp80 or CLEC5C) is a homodimeric C-type lectin receptor (CTLR) expressed virtually on all human NK cells, and a minor subsets of effector memory CD8 alpha/beta T cells and gamma/delta T cells (Vitale et al. 2001). NKp80 binds to the genetically linked receptor C-type lectin domain family 2 member B (CLEC2B also referred as AICL) (Welte et al. 2006). CLEC2B is expressed as a myeloid-specific activating receptor that is upregulated by Toll-like receptor stimulation (Hamann et al. 1997). NKp80-CLEC2B interaction triggers NK cell-mediated cytolysis of malignant myeloid cells. Crosslinking of both NKp80 and CLEC2B was shown to promote an activating cross-talk between NK cells and monocytes in the presence of inflammatory cytokines (Welte et al. 2006, Klimosch et al. 2013).

Literature references

Klimosch, SN., Steinle, A., Bartel, Y., Wiemann, S. (2013). Genetically coupled receptor-ligand pair NKp80-AICL enables autonomous control of human NK cell responses. *Blood, 122*, 2380-9. ↗

Bottino, C., Moretta, A., Moretta, L., Biassoni, R., Semenzato, G., Falco, M. et al. (2001). Identification of NKp80, a novel triggering molecule expressed by human NK cells. *Eur. J. Immunol., 31*, 233-42. ↗

Waldhauer, I., Steinle, A., Welte, S., Kuttruff, S. (2006). Mutual activation of natural killer cells and monocytes mediated by NKp80-AICL interaction. *Nat. Immunol., 7*, 1334-42. ↗

Editions

2015-03-27	Authored, Edited	Garapati, P V.
2015-05-13	Reviewed	Barrow, AD.

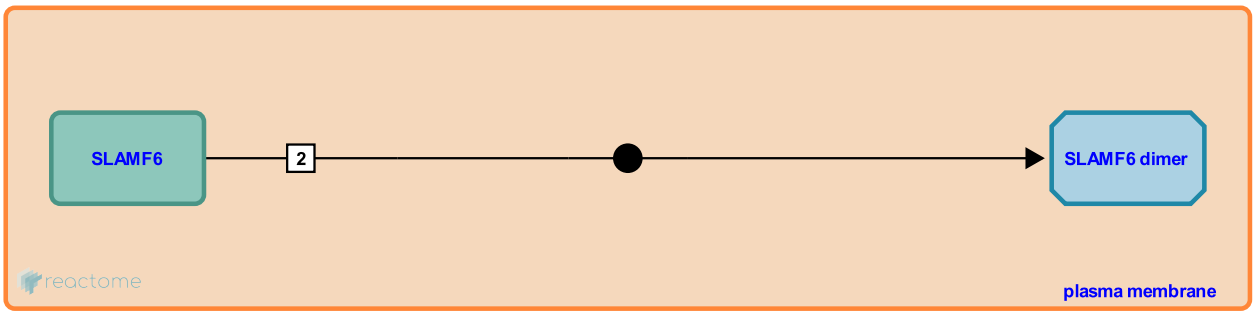
SLAMF6 binds SLAMF6 ↗

Location: Immunoregulatory interactions between a Lymphoid and a non-Lymphoid cell

Stable identifier: R-HSA-5685604

Type: binding

Compartments: plasma membrane



Members of the signaling lymphocytic-activation molecule (SLAM) family, are all encoded in the SLAM locus, and are mostly homotypic self-associating receptors expressed by cells of hemopoietic origin (Veillette et al. 2006). SLAMF6 (also called as NTB-A) is a homophilic receptor that stimulates cytotoxicity in natural killer (NK) cells, regulates bactericidal activities in neutrophils, and potentiates T helper 2 (Th2) responses (Cao et al. 2006).

Followed by: SAP and EAT2 binds SLAMF6

Literature references

Fedorov, E., Cao, E., Lary, JW., Yan, Q., Almo, SC., Cole, JL. et al. (2006). NTB-A receptor crystal structure: insights into homophilic interactions in the signaling lymphocytic activation molecule receptor family. *Immunity, 25*, 559-70. ↗

Mamchak, AA., Wang, N., Julien, A., Wei, DG., Bendelac, A., Rietdijk, S. et al. (2007). Homotypic interactions mediated by Slamf1 and Slamf6 receptors control NKT cell lineage development. *Immunity, 27*, 751-62. ↗

Editions

2015-03-27	Authored, Edited	Garapati, P V.
2015-05-13	Reviewed	Barrow, AD.

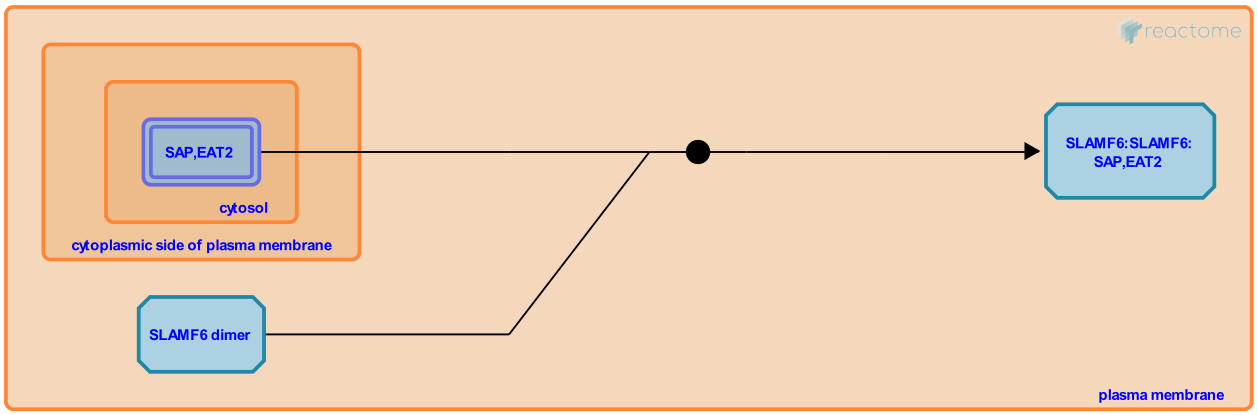
SAP and EAT2 binds SLAMF6 ↗

Location: Immunoregulatory interactions between a Lymphoid and a non-Lymphoid cell

Stable identifier: R-HSA-5685603

Type: binding

Compartments: plasma membrane, cytosol



The cytoplasmic tails of the SLAM-family receptors contain immunoreceptor tyrosine-based switch motifs (ITSMs). These ITSMs act as docking sites for the SH2 domain of SLAM-associated protein (SAP) and the related Ewing's sarcoma-associated transcript (EAT) 2 (Latour & Veillette 2004, Kageyama et al. 2012). Both SAP and EAT2 are expressed in natural killer (NK) cells, and their combined expression is essential for NK cells to kill abnormal hematopoietic cells. SAP mediates this effect by combining SLAM family receptors to the protein kinase FYN and exchange factor VAV, thereby promoting conjugate formation between NK cells and target cells. While EAT2 mediates its effects in NK cells by linking SLAM family receptors to phospholipase C-gamma, calcium fluxes amd ERK kinase (Perez-Quintero et al. 2014).

Preceded by: SLAMF6 binds SLAMF6

Literature references

Latour, S., Veillette, A. (2004). The SAP family of adaptors in immune regulation. *Semin. Immunol., 16,* 409-19. ↗

Bottino, C., Sivori, S., Moretta, A., Moretta, L., Biassoni, R., Falco, M. et al. (2001). NTB-A [correction of GNTB-A], a novel SH2D1A-associated surface molecule contributing to the inability of natural killer cells to kill Epstein-Barr virus-infected B cells in X-linked lymphoproliferative disease. *J. Exp. Med., 194,* 235-46. ↗

Editions

2015-03-27	Authored, Edited	Garapati, P V.
2015-05-13	Reviewed	Barrow, AD.

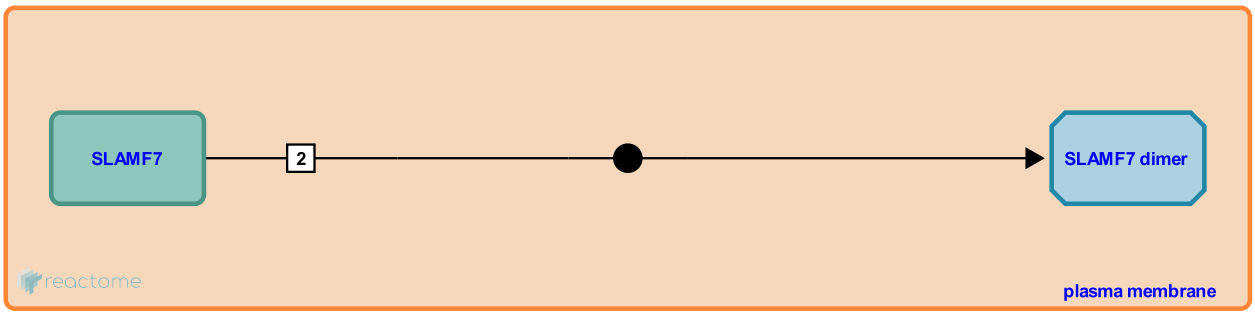
SLAMF7 binds SLAMF7 ↗

Location: Immunoregulatory interactions between a Lymphoid and a non-Lymphoid cell

Stable identifier: R-HSA-5685605

Type: binding

Compartments: plasma membrane



Signaling Lymphocyte Activation Molecule family member F7 (SLAMF7 also called as CS1 or CRACC) is a member of the CD2 family. It is expressed on CD8+ cytotoxic T lymphocytes, activated B cells, NK cells and mature dendritic cells (Boles & Mathew 2001, Bouchon et al. 2001). It has been suggested that CS1 has both activating and inhibitory functions in NK cells. It may activate NK mediated cytotoxicity through an ERK-mediated pathway in a SAP-independent manner (Bouchon et al. 2001). Most of the CD2 members interact homophilically and CS1 is shown to be a self-ligand and that homophilic interaction regulate NK cell cytolytic activity (Kumaresan et al. 2002).

Literature references

Bennett, M., Kumaresan, PR., Mathew, PA., Chuang, SS., Lai, WC. (2002). CS1, a novel member of the CD2 family, is homophilic and regulates NK cell function. *Mol. Immunol., 39*, 1-8. ↗

Horton, NC., Mathew, SO., Mathew, PA., Kim, JR. (2013). CS1 (SLAMF7) inhibits production of proinflammatory cytokines by activated monocytes. *Inflamm. Res., 62*, 765-72. ↗

Editions

2015-03-27	Authored, Edited	Garapati, P V.
2015-05-13	Reviewed	Barrow, AD.

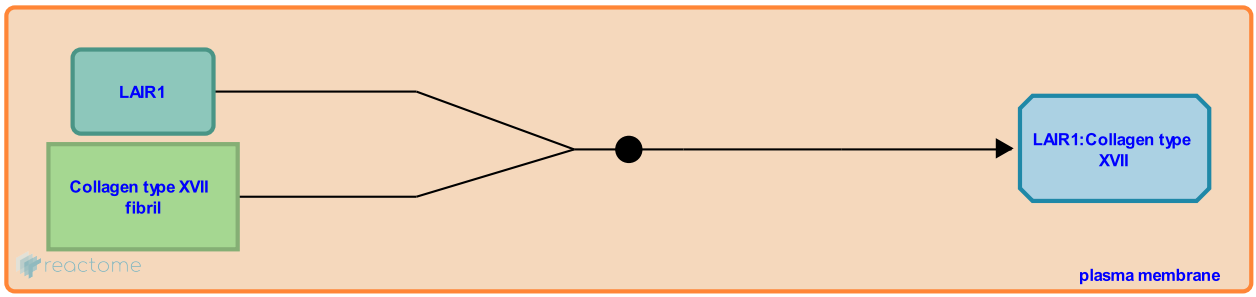
LAIR1 binds collagen ↗

Location: Immunoregulatory interactions between a Lymphoid and a non-Lymphoid cell

Stable identifier: R-HSA-5686625

Type: binding

Compartments: plasma membrane



Leukocyte-associated Ig-like receptor-1 (LAIR1 or CD305) is a member of the Ig superfamily (IgSF), which is expressed on almost all immune cells, mostly on PBMCs and thymocytes (Meyaard et al. 1997). Collagens are functional ligands for LAIR1 and upon their interaction mediate an inhibitory signal to immune cell activation (Lebbink et al. 2006, Meyaard 2008). An interesting implication of the discovery of LAIR1 as an inhibitory collagen receptor is that tumor cells, known to upregulate collagen expression, may use this interaction to downregulate responses directed against the tumor by various effector cells (Meyaard 2010). Upon cross-linking of the receptor with mAbs, LAIR1 gets phosphorylated on the tyrosine residues in the cytoplasmic ITIMs and recruits SHP1 and SHP2 and C-terminal Src Kinase (Csk) (Verbrugge et al. 2006).

Literature references

Adelmeijer, J., van Helvoort, JM., Lenting, PJ., Lebbink, RJ., Meyaard, L., Sonnenberg, A. et al. (2006). Collagens are functional, high affinity ligands for the inhibitory immune receptor LAIR-1. *J. Exp. Med., 203*, 1419-25. ↗

Lanier, LL., Chang, C., Phillips, JH., Sutherland, GR., Meyaard, L., Woollatt, E. et al. (1997). LAIR-1, a novel inhibitory receptor expressed on human mononuclear leukocytes. *Immunity, 7*, 283-90. ↗

Editions

2015-03-27	Authored, Edited	Garapati, P V.
2015-05-13	Reviewed	Barrow, AD.

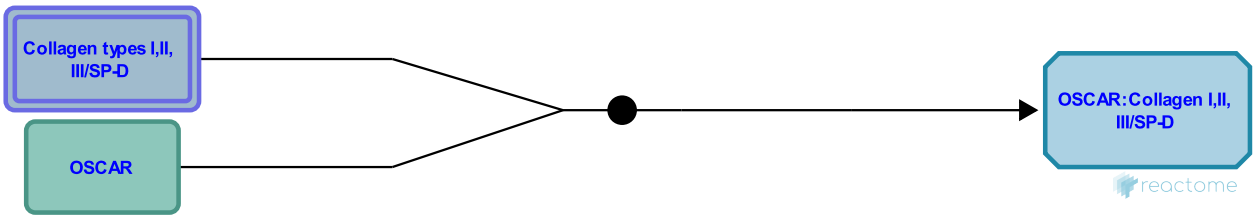
OSCAR binds collagen and SP-D ↗

Location: Immunoregulatory interactions between a Lymphoid and a non-Lymphoid cell

Stable identifier: R-HSA-5696356

Type: binding

Compartments: extracellular region



Osteoclast-associated receptor (OSCAR) is specifically expressed by preosteoclasts and it signals through the ITAM-harboring adaptor protein Fc receptor gamma (FCRG) (Merck et al. 2004). Collagen types (Col)I, II, and III have been described as OSCAR ligands, and this interaction induce costimulatory signaling in receptor activator for NF-kB-dependent osteoclastogenesis (Barrow et al. 2011, Schultz et al. 2015).
Surfactant protein D (SP-D) is a member of the collagenous lectins (collectins), which provide a first line of humoral innate immune defense to pathogens at mucosal surfaces. SP-D is mainly produced by alveolar type II epithelial cells, but is also produced outside of the lung, in the gastrointestinal and genital mucosae, salivary glands, prostate, kidney, pancreas, skin, and endothelial cells (Madsen et al. 2000). Polymorphisms in the SP-D-encoding gene SFTPD have been associated with chronic obstructive pulmonary disease and ulcerative colitis. OSCAR binds with SP-D and is localized in an intracellular compartment of alveolar macrophages.This interaction may trigger TNF-alpha productiion by inflammatory monocytes (Barrow et al. 2015).

Literature references

Palarasah, Y., Byers, DE., Vermi, W., Holehouse, AS., Barrow, AD., Colonna, M. et al. (2015). OSCAR is a receptor for surfactant protein D that activates TNF-α release from human CCR2+ inflammatory monocytes. *J. Immunol., 194*, 3317-26. ↗

Montero-Julian, F., Lebecque, S., Durand, I., Bates, EE., Merck, E., Trinchieri, G. et al. (2004). OSCAR is an FcRgamma-associated receptor that is expressed by myeloid cells and is involved in antigen presentation and activation of human dendritic cells. *Blood, 104*, 1386-95. ↗

Raynal, N., Negishi-Koga, T., Takayanagi, H., Pugh, N., Farndale, RW., Lorenzo, J. et al. (2011). OSCAR is a collagen receptor that costimulates osteoclastogenesis in DAP12-deficient humans and mice. *J. Clin. Invest., 121*, 3505-16. ↗

Editions

2015-05-13	Reviewed	Barrow, AD.
2015-05-28	Authored, Edited	Garapati, P V.

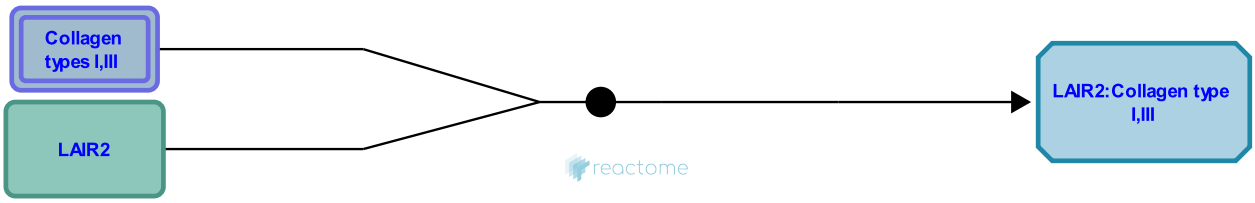
LAIR2 binds collagen ↗

Location: Immunoregulatory interactions between a Lymphoid and a non-Lymphoid cell

Stable identifier: R-HSA-5696357

Type: binding

Compartments: extracellular region



Leukocyte-associated immunoglobulin-like receptor 2 (LAIR2 or CD306) a soluble homolog of LAIR1 protein, also has high affinity for various collagen molecules and this can interfere with collagen-dependent platelet aggregation and adhesion. LAIR-2 may function as a natural competitor for LAIR-1, thereby regulating its inhibitory potential (Lebbink et al. 2008, Lenting et al. 2010).

Literature references

Raynal, N., Lenting, PJ., Lebbink, RJ., Jin, B., Meyaard, L., van Roon, JA. et al. (2008). The soluble leukocyte-associated Ig-like receptor (LAIR)-2 antagonizes the collagen/LAIR-1 inhibitory immune interaction. *J. Immunol., 180*, 1662-9. ↗

Denis, CV., Akkerman, JW., Lenting, PJ., Meyaard, L., Westerlaken, GH. (2010). Efficient inhibition of collagen-induced platelet activation and adhesion by LAIR-2, a soluble Ig-like receptor family member. *PLoS ONE, 5*, e12174. ↗

Editions

2015-05-13	Reviewed	Barrow, AD.
2015-05-28	Authored, Edited	Garapati, P V.

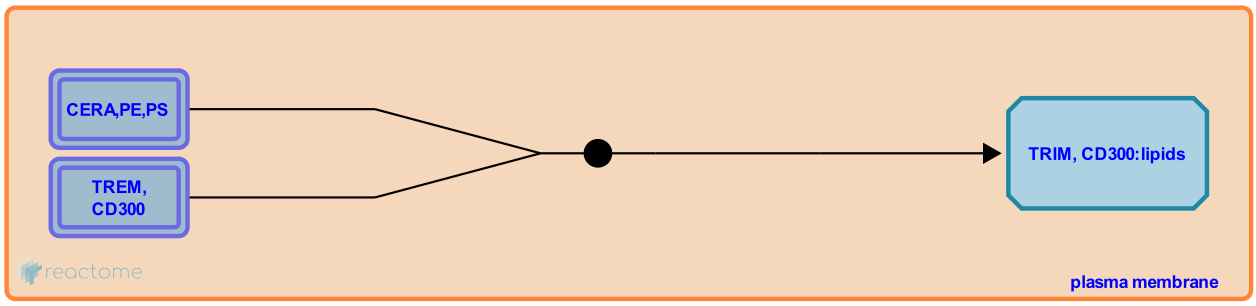
TREM,CD300 binds lipids ↗

Location: Immunoregulatory interactions between a Lymphoid and a non-Lymphoid cell

Stable identifier: R-HSA-5696358

Type: binding

Compartments: plasma membrane



The CD300 glycoproteins are a family of related leucocyte surface molecules that modulate a broad and diverse array of immune cell processes via their paired activating and inhibitory receptor functions (Clark et al. 2000, 2001, 2009a,b). Human CD300 family include 7 members and they have a single Ig-V like domain. Only CD300a and CD300f have long cytoplasmic tails with ITIMs (immunoreceptor tyrosine-based inhibitory motif), whereas the rest of the members have a short cytoplasmic tail and a short transmembrane residue and associate with adaptor proteins such as DDNAX associated protein (DAP)12, DAP10, and the Fc receptor gamma (FCRG) (Clark et al 2009a, Borrego 2013). CD300 receptors bind to polar lipids including extracellular ceramide, phosphatidylserine, and phosphatidylethanolamine, that are exposed on the outer leaflet of the plasma membrane of dead and activated cells. The CD300 gene complex has been linked to PSOR2, a susceptibility locus for psoriasis (Speckman et al. 2003, Tomfohrde et al. 1994).

Literature references

Hart, DN., Clark, GJ., Green, BJ. (2000). The CMRF-35H gene structure predicts for an independently expressed member of an ITIM/ITAM pair of molecules localized to human chromosome 17. *Tissue Antigens, 55*, 101-9. ↗

Tate, C., Ju, X., Hart, DN., Clark, GJ. (2009). The CD300 family of molecules are evolutionarily significant regulators of leukocyte functions. *Trends Immunol., 30*, 209-17. ↗

Tate, C., Ju, X., Azlan, M., Hart, DN., Clark, GJ., Ding, Y. (2009). The CD300 molecules regulate monocyte and dendritic cell functions. *Immunobiology, 214*, 730-6. ↗

Menter, A., Bowcock, AM., Taillon-Miller, P., Duan, S., Kwok, PY., Helms, C. et al. (2003). Novel immunoglobulin superfamily gene cluster, mapping to a region of human chromosome 17q25, linked to psoriasis susceptibility. *Hum. Genet., 112*, 34-41. ↗

Molloy, EJ. (2009). Triggering Receptor Expressed on Myeloid Cells (TREM) family and the application of its antagonists. *Recent Pat Antiinfect Drug Discov, 4*, 51-6. ↗

Editions

2015-05-13	Reviewed	Barrow, AD.
2015-05-28	Authored, Edited	Garapati, P V.

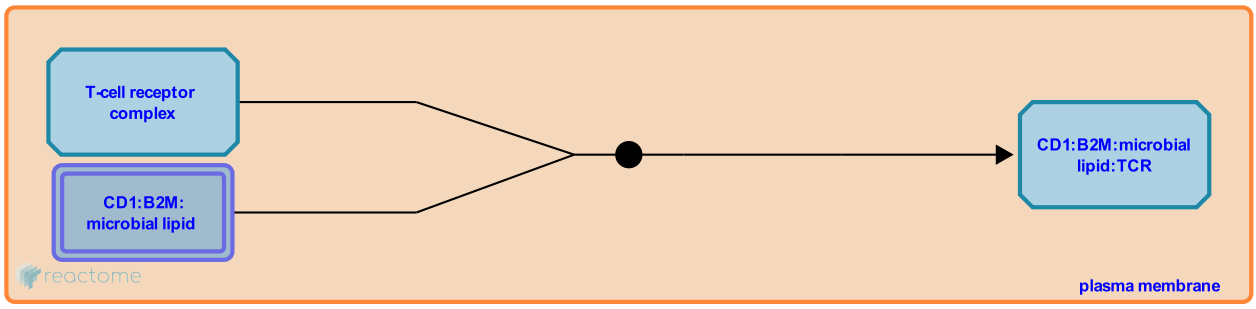
TCR binds microbial lipid-based antigen via CD1 ↗

Location: Immunoregulatory interactions between a Lymphoid and a non-Lymphoid cell

Stable identifier: R-HSA-8850356

Type: binding

Compartments: plasma membrane



The hallmark of T cell activation is the direct binding of T-cell receptor (TCR) to an antigen that is presented by an antigen-presenting molecule. TCRs are able to recognize as antigens a large variety of molecules including peptides, lipids, and vitamin metabolites (Moody DB et al. 2005; Rossjohn J et al. 2015; de Jong A 2015). While TCR responds to peptides when they are presented by classical major histocompatibility complex (MHC)-encoded class I or II molecules, specific recognition of lipids by TCR occurs when lipid-based antigens form antigenic complexes with CD1 antigen-presenting molecules (Garboczi DN et al. 1996; Beckman EM et al. 1994; De Libero G1 & Mori L 2005; Tatituri RV et al. 2013; Van Rhijn I et al. 2015).

Humans express five functional CD1 isotypes (CD1a-e), with CD1e being the only member that does not directly present antigens to T cells (Calabi F et al. 1989; Balk SP et al. 1989; de la Salle H et al. 2005). CD1a, CD1b, CD1c and CD1d are surface expressed proteins that can be found on the plasma membranes of antigen-presenting cells (APC) (Dougan SK et al. 2007). CD1 ectodomains consist of a heavy chain, which folds into three extracellular domains (alpha1, alpha2 and alpha3) noncovalently associated with beta2-microglobulin (B2M) (Moody DB et al. 2005). Antigen-binding grooves nestle between the alpha1 and alpha2 helices and are mostly lined by hydrophobic residues (Zeng Z et al. 1997). This allows the antigenic lipids to be anchored via their hydrophobic chains, so that polar motifs protrude toward the aqueous milieu (Gadola SD et al. 2002; Zajonc DM et al. 2003, 2005; Batuwangala T et al. 2004; Koch M et al. 2005; Zajonc DM et al. 2005; Scharf L et al. 2010; Garcia-Alles LF et al. 2011). Consequently, polar heads establish stimulatory contacts with TCRs, while variation in the number, length and saturation of alkyl chains may contribute to the binding to varying degrees (Borg NA et al. 2007; Garcia-Alles LF et al. 2011; Li Y et al. 2010; Pei B et al 2012; Pierce BG et al. 2014). Each of the four CD1 isoforms that directly present antigens to T cells differ in size of the antigen-binding grooves (Zajonc DM et al. 2005; Gadola SD et al. 2002; Zajonc DM et al. 2003, 2005; Batuwangala T et al. 2004; Koch M et al. 2005; Cheng TY et al. 2006; Borg NA et al. 2007; Scharf L et al. 2010; Garcia-Alles LF et al. 2011), intracellular trafficking patterns (Sugita M et al. 1999; Moody DB & Porcelli SA 2003), lipid ligand repertoire (Im JS et al. 2004; Huang S et al. 2011; Ly D & Moody DB 2014), and tissue distribution of expression (Dougan SK et al. 2007). Together with the observation that multiple CD1 isoforms have been maintained throughout mammalian evolution, this argues that each CD1 isoform plays a non-redundant role in the immune system (Dascher CC 2007; de Jong A 2015).

T cells recognize both endogenous and exogenous (derived from intracellular microbial pathogens) lipid antigens bound to CD1 molecules (Mattner J et al. 2005; Kinjo Y et al. 2005; Chang DH et al. 2008; Cohen NR et al. 2009; De Libero G et al. 2009; Zajonc DM & Girardi E 2015; Birkinshaw RW et al. 2015; de Jong A 2015). Foreign lipid antigens are extremely diverse chemically and include naturally occurring lipopeptide, glycolipids and phospholipid structures that are distinct from mammalian lipids (Moran A 2009). The best studied lipid antigens of microbial origin are glycolipids derived from the cell envelope of Mycobacteria species (De Libero G et al. 2009). They include CD1b-restricted foreign lipid antigens such as lipoarabinomannan (LAM), lipomannan (LM), phosphatidylinositol mannosides (PIM), mycolic acid, glucose monomycolate (GMM), glycerol monomycolate and diacylated sulpholipids (Sieling PA et al. 1995; Moody DB et al. 2000; Layre E et al. 2009; Gilleron M et al. 2004; Kasmar AG et al. 2011). While most mammalian glycolipids have beta-linked carbohydrates attached to the lipid backbone, bacterial glycolipids typically have alpha-linkage. The structural difference in the linkage may contribute to the highly specific interaction of the TCR with the CD1:lipid antigen complex thus dictating the outcome of the immune response (Scott-Browne JP et al. 2007; Zajonc DM et al. 2005, 2007). In addition, lipopeptides, such as didehydroxymycobactin (DDM), an intermediate in the biosynthesis of the mycobacterial iron scavenger mycobactin siderophores, can be recognized by CD1a-restricted T cells (Moody DB et al. 2004; Zajonc DM et al. 2005).

Diacylglycerols, such as the alpha-galactosyldiacylglycerol from the spirochete Borrelia burgdorferi or an alpha-linkage glycosphingolipid (alpha-glucuronosylceramide) found in alpha-proteobacteria can be presented by CD1d to stimulate invariant natural killer T (iNKT) cells (Sriram V et al. 2005; Kinjo Y et al. 2006). The ability of T cells to see lipid antigens bound to CD1 proteins enables these lymphocytes to sense changes in the lipid composition of cells and tissues as a result of infections or inflammation (Mattner J et al. 2005; Kinjo Y et al. 2005; Chang DH et al. 2008; Cohen NR et al. 2009; de Jong A 2015).

The Reactome event shows foreign lipid-based molecules that have been reported to function as antigens for CD1-restricted T cells (Batuwangala T et al. 2004; Roy S et al. 2014; Garcia-Alles LF et al. 2011; Wang J et al. 2010; Sieling PA et al. 1995; Guiard J et al. 2009; Kasmar AG et al. 2011).

Literature references

Girardi, E., Zajonc, DM. (2015). Recognition of Microbial Glycolipids by Natural Killer T Cells. *Front Immunol, 6*, 400. ↗

Bloom, BR., Prigozy, TI., Kronenberg, M., Brennan, PJ., Soriano, T., Brenner, MB. et al. (1995). CD1-restricted T cell recognition of microbial lipoglycan antigens. *Science, 269*, 227-30. ↗

Moody, DB., Zajonc, DM., Wilson, IA. (2005). Anatomy of CD1-lipid antigen complexes. *Nat. Rev. Immunol., 5*, 387-99. ↗

Barral, DC., Brenner, MB. (2007). CD1 antigen presentation: how it works. *Nat. Rev. Immunol., 7*, 929-41. ↗

Moody, DB., van Rhijn, I. (2015). CD1 and mycobacterial lipids activate human T cells. *Immunol. Rev., 264*, 138-53. ↗

Editions

2015-12-19	Authored	Shamovsky, V.
2016-02-10	Reviewed	Zajonc, DM., Adams, EJ., Luoma, AM.
2016-02-22	Edited	Shamovsky, V.

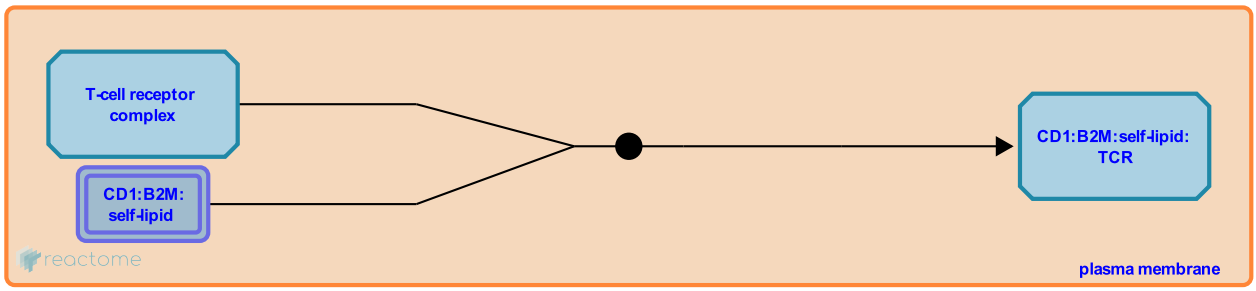
TCR binds self-lipid-based antigen via CD1 ↗

Location: Immunoregulatory interactions between a Lymphoid and a non-Lymphoid cell

Stable identifier: R-HSA-8850326

Type: binding

Compartments: plasma membrane



T lymphocytes have developed the capacity to recognize as antigens a large variety of molecules including peptides, lipids, and vitamin metabolites (Moody DB et al. 2005; Rossjohn J et al. 2015; de Jong A 2015). Specific recognition of lipids by T-cell receptors (TCR) occurs when these molecules form antigenic complexes using functionally nonpolymorphic CD1 molecules (Beckman EM et al. 1994; De Libero G1 & Mori L 2005; Tatituri RV et al. 2013; Van Rhijn I et al. 2015).

Humans express five functional CD1 isotypes (CD1a-e), with CD1e being the only member that does not directly present antigens to T cells (Calabi F et al. 1989; Balk SP et al. 1989; de la Salle H et al. 2005). CD1a, CD1b, CD1c and CD1d are surface expressed proteins that can be found on the plasma membranes of antigen-presenting cells (APC) (Dougan SK et al. 2007). CD1 ectodomains consist of a heavy chain, which folds into three extracellular domains (alpha1, alpha2 and alpha3) noncovalently associated with beta2-microglobulin (B2M) (Moody DB et al. 2005). Antigen-binding grooves nestle between the alpha1 and alpha2 helices and are mostly lined by hydrophobic residues (Zeng Z et al. 1997). This allows the antigenic lipids to be anchored via their hydrophobic chains, so that polar motifs protrude toward the aqueous milieu (Gadola SD et al. 2002; Zajonc DM et al. 2003, 2005; Batuwangala T et al. 2004; Koch M et al. 2005; Zajonc DM et al. 2005; Scharf L et al. 2010; Garcia-Alles LF et al. 2011). Consequently, polar heads establish stimulatory contacts with TCRs, while variation in the number, length and saturation of alkyl chains may contribute to the binding to varying degrees (Borg NA et al. 2007; Garcia-Alles LF et al. 2011; Li Y et al. 2010; Pierce BG et al. 2014). Each of the four CD1 isoforms that directly present antigens to T cells differ in size of the antigen-binding grooves (Zajonc DM et al. 2005; Gadola SD et al. 2002; Zajonc DM et al. 2003, 2005; Batuwangala T et al. 2004; Koch M et al. 2005; Cheng TY et al. 2006; Borg NA et al. 2007; Scharf L et al. 2010; Garcia-Alles LF et al. 2011), intracellular trafficking patterns (Sugita M et al. 1999; Moody DB & Porcelli SA 2003), lipid ligand repertoire (Im JS et al. 2004; Huang S et al. 2011; Ly D & Moody DB 2014), and tissue distribution of expression (Dougan SK et al. 2007). Together with the observation that multiple CD1 isoforms have been maintained throughout mammalian evolution, this argues that each CD1 isoform plays a non-redundant role in the immune system (Dascher CC 2007; de Jong A 2015).

A large spectrum of self- and foreign lipids associates with members of CD1 family (Mattner J et al. 2005; Kinjo Y et al. 2005; Chang DH et al. 2008; Cohen NR et al. 2009; De Libero G et al. 2009; Zajonc DM & Girardi E 2015; Birkinshaw RW et al. 2015; de Jong A 2015). CD1-bound self-derived lipid antigens, including gangliosides, sulfatide, phosphoglycerolipids and sphingomyelin, can stimulate specialized subsets of T cells though the importance of self-lipid interactions with TCRs can vary (Birkinshaw RW et al. 2015; Borg NA et al. 2007; Luoma AM et al. 2013, 2014; Lepore M et al. 2014; Roy S et al. 2016). The ability of of both alphabeta and gammadelta T cells to recognize self lipid loaded CD1 molecules enables these lymphocytes to sense changes in the lipid composition of cells and tissues as a result of infections, inflammation, or malignancies (Brennan PJ et al. 2011; Chang DH et al. 2008; Cohen NR et al. 2009; Luoma et al. 2014; Lepore M et al. 2014; de Jong A 2014, 2015).

The Reactome event shows self lipid-based molecules that have been reported to function as antigens for CD1-restricted T cells (Shamshiev A et al. 2002; Birkinshaw RW et al. 2015; de Jong A 2015).

Literature references

Brown, J., Silk, JD., Salio, M., Cerundolo, V., Jones, EY. (2008). Structural and functional aspects of lipid binding by CD1 molecules. *Annu. Rev. Cell Dev. Biol., 24*, 369-95. ↗

Barral, DC., Brenner, MB. (2007). CD1 antigen presentation: how it works. *Nat. Rev. Immunol., 7*, 929-41. ↗

Moody, DB., Zajonc, DM., Wilson, IA. (2005). Anatomy of CD1-lipid antigen complexes. *Nat. Rev. Immunol., 5*, 387-99. ↗

de Jong, A. (2015). Activation of human T cells by CD1 and self-lipids. *Immunol. Rev., 267*, 16-29. ↗

Editions

2015-12-19	Authored	Shamovsky, V.
2016-02-10	Reviewed	Zajonc, DM., Adams, EJ., Luoma, AM.
2016-02-22	Edited	Shamovsky, V.

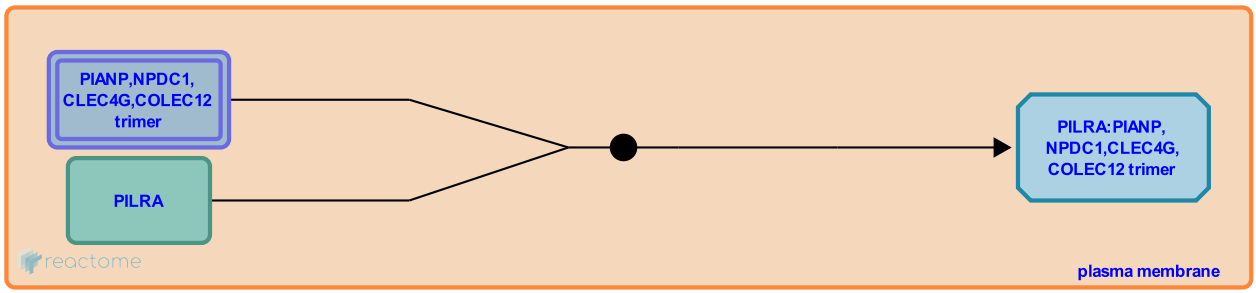
PILRA binds PIANP, COLLEC12 trimer, NPDC1, CLEC4G ↗

Location: Immunoregulatory interactions between a Lymphoid and a non-Lymphoid cell

Stable identifier: R-HSA-8862090

Type: binding

Compartments: plasma membrane



Paired immunoglobulin-like type 2 receptor alpha (PILRA) binds to multiple ligands including CD99 (Shiratori et al. 2004), PILR-associating neural protein (PIANP, PANP) (Kogure et al. 2011), Herpes simplex virus-1 glycoprotein B (Satoh et al. 2008), Collectin-12 (COLEC12), Neural proliferation differentiation and control protein 1 (NPDC1) and C-type lectin domain family 4 member G (CLEC4G) (Sun et al. 2012). Binding studies suggest that PILR recognizes a complex ligand domain involving both silica acid and protein motif(s). Thus, PILR is evolved to engage multiple ligands with common molecular determinants to modulate myeloid cell functions in anatomical settings where PILR ligands are expressed. The precise function of PILRa-Ligand interaction is not well understood (Sun et al. 2012). PILRa negatively regulates inflammation and keeps myeloid system in check. Pilra KO mice produce more pathogenic cytokines during inflammation and are prone to enhanced autoimmune arthritis. Correspondingly, anti-PILRa mAb ameliorated inflammation in mouse arthritis models and suppressed the production of proinflammatory cytokines (Sun et al. 2014).

Literature references

Wang, J., Arase, H., Kogure, A., Lanier, LL., Shiratori, I. (2011). PANP is a novel O-glycosylated PILRα ligand expressed in neural tissues. *Biochem. Biophys. Res. Commun., 405*, 428-33. ↗

Baginski, TK., Sun, Y., Tom, I., Gonzalez, LC., Zarrin, AA., Mukhyala, K. et al. (2012). Evolutionarily conserved paired immunoglobulin-like receptor α (PILRα) domain mediates its interaction with diverse sialylated ligands. *J. Biol. Chem., 287*, 15837-50. ↗

Arase, H., Ogasawara, K., Saito, T., Lanier, LL., Shiratori, I. (2004). Activation of natural killer cells and dendritic cells upon recognition of a novel CD99-like ligand by paired immunoglobulin-like type 2 receptor. *J. Exp. Med., 199*, 525-33. ↗

Editions

2016-02-25	Authored	Jupe, S.
2017-01-30	Edited	Jupe, S.
2017-01-30	Reviewed	Zarrin, AA.

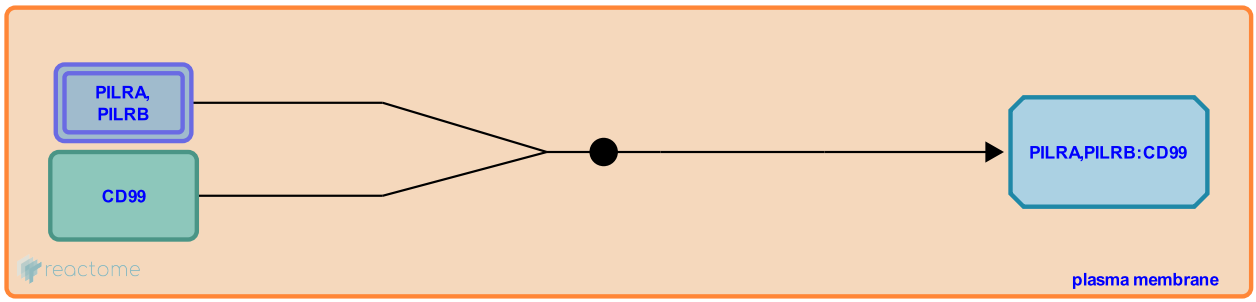
PILRA,PILRB bind CD99

Location: Immunoregulatory interactions between a Lymphoid and a non-Lymphoid cell

Stable identifier: R-HSA-8862084

Type: binding

Compartments: plasma membrane



The paired immunoglobulin-like type 2 receptors (PILR) comprise the inhibitory receptor PILRA and the activating receptor PILRB (Shiratori et al. 2004). The inhibitory PILRA is mainly expressed on macrophages, dendritic cells and granulocytes, whereas the activating PILRB is mainly on activated NK cells. Both recognize mouse CD99 as a ligand, but the binding affinity of PILRB is much lower (Tabata et al. 2008). Mouse NK cells expressing PILRB mediate cytotoxicity against CD99-positive target cells, suggesting that this receptor may be involved in NK cell recognition (Shiratori et al. 2004).

Literature references

Kajikawa, M., Wang, J., Arase, H., Kohda, D., Maenaka, K., Tabata, S. et al. (2008). Biophysical characterization of O-glycosylated CD99 recognition by paired Ig-like type 2 receptors. *J. Biol. Chem., 283*, 8893-901.

Editions

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2017-01-30	Edited	Jupe, S.
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Table of Contents