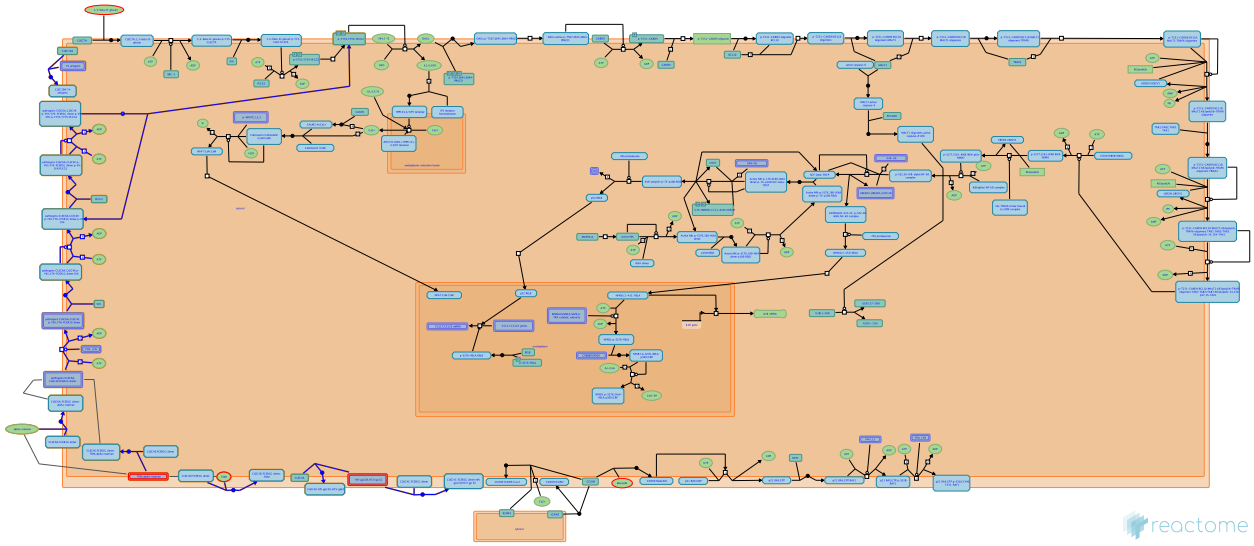
Dectin-2 family



Garapati, P V., Geijtenbeek, TB., Meldal, BH.

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

11/09/2021

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. ↗

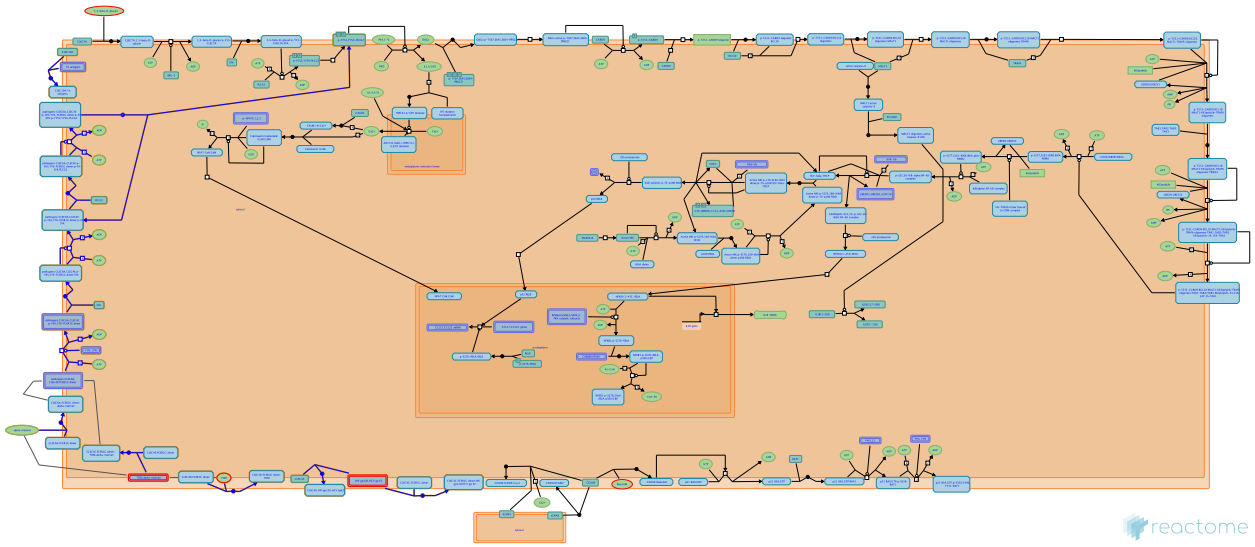
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

Dectin-2 family ↗

Stable identifier: R-HSA-5621480

Compartments: plasma membrane



Dendritic cell-associated C-type lectin-2 (Dectin-2) family of C-type lectin receptors (CLRs) includes Dectin-2 (CLEC6A), blood dendritic antigen 2 (BDCA2/CLEC4C), macrophage C-type lectin (MCL/CLEC4D), Dendritic cell immunoreceptor (DCIR/CLEC4A) and macrophage inducible C-type lectin (Mincle/CLEC4E). These receptors possesses a single extracellular conserved C-type lectin domain (CTLD) with a short cytoplasmic tail that induces intracellular signalling indirectly by binding with the FCERG (High affinity immunoglobulin epsilon receptor subunit gamma) except for DCIR that has a longer cytoplasmic tail with an integral inhibitory signalling motif (Graham & Brown. 2009, Kerschera et al. 2013). CLEC6A (Dectin-2) binds to high mannose containing pathogen-associated molecular patterns (PAMPs) expressed by fungal hyphae, and CLEC4E (mincle) binds to alpha-mannaosyl PAMPs on fungal, mycobacterial and necrotic cell ligands. Both signaling pathways lead to Toll-like receptor (TLR)-independent production of cytokines such as tumor necrosis factor (TNF) and interleukin 6 (IL6). Similarities with Dectin-1 (CLC7A) signaling pathway suggests that both these CLRs couple SYK activation to NF-kB activation using a complex involving CARD9, BCL10 and MALT1 (Geijtenbeek & Gringhuis 2009).

Literature references

Kerscher, B., Willment, JA., Brown, GD. (2013). The Dectin-2 family of C-type lectin-like receptors: an update. *Int. Immunol., 25*, 271-7. ↗

Graham, LM., Brown, GD. (2009). The Dectin-2 family of C-type lectins in immunity and homeostasis. *Cytokine, 48*, 148-55. ↗

Geijtenbeek, TB., Gringhuis, SI. (2009). Signalling through C-type lectin receptors: shaping immune responses. *Nat. Rev. Immunol., 9*, 465-79. ↗

Editions

2014-08-29	Authored, Edited	Garapati, P V.
2014-09-02	Reviewed	Geijtenbeek, TB.

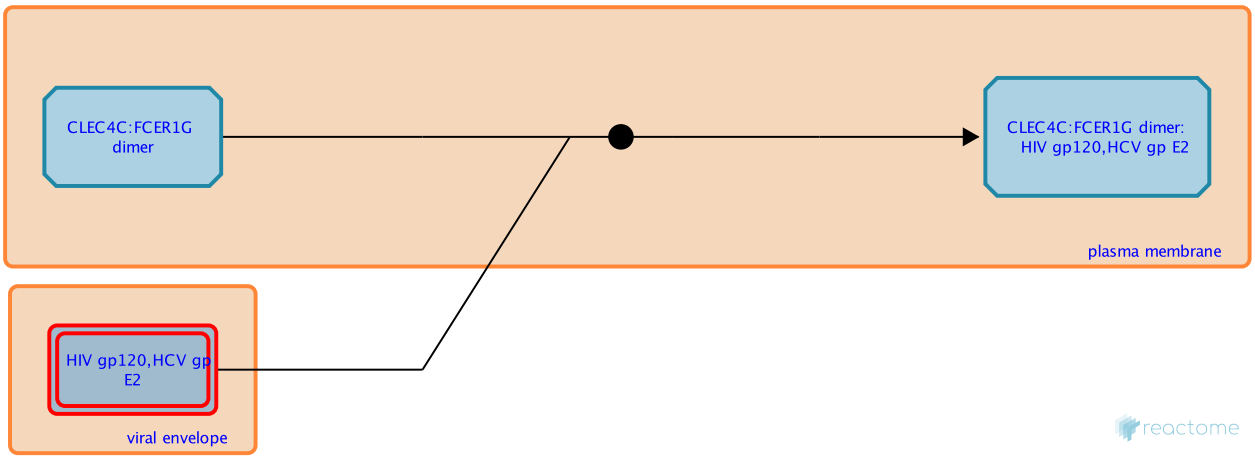
CLEC4C binds HIV and HCV glycoproteins ↗

Location: Dectin-2 family

Stable identifier: R-HSA-5621371

Type: binding

Compartments: plasma membrane, viral envelope



CLEC4C (C-type lectin domain family 4 member C/Blood dendritic cell antigen 2 (BDCA2)) is a member of the Dectin-2 family expressed exclusively on plasmacytoid dendritic cells (pDCs). CLEC4C is capable of binding certain CD14+ monocytes, monocyte-derived DCs and several tumour cell lines by recognising sugars asialo-galactosyl-oligosaccharides with terminal beta1-4- and beta1-3-galactose residues. CLEC4C has also been shown to bind the HIV-1 envelope glycoprotein gp120 and hepatitis C virus (HCV) glycoprotein E2 (Kerscher et al. 2013, Riboldi et al. 2011, Florentin et al. 2011).

CLEC4C lacks signalling motif in its cytoplasmic tail and associates with transmembrane adapter FCERG (High affinity immunoglobulin epsilon receptor subunit gamma) to induce intracellular signal transduction in a B-cell receptor (BCR)-like fashion employing SYK to regulate the immune functions of pDCs. The FCERG-SYK signalling pathway interferes with TLR9-induced activation of pDC, inhibiting type I IFN secretion (Cao et al. 2007, Dzionek et al. 2001, Rock et al. 2007, Riboldi et al. 2011).

Literature references

Florentin, J., Aouar, B., Dental, C., Thumann, C., Firaguay, G., Gondois-Rey, F. et al. (2012). HCV glycoprotein E2 is a novel BDCA-2 ligand and acts as an inhibitor of IFN production by plasmacytoid dendritic cells. *Blood, 120*, 4544-51. ↗

Riboldi, E., Daniele, R., Parola, C., Inforzato, A., Arnold, PL., Bosisio, D. et al. (2011). Human C-type lectin domain family 4, member C (CLEC4C/BDCA-2/CD303) is a receptor for asialo-galactosyl-oligosaccharides. *J. Biol. Chem., 286*, 35329-33. ↗

Editions

2014-08-29	Authored, Edited	Garapati, P V.
2014-09-02	Reviewed	Geijtenbeek, TB.

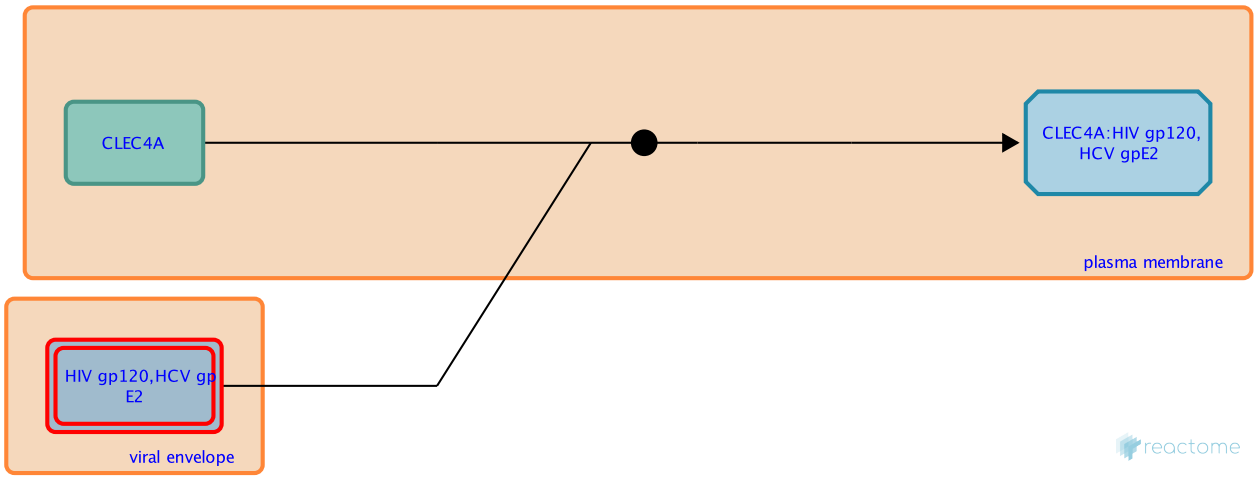
CLEC4A binds HIV and HCV glycoproteins ↗

Location: Dectin-2 family

Stable identifier: R-HSA-5621367

Type: binding

Compartments: plasma membrane, viral envelope



CLEC4A (C-type lectin domain family 4 member A/Dendritic cell immunoreceptor (DCIR)) is expressed by all CD14+ monocytes, CD15+ granulocytes, all dendrite cell (DC) subsets and B cells in peripheral blood. The extracellular domain of CLEC4A has an EPS motif which recognises carbohydrates but the definitive carbohydrate ligands have not been defined. However, it has been identified as an attachment factor for HIV on DCs and hepatitis C virus (HCV) glycoprotein E2 on plasmacytoid dendritic cells (pDCs) (Lambert et al. 2008, Florentin et al. 2012, Kerscher et al. 2013).

Unlike the other Dectin-2 family members, CLEC4A has a long cytoplasmic tail with a classical immunoreceptor tyrosine based inhibitory signalling motif (ITIMs) (Flornes et al. 2004). CLEC4A with its ITIM motif mediates inhibitory signalling through activation of the phosphatases SHP1 and SHP2 (Kanazawa et al 2003, Meyer-Wentrup et al. 2009). Activation of CLEC4A on DCs or pDCs leads to inhibition of TLR8-mediated IL12 and TNF production, and TLR9-induced IFN-alpha production (Lambert et al. 2011, Meyer-Wentrup et al. 2008).

In humans, polymorphisms of CLEC4A have been associated with susceptibility to rheumatoid arthritis (Lorentzen et al. 2007).

Literature references

Florentin, J., Aouar, B., Dental, C., Thumann, C., Firaguay, G., Gondois-Rey, F. et al. (2012). HCV glycoprotein E2 is a novel BDCA-2 ligand and acts as an inhibitor of IFN production by plasmacytoid dendritic cells. *Blood, 120*, 4544-51. ↗

Editions

2014-08-29	Authored, Edited	Garapati, P V.
2014-09-02	Reviewed	Geijtenbeek, TB.

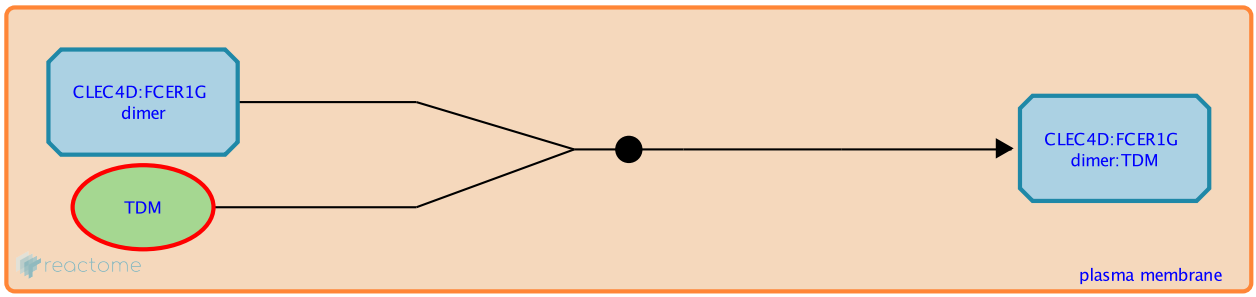
CLEC4D binds mycobacterial trehalose-6,6'-dimycolate (TDM) ↗

Location: Dectin-2 family

Stable identifier: R-HSA-5621353

Type: binding

Compartments: plasma membrane



CLEC4D (Macrophage C-type lectin (MCL)) is a member of the C-type lectin that recognises mycobacterial trehalose-6,6'-dimycolate (TDM) or cord factor likely to arise from gene duplication of CLEC4E (also called Minicle). CLEC4D is constitutively expressed on myeloid cells. It couples with FCERG (High affinity immunoglobulin epsilon receptor subunit gamma) and acts as an activating receptor (Miyake et al. 2013).

Literature references

Miyake, Y., Toyonaga, K., Mori, D., Kakuta, S., Hoshino, Y., Oyamada, A. et al. (2013). C-type lectin MCL is an FcR?-coupled receptor that mediates the adjuvanticity of mycobacterial cord factor. *Immunity, 38*, 1050-62. ↗

Editions

2014-08-29	Authored, Edited	Garapati, P V.
2014-09-02	Reviewed	Geijtenbeek, TB.

CLEC6A binds alpha-mannan in fungal cell walls ↗

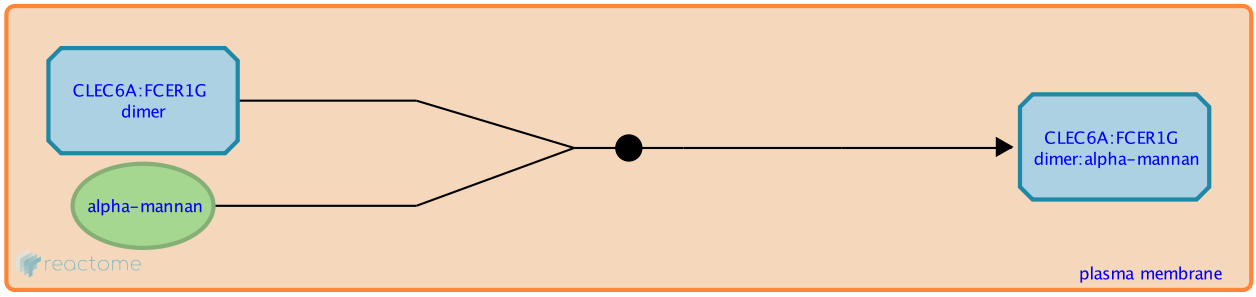
Location: Dectin-2 family

Stable identifier: R-HSA-5621352

Type: binding

Compartments: plasma membrane

Inferred from: Clec6a binds alpha-mannan in fungal cell walls (Mus musculus)



CLEC6A (C-type lectin domain family 6 member A/Dectin-2 (Dendritic cell-associated C-type lectin 2)) a C-type lectin expressed by dendritic cells (DCs) and activated macrophages has been shown to bind structures with high mannose content (McGreal et al. 2006). It is reported to recognise a variety of pathogens including Candida albicans, Saccharomyces cerevisiae, Mycobacterium tuberculosis, Paracoccidioides brasiliensis, Histoplasma capsulatum, Aspergillus fumigatus, non-encapsulated Cryptococcus neoformans, Microsporum audouinii, Trichophyton rubrum, Schistosoma mansoni and house dust mite allergens (Sato et al. 2006, Gorjestani et al. 2011, Ritter et al. 2010, McGreal et al. 2006, Kerscher et al. 2013).

Like other members of the Dectin-2 family, cytoplasmic region of CLEC6A has no obvious signalling motif and it associates with transmembrane adapter FCERG (High affinity immunoglobulin epsilon receptor subunit gamma) to transduce a CLEC6A/Dectin-2 signalling.

Followed by: LYN and FYN phosphorylate FCER1G in CLEC6A:FCERG and CLEC4E:FCERG

Editions

2014-08-29	Authored, Edited	Garapati, P V.
2014-09-02	Reviewed	Geijtenbeek, TB.

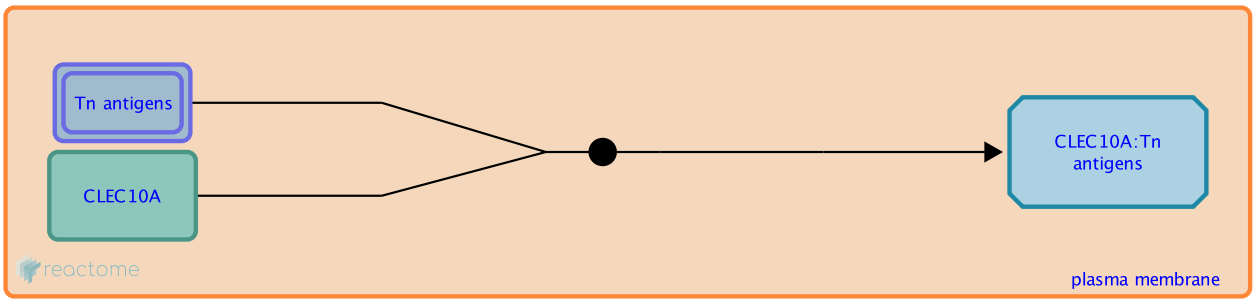
CLEC10A binds Tn-MUC1 ↗

Location: Dectin-2 family

Stable identifier: R-HSA-8858500

Type: binding

Compartments: plasma membrane



Glycoproteins in human tumors often exhibit abnormal glycosylation patters, e.g. certain Lewis structures, TF antigen, Tn antigen and/or their sialylated forms, which creates additional binding sites for glycoreceptors. The C-type lectin domain family 10 member A (CLEC10A/MGL/CD301) is a calcium-type (C-type) lectin glycoreceptor expressed on dendritic cells (DCs) (Suzuki et al. 1996). It recognizes glycoproteins from both altered self and pathogens due to its monosaccharide specificity for galactose (Gal) and N-acetylgalactosamine (GalNAc). CLEC10A specifically binds glycans with terminal GalNAc residues such as Tn antigen (GalNAcalpha-serine/threonine), 6-sulfo-Tn, Lac-di-NAc (Galbeta1,4-GlcNAc) as well as core 5 (GalNAcalpha1-3GalNAcalpha-) and core 6 (GlcNAcbeta1-6GalNAcalpha-) that are expressed in human tumors (Mortezai et al. 2013, van Vliet et al. 2005). CLEC10A on immature human monocyte-derived DCs has been shown to recognize and internalize the three tandem repeat peptides of Mucin-1 carrying Tn (Tn-MUC1) (Denda-Nagai et al. 2010).

Literature references

Suzuki, N., Yamamoto, K., Toyoshima, S., Osawa, T., Irimura, T. (1996). Molecular cloning and expression of cDNA encoding human macrophage C-type lectin. Its unique carbohydrate binding specificity for Tn antigen. *J. Immunol., 156*, 128-35. ↗

Mortezai, N., Behnken, HN., Kurze, AK., Ludewig, P., Buck, F., Meyer, B. et al. (2013). Tumor-associated Neu5Ac-Tn and Neu5Gc-Tn antigens bind to C-type lectin CLEC10A (CD301, MGL). *Glycobiology, 23*, 844-52. ↗

Editions

2016-02-19	Authored, Edited	Garapati, P V.
2016-09-14	Reviewed	Meldal, BH.

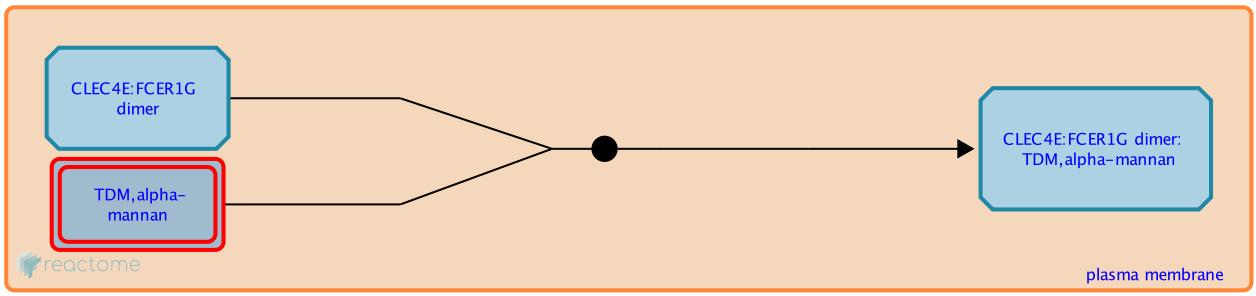
CLEC4E binds alpha-mannan and trehalose-6-6'-dimycolate ↗

Location: Dectin-2 family

Stable identifier: R-HSA-5621354

Type: binding

Compartments: plasma membrane



CLEC4E (also called Mincle or CLECSF9) is a C-type lectin receptor (CLR) expressed in activated macrophages and dendritic cells (DCs) in response to several inflammatory stimuli, including LPS, TNF, IL6, IFN-gamma and cellular stresses (Matsumoto et al. 1999). Like the other activating receptors in the Dectin-2 family, CLEC4E is coupled with the FCERG (High affinity immunoglobulin epsilon receptor subunit gamma) to transduce intracellular signalling (Yamasaki et al. 2008). CLEC4E possesses a typical carbohydrate recognition domain (CRD) containing an EPN (Glu-Pro-Asn) motif which is capable of recognising several types of carbohydrates, particularly those containing alpha-mannose. CLEC4E can recognise fungal (Candida albicans and Malassezia), mycobacterial (trehalose-6,6?-dimycolate (TDM)) and necrotic cell ligands implicating this receptor in anti-microbial immunity and homeostasis (Schoenen et al. 2010, Yamasaki et al. 2009, Graham & Brown. 2009).

Followed by: LYN and FYN phosphorylate FCER1G in CLEC6A:FCERG and CLEC4E:FCERG

Literature references

Wells, CA., Salvage-Jones, JA., Li, X., Hitchens, K., Butcher, S., Murray, RZ. et al. (2008). The macrophage-inducible C-type lectin, mincle, is an essential component of the innate immune response to Candida albicans. *J. Immunol., 180*, 7404-13. ↗

Editions

2014-08-29	Authored, Edited	Garapati, P V.
2014-09-02	Reviewed	Geijtenbeek, TB.

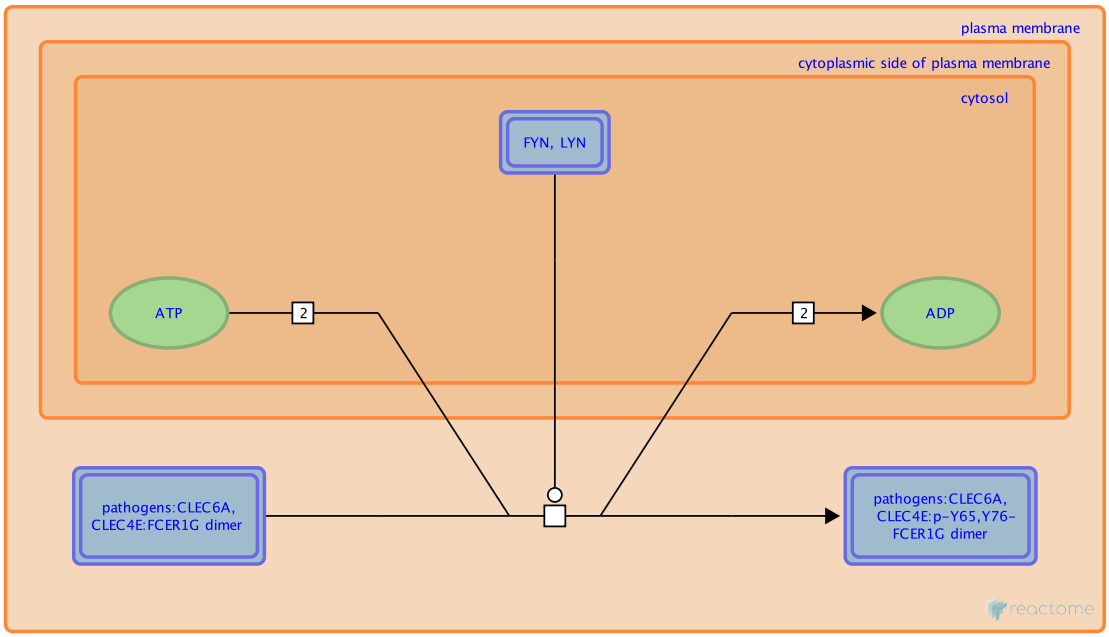
LYN and FYN phosphorylate FCER1G in CLEC6A:FCERG and CLEC4E:FCERG ↗

Location: Dectin-2 family

Stable identifier: R-HSA-5621355

Type: transition

Compartments: plasma membrane, cytosol



Ligation of CLEC6A (C-type lectin domain family 6 member A/Dectin-2) and CLEC4E (Mincle) with their appropriate ligands trigger the tyrosine phosphorylation of the immune receptor tyrosine-based activation motif (ITAM) in the cytoplasmic tail of FCER1G chain. Tyrosine Y65 and Y76 in the ITAM are phosphorylated and this phosphorylation is mediated by Src kinases Lyn and Fyn (Sato et al. 2006, Yamasaki et al. 2008, Quek et al. 1998).

Preceded by: CLEC4E binds alpha-mannan and trehalose-6-6'-dimycolate, CLEC6A binds alpha-mannan in fungal cell walls

Followed by: SYK binds to p-Y65,Y76-FCER1G

Literature references

Sato, K., Yang, XL., Yudate, T., Chung, JS., Wu, J., Luby-Phelps, K. et al. (2006). Dectin-2 is a pattern recognition receptor for fungi that couples with the Fc receptor gamma chain to induce innate immune responses. *J. Biol. Chem., 281*, 38854-66. ↗

Yamasaki, S., Ishikawa, E., Sakuma, M., Hara, H., Ogata, K., Saito, T. (2008). Mincle is an ITAM-coupled activating receptor that senses damaged cells. *Nat. Immunol., 9*, 1179-88. ↗

Quek, LS., Pasquet, JM., Hers, I., Cornall, R., Knight, G., Barnes, M. et al. (2000). Fyn and Lyn phosphorylate the Fc receptor gamma chain downstream of glycoprotein VI in murine platelets, and Lyn regulates a novel feedback pathway. *Blood, 96*, 4246-53. ↗

Editions

2014-08-29	Authored, Edited	Garapati, P V.
2014-09-02	Reviewed	Geijtenbeek, TB.

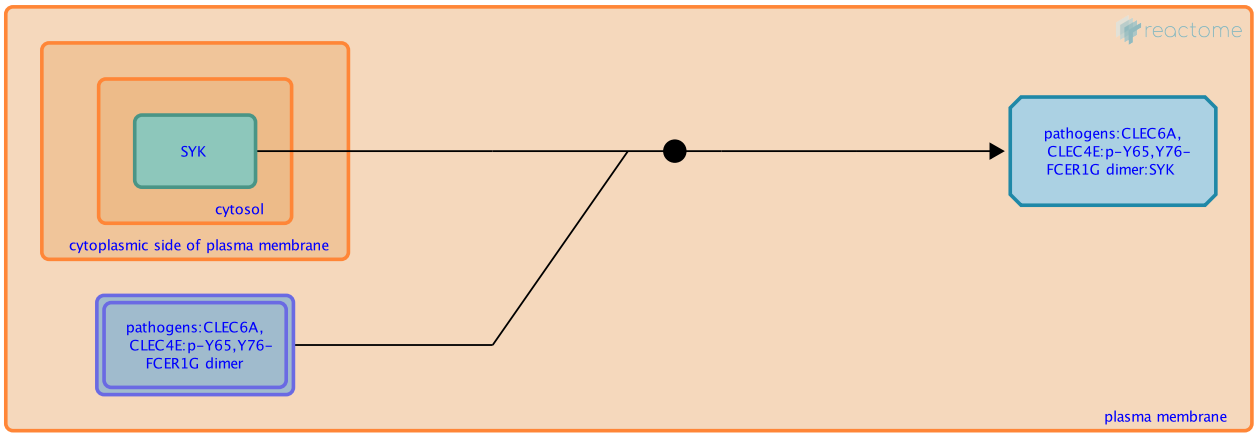
SYK binds to p-Y65,Y76-FCER1G ↗

Location: Dectin-2 family

Stable identifier: R-HSA-5621366

Type: binding

Compartments: plasma membrane, cytosol



SYK is a cytoplasmic tyrosine kinase related to ZAP70 that is expressed in all hematopoietic cells and coimmunoprecipitates with the gamma chain associated with FCGRIIIA in macrophages and with FCERI in mast cells. Tyrosine phosphorylation of the FCER1G ITAM recruits SYK and initiates a signaling cascade, leading to the activation of transcription factors such as NF-kB via CARD9-BCL10-MALT1 (Kerscher et al. 2013).

Preceded by: LYN and FYN phosphorylate FCER1G in CLEC6A:FCERG and CLEC4E:FCERG

Followed by: SYK autophosphorylates

Literature references

Sato, K., Yang, XL., Yudate, T., Chung, JS., Wu, J., Luby-Phelps, K. et al. (2006). Dectin-2 is a pattern recognition receptor for fungi that couples with the Fc receptor gamma chain to induce innate immune responses. *J. Biol. Chem., 281*, 38854-66. ↗

Yamasaki, S., Ishikawa, E., Sakuma, M., Hara, H., Ogata, K., Saito, T. (2008). Mincle is an ITAM-coupled activating receptor that senses damaged cells. *Nat. Immunol., 9*, 1179-88. ↗

Editions

2014-08-29	Authored, Edited	Garapati, P V.
2014-09-02	Reviewed	Geijtenbeek, TB.

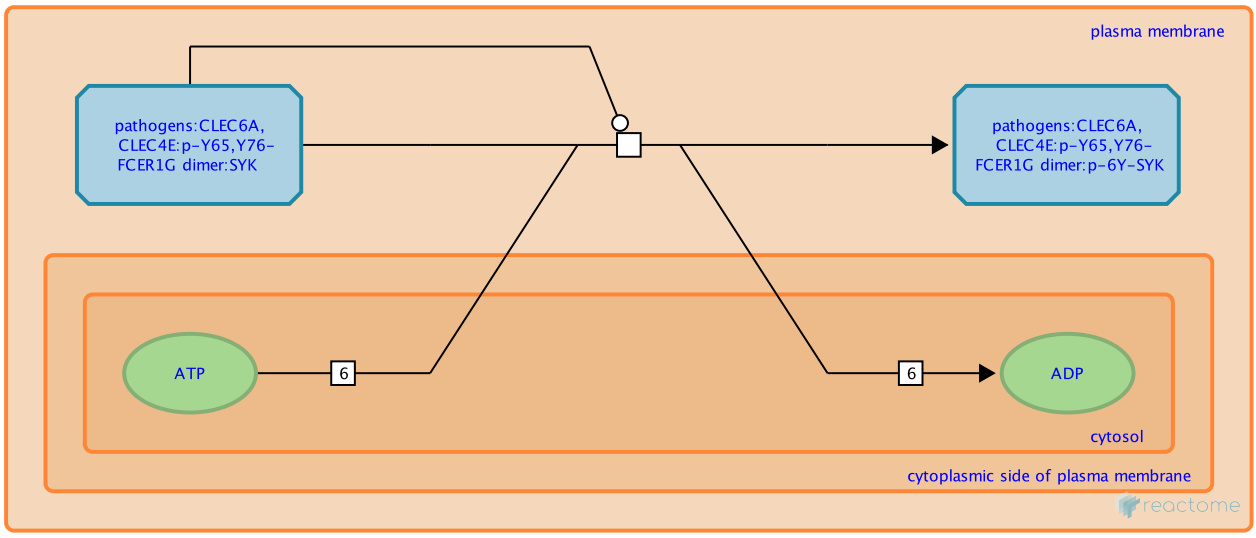
SYK autophosphorylates ↗

Location: Dectin-2 family

Stable identifier: R-HSA-5621370

Type: transition

Compartments: plasma membrane, cytosol



SYK can autophosphorylate and autophosphorylation increases its activity. It is more readily activated by autophosphorylation although it is rapidly activated by Src family kinases. SYK has multiple sites of phosphorylation which both regulate its activity and serve as docking sites for other proteins (Sada et al. 2001). Some of these sites include Y131 of interdomain A, Y323, Y348, and Y352 of interdomain B, and Y525 and Y526 within the activation loop of the kinase domain and Y630 in the C-terminus (Zhang et al. 2002, Lupher et al. 1998, Furlong et al. 1997).

Preceded by: SYK binds to p-Y65,Y76-FCER1G

Followed by: PLCG1 binds p-6Y-SYK:p-Y65,Y76-FCER1G

Literature references

Furlong, MT., Mahrenholz, AM., Kim, KH., Ashendel, CL., Harrison, ML., Geahlen, RL. (1997). Identification of the major sites of autophosphorylation of the murine protein-tyrosine kinase Syk. *Biochim Biophys Acta, 1355*, 177-90. ↗

Tsang, E., Giannetti, AM., Shaw, D., Dinh, M., Tse, JK., Gandhi, S. et al. (2008). Molecular mechanism of the Syk activation switch. *J Biol Chem, 283*, 32650-9. ↗

Editions

2014-08-29	Authored, Edited	Garapati, P V.
2014-09-02	Reviewed	Geijtenbeek, TB.

PLCG1 binds p-6Y-SYK:p-Y65,Y76-FCER1G ↗

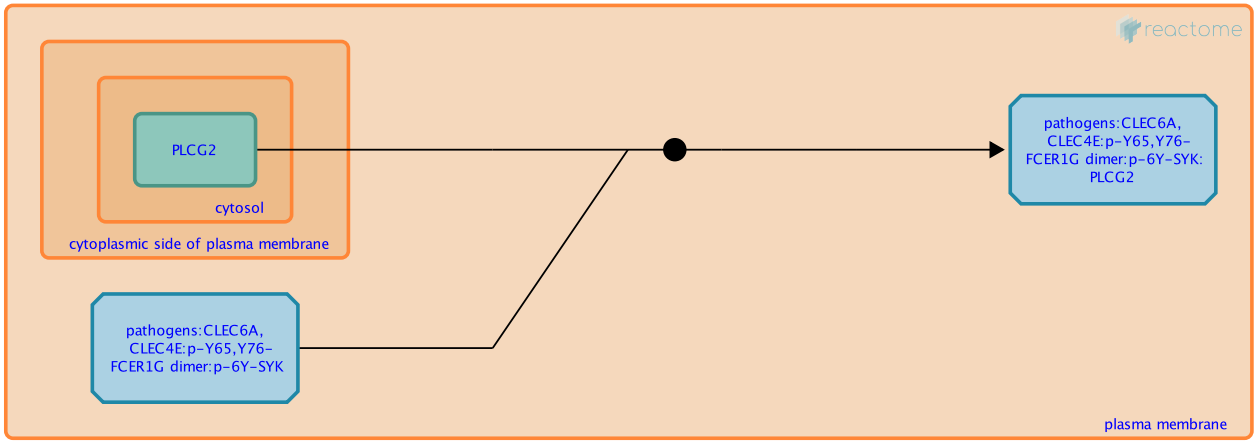
Location: Dectin-2 family

Stable identifier: R-HSA-5621356

Type: binding

Compartments: plasma membrane, cytosol

Inferred from: Plcg1 binds p-Y348,352,525,526-Syk (Mus musculus)



Phospholipase C-gamma (PLCG) binds to phosphorylated Tyr-348 (Tyr-342 in mouse) and Tyr-352 (Tyr-346 in mouse) in SYK with its C-terminal SH2 domain (Law et al. 1996). PLCG2 functions downstream of CLEC6A/Dectin-2 and triggers cytokine production in response to the infection by Candida albicans. PLCG2 deficiency results in the defective production of NF-kB and significantly reduced production of reactive oxygen species (ROS) following infection (Gorjestani et al. 2011).

Preceded by: SYK autophosphorylates

Followed by: SYK phosphorylates PLCG2 in p-6Y-SYK:p-Y65,Y76-FCER1G:PLCG2

Editions

2014-08-29	Authored, Edited	Garapati, P V.
2014-09-02	Reviewed	Geijtenbeek, TB.

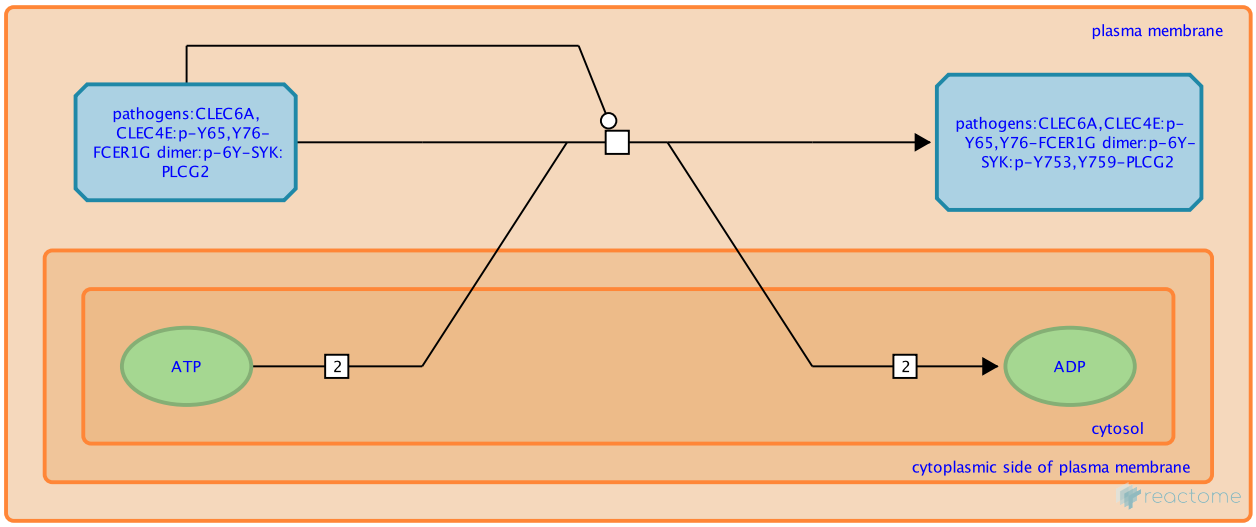
SYK phosphorylates PLCG2 in p-6Y-SYK:p-Y65,Y76-FCER1G:PLCG2 ↗

Location: Dectin-2 family

Stable identifier: R-HSA-5621363

Type: transition

Compartments: plasma membrane, cytosol



Activation of SYK triggers multiple cascades, which induces NF-kB activation through a CARD9-dependent pathway. Phospholipase C-gamma 2 (PLCG2) is one of the key signaling components of the CLEC4E (Mincle)/CLEC6A (Dectin-2) pathway that connects SYK activation to CARD9 recruitment. PLCG2 is activated upon CLEC4E (Mincle)/CLEC6A (Dectin-2) engagement and triggers an intracellular Ca2+ flux. SYK and Src family kinases are upstream of PLCG2. SYK phosphorylates PLCG2 on Y753 and Y759, enhancing the activity of PLCG2 (Gorjestani et al. 2011, Suzuki-Inoue et al. 2004).

Preceded by: PLCG1 binds p-6Y-SYK:p-Y65,Y76-FCER1G

Followed by: PLCG2 translocates from cytosol to plasma membrane

Literature references

Suzuki-Inoue, K., Wilde, JI., Andrews, RK., Auger, JM., Siraganian, RP., Sekiya, F. et al. (2004). Glycoproteins VI and Ib-IX-V stimulate tyrosine phosphorylation of tyrosine kinase Syk and phospholipase Cgamma2 at distinct sites. *Biochem J, 378*, 1023-9. ↗

Gorjestani, S., Yu, M., Tang, B., Zhang, D., Wang, D., Lin, X. (2011). Phospholipase C?2 (PLC?2) is key component in Dectin-2 signaling pathway, mediating anti-fungal innate immune responses. *J. Biol. Chem., 286*, 43651-9. ↗

Editions

2014-08-29	Authored, Edited	Garapati, P V.
2014-09-02	Reviewed	Geijtenbeek, TB.

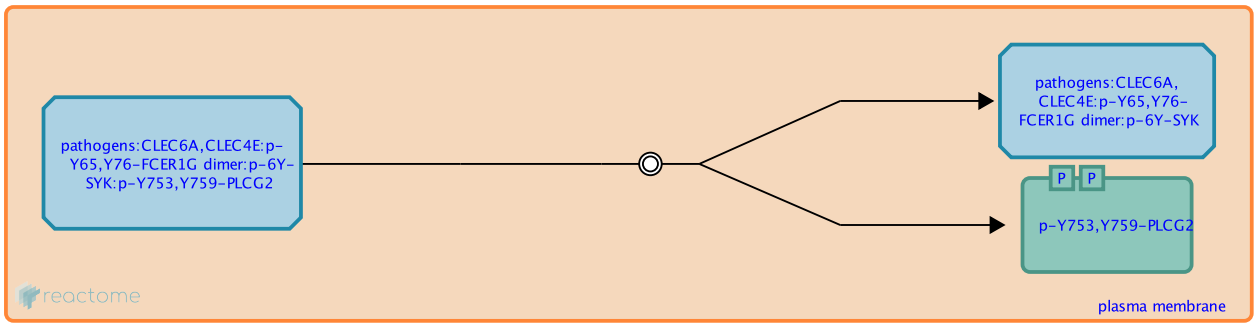
PLCG2 translocates from cytosol to plasma membrane ↗

Location: Dectin-2 family

Stable identifier: R-HSA-5621347

Type: dissociation

Compartments: plasma membrane



Tyrosine-phosphorylated Phospholipase C-gamma 2 (PLCG2) translocates from the cytosol to the plasma membrane. At the membrane PLCG2 is in close proximity to phosphatidylinositol 4,5-bisphosphate (PIP2) and its other substrates generating the second messengers IP3 and DAG (Rhee 2001). This leads to the activation of CARD9-BCL10-MALT1/NF-kB signaling.

Preceded by: SYK phosphorylates PLCG2 in p-6Y-SYK:p-Y65,Y76-FCER1G:PLCG2

Literature references

Kawakami, N., Shimohama, S., Hayakawa, T., Sumida, Y., Fujimoto, S. (1996). Tyrosine phosphorylation and translocation of phospholipase C-gamma 2 in polymorphonuclear leukocytes treated with pervanadate. *Biochim. Biophys. Acta, 1314*, 167-74. ↗

Rodriguez, R., Matsuda, M., Perisic, O., Bravo, J., Paul, A., Jones, NP. et al. (2001). Tyrosine residues in phospholipase Cgamma 2 essential for the enzyme function in B-cell signaling. *J Biol Chem, 276*, 47982-92. ↗

Editions

2014-08-29	Authored, Edited	Garapati, P V.
2014-09-02	Reviewed	Geijtenbeek, TB.

Table of Contents