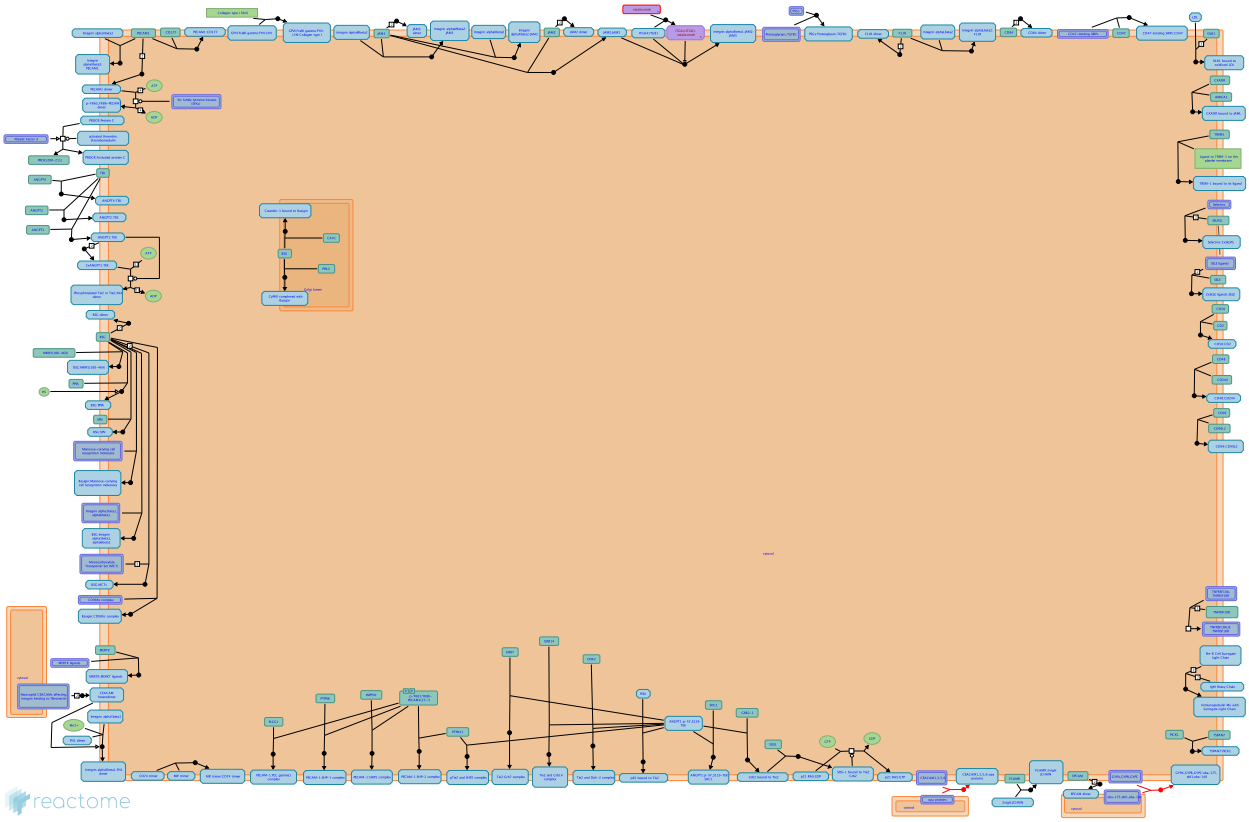
# Cell surface interactions at the vascular wall



Akkerman, JW., Garapati, P V., Gillespie, ME., Harper, MT., Humphries, MJ., Hynes, R., Jassal, B., Jones, ML., Jupe, S., Meldal, BH., Orlic-Milacic, M., Ouwehand, WH., Poole, AW., Reinhardt, DP., Shamovsky, V., Shoichet, BK., Trowsdale, J., Virgen-Slane, R., Ware, CF., Yamada, KM., Zwaginga, JJ., de Bono, B.

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



01/09/2021

# 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. ↗

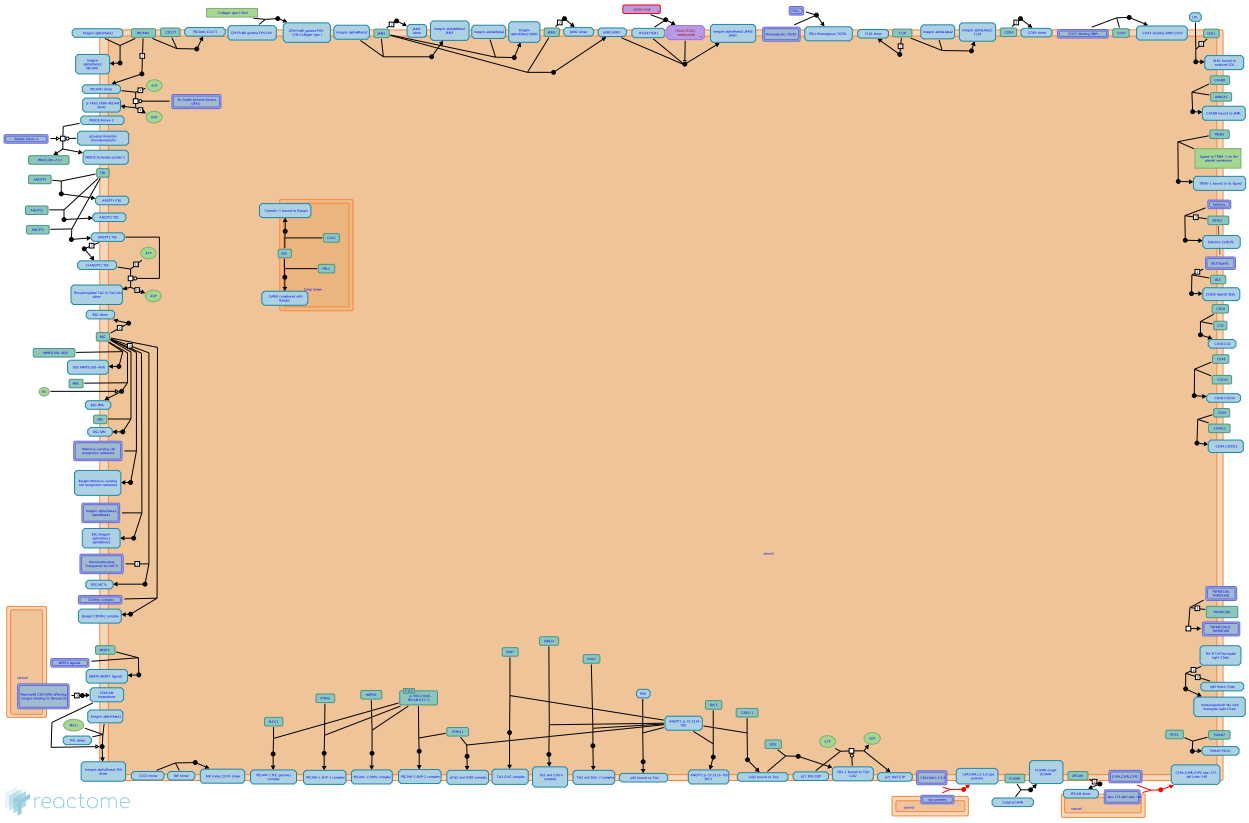
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

## Cell surface interactions at the vascular wall ↗

**Stable identifier:** R-HSA-202733

**Compartments:** plasma membrane



Leukocyte extravasation is a rigorously controlled process that guides white cell movement from the vascular lumen to sites of tissue inflammation. The powerful adhesive interactions that are required for leukocytes to withstand local flow at the vessel wall is a multistep process mediated by different adhesion molecules. Platelets adhered to injured vessel walls form strong adhesive substrates for leukocytes. For instance, the initial tethering and rolling of leukocytes over the site of injury are mediated by reversible binding of selectins to their cognate cell-surface glycoconjugates.

Endothelial cells are tightly connected through various proteins, which regulate the organization of the junctional complex and bind to cytoskeletal proteins or cytoplasmic interaction partners that allow the transfer of intracellular signals. An important role for these junctional proteins in governing the transendothelial migration of leukocytes under normal or inflammatory conditions has been established.

This pathway describes some of the key interactions that assist in the process of platelet and leukocyte interaction with the endothelium, in response to injury.

## Literature references

Jackson, SP., Mistry, N., Yuan, Y. (2000). Platelets and the injured vessel wall-- "rolling into action": focus on glycoprotein Ib/V/IX and the platelet cytoskeleton. *Trends Cardiovasc Med, 10*, 192-7. ↗

Furie, B., Furie, BC. (1995). The molecular basis of platelet and endothelial cell interaction with neutrophils and monocytes: role of P-selectin and the P-selectin ligand, PSGL-1. *Thromb Haemost, 74*, 224-7. ↗

Becker, BF., Heindl, B., Kupatt, C., Zahler, S. (2000). Endothelial function and hemostasis. *Z Kardiol, 89*, 160-7. ↗

Schober, A., Weber, C. (2005). Mechanisms of monocyte recruitment in vascular repair after injury. *Antioxid Redox Signal, 7*, 1249-57. ↗

Weber, C., Fraemohs, L., Dejana, E. (2007). The role of junctional adhesion molecules in vascular inflammation. *Nat Rev Immunol, 7*, 467-77. ↗

## Editions

| | | |
|---|---|---|
| 2007-11-12 | Authored | Ouwehand, WH. |
| 2007-11-12 | Reviewed | Zwaginga, JJ. |
| 2013-11-20 | Revised | Shamovsky, V. |
| 2016-09-05 | Revised | Meldal, BH. |

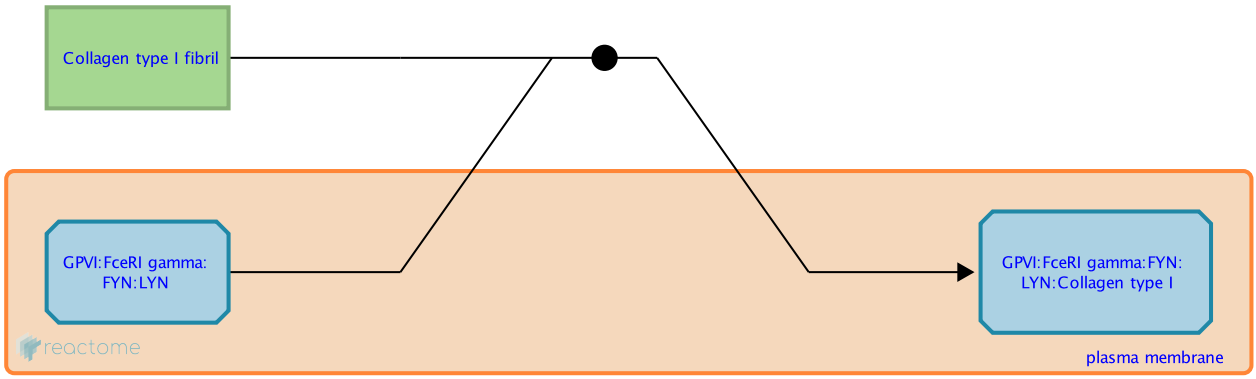
## Binding of GPVI:Fc Epsilon R1 gamma receptor complex with collagen ↗

**Location:** Cell surface interactions at the vascular wall

**Stable identifier:** R-HSA-114577

**Type:** binding

**Compartments:** extracellular region, plasma membrane




GPVI receptor has little affinity for soluble forms of collagen but binds collagen fibrils. Recent structural models indicate that each GPVI receptor complex could bind up to 3 collagen fibrils (Jung & Moroi 2008). The Src family kinases Fyn and Lyn constitutively associate with the GPVI-FceRIgamma complex in platelets and initiate platelet activation through phosphorylation of the immunoreceptor tyrosine-based activation motif (ITAM) in the FceRIgamma chain, leading to binding and activation of the tyrosine kinase Syk. Downstream of Syk, a series of adapter molecules and effectors lead to platelet activation.

### Literature references

Tsuji, M., Ezumi, Y., Arai, M., Takayama, H. (1997). A novel association of Fc receptor gamma-chain with glycoprotein VI and their co-expression as a collagen receptor in human platelets. *J Biol Chem, 272,* 23528-31. ↗

### Editions

| | | |
|---|---|---|
| 2007-11-12 | Authored | Ouwehand, WH. |
| 2009-11-02 | Reviewed | Jones, ML., Harper, MT. |
| 2009-11-02 | Edited | Jupe, S. |
| 2009-11-02 | Reviewed | Poole, AW. |

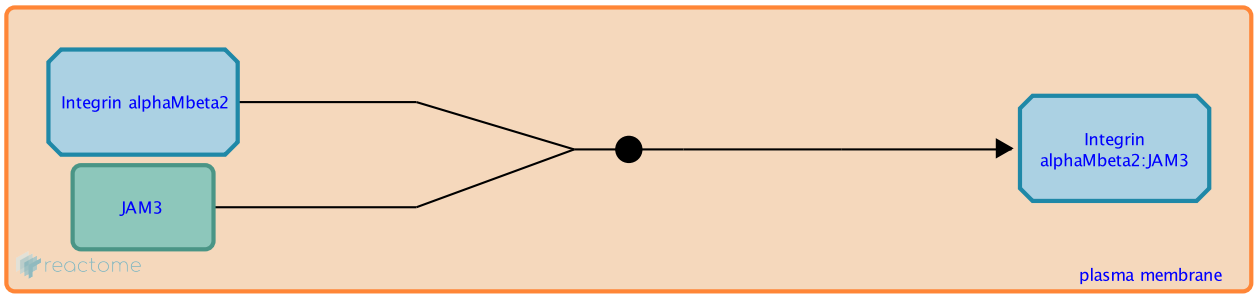
## Integrin alphaMbeta2 (MAC1) binds JAM3 ↗

**Location:** Cell surface interactions at the vascular wall

**Stable identifier:** R-HSA-202727

**Type:** binding

**Compartments:** plasma membrane




Recruitment of monocytic cells to the vessel wall by platelets is mediated via CD11b/CD18 (Mac-1) and platelet JAM-C. In the case of dendritic cells, this interaction leads to their activation and platelet phagocytosis. This process may be of importance for progression of atherosclerotic lesions.

## Literature references

Weber, C., Fraemohs, L., Dejana, E. (2007). The role of junctional adhesion molecules in vascular inflammation. *Nat Rev Immunol, 7*, 467-77. ↗

Langer, HF., Daub, K., Braun, G., Schonberger, T., May, AE., Schaller, M. et al. (2007). Platelets recruit human dendritic cells via Mac-1/JAM-C interaction and modulate dendritic cell function in vitro. *Arterioscler Thromb Vasc Biol, 27*, 1463-70. ↗

## Editions

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

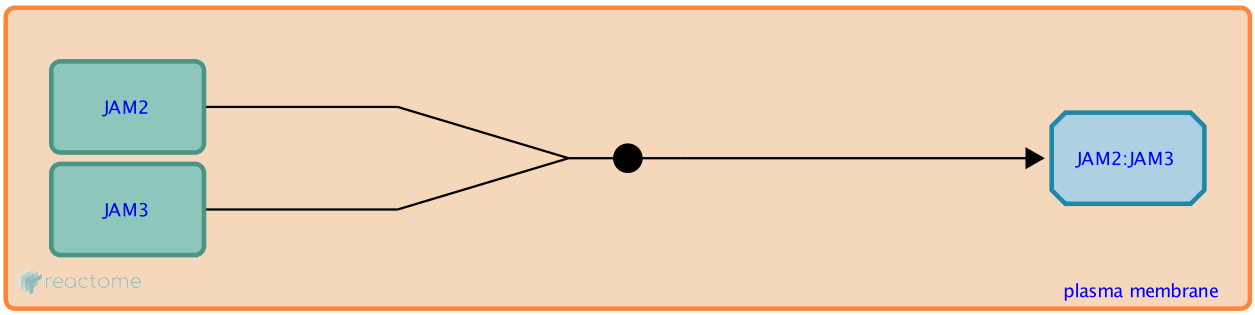
## JAM2 binds JAM3 ↗

**Location:** Cell surface interactions at the vascular wall

**Stable identifier:** R-HSA-202721

**Type:** binding

**Compartments:** plasma membrane




JAM2 and JAM3 bind each other and are strongly expressed by endothelial cells of high endothelial venules, the predominant site of leukocyte extravasation. JAM2 and JAM3 also bind to the leukocyte integrins VLA-4 and Mac-1 respectively.

**Followed by:** Integrin alpha4beta1 binds JAM2:JAM3

### Literature references

Weber, C., Fraemohs, L., Dejana, E. (2007). The role of junctional adhesion molecules in vascular inflammation. *Nat Rev Immunol, 7*, 467-77. ↗

Ludwig, RJ., Zollner, TM., Santoso, S., Hardt, K., Gille, J., Baatz, H. et al. (2005). Junctional adhesion molecules (JAM)-B and -C contribute to leukocyte extravasation to the skin and mediate cutaneous inflammation. *J Invest Dermatol, 125*, 969-76. ↗

### Editions

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

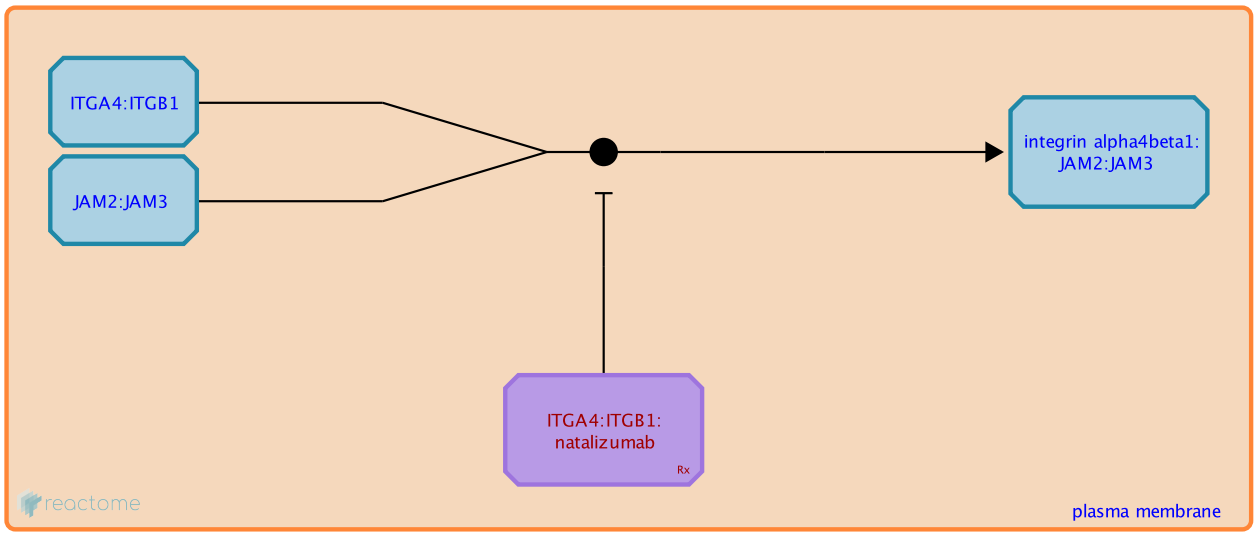
## Integrin alpha4beta1 binds JAM2:JAM3 ↗

**Location:** Cell surface interactions at the vascular wall

**Stable identifier:** R-HSA-202706

**Type:** binding

**Compartments:** plasma membrane




Several key IgSF cell adhesion molecules engage integrin and in so doing impact on the multi-step paradigm of leukocyte emigration. The interaction between JAM2 (JAM-B) and Integrin alpha4beta1 (VLA-4) requires prior binding of JAM2 to JAM3 (JAM-C).

**Preceded by:** JAM2 binds JAM3

### Literature references


Weber, C., Fraemohs, L., Dejana, E. (2007). The role of junctional adhesion molecules in vascular inflammation. *Nat Rev Immunol, 7*, 467-77. ↗

Cunningham, SA., Rodriguez, JM., Arrate, MP., Tran, TM., Brock, TA. (2002). JAM2 interacts with alpha4beta1. Facilitation by JAM3. *J Biol Chem, 277*, 27589-92. ↗


### Editions

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| 2007-11-12 | Authored | Ouwehand, WH. |
| 2008-05-07 | Reviewed | Humphries, MJ., Yamada, KM., Hynes, R. |

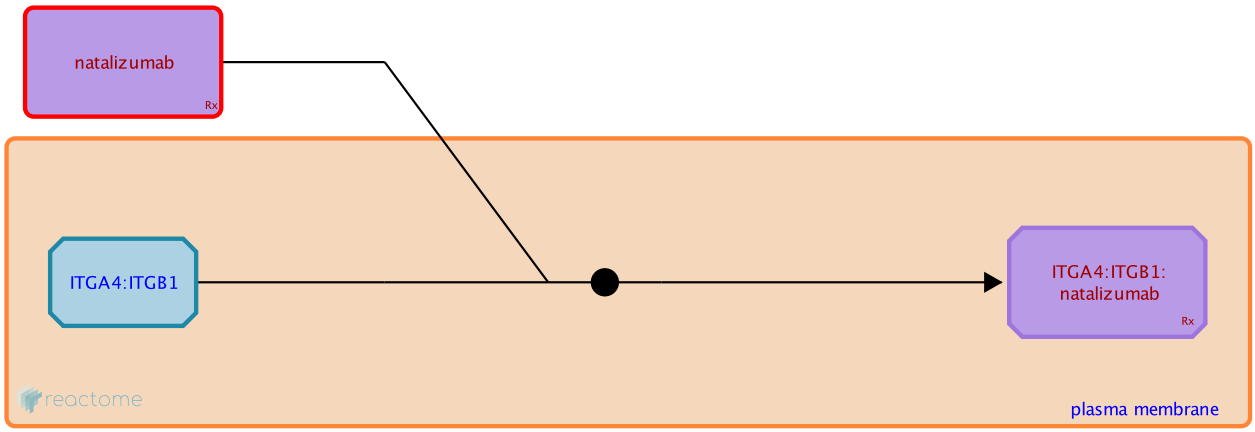
## ITGA4:ITGB1 binds natalizumab ↗

**Location:** Cell surface interactions at the vascular wall

**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

Rice, GP., Hartung, HP., Calabresi, PA. (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. |

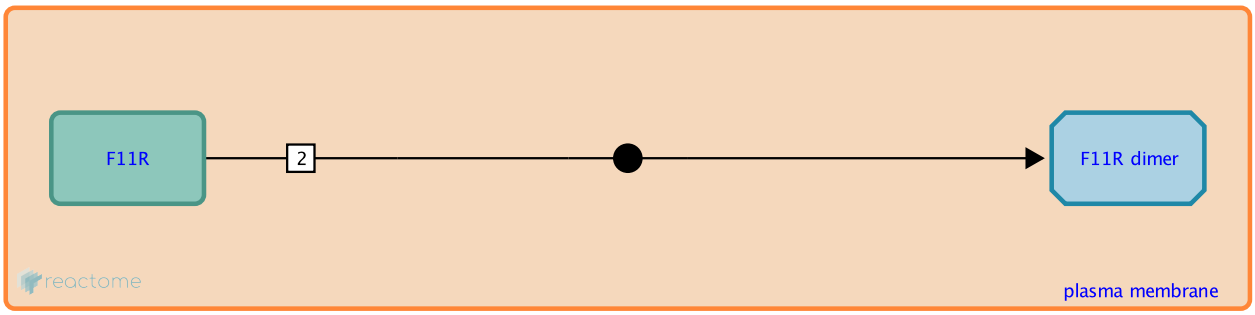
## F11R dimerises ↗

**Location:** Cell surface interactions at the vascular wall

**Stable identifier:** R-HSA-202726

**Type:** binding

**Compartments:** plasma membrane




F11R (JAM-A) is the most widely expressed member of the family, and has been shown to be expressed on endothelial and epithelial cells, on platelets, and on a number of leukocyte subsets. In endothelial cells, F11R locates to the tight junctions, where it appears to engage in homophilic binding to F11R on adjacent cells, an interaction that is considered to play a critical role in angiogenesis.

## Literature references


Weber, C., Fraemohs, L., Dejana, E. (2007). The role of junctional adhesion molecules in vascular inflammation. *Nat Rev Immunol, 7*, 467-77. ↗

Bradfield, PF., Nourshargh, S., Aurrand-Lions, M., Imhof, BA. (2007). JAM family and related proteins in leukocyte migration (Vestweber series). *Arterioscler Thromb Vasc Biol, 27*, 2104-12. ↗

Woodfin, A., Reichel, CA., Khandoga, A., Corada, M., Voisin, MB., Scheiermann, C. et al. (2007). JAM-A mediates neutrophil transmigration in a stimulus-specific manner in vivo: evidence for sequential roles for JAM-A and PECAM-1 in neutrophil transmigration. *Blood, 110*, 1848-56. ↗

Huang, H., Cruz, F., Bazzoni, G. (2006). Junctional adhesion molecule-A regulates cell migration and resistance to shear stress. *J Cell Physiol, 209*, 122-30. ↗


## Editions

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

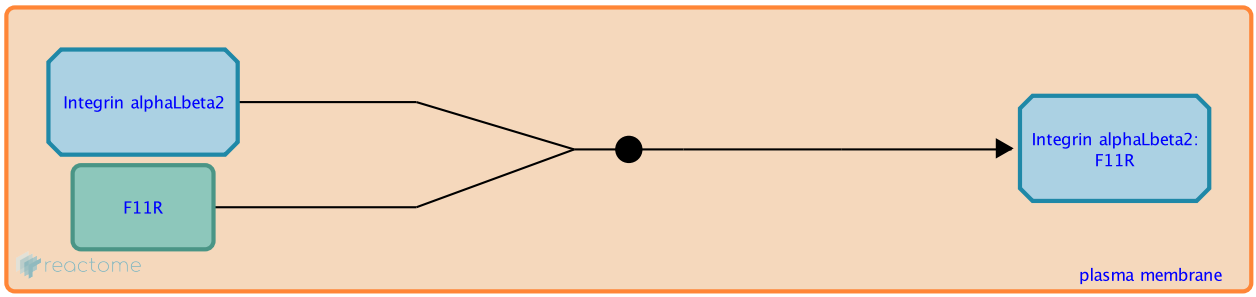
## Integrin alphaLbeta2 (LFA-1) binds F11R (JAM-A) ↗

**Location:** Cell surface interactions at the vascular wall

**Stable identifier:** R-HSA-202718

**Type:** binding

**Compartments:** plasma membrane




JAM-A plays a key role in leukocyte transmigration and inflammatory extravasation. Transmigration of human leukocytes has been shown to involve heterophilic interactions of JAM-A with its integrin receptor LFA-1.

## Literature references


Weber, C., Fraemohs, L., Dejana, E. (2007). The role of junctional adhesion molecules in vascular inflammation. *Nat Rev Immunol, 7*, 467-77. ↗

Ostermann, G., Fraemohs, L., Baltus, T., Schober, A., Lietz, M., Zernecke, A. et al. (2005). Involvement of JAM-A in mononuclear cell recruitment on inflamed or atherosclerotic endothelium: inhibition by soluble JAM-A. *Arterioscler Thromb Vasc Biol, 25*, 729-35. ↗

Fraemohs, L., Koenen, RR., Ostermann, G., Heinemann, B., Weber, C. (2004). The functional interaction of the beta 2 integrin lymphocyte function-associated antigen-1 with junctional adhesion molecule-A is mediated by the I domain. *J Immunol, 173*, 6259-64. ↗

Ostermann, G., Weber, KS., Zernecke, A., Schroder, A., Weber, C. (2002). JAM-1 is a ligand of the beta(2) integrin LFA-1 involved in transendothelial migration of leukocytes. *Nat Immunol, 3*, 151-8. ↗


## Editions

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

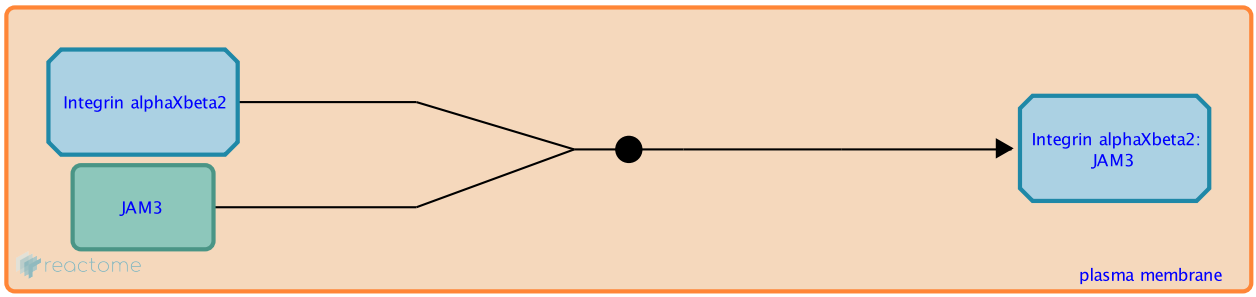
## Integrin alphaXbeta2 binds JAM3 ↗

**Location:** Cell surface interactions at the vascular wall

**Stable identifier:** R-HSA-202704

**Type:** binding

**Compartments:** plasma membrane




Although JAM-C is better known for its interaction with MAC-1, an interaction with CD11c/CD18 (known as alpha X beta 2), has also been described.

## Literature references


Weber, C., Fraemohs, L., Dejana, E. (2007). The role of junctional adhesion molecules in vascular inflammation. *Nat Rev Immunol, 7*, 467-77. ↗

Bradfield, PF., Scheiermann, C., Nourshargh, S., Ody, C., Luscinskas, FW., Rainger, GE. et al. (2007). JAM-C regulates unidirectional monocyte transendothelial migration in inflammation. *Blood, 110*, 2545-55. ↗

Santoso, S., Sachs, UJ., Kroll, H., Linder, M., Ruf, A., Preissner, KT. et al. (2002). The junctional adhesion molecule 3 (JAM-3) on human platelets is a counterreceptor for the leukocyte integrin Mac-1. *J Exp Med, 196*, 679-91. ↗


## Editions

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

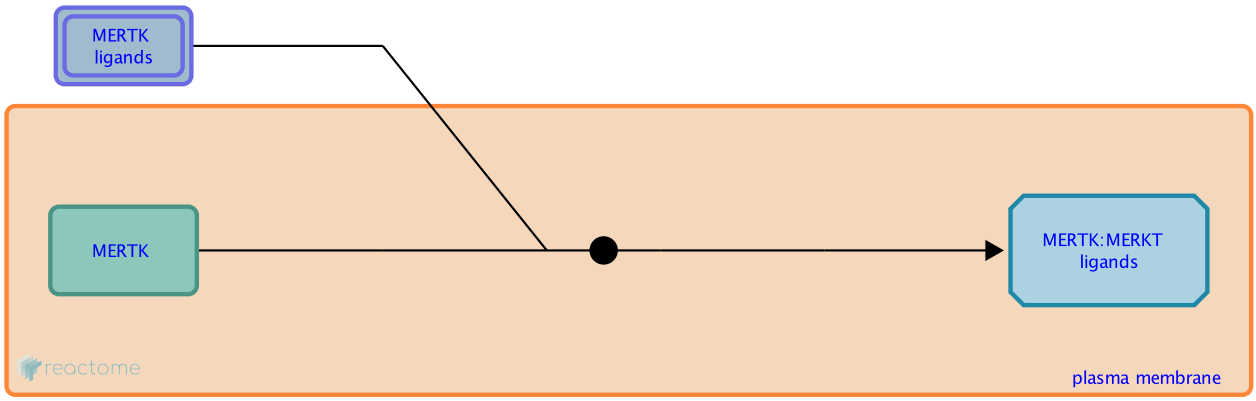
## MERTK receptor binds ligands (Gas6 or Protein S) ↗

**Location:** Cell surface interactions at the vascular wall

**Stable identifier:** R-HSA-202710

**Type:** binding

**Compartments:** plasma membrane, extracellular region




MerTK appears to be required for ingestion of apoptotic cells by professional phagocytes such as monocytes/macrophages, retinal pigment epithelial cells and dendritic cells. Mer appears to be able to induce the cytoskeletal remodelling that is required for engulfment during phagocytosis. For instance, a deletion in the MERTK gene was identified as the underlying cause for retinal dystrophy which involves an impairment in the ingestion of shed photoreceptor cell fragments by retinal pigment epithelial cells.

The biological ligands for MerTK are two highly similar vitamin K-dependent proteins, Gas6 and protein S (PS), a negative regulator of blood coagulation. Both proteins are composed an N-terminal region containing multiple post-translationally modified gamma-carboxyglutamic acid residues (Gla). The Gla region possesses the ability to interact in a conformationally specific manner with negatively charged membrane phospholipids, which is thought to mediate the binding of both Gas6 and PS to apoptotic cells. In this way, they are thought to act as recognition bridges between apoptotic cells and the phagocyte cell that ingest them.

### Literature references

Hafizi, S., Dahlback, B. (2006). Signalling and functional diversity within the Axl subfamily of receptor tyrosine kinases. *Cytokine Growth Factor Rev, 17*, 295-304. ↗

Hafizi, S., Dahlback, B. (2006). Gas6 and protein S. Vitamin K-dependent ligands for the Axl receptor tyrosine kinase subfamily. *FEBS J, 273*, 5231-44. ↗

Seitz, HM., Camenisch, TD., Lemke, G., Earp, HS., Matsushima, GK. (2007). Macrophages and dendritic cells use different Axl/Mertk/Tyro3 receptors in clearance of apoptotic cells. *J Immunol, 178*, 5635-42. ↗

### Editions

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

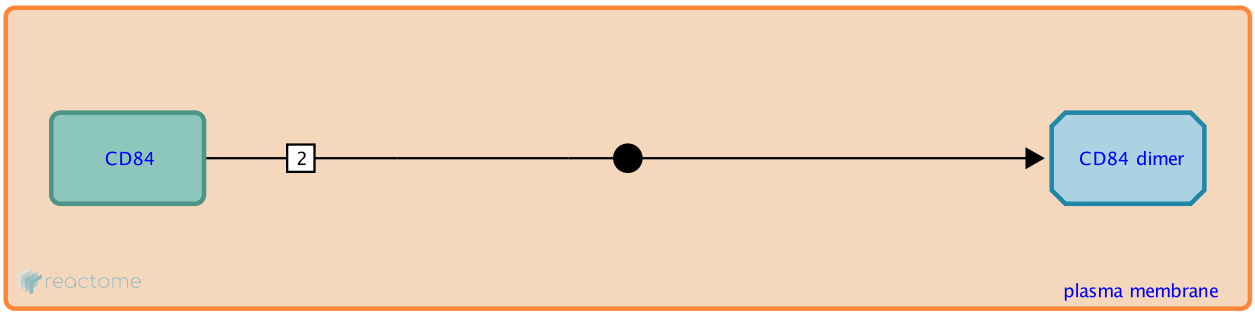
## CD84 homodimerises ↗

**Location:** Cell surface interactions at the vascular wall

**Stable identifier:** R-HSA-202713

**Type:** binding

**Compartments:** plasma membrane




CD84 is a homophilic receptor expressed on T cells, B cells, dendritic cells, monocytes, macrophages, eosinophils, mast cells, granulocytes, and platelets. CD84 expression increases following activation of T cells, B cells, and dendritic cells. CD84 homophilic engagement is known to induce platelet stimulation.

## Literature references


Martin, M., Romero, X., de la Fuente, MA., Tovar, V., Zapater, N., Esplugues, E. et al. (2001). CD84 functions as a homophilic adhesion molecule and enhances IFN-gamma secretion: adhesion is mediated by Ig-like domain 1. *J Immunol, 167*, 3668-76. ↗

Yan, Q., Malashkevich, VN., Fedorov, A., Fedorov, E., Cao, E., Lary, JW. et al. (2007). Structure of CD84 provides insight into SLAM family function. *Proc Natl Acad Sci U S A, 104*, 10583-8. ↗


## Editions

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

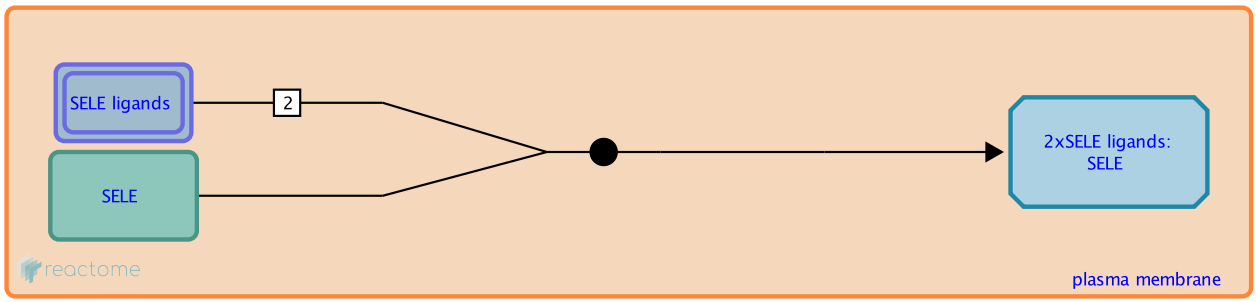
## E-selectin binds E-selectin ligand ↗

**Location:** Cell surface interactions at the vascular wall

**Stable identifier:** R-HSA-2870221

**Type:** binding

**Compartments:** plasma membrane




E-selectin is an adhesion molecule on the cell surface of endothelial cells. It participates in the binding of leukocytes to activated blood vascular endothelium during inflammation or metastasis (Haraldsen G et al. 1996). Leucocytes express  E-selectin ligand 1 (ESL-1) and P-selectin glycoprotein ligand-1 (PCGL-1) which were identified as the ligands for E-selectin (Graves BJ et al 1994; Asa D et al 1995). E-selectin has been also implicated in mediating tissue-specific homing primitive hematopoietic progenitor cells (HPCs) into bone marrow (BM). PCGL-1, CD43, CD44 were shown to function as E-selectin ligands on human BM cells (Dimitroff CJ et al. 2001; Katayama Y et al. 2003; Merzaban JS et al. 2011).

## Literature references

Graves, BJ., Crowther, RL., Chandran, C., Rumberger, JM., Li, S., Huang, KS. et al. (1994). Insight into E-selectin/ligand interaction from the crystal structure and mutagenesis of the lec/EGF domains. *Nature, 367*, 532-8. ↗

Merzaban, JS., Burdick, MM., Gadhoum, SZ., Dagia, NM., Chu, JT., Fuhlbrigge, RC. et al. (2011). Analysis of glycoprotein E-selectin ligands on human and mouse marrow cells enriched for hematopoietic stem/progenitor cells. *Blood, 118*, 1774-83. ↗

## Editions

| | | |
|---|---|---|
| 2012-12-20 | Reviewed | Gillespie, ME. |
| 2012-12-20 | Authored | Shamovsky, V. |
| 2013-11-05 | Edited | Shamovsky, V. |
| 2013-11-05 | Reviewed | Zwaginga, JJ. |

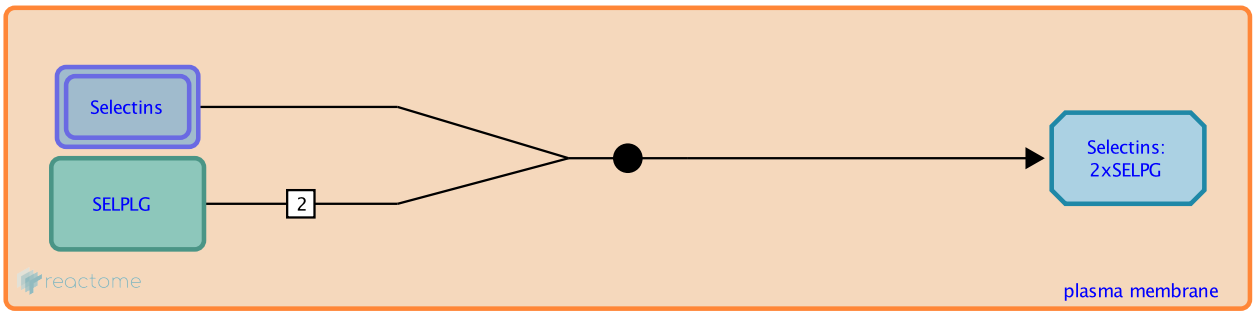
## P-selectin binds P-selectin ligand ↗

**Location:** Cell surface interactions at the vascular wall

**Stable identifier:** R-HSA-202724

**Type:** binding

**Compartments:** plasma membrane




PSGL-1 is expressed as a homodimer of two 120-kDa subunits that binds all four selectins, with the highest affinity for P-selectin, and is known to be constitutively expressed on the surface of platelets and most types of leukocytes. Besides playing a critical role in the inflammatory response by mediating leukocyte-leukocyte and leukocyte-endothelium interactions, PSGL-1 also participates in the hemostatic process by mediating leukocyte-platelet interactions.

## Literature references


da Costa Martins, P., Garcia-Vallejo, JJ., van Thienen, JV., Fernandez-Borja, M., van Gils, JM., Beckers, C. et al. (2007). P-selectin glycoprotein ligand-1 is expressed on endothelial cells and mediates monocyte adhesion to activated endothelium. *Arterioscler Thromb Vasc Biol, 27*, 1023-9. ↗

da Costa Martins, P., van den Berk, N., Ulfman, LH., Koenderman, L., Hordijk, PL., Zwaginga, JJ. (2004). Platelet-monocyte complexes support monocyte adhesion to endothelium by enhancing secondary tethering and cluster formation. *Arterioscler Thromb Vasc Biol, 24*, 193-9. ↗

Moore, KL., Eaton, SF., Lyons, DE., Lichenstein, HS., Cummings, RD., McEver, RP. (1994). The P-selectin glycoprotein ligand from human neutrophils displays sialylated, fucosylated, O-linked poly-N-acetyllactosamine. *J. Biol. Chem., 269*, 23318-27. ↗


## Editions

| | | |
|---|---|---|
| 2007-11-12 | Authored | Ouwehand, WH. |
| 2012-12-20 | Reviewed | Gillespie, ME. |
| 2012-12-20 | Edited | Shamovsky, V. |
| 2013-11-05 | Reviewed | Zwaginga, JJ. |

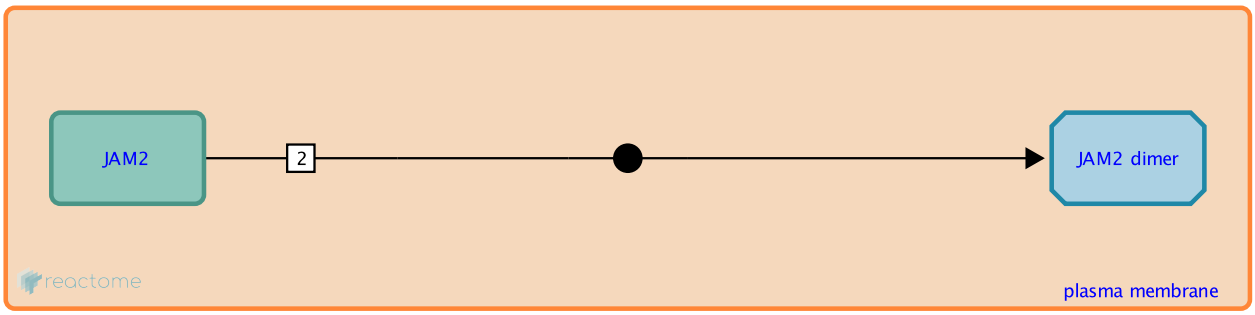
## JAM2 dimerises ↗

**Location:** Cell surface interactions at the vascular wall

**Stable identifier:** R-HSA-202709

**Type:** binding

**Compartments:** plasma membrane




Apart from its well-established interaction with Integrin alpha4beta1 (VLA-4), JAM2 (JAM-B) is also known to homodimerize.

## Literature references

Weber, C., Fraemohs, L., Dejana, E. (2007). The role of junctional adhesion molecules in vascular inflammation. *Nat Rev Immunol, 7*, 467-77. ↗

## Editions

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

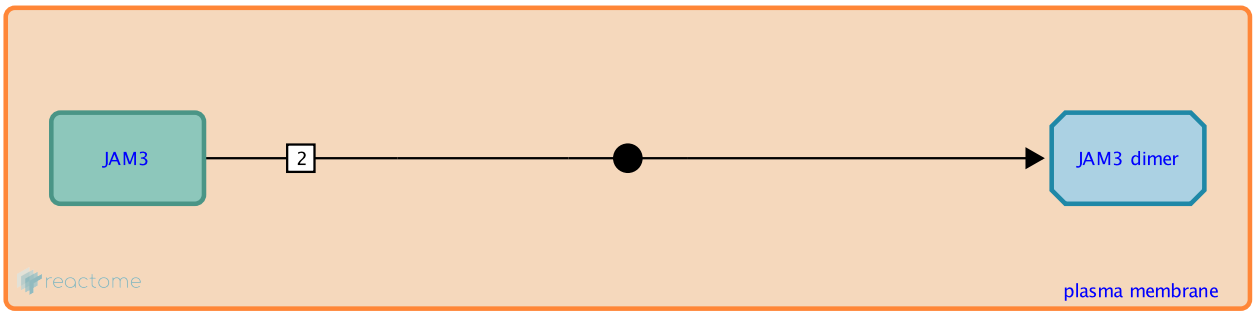
## JAM3 dimerises ↗

**Location:** Cell surface interactions at the vascular wall

**Stable identifier:** R-HSA-202731

**Type:** binding

**Compartments:** plasma membrane




JAM-C has been detected in epithelial-cell desmosomes. JAM-C homodimers are prominently located in endothelial-cell tight junctions.

## Literature references

Weber, C., Fraemohs, L., Dejana, E. (2007). The role of junctional adhesion molecules in vascular inflammation. *Nat Rev Immunol, 7*, 467-77. ↗

Mandicourt, G., Iden, S., Ebnet, K., Aurrand-Lions, M., Imhof, BA. (2007). JAM-C regulates tight junctions and integrin-mediated cell adhesion and migration. *J Biol Chem, 282*, 1830-7. ↗

## Editions

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

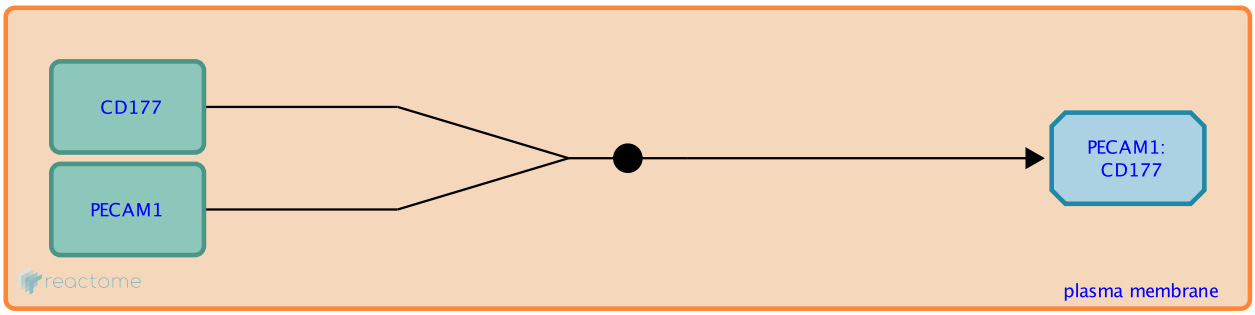
## CD177 binds PECAM-1 ↗

**Location:** Cell surface interactions at the vascular wall

**Stable identifier:** R-HSA-202702

**Type:** binding

**Compartments:** plasma membrane




CD177 is a 58- to 64-kDa glycosylphosphatidylinositol-anchored glycoprotein expressed exclusively by neutrophils, neutrophilic metamyelocytes, and myelocytes, but not by any other blood cells. It has been shown that neutrophil-specific CD177 is a heterophilic binding partner of PECAM-1, constituting a novel pathway that promotes neutrophil transmigration.

## Literature references

Sachs, UJ., Andrei-Selmer, CL., Maniar, A., Weiss, T., Paddock, C., Orlova, VV. et al. (2007). The neutrophil-specific antigen CD177 is a counter-receptor for platelet endothelial cell adhesion molecule-1 (CD31). *J Biol Chem, 282*, 23603-12. ↗

Kalinowska, A., Losy, J. (2006). PECAM-1, a key player in neuroinflammation. *Eur J Neurol, 13*, 1284-90. ↗

## Editions

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

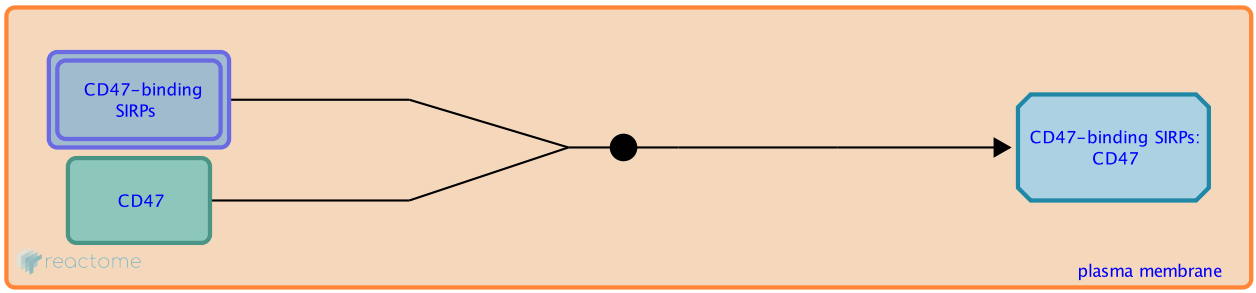
## CD47 binds SIRP ↗

**Location:** Cell surface interactions at the vascular wall

**Stable identifier:** R-HSA-202703

**Type:** binding

**Compartments:** plasma membrane




Integrin-associated protein (IAP or CD47) is a receptor for thrombospondin family members, a ligand for the transmembrane signaling protein SIRP-alpha and -gamma, and a component of a supramolecular complex containing specific integrins, heterotrimeric G proteins and cholesterol.

## Literature references

Barclay, AN., Brown, MH. (2006). The SIRP family of receptors and immune regulation. *Nat Rev Immunol, 6*, 457-64. ↗

## Editions

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

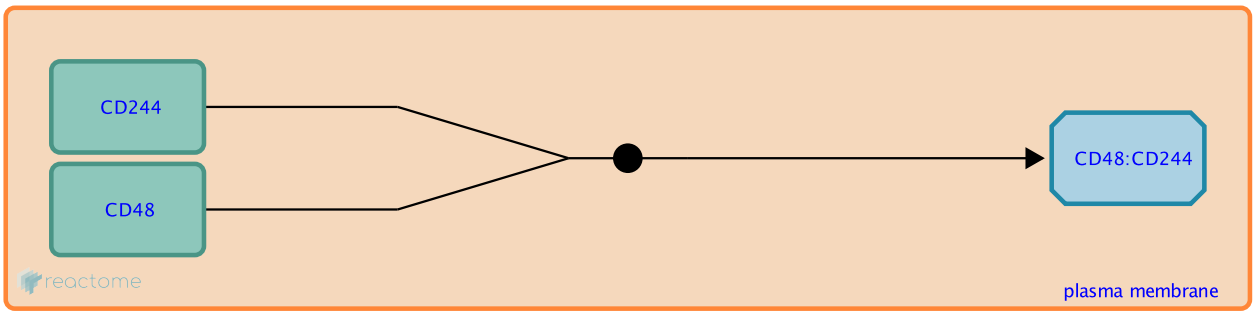
## CD48 binds CD244 ↗

**Location:** Cell surface interactions at the vascular wall

**Stable identifier:** R-HSA-202722

**Type:** binding

**Compartments:** plasma membrane




CD2, CD48, CD84, CD244 and CD58 have a similar extracellular domain arichitecture consisting of two Ig-SF domains. CD244 is closely related to CD84 in having a long cytoplasmic tail with tyrosine-based motifs (TxYxxI/V) resembling immunoreceptor tyrosine-based inhibitory motifs (ITIMs). CD2 has a cytoplasmic domain with proline-rich regions which recruit an Src homology 3 (SH3)- containing protein called CD2-associated protein (CD2AP). CD48 is glycosyl-phosphatidyl-inositol (GPI)-anchored to the membrane.

CD244 is known to be activated by binding to CD48 in humans.

### Literature references

Tangye, SG., Phillips, JH., Lanier, LL. (2000). The CD2-subset of the Ig superfamily of cell surface molecules: receptor-ligand pairs expressed by NK cells and other immune cells. *Semin Immunol, 12*, 149-57. ↗

Messmer, B., Eissmann, P., Stark, S., Watzl, C. (2006). CD48 stimulation by 2B4 (CD244)-expressing targets activates human NK cells. *J Immunol, 176*, 4646-50. ↗

### Editions

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

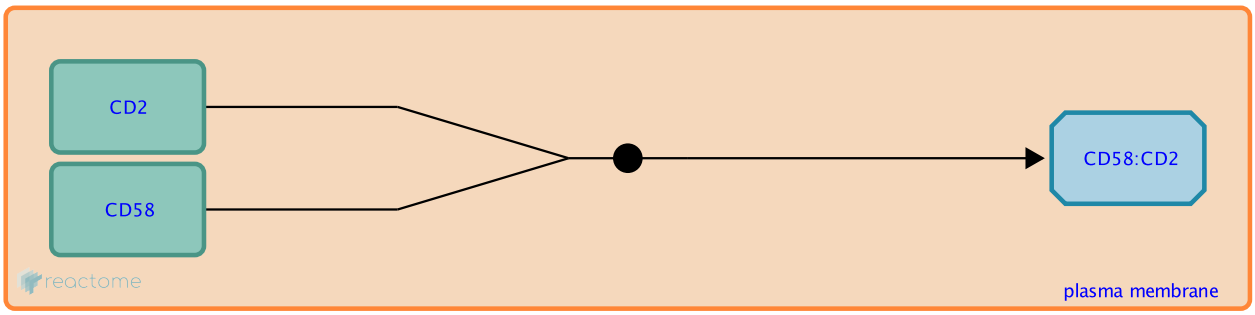
## CD58 binds CD2 ↗

**Location:** Cell surface interactions at the vascular wall

**Stable identifier:** R-HSA-202714

**Type:** binding

**Compartments:** plasma membrane




The crystal structure of the human CD2-CD58 complex also shows that most of the residues at the interface between these two proteins are charged and form several inter-protein salt bridges.

## Literature references

Bayas, MV., Kearney, A., Avramovic, A., van der Merwe, PA., Leckband, DE. (2007). Impact of salt bridges on the equilibrium binding and adhesion of human CD2 and CD58. *J Biol Chem, 282*, 5589-96. ↗

Wilkins, AL., Yang, W., Yang, JJ. (2003). Structural biology of the cell adhesion protein CD2: from molecular recognition to protein folding and design. *Curr Protein Pept Sci, 4*, 367-73. ↗

## Editions

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

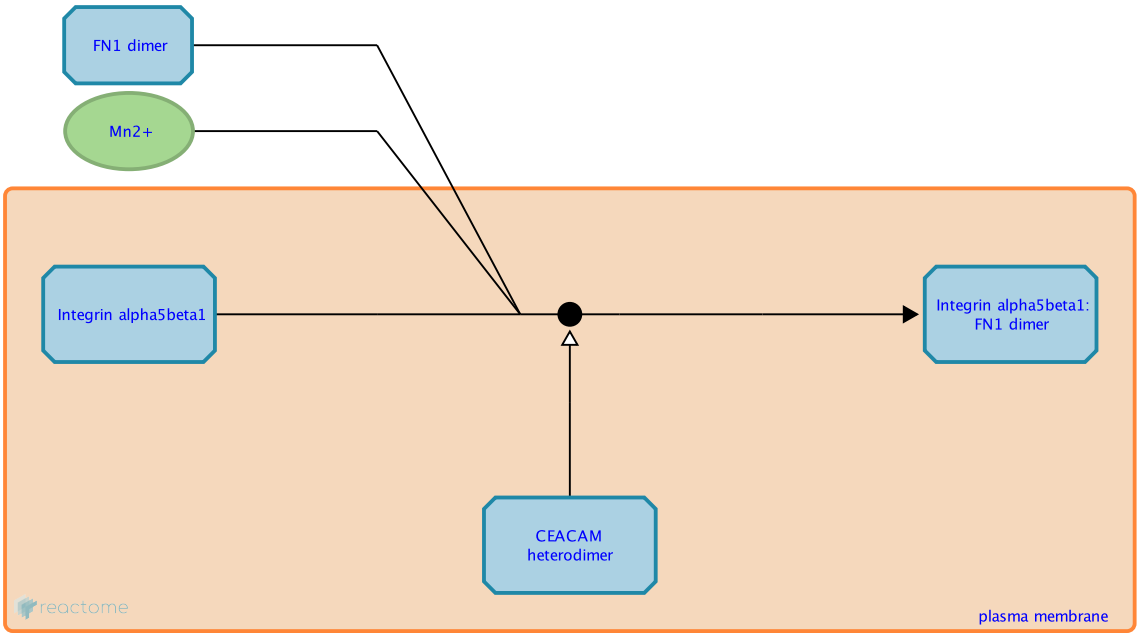
## Integrin alpha5beta1 binds FN1 dimer ↗

**Location:** Cell surface interactions at the vascular wall

**Stable identifier:** R-HSA-202723

**Type:** binding

**Compartments:** plasma membrane, extracellular region




Alpha5beta1 integrin was the first integrin shown to bind fibronectin (FN1). Unlike other FN1-binding integrins it is a specialist at this task. In solution FN1 occurs as a dimer. Binding to alpha5beta1 integrin stimulates FN1 self-association; blocking the RGD-cell binding domain of FN1 blocks fibril formation (Fogerty et al. 1990). FN1 binding is believed to induce integrin clustering, which promotes FN1-FN1 interactions. Integrin clustering is mediated by association between integrins and intracellular actin stress fibers (Calderwood et al. 2000). Binding of integrins to each of the monomers in the FN1 dimer pair is thought to trigger a conformational change in FN1 that exposes 'cryptic' FN1 binding sites that allow additional fibronectin dimers to bind without the requirement for pre-association with integrins (Singh et al. 2010). This non-covalent interaction may involve interactions with fibrillin (Ohashi & Erickson 2009). I1-5 functions as a unit that is the primary FN matrix assembly domain (Sottile et al. 1991) but other units are likely to be involved (Singh et al. 2010). Other integrins able to bind FN1 include alphaIIbBeta3, which is highly expressed on platelets where it predominantly binds fibrinogen leading to thrombus formation but also binds FN1 (Savage et al. 1996). Alpha4beta1 mediates cell-cell contacts and cell-matrix contacts through the ligands VCAM-1 and FN1, respectively (Humphries et al. 1995). Integrins alpha3beta1, alpha4beta7, alphaVbeta1, 3 (Johansson et al. 1997), 6 (Busk et al. 1992) and alpha8beta1 (Muller et al. 1995, Farias et al. 2005) are all able to bind FN1.

Tenacious binding of free fibronectin to cells leads to enhanced fibronectin matrix assembly and the formation of a polymerized fibronectin "cocoon" around the cells. This process is enhanced in the presence of CEACAM molecules.

## Literature references

Brakebusch, C., Fassler, R. (2005). beta 1 integrin function in vivo: adhesion, migration and more. *Cancer Metastasis Rev, 24*, 403-11. ↗

Zhang, Z., Morla, AO., Vuori, K., Bauer, JS., Juliano, RL., Ruoslahti, E. (1993). The alpha v beta 1 integrin functions as a fibronectin receptor but does not support fibronectin matrix assembly and cell migration on fibronectin. *J Cell Biol, 122*, 235-42. ↗

Ordonez, C., Zhai, AB., Camacho-Leal, P., Demarte, L., Fan, MM., Stanners, CP. (2007). GPI-anchored CEA family glycoproteins CEA and CEACAM6 mediate their biological effects through enhanced integrin alpha5beta1-fibronectin interaction. *J Cell Physiol, 210*, 757-65. ↗

Farias, E., Lu, M., Li, X., Schnapp, LM. (2005). Integrin alpha8beta1-fibronectin interactions promote cell survival via PI3 kinase pathway. *Biochem Biophys Res Commun, 329*, 305-11. ↗

## Editions

| | | |
|---|---|---|
| 2007-11-12 | Authored | Ouwehand, WH. |
| 2007-11-12 | Reviewed | Zwaginga, JJ. |
| 2008-05-07 | Reviewed | Humphries, MJ., Yamada, KM., Hynes, R. |
| 2010-01-21 | Edited | Jupe, S. |
| 2013-02-08 | Reviewed | Reinhardt, DP. |
| 2013-08-13 | Revised | Jupe, S. |

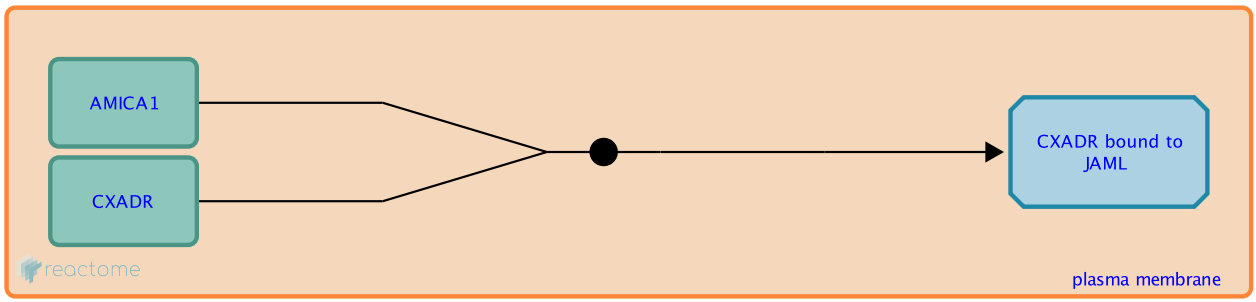
## CXADR binds to AMICA1 ↗

**Location:** Cell surface interactions at the vascular wall

**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

Zen, K., Liu, Y., McCall, IC., Wu, T., Lee, W., Babbin, BA. 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. |

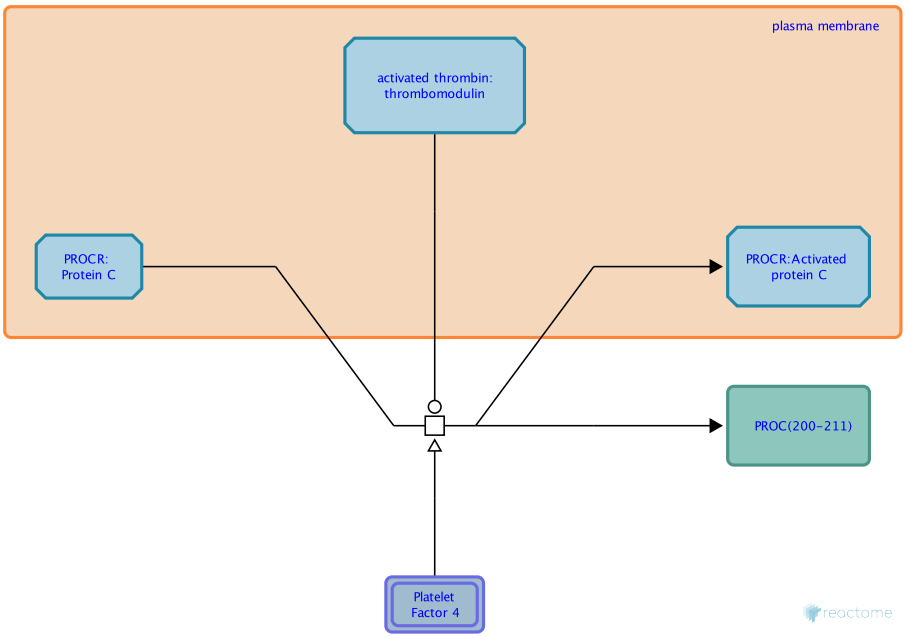
## Activated thrombin:thrombomodulin cleaves PROCR:Protein C to PROCR:Activated protein C ↗

**Location:** Cell surface interactions at the vascular wall

**Stable identifier:** R-HSA-141040

**Type:** transition

**Compartments:** extracellular region, plasma membrane




Thrombin complexed with thrombomodulin at the endothelial cell surface cleaves the heavy chain of protein C, generating activated protein C and an activation peptide. The activation peptide has no known function.

### Literature references


Esmon, CT. (1989). The roles of protein C and thrombomodulin in the regulation of blood coagulation. *J Biol Chem, 264*, 4743-6. ↗

Kisiel, W. (1979). Human plasma protein C: isolation, characterization, and mechanism of activation by alpha-thrombin. *J Clin Invest, 64*, 761-9. ↗


### Editions

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

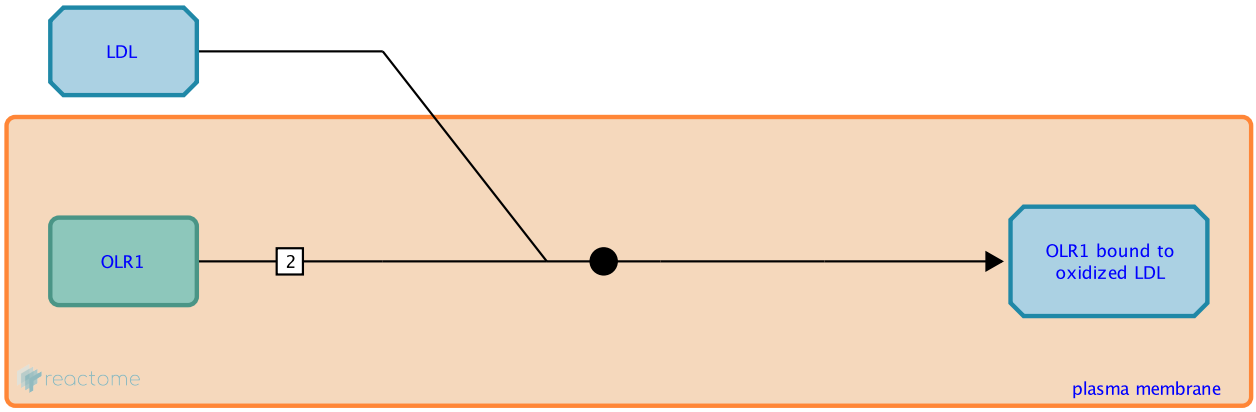
## OLR1 binds to oxidized LDL ↗

**Location:** Cell surface interactions at the vascular wall

**Stable identifier:** R-HSA-203130

**Type:** binding

**Compartments:** plasma membrane, extracellular region




The lectin-like oxidized low density lipoprotein receptor- 1 (Lox-1) mediates the recognition and internalization of oxidatively modified low density lipoprotein. This interaction results in a number of pro-atherogenic cellular responses that probably play a significant role in the pathology of atherosclerosis.

## Literature references


Sawamura, T., Kume, N., Aoyama, T., Moriwaki, H., Hoshikawa, H., Aiba, Y. et al. (1997). An endothelial receptor for oxidized low-density lipoprotein. *Nature, 386*, 73-7. ↗

Xie, Q., Matsunaga, S., Niimi, S., Ogawa, S., Tokuyasu, K., Sakakibara, Y. et al. (2004). Human lectin-like oxidized low-density lipoprotein receptor-1 functions as a dimer in living cells. *DNA Cell Biol, 23*, 111-7. ↗

Yoshida, H., Kondratenko, N., Green, S., Steinberg, D., Quehenberger, O. (1998). Identification of the lectin-like receptor for oxidized low-density lipoprotein in human macrophages and its potential role as a scavenger receptor. *Biochem J, 334*, 9-13. ↗

Shi, X., Niimi, S., Ohtani, T., Machida, S. (2001). Characterization of residues and sequences of the carbohydrate recognition domain required for cell surface localization and ligand binding of human lectin-like oxidized LDL receptor. *J Cell Sci, 114*, 1273-82. ↗

Moriwaki, H., Kume, N., Sawamura, T., Aoyama, T., Hoshikawa, H., Ochi, H. et al. (1998). Ligand specificity of LOX-1, a novel endothelial receptor for oxidized low density lipoprotein. *Arterioscler Thromb Vasc Biol, 18*, 1541-7. ↗


## Editions

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

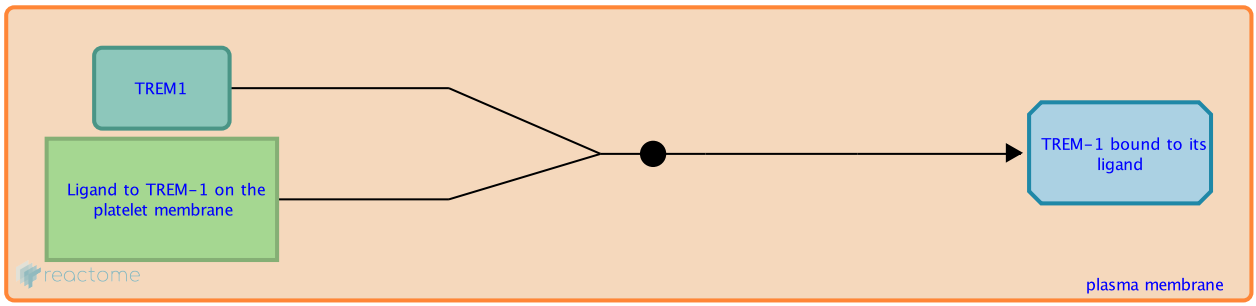
## Platelet-derived TREM-1 ligand binds to TREM-1 ↗

**Location:** Cell surface interactions at the vascular wall

**Stable identifier:** R-HSA-203156

**Type:** binding

**Compartments:** plasma membrane




The triggering receptor expressed on myeloid cells 1 (TREM-1) plays an important role in the innate immune response related to severe infections and sepsis. Although the identity and occurrence of the natural TREM-1 ligands are so far unknown, the presence of a ligand for TREM-1 on human platelets has been established. It has been suggested that TREM1 recognizes soluble proteins or cell-surface proteins which are upregulated as a result of inflammation and/or tissue damage and also bacterial LPS (Tessarz & Cerwenka 2008).

## Literature references

Haselmayer, P., Grosse-Hovest, L., von Landenberg, P., Schild, H., Radsak, MP. (2007). TREM-1 ligand expression on platelets enhances neutrophil activation. *Blood, 110*, 1029-35. ↗

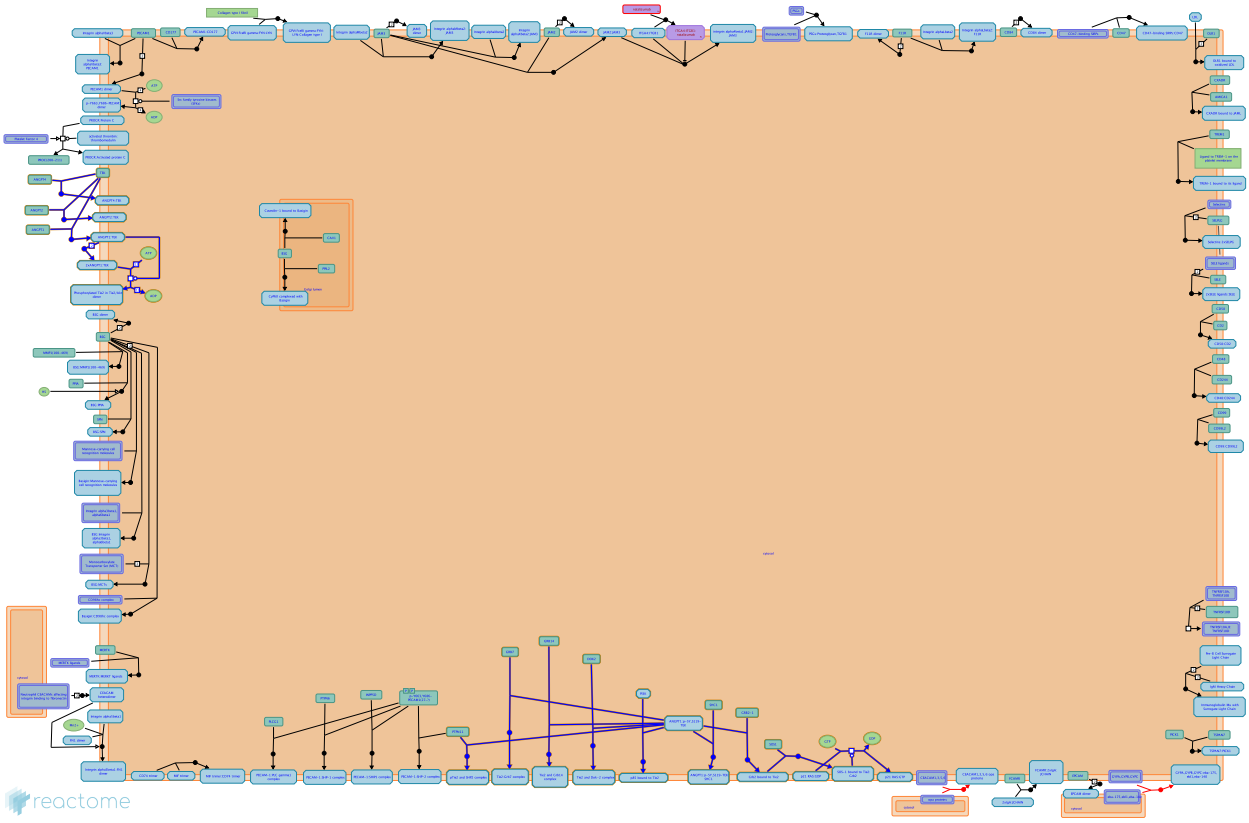
## Editions

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

## Tie2 Signaling ↗

**Location:** Cell surface interactions at the vascular wall

**Stable identifier:** R-HSA-210993



The Tie2/Tek receptor tyrosine kinase plays a pivotal role in vascular and hematopoietic development and is expressed exclusively on endothelial lineage. Tie2 interacts with a group of ligands belonging to angiopoietin family and undergoes activation.

These ligands show opposing actions, angiopoietin 1 and angiopoietin 4 stimulate the Tie2 phosphorylation and angiopoietin 2 inhibits it. Upon tyrosine phosphorylation Tie2 acts as a scaffold for various signaling proteins involved in different signal transduction cascades that can effect survival of endothelium and angiogenic sprout formation.

## Literature references


Loughna, S., Sato, TN. (2001). Angiopoietin and Tie signaling pathways in vascular development. *Matrix Biol, 20*, 319-25. ↗

Jones, N., Dumont, DJ. (2000). Tek/Tie2 signaling: new and old partners. *Cancer Metastasis Rev, 19*, 13-7. ↗

Jones, N., Dumont, DJ. (1998). The Tek/Tie2 receptor signals through a novel Dok-related docking protein, Dok-R. *Oncogene, 17*, 1097-108. ↗

Ward, NL., Dumont, DJ. (2002). The angiopoietins and Tie2/Tek: adding to the complexity of cardiovascular development. *Semin Cell Dev Biol, 13*, 19-27. ↗

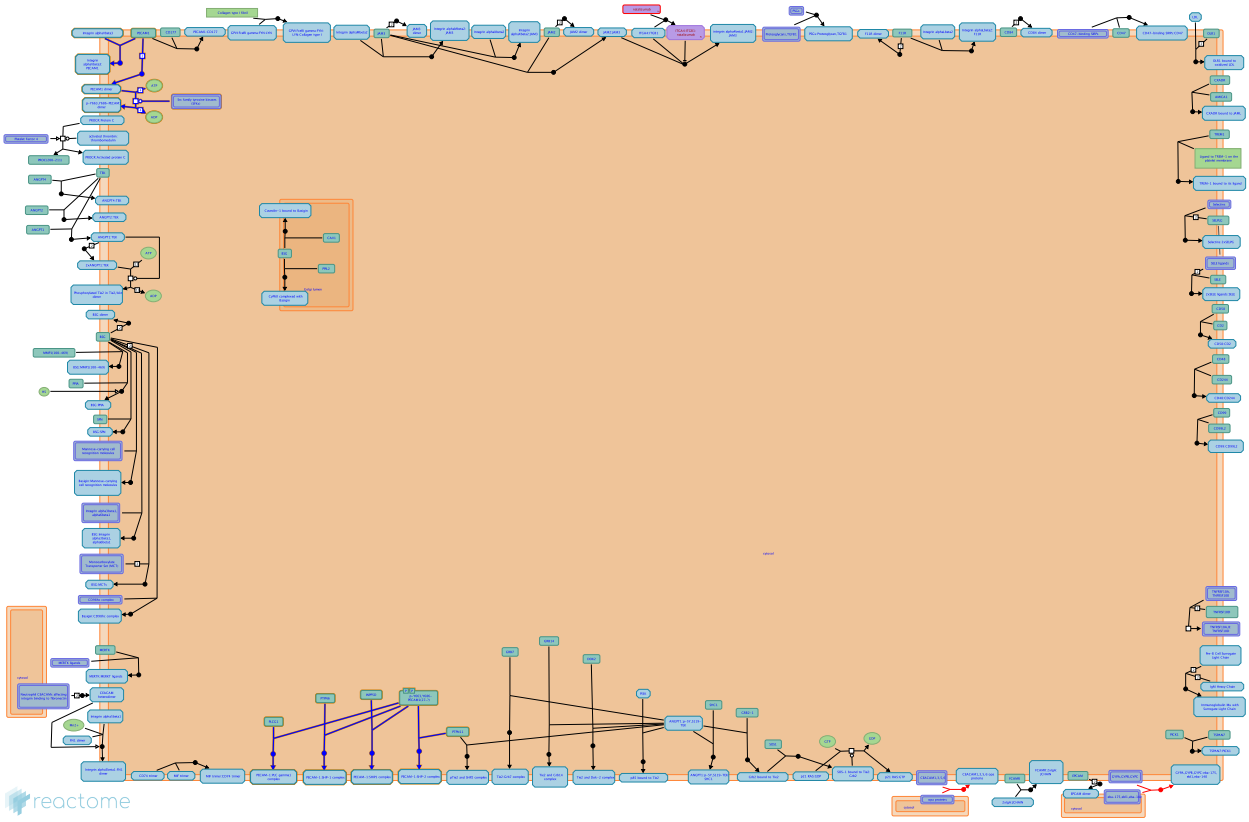

## Editions

| | | |
|---|---|---|
| 2008-02-26 | Reviewed | Trowsdale, J. |
| 2008-03-05 | Authored | de Bono, B., Garapati, P V. |

## PECAM1 interactions ↗

**Location:** Cell surface interactions at the vascular wall

**Stable identifier:** R-HSA-210990



PECAM-1/CD31 is a member of the immunoglobulin superfamily (IgSF) and has been implicated to mediate the adhesion and trans-endothelial migration of T-lymphocytes into the vascular wall, T cell activation and angiogenesis. It has six Ig homology domains within its extracellularly and an ITIM motif within its cytoplasmic region. PECAM-1 mediates cellular interactions by both homophilic and heterophilic interactions. The cytoplasmic domain of PECAM-1 contains tyrosine residues which serves as docking sites for recruitment of cytosolic signaling molecules. Under conditions of platelet activation, PECAM-1 is phosphorylated by Src kinase members. The tyrosine residues 663 and 686 are required for recruitment of the SH2 domain containing PTPs.

## Literature references


Gong, N., Chatterjee, S. (2003). Platelet endothelial cell adhesion molecule in cell signaling and thrombosis. *Mol Cell Biochem, 253*, 151-8. ↗

Jackson, DE. (2003). The unfolding tale of PECAM-1. *FEBS Lett, 540*, 7-14. ↗


## Editions

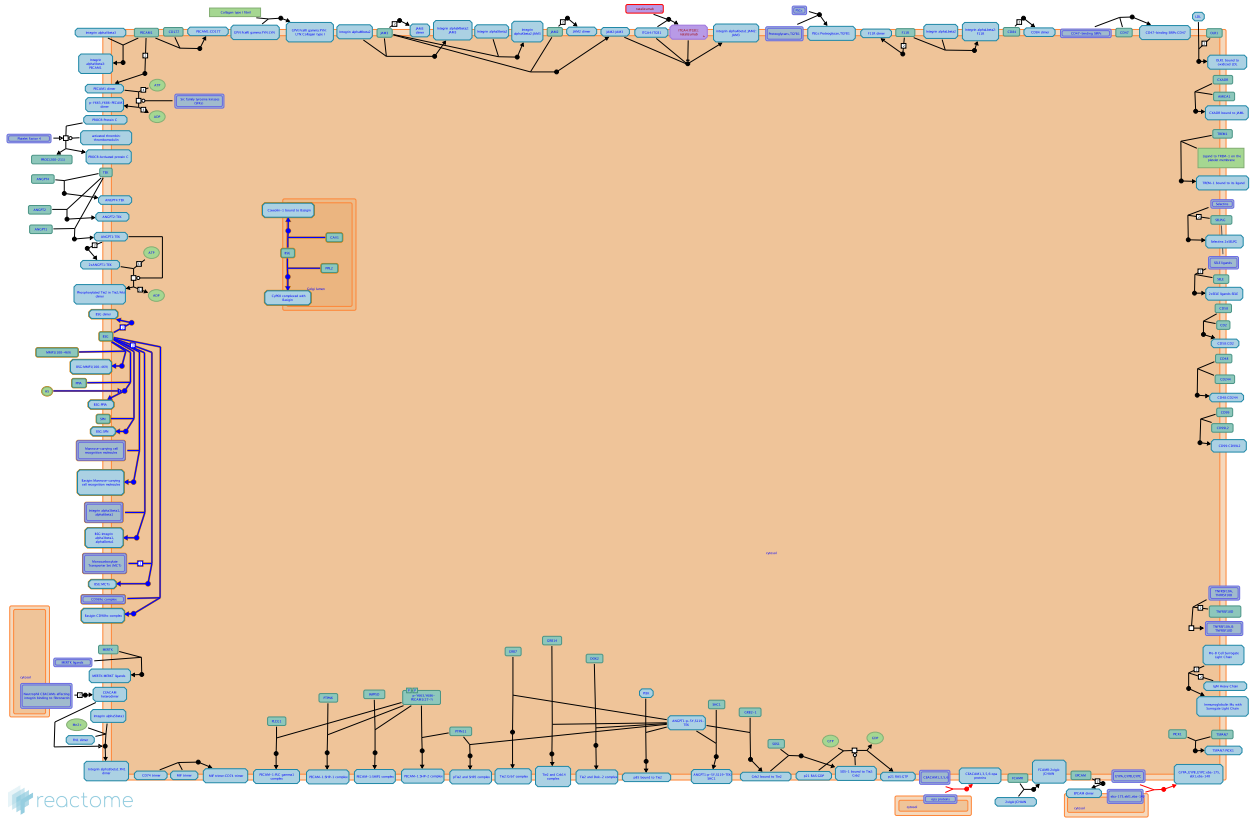
| | | |
|---|---|---|
| 2008-02-26 | Reviewed | Trowsdale, J. |
| 2008-02-26 | Authored | de Bono, B., Garapati, P V. |

## Basigin interactions ↗

**Location:** Cell surface interactions at the vascular wall

**Stable identifier:** R-HSA-210991

**Compartments:** plasma membrane



Basigin is a widely expressed transmembrane glycoprotein that belongs to the Ig superfamily and is highly enriched on the surface of epithelial cells. Basigin is involved in intercellular interactions involved in various immunologic phenomena, differentiation, and development, but a major function of basigin is stimulation of synthesis of several matrix metalloproteinases. Basigin also induces angiogenesis via stimulation of VEGF production.

Basigin has an extracellular region with two Ig-like domains of which the N-term Ig-like domain is involved in interactions. It undergoes interactions between basigin molecules on opposing cells or on neighbouring cells. It also interacts with a variety of other proteins like caveolin-1, cyclophilins, integrins and annexin II that play important roles in cell proliferation, energy metabolism, migration, adhesion and motion, especially in cancer metastasis.

## Literature references

Jiang, JL., Tang, J. (2007). CD147 and its interacting proteins in cellular functions. *Sheng Li Xue Bao, 59*, 517-23. ↗

## Editions

| | | |
|---|---|---|
| 2008-02-26 | Reviewed | Trowsdale, J. |
| 2008-02-26 | Authored | de Bono, B., Garapati, P V. |
| 2009-03-16 | Edited | Garapati, P V. |

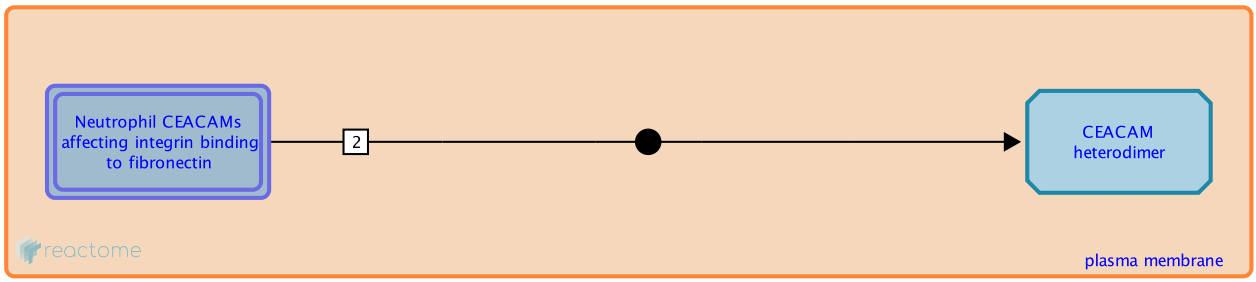
## Heterodimerization of CEACAMs ↗

**Location:** Cell surface interactions at the vascular wall

**Stable identifier:** R-HSA-202717

**Type:** binding

**Compartments:** plasma membrane




The presence of CEACAM dimers was shown to lead to an increase in the binding of the integrin alph5 beta1 receptor to its ligand fibronectin, without changing its cell surface levels, resulting in increased adhesion of these cells to fibronectin.

## Literature references

Ordonez, C., Zhai, AB., Camacho-Leal, P., Demarte, L., Fan, MM., Stanners, CP. (2007). GPI-anchored CEA family glycoproteins CEA and CEACAM6 mediate their biological effects through enhanced integrin alpha5beta1-fibronectin interaction. *J Cell Physiol, 210,* 757-65. ↗

## Editions

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

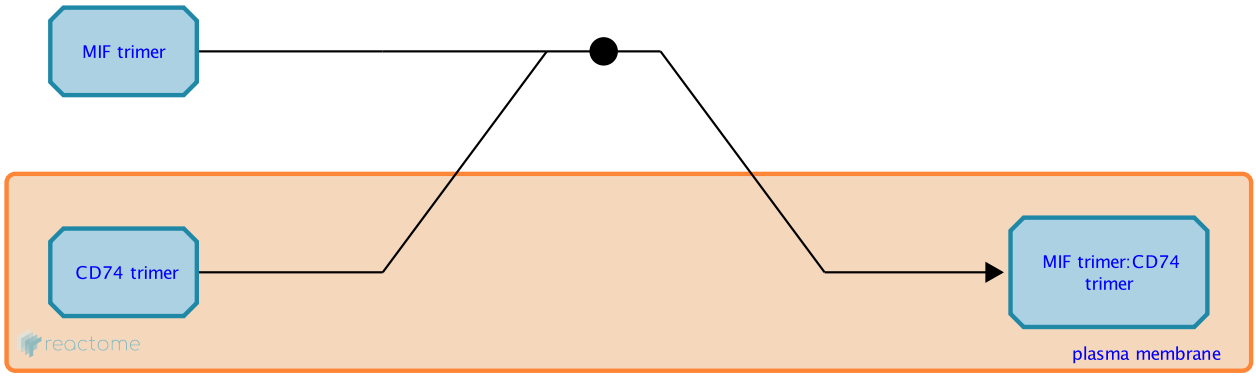
## CD74 binds MIF ↗

**Location:** Cell surface interactions at the vascular wall

**Stable identifier:** R-HSA-5676133

**Type:** binding

**Compartments:** extracellular region, plasma membrane




Macrophage migration inhibitory factor (MIF), one of the first cytokines to be described (George & Vaughan 1962), is an important regulator of innate and adaptive immunity. MIF is an upstream activator of monocytes/macrophages, centrally involved in the pathogenesis of septic shock, arthritis, and other inflammatory conditions (Nishihira 2000, Sanchez-Niño et al. 2013). High-expression Mif alleles are linked to severe rheumatoid arthritis (Morand & Leech 2005). MIF promotes monocyte/macrophage activation and it is required for the optimal expression of TNF-alpha, IL-1, and PGE2 (Calandra & Bucala 1997). MIF-treated macrophages are more phagocytic and better able to destroy intracellular pathogens, such as Leishmania (Rosado & Rodriguez-Sosa 2011). Active MIF is a 37.5 kDa homotrimer.

MIF can bind to CD74 (Leng et al. 2003) and the chemokine receptors CXCR2 and CXCR4 (Bernhagen et al. 2007). Leukocyte recruitment by MIF is mediated by interaction with CXCR2 and CXCR4 (Bernhagen et al. 2007). MIF interaction with CD74 mediates its proproliferative and antiproliferative effects, regulation of B-cell and tumor cell survival, fibrosis and angiogenesis (Starlets et al. 2006). MIF can suppress the immunosuppressive effects of glucocorticoids, inducing a sustained pattern of ERK-1/2 MAP kinase activation (Bach et al. 2009).

MIF is endocytosed to bind the cytosolic protein JAB1 (Schwartz et al. 2012), negatively regulating JAB1-controlled pathways (Kleemann et al. 2000). MIF inhibits JAB1-induced JNK activity, AP-1 activity and JAB1-dependent cell-cycle regulation by stabilizing p27Kip1 protein (Nguyen et al. 2003). Consequently, MIF blocks JAB1-mediated rescue of fibroblasts from growth arrest (Kleemann et al. 2000).

## Literature references

Leng, L., Metz, CN., Fang, Y., Xu, J., Donnelly, S., Baugh, J. et al. (2003). MIF signal transduction initiated by binding to CD74. *J. Exp. Med., 197*, 1467-76. ↗

## Editions

| | | |
|---|---|---|
| 2014-11-18 | Authored | Jupe, S. |
| 2015-09-01 | Edited | Jupe, S. |
| 2015-11-09 | Reviewed | Akkerman, JW. |

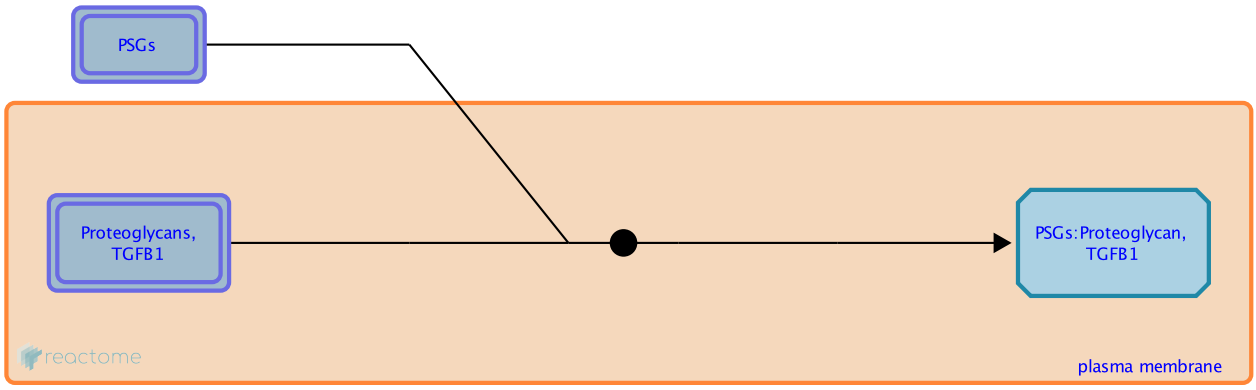
## PSGs bind proteoglycans and TGF-beta1 ↗

**Location:** Cell surface interactions at the vascular wall

**Stable identifier:** R-HSA-8870732

**Type:** binding

**Compartments:** plasma membrane, extracellular region




The pregnancy-specific glycoproteins (PSGs) are the most abundant trophoblastic proteins in maternal blood during human pregnancy. They are secreted by the syncytiotrophoblast and are detected around day 14 post fertilization. The PSG family belongs to the carcinoembryonic antigen family. There are ten human protein-coding PSG genes (PSG1- PSG9, PSG11) (Thompson et al. 1990). Several studies indicate that PSGs have immunoregulatory, proangiogenic, and anti-platelet functions. PSGs (PSG1) binds to cell surface proteoglycans that have covalently attached glycosaminoglycans (GAGs), specifically to syndecans 1-4 and glypican-1, to induce endothelial tube formation (Lisboa et al. 2011). PSG1 interacts with and activates Transforming growth factor beta 1 (TGFB1) (Blois et al. 2014, Moore & Dveksler 2014). During pregnancy, TGFB1 regulates many processes essential for pregnancy success including trophoblast invasion and proliferation, angiogenesis, extracellular matrix formation and tolerance to the foetal semi-allograft (Jones et al. 2006). TGFB1 also regulates the production of vascular endothelial growth factor (VEGF) and this may contribute to  PSG1-induced VEGF-A secretion (Ha et al. 2010). Therefore the pro-angiogenic properties of some PSGs are mediated by two different mechanisms, TGF-beta mediated induction of VEGF-A, and direct interaction of PSGs with GAGs on the surface of endothelial cells.

## Literature references

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Blois, SM., Sulkowski, G., Tirado-González, I., Warren, J., Freitag, N., Klapp, BF. et al. (2014). Pregnancy-specific glycoprotein 1 (PSG1) activates TGF-? and prevents dextran sodium sulfate (DSS)-induced colitis in mice. *Mucosal Immunol, 7*, 348-58. ↗

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

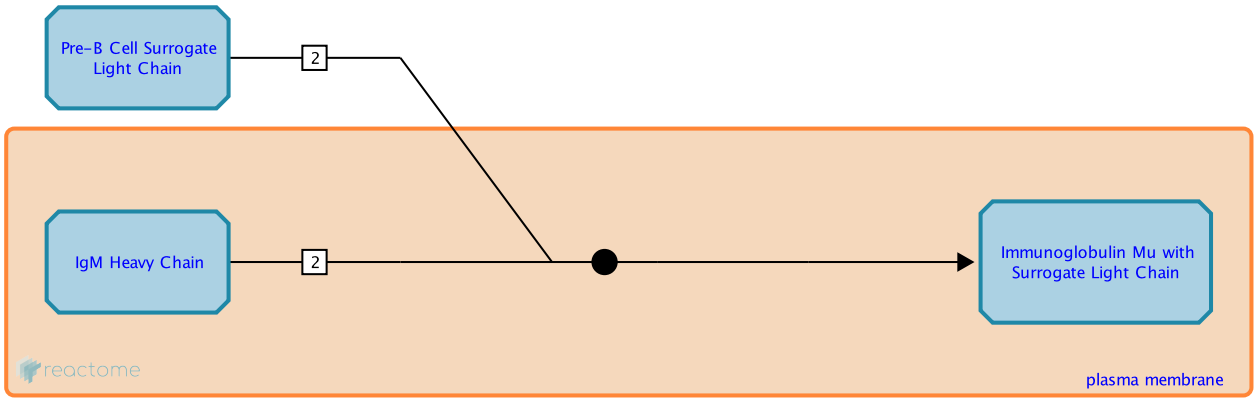
## SL (surrogate light chain) binds IgH to form pre-BCR ↗

**Location:** Cell surface interactions at the vascular wall

**Stable identifier:** R-HSA-8858498

**Type:** binding

**Compartments:** plasma membrane




The pre-BCR is a heterodimer composed of an immunoglobulin (Ig) heavy chain molecule (IgH) covalently associated with an immunoglobulin light chain-like molecule called the surrogate light chain (SL). The SL consists of two non-covalently associated proteins called lamda-5 (CD179a) and VPREB (CD179b) (Melchers 1993). Pre-BCR signalling promotes the generation of a large pool of precursor cells that can undergo light-chain gene rearrangement (Rickert 2013).

### Literature references

Melchers, F., Karasuyama, H., Haasner, D., Bauer, S., Kudo, A., Sakaguchi, N. et al. (1993). The surrogate light chain in B-cell development. *Immunol. Today, 14*, 60-8. ↗

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

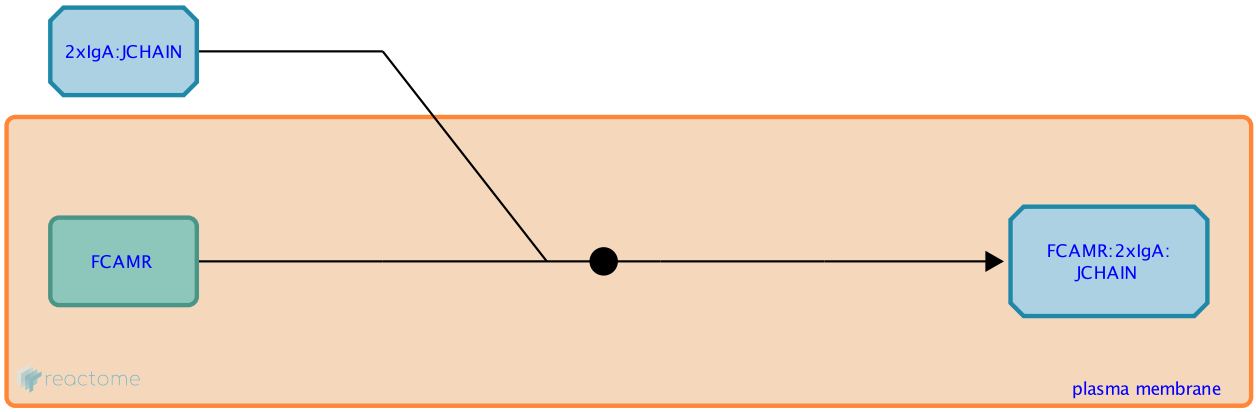
## FCAMR binds IgA ↗

**Location:** Cell surface interactions at the vascular wall

**Stable identifier:** R-HSA-8858428

**Type:** binding

**Compartments:** plasma membrane, extracellular region




IgA nephropathy (IgAN), the most common glomerulonephritis, is characterized by the deposition of IgA immune complexes in the glomerular mesangium. This is the result of High affinity immunoglobulin alpha and immunoglobulin mu Fc receptor (FCAMR, CD351) binding to IgA (McDonald et al. 2002).

## Literature references

McDonald, KJ., Cameron, AJ., Allen, JM., Jardine, AG. (2002). Expression of Fc alpha/mu receptor by human mesangial cells: a candidate receptor for immune complex deposition in IgA nephropathy. *Biochem. Biophys. Res. Commun., 290*, 438-42. ↗

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

## TSPAN7 binds PICK1 ↗

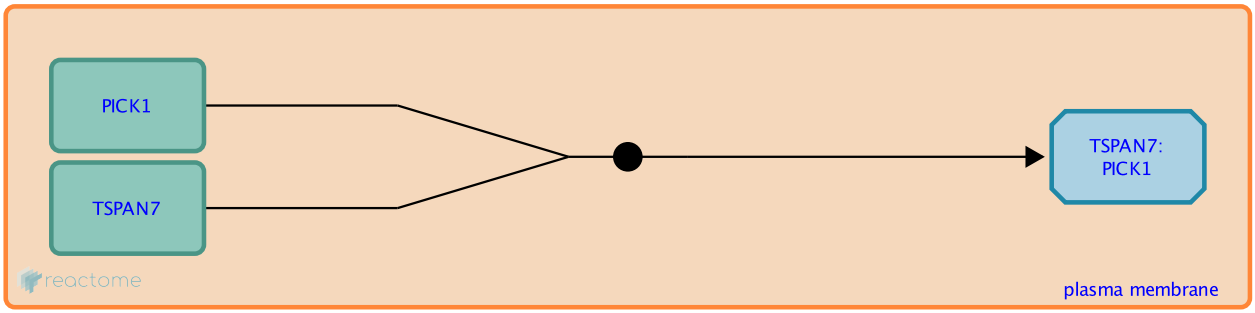
**Location:** Cell surface interactions at the vascular wall

**Stable identifier:** R-HSA-8858435

**Type:** binding

**Compartments:** plasma membrane

**Inferred from:** Tspan7 binds Pick1 (Rattus norvegicus)




Tetraspanin 7 (TSPAN7) a member of the tetraspanin superfamily associates dynamically with numerous partner proteins in tetraspanin-enriched microdomains (TEMs) of the plasma membrane (Boucheix and Rubinstein, 2001). TSPAN7 promotes filopodia and dendritic spine formation in cultured hippocampal neurons, and is required for spine stability and normal synaptic transmission. Via its C-terminus, TSPAN7 interacts with the PDZ domain of protein interacting with C kinase 1 (PICK1), to regulate PICK1 and GluR2/3 association and AMPA receptor trafficking (Bassani et al. 2012). PICK1 is involved in the internalization and recycling of AMPA receptors (AMPARs) (Perez et al. 2001). In hippocampal neurons, TSPAN7 may regulate AMPA receptor trafficking by limiting PICK1 accessibility to AMPA receptors and suggest an additional mechanism for the functional maturation of glutamatergic synapses, whose impairment is implicated in intellectual disability (Bassani et al. 2012).

### Editions

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

## Glycophorins bind plasmodium falciparum Ags ↗

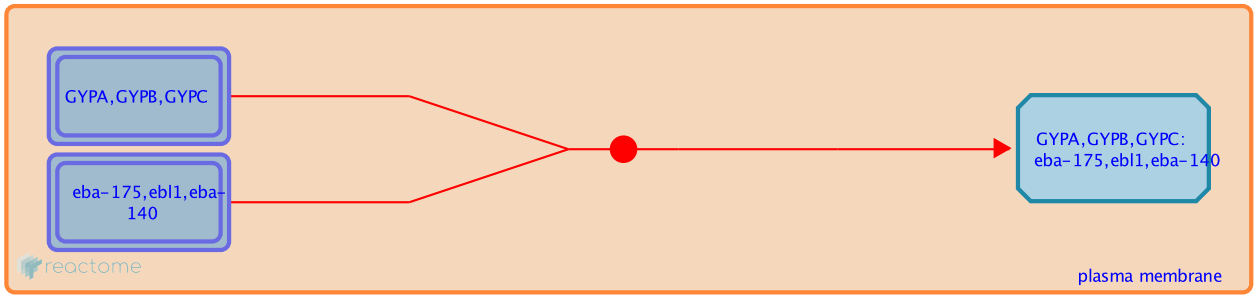
**Location:** Cell surface interactions at the vascular wall

**Stable identifier:** R-HSA-8867098

**Type:** binding

**Compartments:** plasma membrane

**Diseases:** malaria




Red blood cell (RBC) glycophorins are integral membrane proteins that are rich in sialic acids. They carry blood group antigenic determinants and serve as ligands for viruses, bacteria, and parasites. They are used as markers to study normal and pathological differentiation of erythroid tissue. RBC glycophorins include glycophorins A (GPYA) to E and are divided into two groups. GPYA and GPYB carry MN and Ss blood group antigens and may act as receptors for Plasmodium falciparum (Cartron & Rahuel 1992). GPYA and GPYB are recognized by P. falciparum erythrocyte-binding antigen 175 (EBA-175) (Wanaguru et al. 2013) and erythrocyte-binding ligand 1 (EBL-1) (Mayer et al. 2009), respectively. GLYC codes for the Gerbich (Ge) blood group antigens and is a receptor for P. falciparum invasion, recognizing EBA-140 on the surface of merozoites (Maier et al. 2003).

## Literature references

Mayer, DC., Cofie, J., Jiang, L., Hartl, DL., Tracy, E., Kabát, J. et al. (2009). Glycophorin B is the erythrocyte receptor of Plasmodium falciparum erythrocyte-binding ligand, EBL-1. *Proc. Natl. Acad. Sci. U.S.A., 106*, 5348-52. ↗

Cartron, JP., Rahuel, C. (1992). Human erythrocyte glycophorins: protein and gene structure analyses. *Transfus Med Rev, 6*, 63-92. ↗

Maier, AG., Duraisingh, MT., Reeder, JC., Patel, SS., Kazura, JW., Zimmerman, PA. et al. (2003). Plasmodium falciparum erythrocyte invasion through glycophorin C and selection for Gerbich negativity in human populations. *Nat. Med., 9*, 87-92. ↗

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

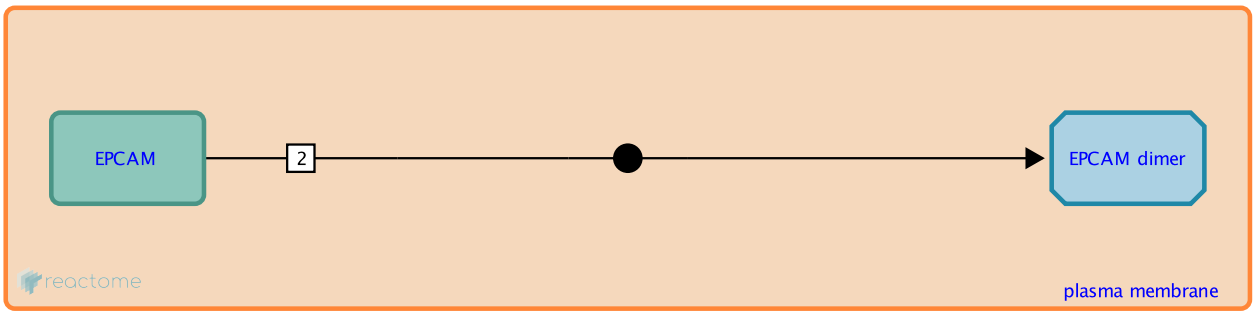
## EPCAM binds itself to form homotypic cell adhesion ↗

**Location:** Cell surface interactions at the vascular wall

**Stable identifier:** R-HSA-8867240

**Type:** binding

**Compartments:** plasma membrane




Epithelial cell adhesion molecule (EPCAM) is a type I membrane protein expressed in a variety of human epithelial tissues, cancers, and progenitor and stem cells. It consists of an extracellular domain with epidermal growth factor (EGF)-like and thyroglobulin repeat-like domains, a single transmembrane domain, and a short 26-amino acid intracellular domain called EpICD (Balzar et al. 1999). In normal cells EPCAM is predominantly present at the surfaces of intercellular spaces where epithelial cells form very tight junctions. The extracellular domain of EPCAM interacts with a second EPCAM molecule resulting in homotypic cell-cell adhesion (Litvinov et al. 1994, 1997). Formation of EPCAM-mediated adhesions has a negative regulatory effect on adhesions mediated by classic cadherins, which may have strong effects on the differentiation and growth of epithelial cells (Balzar et al. 1999).

### Literature references

Litvinov, SV., Velders, MP., Bakker, HA., Fleuren, GJ., Warnaar, SO. (1994). Ep-CAM: a human epithelial antigen is a homophilic cell-cell adhesion molecule. *J. Cell Biol., 125*, 437-46. ↗

Litvinov, SV., Balzar, M., Winter, MJ., Bakker, HA., Briaire-de Bruijn, IH., Prins, F. et al. (1997). Epithelial cell adhesion molecule (Ep-CAM) modulates cell-cell interactions mediated by classic cadherins. *J. Cell Biol., 139*, 1337-48. ↗

Trzpis, M., McLaughlin, PM., de Leij, LM., Harmsen, MC. (2007). Epithelial cell adhesion molecule: more than a carcinoma marker and adhesion molecule. *Am. J. Pathol., 171*, 386-95. ↗

Balzar, M., Winter, MJ., de Boer, CJ., Litvinov, SV. (1999). The biology of the 17-1A antigen (Ep-CAM). *J. Mol. Med., 77* , 699-712. ↗

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

## CD99 binds CD99L2 ↗

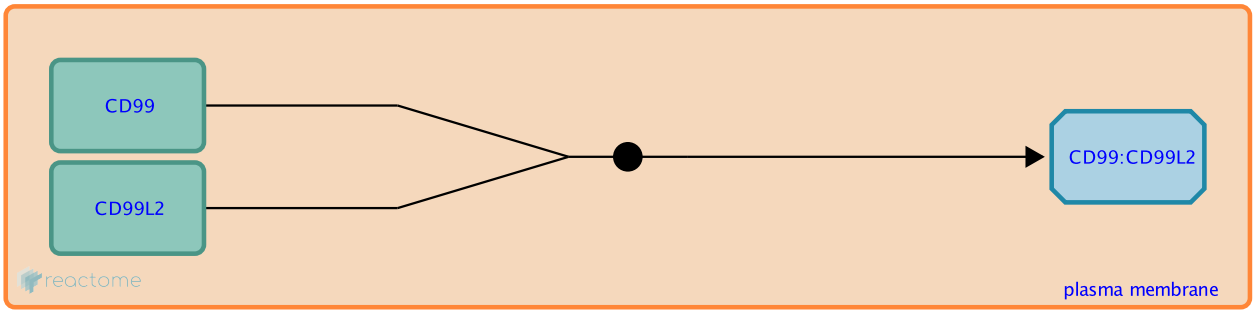
**Location:** Cell surface interactions at the vascular wall

**Stable identifier:** R-HSA-8867097

**Type:** binding

**Compartments:** plasma membrane

**Inferred from:** Cd99 binds Cd99l2 (Mus musculus)




CD99 is a glycoprotein found on the leukocytes surface. It has been variously described as a human thymus leukemia Ag (Levy et al. 1979), a Ewing's sarcoma-specific membrane marker molecule (Hamilton et al. 1988) and a putative adhesion molecule (termed E2) involved in spontaneous rosette formation of T cells with erythrocytes (Aubrit et al. 1989, Bernard et al. 1988). CD99L2 is a paralog of CD99 that directly interacts with CD99 to form a heterodimer via its cytoplasmic domain. This interaction positively regulates CD99L2 trafficking to cell surfaces (Nam et al. 2013).

### Editions

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

## CEACAM1,3,5,6 bind opa proteins ↗

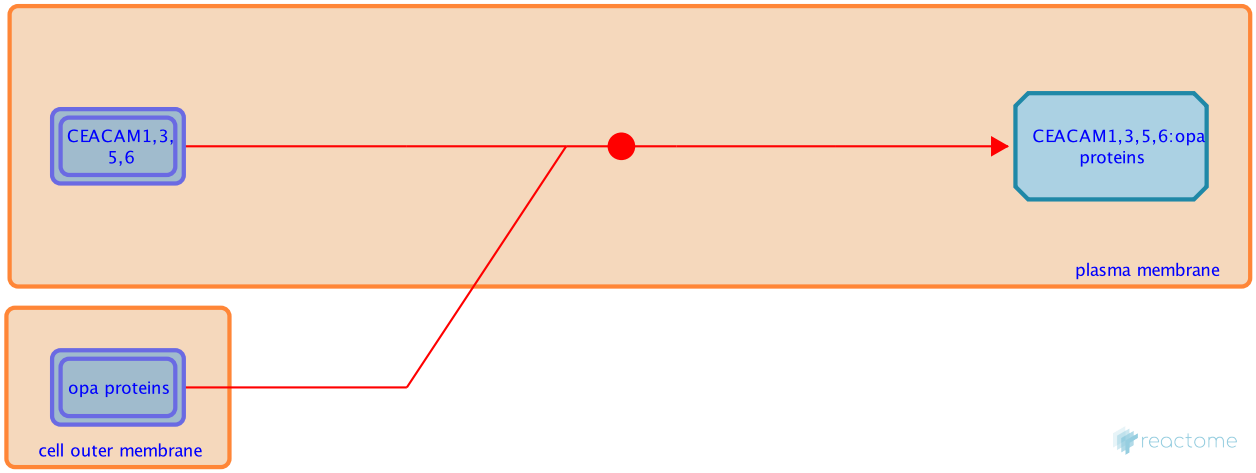
**Location:** Cell surface interactions at the vascular wall

**Stable identifier:** R-HSA-8867135

**Type:** binding

**Compartments:** plasma membrane

**Diseases:** gonorrhea




The carcinoembryonic antigen (CEA) gene family, part of the immunoglobulin (Ig) gene superfamily, is a diverse set of highly glycosylated glycoproteins. Two types of membrane anchorage are found in the CEA subgroup of CEACAM proteins. CEACAM1 and CEACAM3 contain a hydrophobic transmembrane domain followed by a cytoplasmic domain, while CEA (also known as CEACAM5) and CEACAM6 are attached to the cell surface via a glycosylphosphatidylinositol (GPI) moiety (Hammarstrom et al. 1999). CEA, CEACAM1, CEACAM3, and CEACAM6 have been shown to serve as receptors for the neisserial phase-variable opacity-associated (Opa) adhesin proteins (Chen & Gotschlich, 1996, Bos et al. 1997, Popp et al. 1999). These adhesin proteins are a major surface component of Neisseria meningitidis and Neisseria gonorrhoeae, and are responsible for bacterial adherence and entry into host cells and interactions with the host immune system. These receptors also bind to DraE adhesin of Escherichia coli (Berger et al. 2004).

## Literature references

Bos, MP., Grunert, F., Belland, RJ. (1997). Differential recognition of members of the carcinoembryonic antigen family by Opa variants of Neisseria gonorrhoeae. *Infect. Immun., 65*, 2353-61. ↗

Popp, A., Dehio, C., Grunert, F., Meyer, TF., Gray-Owen, SD. (1999). Molecular analysis of neisserial Opa protein interactions with the CEA family of receptors: identification of determinants contributing to the differential specificities of binding. *Cell. Microbiol., 1*, 169-81. ↗

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

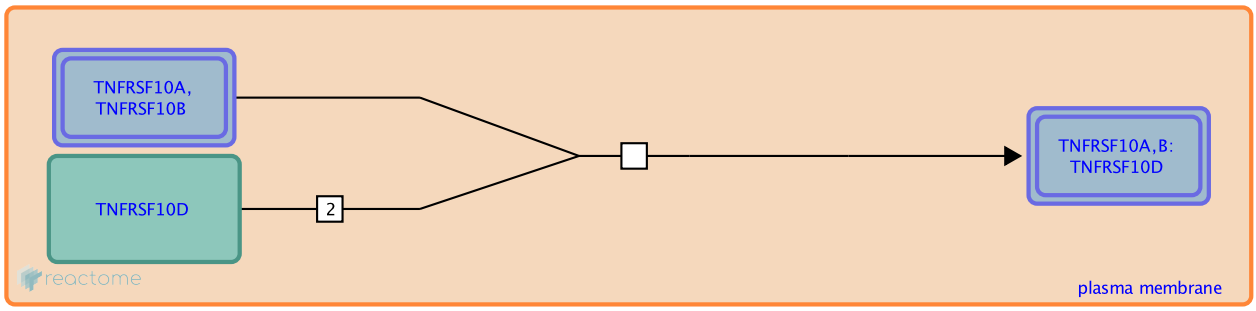
## TRAIL receptor-4 binds TRAIL receptor-1 or TRAIL receptor-2 ↗

**Location:** Cell surface interactions at the vascular wall

**Stable identifier:** R-HSA-5635741

**Type:** transition

**Compartments:** plasma membrane




TNFRSF10D (also known as DcR2 or TRAILR4) inhibits pro-apoptotic signaling by TRAIL (TNFSF10) receptors TNFRSF10A (TRAILR1, DR4) and TNFRSF10B (TRAILR2, DR5). TNFRSF10D has a truncated death domain (DD) but has the motifs involved in oligomerization of TRAIL receptors. While it was initially thought that TNFRSF10D functions as a decoy receptor that competes with TNFRSF10A and TNFRSF10B for ligand binding (Pan et al. 1997), latest studies indicate that it prevents TRAIL signaling by forming heterodimers with TNFRSF10A and TNFRSF10B and thus preventing formation of functional homotrimeric TRAIL ligand:receptor complexes (Neumann et al. 2014).

## Literature references

Neumann, S., Hasenauer, J., Pollak, N., Scheurich, P. (2014). Dominant negative effects of tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) receptor 4 on TRAIL receptor 1 signaling by formation of heteromeric complexes. *J. Biol. Chem., 289*, 16576-87. ↗

Pan, G., Ni, J., Wei, YF., Yu, G., Gentz, R., Dixit, VM. (1997). An antagonist decoy receptor and a death domain-containing receptor for TRAIL. *Science, 277*, 815-8. ↗

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| 2014-10-29 | Authored | Orlic-Milacic, M. |
| 2015-05-12 | Reviewed | Ware, CF., Virgen-Slane, R. |
| 2016-11-17 | Edited | Jupe, S. |

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