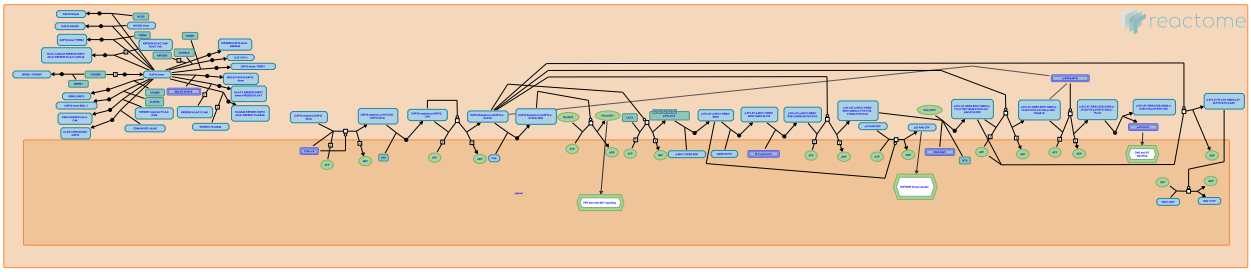
DAP12 interactions



Barclay, AN., Garapati, P V., Lanier, LL.

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

This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the Reactome Textbook.

02/05/2024

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. ↗

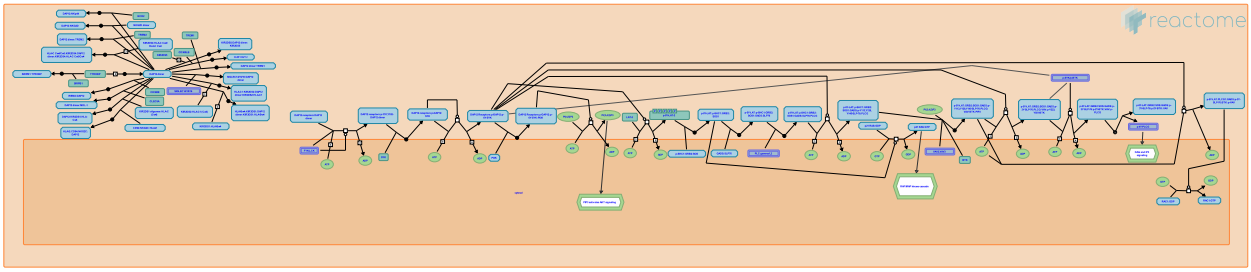
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

DAP12 interactions ↗

Stable identifier: R-HSA-2172127



DNAX activation protein of 12kDa (DAP12) is an immunoreceptor tyrosine-based activation motif (ITAM)-bearing adapter molecule that transduces activating signals in natural killer (NK) and myeloid cells. It mediates signalling for multiple cell-surface receptors expressed by these cells, associating with receptor chains through complementary charged transmembrane amino acids that form a salt-bridge in the context of the hydrophobic lipid bilayer (Lanier et al. 1998). DAP12 homodimers associate with a variety of receptors expressed by macrophages, monocytes and myeloid cells including TREM2, Siglec H and SIRP-beta, as well as activating KIR, LY49 and the NKG2C proteins expressed by NK cells. DAP12 is expressed at the cell surface, with most of the protein lying on the cytoplasmic side of the membrane (Turnbull & Colonna 2007, Tessarz & Cerwenka 2008).

Literature references

Lanier, LL., Phillips, JH., Corliss, BC., Leong, C., Wu, J. (1998). Immunoreceptor DAP12 bearing a tyrosine-based activation motif is involved in activating NK cells. *Nature, 391*, 703-7. ↗

Vivier, E., Tomasello, E. (2005). KARAP/DAP12/TYROBP: three names and a multiplicity of biological functions. *Eur J Immunol, 35*, 1670-7. ↗

Colonna, M., Turnbull, IR. (2007). Activating and inhibitory functions of DAP12. *Nat. Rev. Immunol., 7*, 155-61. ↗

Lanier, LL. (2009). DAP10- and DAP12-associated receptors in innate immunity. *Immunol. Rev., 227*, 150-60. ↗

Tessarz, AS., Cerwenka, A. (2008). The TREM-1/DAP12 pathway. *Immunol Lett, 116*, 111-6. ↗

Editions

2012-05-25	Authored, Edited	Garapati, P V.
2012-08-09	Reviewed	Lanier, LL.

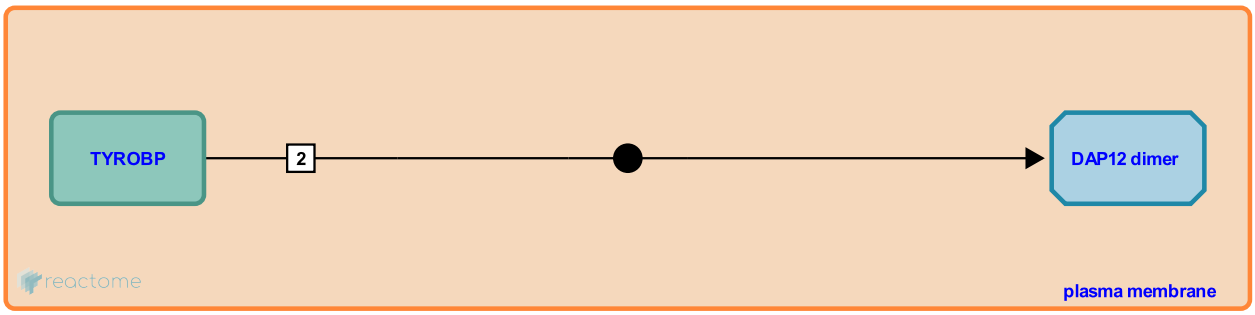
Dimerization of DAP12 ↗

Location: DAP12 interactions

Stable identifier: R-HSA-2130151

Type: binding

Compartments: plasma membrane



DAP12 is expressed as a disulfide-bonded homodimer on NK cells, myeloid cells and a subset of T cells. Cystine-7 in the extracellular domain is involved in the interchain disulphide bond (numbering according to Lanier et al. 1998).

Followed by: Interaction of DAP12 and NKp44, Interaction of DAP12 and TREM1, Interaction of DAP12 and KIR2DS4, Interaction of DAP12 and KIR2DS2, Interaction of DAP12 and KIR2DS5, Interaction of DAP12 and CLM7, Interaction of SIGLEC14/15/16 and DAP12, Interaction of DAP12 and KIR2DS1, Interaction of DAP12 and IREM2, Interaction of DAP12 and MDL-1, Interaction of DAP12 and KIR3DS1, SIRP beta binds TYROBP, Interaction of DAP12 and TREM2, DAP12 interacts with NKG2C, Interaction of DAP12 and NKG2D

Literature references

Lanier, LL., Phillips, JH., Corliss, BC., Leong, C., Wu, J. (1998). Immunoreceptor DAP12 bearing a tyrosine-based activation motif is involved in activating NK cells. *Nature, 391*, 703-7. ↗

Wucherpfennig, KW., Chou, JJ., Call, ME. (2010). The structural basis for intramembrane assembly of an activating immunoreceptor complex. *Nat Immunol, 11*, 1023-9. ↗

Wucherpfennig, KW., Call, ME., Feng, J. (2006). The assembly of diverse immune receptors is focused on a polar membrane-embedded interaction site. *PLoS Biol, 4*, e142. ↗

Editions

2012-05-25	Authored, Edited	Garapati, P V.
2012-08-09	Reviewed	Lanier, LL.

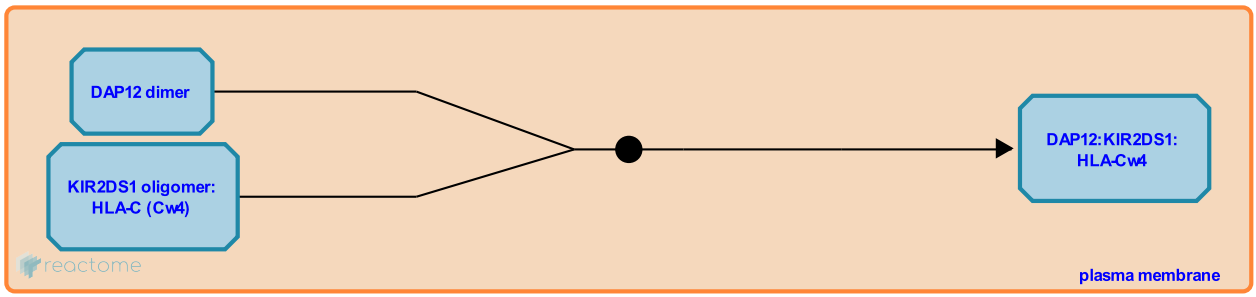
Interaction of DAP12 and KIR2DS1 ↗

Location: DAP12 interactions

Stable identifier: R-HSA-2272795

Type: binding

Compartments: plasma membrane



Killer cell immunoglobulin-like two-domain short-tail receptor 1 (KIR2DS1) is one of the activating KIR receptors expressed on the surface of NK cells. It recognizes and binds to ligand HLA-C2:peptide complexes. KIR2DS1 oligomerizes upon interaction with its HLA-Class I ligands. The interaction between the peptide-HLA and KIR2DS1 oligomers leads to activation of the DAP12 signaling cascade. The engagement of KIR2DS1 with HLA-C2 is not sufficient to drive NK cell cytotoxicity or IFN-gamma production (Stewart et al. 2005). Recognition of HLA-C2 by KIR2DS1 is involved in the anti-leukemic activity of alloreactive NK cells and associated with protection against Hodgkin's lymphoma (Cognet et al. 2010). The presence of the HLA-C2 allele HLA-Cw6 in combination with KIR2DS1 is a major risk factor for psoriasis (Ploski et al. 2006).

Preceded by: Dimerization of DAP12

Literature references

Gauthier, L., Rieux-Laucat, F., Magérus-Chatinet, A., André, P., Farnarier, C., Schleinitz, N. et al. (2010). Expression of the HLA-C2-specific activating killer-cell Ig-like receptor KIR2DS1 on NK and T cells. *Clin. Immunol., 135*, 26-32 . ↗

Editions

2012-05-25	Authored, Edited	Garapati, P V.
2012-08-09	Reviewed	Lanier, LL.

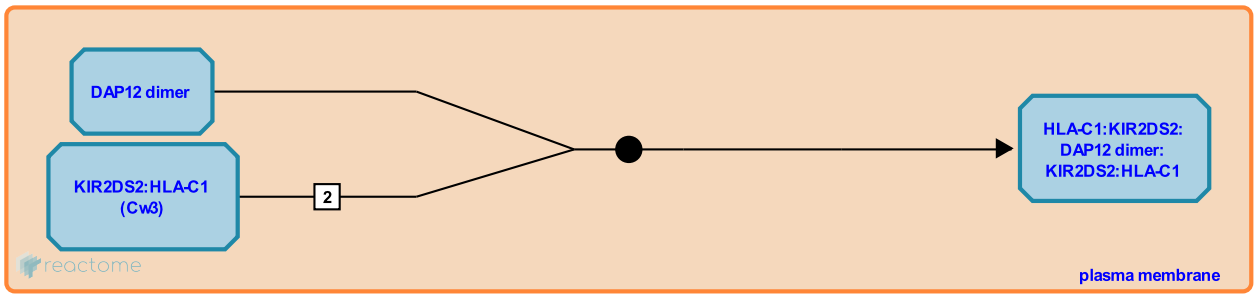
Interaction of DAP12 and KIR2DS2 ↗

Location: DAP12 interactions

Stable identifier: R-HSA-210309

Type: binding

Compartments: plasma membrane



Killer cell immunoglobulin-like two-domain short-tail receptor 2 (KIR2DS2) is an activating KIR receptor invariably expressed on the cell surface of NK cells and subsets of T cells. The ligand specificity of KIR2DS2 is unknown; it does not bind the HLA-Cw3 molecules recognised by the inhibitory receptor KIR2DL2, despite 99% extracellular amino acid identity (Saulquin et al. 2003). In the presence of DAP12, cross-linking of KIR2DS2 with monoclonal antibody leads to phosphorylation of JNK and ERK and activation of both cytotoxicity and IFN-production.

Preceded by: Dimerization of DAP12

Literature references

Vivier, E., Gastinel, LN., Saulquin, X. (2003). Crystal structure of the human natural killer cell activating receptor KIR2DS2 (CD158j). *J Exp Med, 197*, 933-8. ↗

Editions

2012-05-25	Authored, Edited	Garapati, P V.
2012-08-09	Reviewed	Lanier, LL.

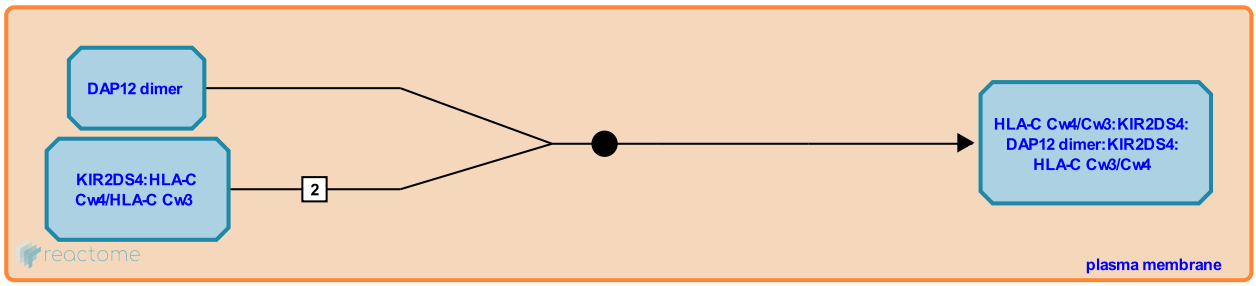
Interaction of DAP12 and KIR2DS4 ↗

Location: DAP12 interactions

Stable identifier: R-HSA-2272753

Type: binding

Compartments: plasma membrane



Killer cell immunoglobulin-like two-domain short-tail receptor 4 (KIR2DS4) is the most prevalent lineage III-activating KIR receptor. It interacts weakly but specifically with HLA-Cw3 and HLA-Cw4 and may also bind to an uncharacterised non-MHC molecule. It can associate with DAP12, activating NK cells.

Preceded by: Dimerization of DAP12

Literature references

Norman, PJ., Abi-Rached, L., Hammond, JA., Graef, T., Parham, P., Robinson, PJ. et al. (2009). KIR2DS4 is a product of gene conversion with KIR3DL2 that introduced specificity for HLA-A*11 while diminishing avidity for HLA-C. *J. Exp. Med., 206*, 2557-72. ↗

Tarcic, G., Mandelboim, O., Drize, O., Achdout, H., Merims, S., Gruda, R. et al. (2004). MHC class I-independent recognition of NK-activating receptor KIR2DS4. *J. Immunol., 173*, 1819-25. ↗

Editions

2012-05-25	Authored, Edited	Garapati, P V.
2012-08-09	Reviewed	Lanier, LL.

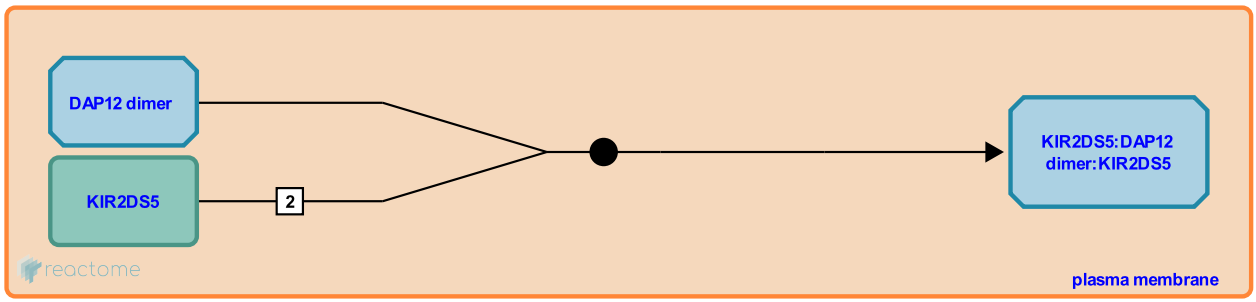
Interaction of DAP12 and KIR2DS5 ↗

Location: DAP12 interactions

Stable identifier: R-HSA-2272668

Type: binding

Compartments: plasma membrane



Killer cell immunoglobulin-like two-domain short-tail receptor 5 (KIR2DS5) is an activating KIR receptor expressed on natural killer (NK) cells and subpopulations of T lymphocytes (Nowak et al. 2010). KIR2DS5 has two Ig domains of the D1-D2 type, a short cytoplasmic tail and a positive charged transmembrane (TM) portion.
No physiological ligand has yet been identified for KIR2DS5 but it is able to associate with DAP12 and induce both cytotoxicity and cytokine release when KIR2DS5 is cross-linked with monoclonal antibody (Della Chiesa et al. 2008).

Preceded by: Dimerization of DAP12

Literature references

Vitale, M., Falco, M., Moretta, A., Romeo, E., Balsamo, M., Bottino, C. et al. (2008). Evidence that the KIR2DS5 gene codes for a surface receptor triggering natural killer cell function. *Eur. J. Immunol., 38*, 2284-9. ↗

Jankowska, R., Tchórzewski, H., Malinowski, A., Wilczyński, J., Kurpisz, M., Nowak, I. et al. (2010). Does the KIR2DS5 gene protect from some human diseases?. *PLoS ONE, 5*, e12381. ↗

Editions

2012-05-25	Authored, Edited	Garapati, P V.
2012-08-09	Reviewed	Lanier, LL.

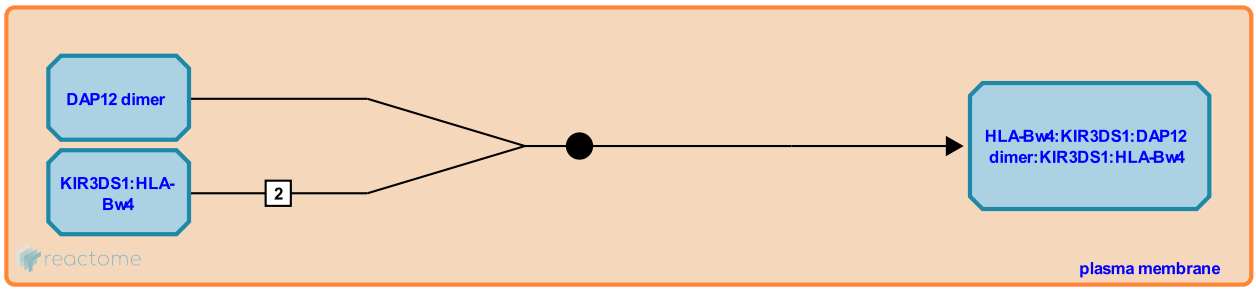
Interaction of DAP12 and KIR3DS1 ↗

Location: DAP12 interactions

Stable identifier: R-HSA-210298

Type: binding

Compartments: plasma membrane



Killer cell immunoglobulin-like three-domain short-tail receptor 1 (KIR3DS1) is a member of the KIR family expressed on peripheral natural killer (NK) cells and implicated in protection against HIV (Carr et al. 2007, Pascal et al. 2007). The physiological ligand for KIR3DS1 is not clearly determined but it has been suggested to bind HLA-B Bw4-80I on HIV-1-infected target cells (Qi et al. 2006). KIR3DS1 associates with DAP12 and this association enhances its cell surface expression. Crosslinking KIR3DS1 with a monoclonal antibody stimulates NK cell-mediated cytolysis and IFN-gamma production (Carr et al. 2007).

Preceded by: Dimerization of DAP12

Literature references

Gao, X., O'Brien, SJ., Trowsdale, J., Martin, MP., Buchbinder, S., Carrington, M. et al. (2006). KIR/HLA pleiotropism: protection against both HIV and opportunistic infections. *PLoS Pathog, 2*, e79. ↗

Baseler, MW., Anderson, SK., Alter, G., Martin, MP., Metcalf, JA., Altfeld, M. et al. (2007). Detection of KIR3DS1 on the cell surface of peripheral blood NK cells facilitates identification of a novel null allele and assessment of KIR3DS1 expression during HIV-1 infection. *J Immunol, 179*, 1625-33. ↗

Lanier, LL., Rosen, DB., Nixon, DF., Michaelsson, J., Arase, H., Carr, WH. (2007). Cutting Edge: KIR3DS1, a gene implicated in resistance to progression to AIDS, encodes a DAP12-associated receptor expressed on NK cells that triggers NK cell activation. *J Immunol, 178*, 647-51. ↗

Editions

2012-05-25	Authored, Edited	Garapati, P V.
2012-08-09	Reviewed	Lanier, LL.

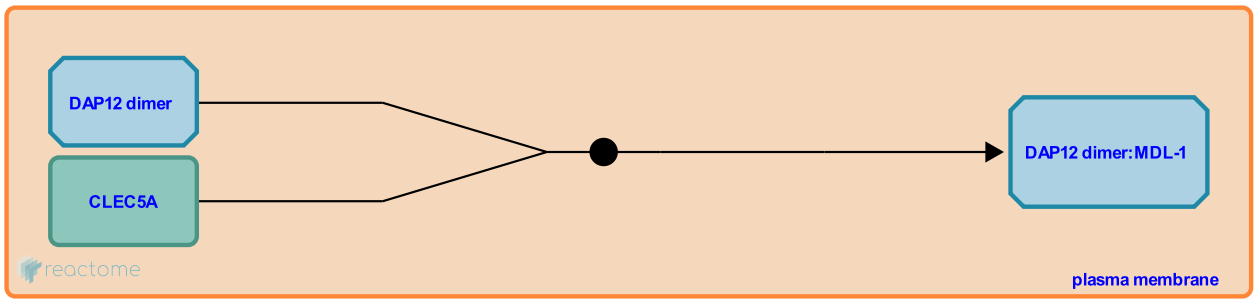
Interaction of DAP12 and MDL-1 ↗

Location: DAP12 interactions

Stable identifier: R-HSA-210271

Type: binding

Compartments: plasma membrane



Myeloid DAP12-associating lectin (MDL)-1, also designated CLEC5A, is a type II transmembrane protein belonging to the C-type lectin superfamily and expressed exclusively in monocytes and macrophages. MDL-1 contains a charged residue in the transmembrane region and this enables it to pair with DAP12 dimers. MDL-1's natural mammalian ligand is unknown, but MDL-1 is a receptor for Dengue virus CLEC5A is critical for dengue-virus-induced lethal disease (Chen et al 2008). Engagement with DAP12 has been shown to regulate osteoclastogenesis and myeloid cell-associated inflammatory responses (Bakker et al. 1999, Aoki et al. 2009, Inui et al 2009, Joyce-Shaikh et al. 2010, Cheung et al. 2011).

Preceded by: Dimerization of DAP12

Literature references

Vivier, E., Tomasello, E. (2005). KARAP/DAP12/TYROBP: three names and a multiplicity of biological functions. *Eur J Immunol, 35*, 1670-7. ↗

Lanier, LL., Phillips, JH., Baker, E., Bakker, AB., Sutherland, GR. (1999). Myeloid DAP12-associating lectin (MDL)-1 is a cell surface receptor involved in the activation of myeloid cells. *Proc Natl Acad Sci U S A, 96*, 9792-6. ↗

Editions

2012-05-25	Authored, Edited	Garapati, P V.
2012-08-09	Reviewed	Lanier, LL.

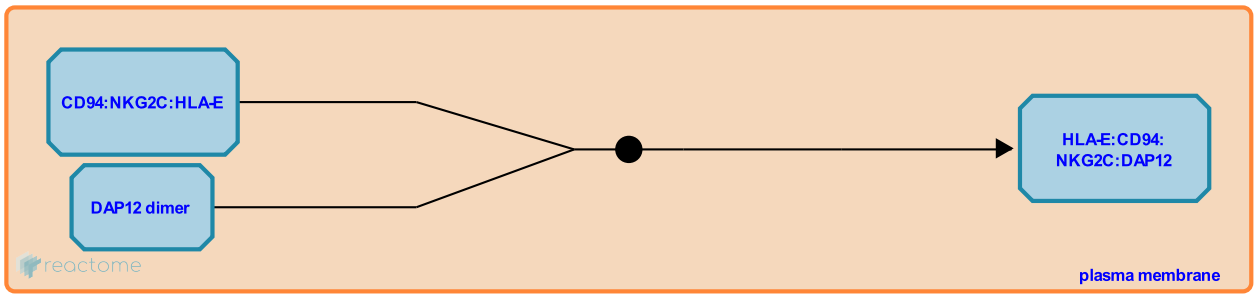
DAP12 interacts with NKG2C ↗

Location: DAP12 interactions

Stable identifier: R-HSA-2172126

Type: binding

Compartments: plasma membrane



NKG2C, a C-type lectin-like surface receptor, is a member of the NKG2 family and forms heterodimers with CD94 that is expressed on NK cells and a subset of T cells. The CD94/NKG2C killer lectin-like receptor (KLR) perform an important role in immunosurveillance by binding to HLA-E complexes that present peptides derived from the signal sequences of other HLA class I molecules (A, B, C, G), thereby monitoring MHC class I expression. It has been proposed that the activating receptor CD94/NKG2C may contribute with other NK stimulatory molecules (like NKp46, NKp44 and NKp30 and NKG2D) to trigger effector functions when the control exerted by inhibitory receptors is overcome (Guma et al. 2005). NKG2C/CD94 associates with the ITAM-containing adapter protein DAP12 and this leads to cell activation and cytotoxic function. The charged residues in the transmembrane domains of DAP12 and NKG2C are necessary for this interaction (Lanier et al. 1998). NK cells expressing the CD94/NKG2C receptor are preferentially expanded during cytomegalovirus infection in humans (Lopez-Verges et al. 2011)

Preceded by: Dimerization of DAP12

Literature references

Lanier, LL., Phillips, JH., Corliss, B., Wu, J. (1998). Association of DAP12 with activating CD94/NKG2C NK cell receptors. *Immunity, 8*, 693-701. ↗

Busch, LK., García, P., Bellosillo, B., Gumá, M., López-Botet, M., Salazar-Fontana, LI. et al. (2005). The CD94/NKG2C killer lectin-like receptor constitutes an alternative activation pathway for a subset of CD8+ T cells. *Eur. J. Immunol., 35*, 2071-80. ↗

Editions

2012-05-25	Authored, Edited	Garapati, P V.
2012-08-09	Reviewed	Lanier, LL.

Interaction of DAP12 and NKG2D ↗

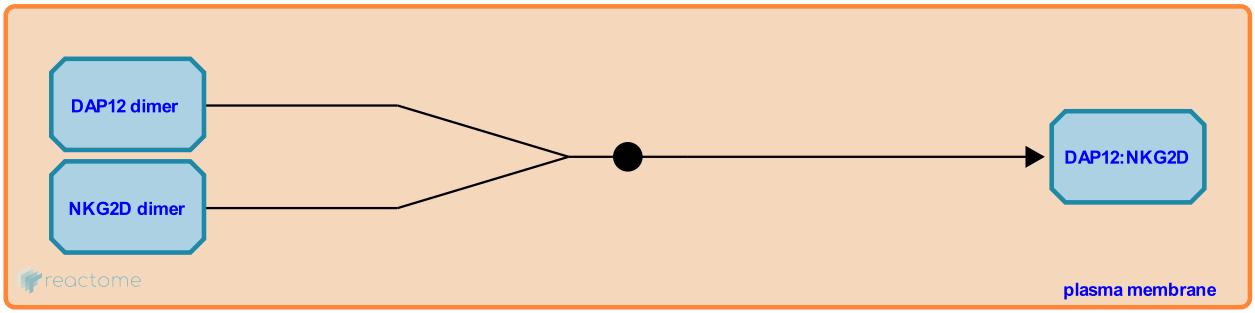
Location: DAP12 interactions

Stable identifier: R-HSA-210295

Type: binding

Compartments: plasma membrane

Inferred from: Interaction of DAP12 and NKG2D (Mus musculus)



NKG2D is a member of the NKG2 family of C-type lectin-like surface receptors. It is a homodimeric activating receptor expressed on natural killer (NK) cells, gamma/delta T-cells and CD8+ alpha/beta T-cells. NKG2D can mediate NK activation and cytotoxicity. NKG2D interacts with the stress-induced class I like molecules MICA, MICB and ULBPs expressed on target cells. Interaction of NKG2D and NKG2D ligands leads to NK cell activation (Cosman et al. 2001, Steinle et al. 2001, Long. 2002). In mice there are two alternatively spliced isoforms of NKG2D, designated NKG2D-S and NKG2D-L. DAP12 interacts with NKG2D-S, but not NKG2D-L, whereas the DAP10 adapter associates with both NKG2D-S and NKG2D-L (Gilfillan et al. 2002, Diefenbach et al. 2002). Humans only express an NKG2D-L isoform and exclusively associate with DAP10, and not DAP12 A Structural basis for the association of DAP12 with mouse, but not human, NKG2D (Rosen et al. 2004).

Preceded by: Dimerization of DAP12

Editions

2012-05-25	Authored, Edited	Garapati, P V.
2012-08-09	Reviewed	Lanier, LL.

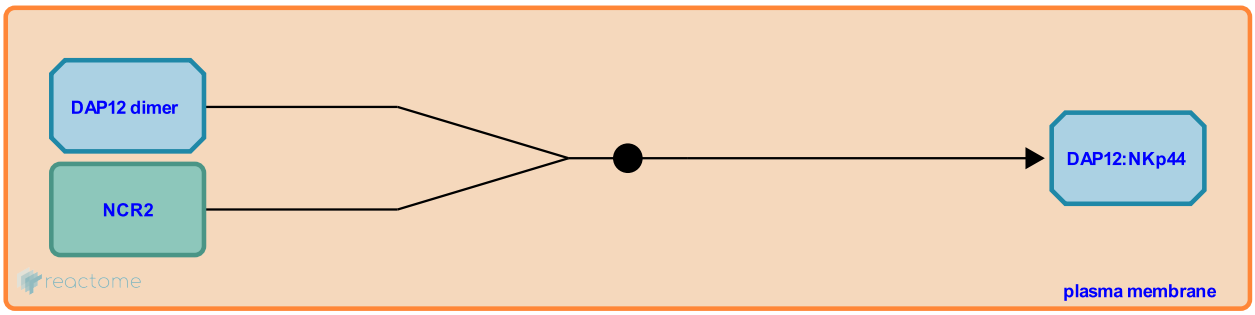
Interaction of DAP12 and NKp44 ↗

Location: DAP12 interactions

Stable identifier: R-HSA-210273

Type: binding

Compartments: plasma membrane



NKp44 is a natural cytotoxicity receptor (NCR) family member selectively expressed by IL-2-activated NK cells. It is a transmembrane receptor involved in recognizing unidentified non-MHC ligands on tumor cells, mediating tumor cell lysis by activated NK cells. NKp44 is coupled to cytoplasmic signal transduction machinery via association with DAP12. Lysine-183 in the transmembrane region of NKp44 may be involved in the association with DAP12. The interaction with DAP12 influences NKp44 surface expression and hence NK cell activation (Campbell et al. 2004, Cantoni et al. 1999, Vitale et al. 1998).

Preceded by: Dimerization of DAP12

Literature references

Parolini, S., Malaspina, A., Vitale, M., Cantoni, C., Bottino, C., Moretta, L. et al. (1999). NKp44, a triggering receptor involved in tumor cell lysis by activated human natural killer cells, is a novel member of the immunoglobulin superfamily. *J Exp Med, 189*, 787-96. ↗

Kikuchi-Maki, A., Yusa, S., Catina, TL., Campbell, KS. (2004). NKp44 triggers NK cell activation through DAP12 association that is not influenced by a putative cytoplasmic inhibitory sequence. *J Immunol, 172*, 899-906. ↗

Bottino, C., Sivori, S., Moretta, A., Moretta, L., Sanseverino, L., Augugliaro, R. et al. (1998). NKp44, a novel triggering surface molecule specifically expressed by activated natural killer cells, is involved in non-major histocompatibility complex-restricted tumor cell lysis. *J. Exp. Med., 187*, 2065-72. ↗

Editions

2012-05-25	Authored, Edited	Garapati, P V.
2012-08-09	Reviewed	Lanier, LL.

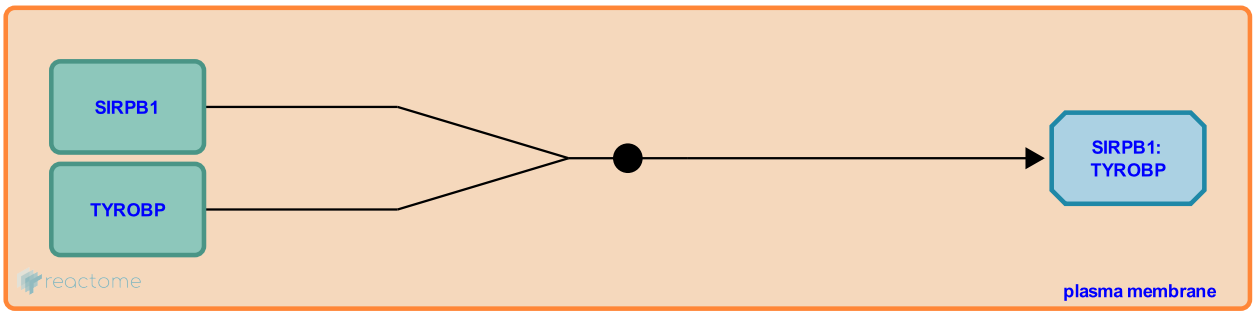
SIRP beta binds TYROBP ↗

Location: DAP12 interactions

Stable identifier: R-HSA-210274

Type: binding

Compartments: plasma membrane



SIRP beta (SIRPB, CD172b) is expressed mainly on myeloid cells and has a very short cytoplasmic region of only six amino acids, lacking the signaling motifs required for association with phosphatases that are found in SIRPA. Instead, SIRPB associates with a dimeric protein TYROBP (DAP12) to transmit activating signals via its ITAM motif. A positively charged amino acid in the transmembrane domain of TYROBP associates with a basic amino acid in the transmembrane region of SIRPB.

Preceded by: Dimerization of DAP12

Literature references

Buhring, HJ., Colonna, M., Dietrich, J., Seiffert, M., Cella, M. (2000). Cutting edge: signal-regulatory protein beta 1 is a DAP12-associated activating receptor expressed in myeloid cells. *J Immunol, 164*, 9-12. ↗

Vivier, E., Cant, C., Vely, F., Ullrich, A., Buhring, HJ., Andre, P. et al. (2000). Association of signal-regulatory proteins beta with KARAP/DAP-12. *Eur J Immunol, 30*, 2147-56. ↗

Editions

2009-02-12	Authored, Edited	Garapati, P V.
2010-05-20	Reviewed	Barclay, AN.

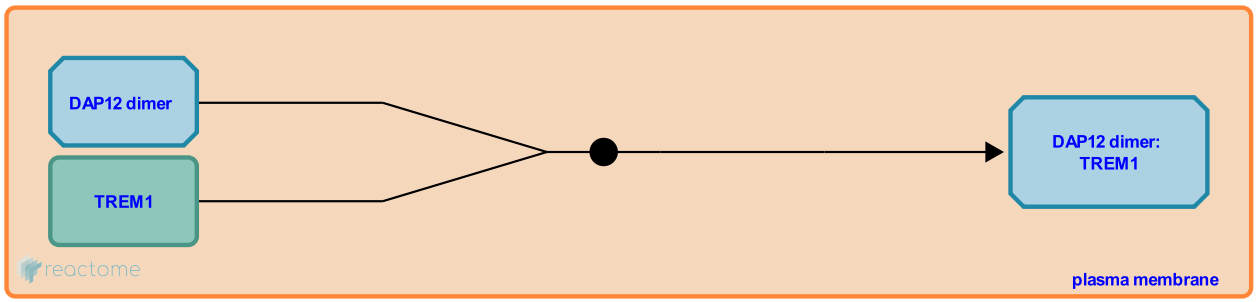
Interaction of DAP12 and TREM1 ↗

Location: DAP12 interactions

Stable identifier: R-HSA-210292

Type: binding

Compartments: plasma membrane



TREM proteins (triggering receptors expressed on myeloid cells) are a family of cell surface receptors involved in innate immune responses. They are expressed in myeloid cells and have both positive and negative functions in regulating myeloid cell activation and differentiation. Humans have two members, TREM1 and TREM2. TREM1 is considered an amplifier of the immune response, while TREM2 is believed to be a negative regulator of inflammatory responses (Sharif & Knaap 2008). TREM proteins consist of a single extracellular V-type Ig-like domain, a transmembrane region and a short cytoplasmic tail lacking any signalling motifs (Kelker et al. 2004). Both receptors associate with DAP12 for signalling.
The ligand for TREM1 is unknown. TREM1 associates with DAP12 dimer. This interaction is mediated by aspartic acid and adjacent threonine residues in the DAP12 dimer that interface with lysine residues in the TREM1 transmembrane region. TREM1 engagement triggers the production of inflammatory chemokines and cytokines such as IL-8 and myeloperoxidase (MPO) in neutrophils and IL-8, MCP-1, and TNF in monocytes (Tessarz & Cerwenka 2008, Bouchon et al. 2000).

Preceded by: Dimerization of DAP12

Literature references

Klesney-Tait, J., Colonna, M., Turnbull, IR. (2006). The TREM receptor family and signal integration. *Nat Immunol, 7*, 1266-73. ↗

Vivier, E., Tomasello, E. (2005). KARAP/DAP12/TYROBP: three names and a multiplicity of biological functions. *Eur J Immunol, 35*, 1670-7. ↗

Colonna, M. (2003). TREMs in the immune system and beyond. *Nat Rev Immunol, 3*, 445-53. ↗

Editions

2012-05-25	Authored, Edited	Garapati, P V.
2012-08-09	Reviewed	Lanier, LL.

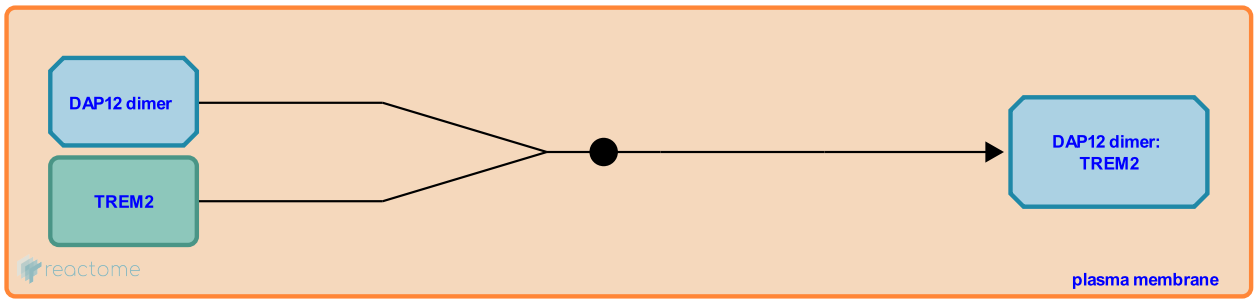
Interaction of DAP12 and TREM2 ↗

Location: DAP12 interactions

Stable identifier: R-HSA-210300

Type: binding

Compartments: plasma membrane



TREM2 (triggering receptor expressed on myeloid cells 2 protein) is expressed on the cell membrane of a subset of myeloid cells - namely, immature dendritic cells, osteoclasts, tissue macrophages, and microglia. Like TREM1 the ligand for TREM2 is unknown. TREM2 signals through DAP12, leading to an increase in intracellular calcium and phosphorylation of ERK1/2 (Sharif & Knapp. 2008). It recognises anionic lipopolysacharides in the cell wall of bacteria and triggers the phagocytic uptake of bacteria and the release of reactive oxygen species (Neumann & Daly 2013). TREM2 on immature dendritic cells triggers upregulation of molecules involved in T cell co-stimulation such as CD86, CD40 and MHC class II, as well as up-regulation of the chemokine receptor CCR7 (Bouchon et al. 2001). In macrophages TREM2 is a negative regulator of inflammatory responses (Hamerman et al. 2006, Turnbull et al. 2006). From genome wide association studies, a TREM2 variant (encoding a substitution of arginine by histidine at residue 47 [R47H]) has been reported to be implicated in late-onset Alzheumer's disease (Neumann & Daly 2013).

Preceded by: Dimerization of DAP12

Literature references

Colonna, M., Cella, M., Hernández-Munain, C., Bouchon, A. (2001). A DAP12-mediated pathway regulates expression of CC chemokine receptor 7 and maturation of human dendritic cells. *J. Exp. Med., 194*, 1111-22. ↗

Editions

2012-05-25	Authored, Edited	Garapati, P V.
2012-08-09	Reviewed	Lanier, LL.

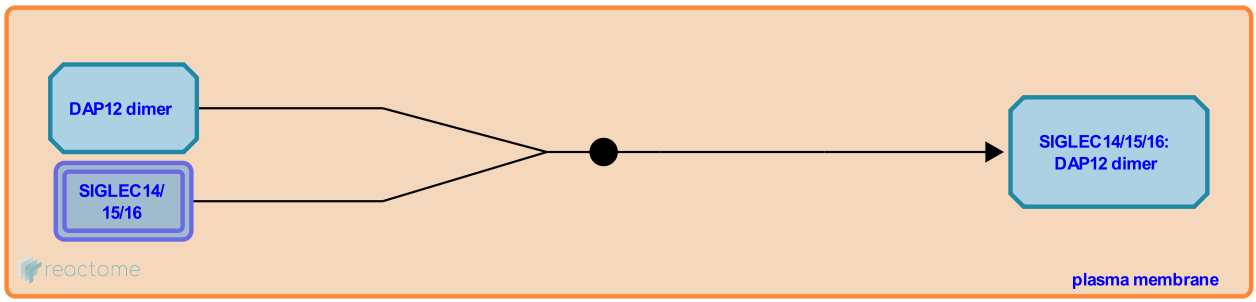
Interaction of SIGLEC14/15/16 and DAP12 ↗

Location: DAP12 interactions

Stable identifier: R-HSA-2172123

Type: binding

Compartments: plasma membrane



SIGLECs are sialic acid-recognizing receptors of the immunoglobulin (Ig) superfamily expressed on immune cells. SEGLEC14 and SEGLEC15 preferentially recognise ligands containing the glycans N-acetylneuraminic acid (Neu5Ac). SEGLEC14, SEGLEC15 and SEGLEC16 are expressed by myeloid cells and associate with the activating adapter protein DAP12 via the arginine residue in their transmembrane domains (Angata et al. 2006, Angata et al. 2007, Cao et al. 2008).

Preceded by: Dimerization of DAP12

Literature references

Lakner, U., Barrow, AD., Traherne, JA., Cao, H., de Bono, B., Trowsdale, J. (2008). SIGLEC16 encodes a DAP12-associated receptor expressed in macrophages that evolved from its inhibitory counterpart SIGLEC11 and has functional and non-functional alleles in humans. *Eur. J. Immunol., 38*, 2303-15. ↗

Nakamura, M., Yamanaka, M., Angata, T., Hayakawa, T., Varki, A. (2006). Discovery of Siglec-14, a novel sialic acid receptor undergoing concerted evolution with Siglec-5 in primates. *FASEB J., 20*, 1964-73. ↗

Tabuchi, Y., Nakamura, M., Angata, T., Nakamura, K. (2007). Siglec-15: an immune system Siglec conserved throughout vertebrate evolution. *Glycobiology, 17*, 838-46. ↗

Editions

2012-05-25	Authored, Edited	Garapati, P V.
2012-08-09	Reviewed	Lanier, LL.

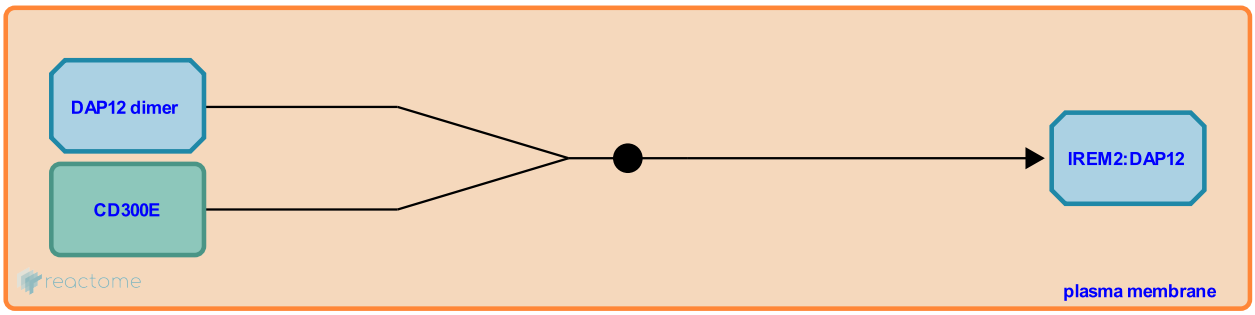
Interaction of DAP12 and IREM2 ↗

Location: DAP12 interactions

Stable identifier: R-HSA-2426569

Type: binding

Compartments: plasma membrane



Immune receptor expressed by myeloid cells 2 (IREM-2), is a member of the Ig-superfamily expressed on myeloid cells. The extracellular region contains a single Ig variable and a positively charged amino acid lysine in its transmembrane region followed by a short cytoplasmic tail. IREM-2 associates with activating adaptor DAP12, through the transmembrane basic amino acid residue. This association induces NFAT transcriptional activity (Aguilar et al. 2004).

Preceded by: Dimerization of DAP12

Literature references

García-Montero, AC., Orfao, A., López-Botet, M., Alvarez-Errico, D., Aguilar, H., Sayós, J. (2004). Molecular characterization of a novel immune receptor restricted to the monocytic lineage. *J. Immunol., 173*, 6703-11. ↗

Editions

2012-05-25	Authored, Edited	Garapati, P V.
2012-08-09	Reviewed	Lanier, LL.

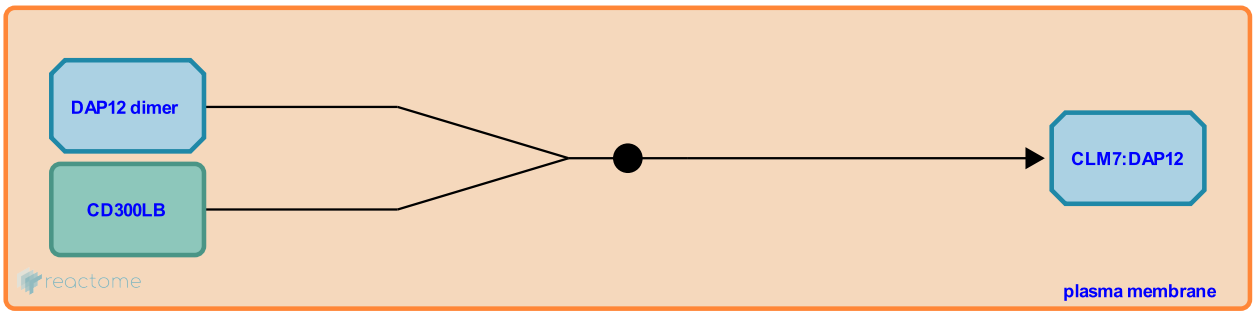
Interaction of DAP12 and CLM7 ↗

Location: DAP12 interactions

Stable identifier: R-HSA-2426566

Type: binding

Compartments: plasma membrane



CLM7/TREM5 is a member of the CMRF-35/immune receptor expressed by myeloid cell (IREM) multigene family of immune receptors expressed on myeloid cells. It has a basic residue in its transmembrane domain and a functional tyrosine-based motif in its short cytoplasmic tail. This structural arrangement confers CLM7 the ability to signal through two independent pathways: one through associating with activating adaptor protein DAP12 and the other through the tyrosine motif in its cytoplasmic tail (Martinez-Barriocanal & Sayos 2006).

Preceded by: Dimerization of DAP12

Literature references

Martínez-Barriocanal, A., Sayós, J. (2006). Molecular and functional characterization of CD300b, a new activating immunoglobulin receptor able to transduce signals through two different pathways. *J. Immunol., 177*, 2819-30. ↗

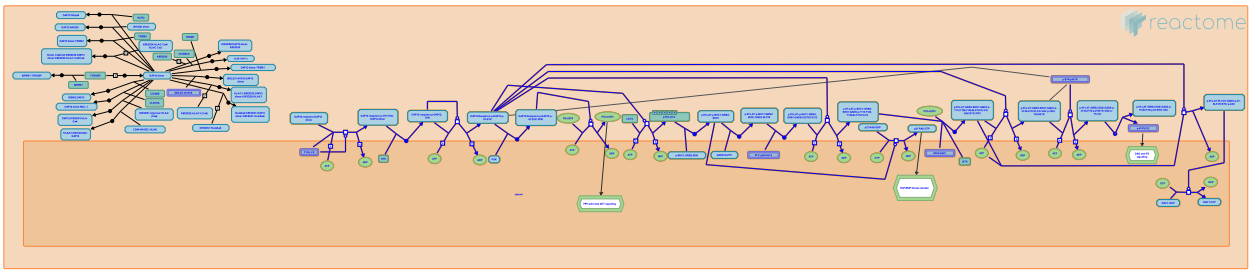
Editions

2012-05-25	Authored, Edited	Garapati, P V.
2012-08-09	Reviewed	Lanier, LL.

DAP12 signaling ↗

Location: DAP12 interactions

Stable identifier: R-HSA-2424491



In response to receptor ligation, the tyrosine residues in DAP12's immunoreceptor tyrosine-based activation motif (ITAM) are phosphorylated by Src family kinases. These phosphotyrosines form the docking site for the protein tyrosine kinase SYK in myeloid cells and SYK and ZAP70 in NK cells. DAP12-bound SYK autophosphorylates and phosphorylates the scaffolding molecule LAT, recruiting the proximal signaling molecules phosphatidylinositol-3-OH kinase (PI3K), phospholipase-C gamma (PLC-gamma), GADS (GRB2-related adapter downstream of SHC), SLP76 (SH2 domain-containing leukocyte protein of 76 kDa), GRB2:SOS (Growth factor receptor-bound protein 2:Son of sevenless homolog 1) and VAV. All of these intermediate signalling molecules result in the recruitment and activation of kinases AKT, CBL (Casitas B-lineage lymphoma) and ERK (extracellular signal-regulated kinase), and rearrangement of the actin cytoskeleton (actin polymerization) finally leading to cellular activation. PLC-gamma generates the secondary messengers diacylglycerol (DAG) and inositol-1,4,5-trisphosphate (InsP3), leading to activation of protein kinase C (PKC) and calcium mobilization, respectively (Turnbull & Colonna 2007, Klesney-Tait et al. 2006).

Literature references

Colonna, M., Turnbull, IR. (2007). Activating and inhibitory functions of DAP12. *Nat. Rev. Immunol., 7*, 155-61. ↗

Vivier, E., Tomasello, E. (2005). KARAP/DAP12/TYROBP: three names and a multiplicity of biological functions. *Eur J Immunol, 35*, 1670-7. ↗

Klesney-Tait, J., Colonna, M., Turnbull, IR. (2006). The TREM receptor family and signal integration. *Nat Immunol, 7*, 1266-73. ↗

Editions

2012-05-25	Authored, Edited	Garapati, P V.
2012-08-09	Reviewed	Lanier, LL.

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