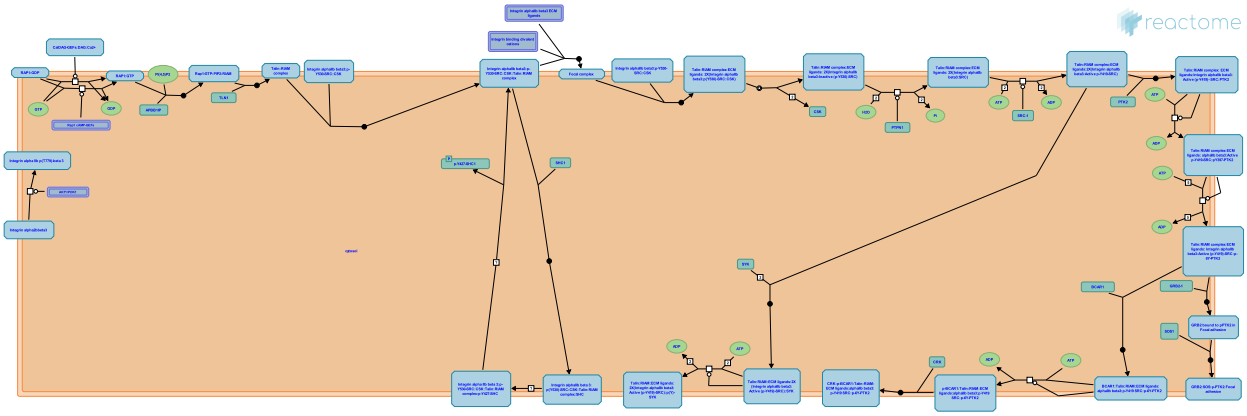
Integrin signaling



Akkerman, JW., Garapati, P V., Heemskerk, JW., Jupe, S., Shattil, SJ.

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25/04/2024

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. ↗

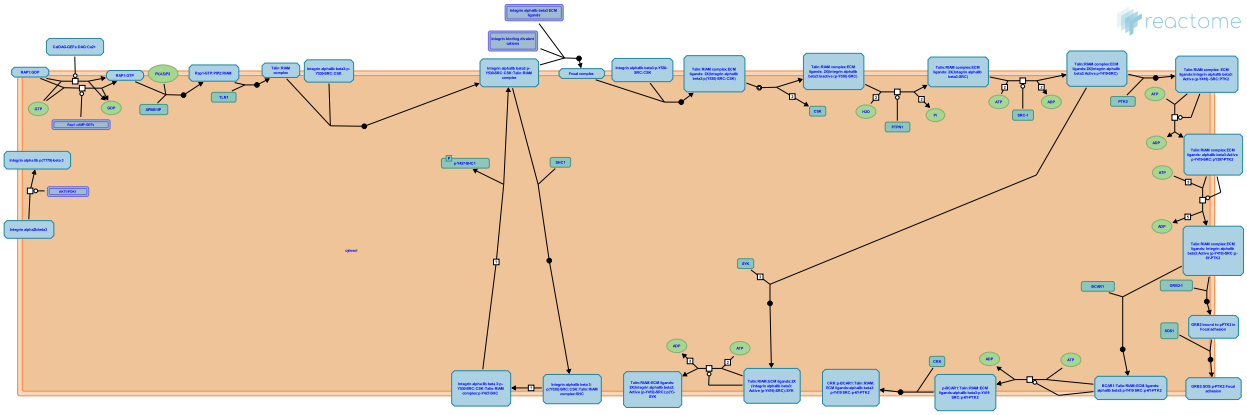
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

Integrin signaling ↗

Stable identifier: R-HSA-354192



Integrins are a major family of cell surface receptors that modulate cell adhesion, migration, proliferation and survival through interaction with the extracellular matrix (ECM) and the actin cytoskeleton. Integrins are type 1 transmembrane proteins that exist at the cell surface as heterodimers of alpha and beta subunits, of which there are 18 and 8 different isoforms, respectively, in human cells. In addition to their mechanical role in mediating contact between the ECM and the cytoskeleton, integrins also modulate intracellular signaling pathways governing cytoskeletal rearrangements and pro-survival and mitogenic signaling (reviewed in Hehlgans et al, 2007; Harburger and Calderwood, 2009; Ata and Antonescu, 2017).
In this pathway, we describe signaling through integrin alphaIIb beta3 as a representative example.
At the sites of vascular injury bioactive molecules such as thrombin, ADP, collagen, fibrinogen and thrombospondin are generated, secreted or exposed. These stimuli activate platelets, converting the major platelet integrin alphaIIbbeta3 from a resting state to an active conformation, in a process termed integrin priming or 'inside-out signalling'. Integrin activation refers to the change required to enhance ligand-binding activity. The activated alphaIIbbeta3 interacts with the fibrinogen and links platelets together in an aggregate to form a platelet plug. AlphaIIbbeta3 bound to fibrin generates more intracellular signals (outside-in signalling), causing further platelet activation and platelet-plug retraction.
In the resting state the alpha and beta tails are close together. This interaction keeps the membrane proximal regions in a bent conformation that maintains alphaIIbbeta3 in a low affinity state.
Integrin alphaIIbbeta3 is released from its inactive state by interaction with the protein talin. Talin interacts with the beta3 cytoplasmic domain and disrupts the salt bridge between the alpha and beta chains. This separation in the cytoplasmic regions triggers the conformational change in the extracellular domain that increases its affinity to fibrinogen.
Much of talin exists in an inactive cytosolic pool, and the Rap1 interacting adaptor molecule (RIAM) is implicated in talin activation and translocation to beta3 integrin cytoplasmic domain.

Literature references

Auger, JM., Watson, SP., Pearce, AC., McCarty, OJ. (2005). GPVI and integrin alphaIIb beta3 signaling in platelets. *J Thromb Haemost, 3*, 1752-62. ↗

Parise, LV. (1999). Integrin alpha(IIb)beta(3) signaling in platelet adhesion and aggregation. *Curr Opin Cell Biol, 11*, 597-601. ↗

Cordes, N., Haase, M., Hehlgans, S. (2007). Signalling via integrins: implications for cell survival and anticancer strategies. *Biochim Biophys Acta, 1775*, 163-80. ↗

Calderwood, DA., Harburger, DS. (2009). Integrin signalling at a glance. *J. Cell. Sci., 122*, 159-63. ↗

Ata, R., Antonescu, CN. (2017). Integrins and Cell Metabolism: An Intimate Relationship Impacting Cancer. *Int J Mol Sci, 18*. ↗

Editions

2008-06-16	Authored, Edited	Garapati, P V.
2008-09-16	Reviewed	Shattil, SJ.
2011-02-13	Revised	Garapati, P V.

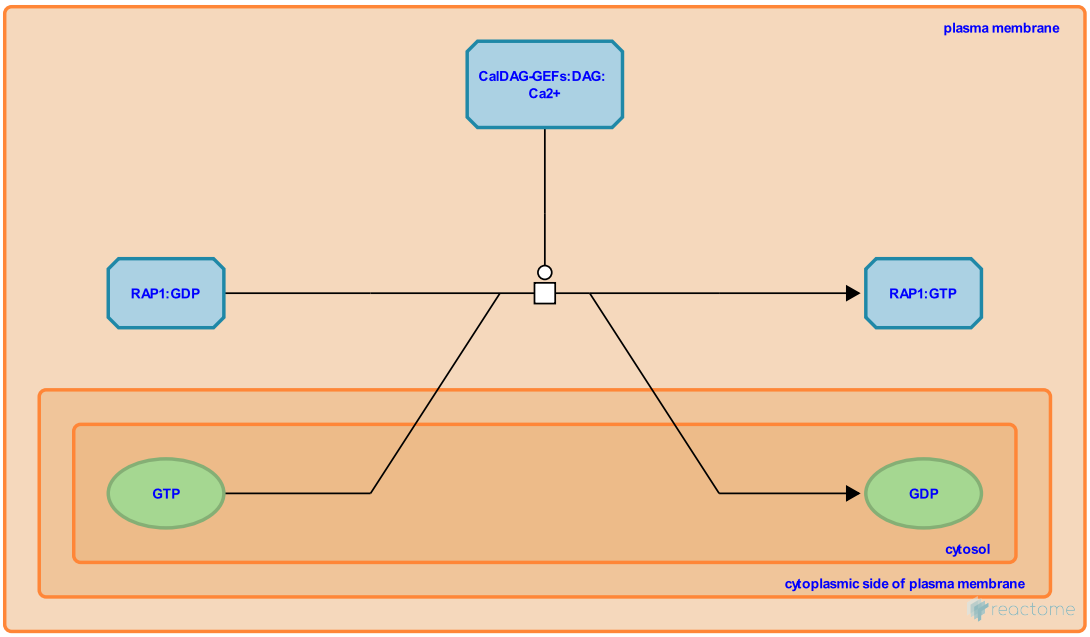
Activation of Rap1 by cytosolic GEFs ↗

Location: Integrin signaling

Stable identifier: R-HSA-354173

Type: transition

Compartments: plasma membrane, cytosol



Signals from agonist receptors (such as GPVI) trigger the production of PIP3, DAG, cAMP and elevated Ca++ levels. This leads to the activation and translocation of active Rap1-GTP to the plasma membrane. Rap-GEFs stimulate the replacement of GDP for GTP, activating Rap1. Several Rap1 GEFs have been identified enabling Rap1 to respond to diverse stimuli. CalDAG-GEFs activate Rap1 in response to calcium and DAG, downstream of Phospholipase C. EPAC (exchange proteins directly activated by cAMP) GEFs are activated by binding cAMP.

Followed by: Translocation of RIAM to plasma membrane

Literature references

Boussiotis, VA., Lafuente, E. (2006). Rap1 regulation of RIAM and cell adhesion. *Methods Enzymol, 407*, 345-58. ↗

Stork, PJ., Dillon, TJ. (2005). Multiple roles of Rap1 in hematopoietic cells: complementary versus antagonistic functions. *Blood, 106*, 2952-61. ↗

Zhang, Y., Housman, DE., Liang, Y., Piffath, CL., Graybiel, AM., Wagner, DD. et al. (2004). CalDAG-GEFI integrates signaling for platelet aggregation and thrombus formation. *Nat Med, 10*, 982-6. ↗

Constantine, E., Krause, M., van Puijenbroek, AA., Springer, TA., Lafuente, EM., Gertler, FB. et al. (2004). RIAM, an Ena/VASP and Profilin ligand, interacts with Rap1-GTP and mediates Rap1-induced adhesion. *Dev Cell, 7*, 585-95. ↗

Editions

2008-06-16	Authored, Edited	Garapati, P V.
2008-09-16	Reviewed	Shattil, SJ.

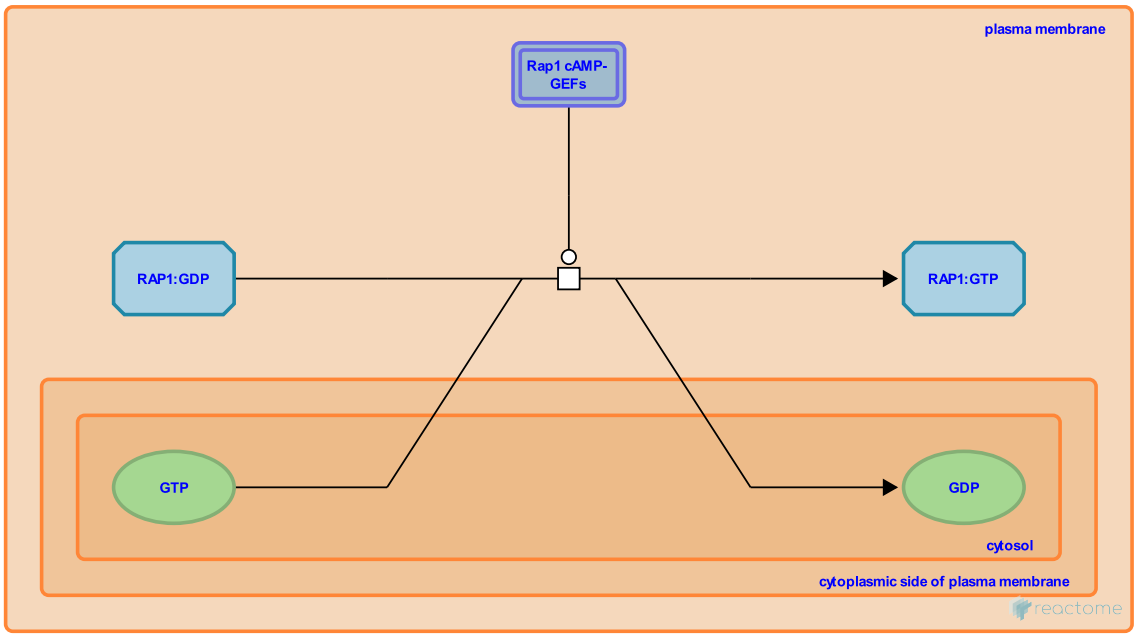
Activation of Rap1 by membrane-associated GEFs ↗

Location: Integrin signaling

Stable identifier: R-HSA-939265

Type: transition

Compartments: plasma membrane, cytosol



Signals from agonist receptors (such as GPVI) trigger the production of PIP3, DAG, cAMP and elevated Ca++ levels. This leads to the activation and translocation of active Rap1-GTP to the plasma membrane. Rap-GEFs stimulate the replacement of GDP for GTP, activating Rap1. Several Rap1 GEFs have been identified enabling Rap1 to respond to diverse stimuli. CalDAG-GEFs activate Rap1 in response to calcium and DAG, downstream of Phospholipase C. EPAC (exchange proteins directly activated by cAMP) GEFs are activated by binding cAMP.

Followed by: Translocation of RIAM to plasma membrane

Literature references

Boussiotis, VA., Lafuente, E. (2006). Rap1 regulation of RIAM and cell adhesion. *Methods Enzymol, 407*, 345-58. ↗

Stork, PJ., Dillon, TJ. (2005). Multiple roles of Rap1 in hematopoietic cells: complementary versus antagonistic functions. *Blood, 106*, 2952-61. ↗

Zhang, Y., Housman, DE., Liang, Y., Piffath, CL., Graybiel, AM., Wagner, DD. et al. (2004). CalDAG-GEFI integrates signaling for platelet aggregation and thrombus formation. *Nat Med, 10*, 982-6. ↗

Constantine, E., Krause, M., van Puijenbroek, AA., Springer, TA., Lafuente, EM., Gertler, FB. et al. (2004). RIAM, an Ena/VASP and Profilin ligand, interacts with Rap1-GTP and mediates Rap1-induced adhesion. *Dev Cell, 7*, 585-95. ↗

Editions

2008-09-16	Reviewed	Shattil, SJ.
2010-09-01	Authored, Edited	Jupe, S.

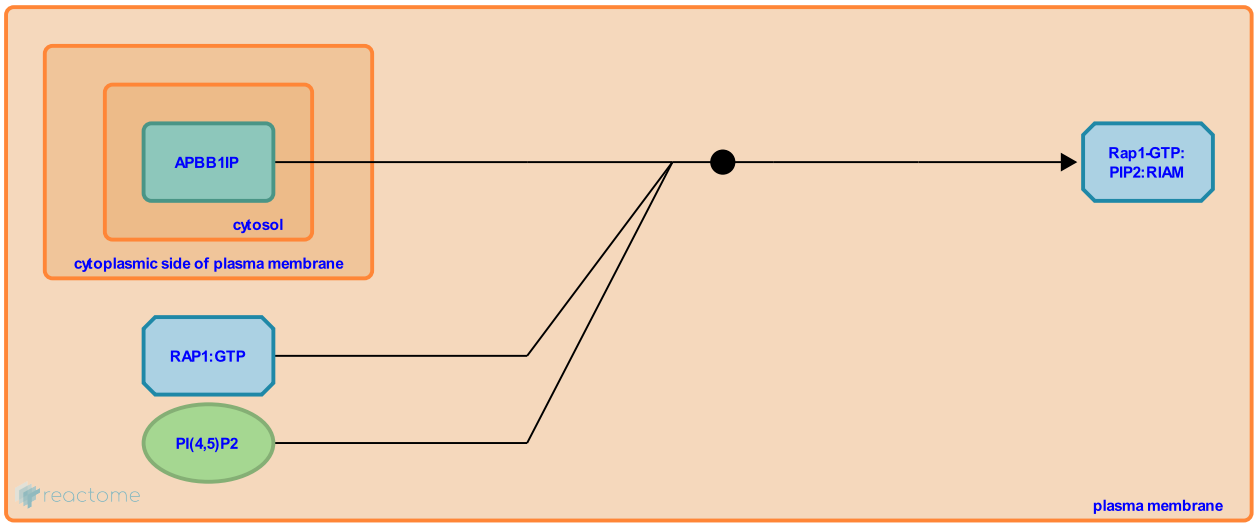
Translocation of RIAM to plasma membrane ↗

Location: Integrin signaling

Stable identifier: R-HSA-354060

Type: binding

Compartments: plasma membrane, cytosol



Upon the production of activated Rap1A at the plasma membrane, RIAM interacts with Rap1A-GTP with its N-ter RA domain, and with its C-ter PH domain it interacts with PIP2.

Preceded by: Activation of Rap1 by membrane-associated GEFs, Activation of Rap1 by cytosolic GEFs

Followed by: Activation of Talin

Literature references

Boussiotis, VA., Lafuente, E. (2006). Rap1 regulation of RIAM and cell adhesion. *Methods Enzymol, 407*, 345-58. ↗

Kasirer-Friede, A., Kahn, ML., Shattil, SJ. (2007). Platelet integrins and immunoreceptors. *Immunol Rev, 218*, 247-64. ↗

Constantine, E., Krause, M., van Puijenbroek, AA., Springer, TA., Lafuente, EM., Gertler, FB. et al. (2004). RIAM, an Ena/VASP and Profilin ligand, interacts with Rap1-GTP and mediates Rap1-induced adhesion. *Dev Cell, 7*, 585-95. ↗

Editions

2008-06-16	Authored, Edited	Garapati, P V.
2008-09-16	Reviewed	Shattil, SJ.

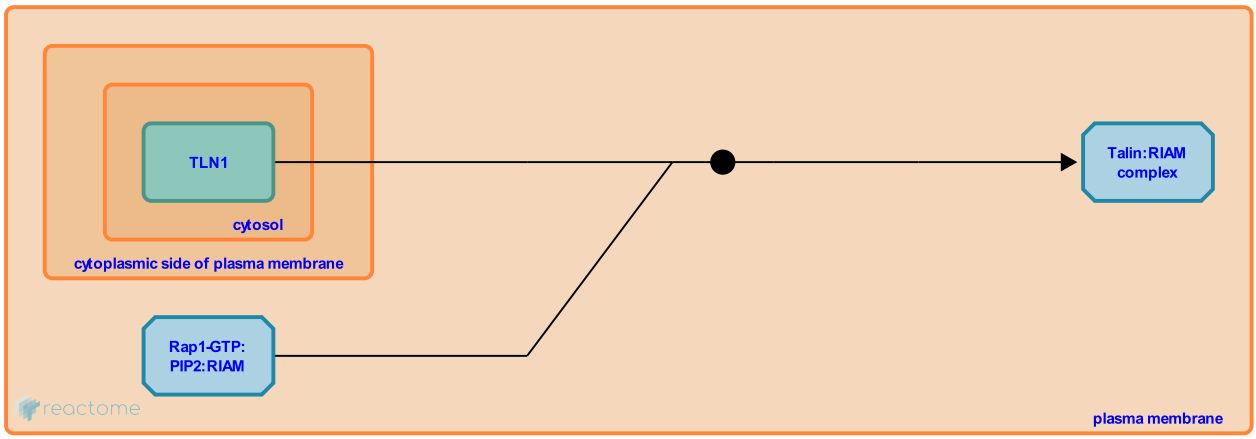
Activation of Talin ↗

Location: Integrin signaling

Stable identifier: R-HSA-354097

Type: binding

Compartments: plasma membrane, cytosol



Talin is one of the major cytoskeletal proteins involved in integrin activation and linking the resulting focal adhesion (FA) with cytoskeleton. Talin comprises an N-ter head region and a flexible rod domain. The head region has the FERM domain (subdivided into F1, F2 and F3 subdomains), which has the binding sites for beta integrin cytoplasmic regions and actin binding sites close to the C-terminal rod domain.
Talin exists in closed inactive conformation, where the head region interacts with the rod domain masking the integrin binding sites. At the plasma membrane the RIAM bound to active Rap1 recruits talin to form the integrin activation complex. This interaction exposes the integrin-binding site in talin F3 domain leading to integrin activation.

Preceded by: Translocation of RIAM to plasma membrane

Followed by: Integrin alphaIIb beta3 activation

Literature references

Kasirer-Friede, A., Kahn, ML., Shattil, SJ. (2007). Platelet integrins and immunoreceptors. *Immunol Rev, 218,* 247-64. ↗

Gingras, AR., Critchley, DR. (2008). Talin at a glance. *J Cell Sci, 121,* 1345-7. ↗

Editions

2008-06-16	Authored, Edited	Garapati, P V.
2008-09-16	Reviewed	Shattil, SJ.

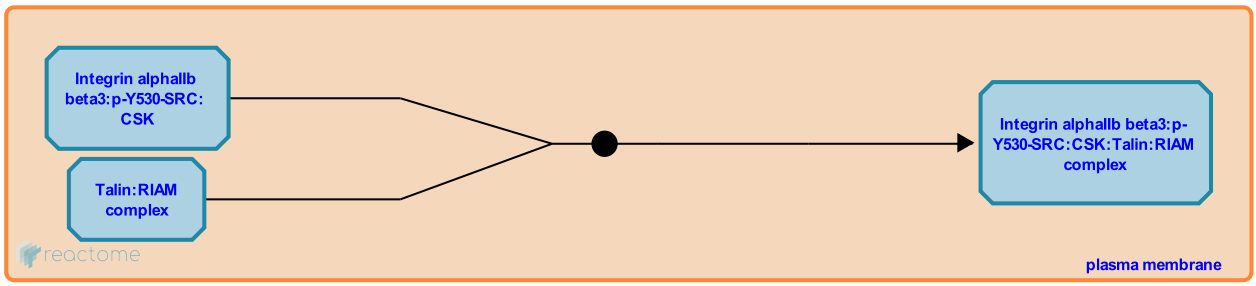
Integrin alphaIIb beta3 activation ↗

Location: Integrin signaling

Stable identifier: R-HSA-354077

Type: binding

Compartments: plasma membrane



The interaction between talin and integrin alphaIIb beta3 breaks the putative salt bridge between the alphaIIb (R995) and beta3 (D723) integrin chains and induces conformational changes in their external domains increasing their affinity for fibrinogen and other ECM ligands. Breaking of this salt bridge is necessary but not sufficient for full activation.
The Talin F3 subdomain of the FERM domain has a phosphotyrosine binding (PTB) domain fold. This domain interacts with the membrane-proximal (MP) region within the integrin beta3 chain. The primary function of this interaction is to provide an initial strong linkage between talin and integrin and this interaction holds the key to the molecular recognition required for activation. In platelets SRC kinase and its negative regulator CSK associates constitutively with integrin alphaIIbbeta3. SRC is involved in alphaIIbbeta3 dependent activation of SYK, and both SRC and SYK are required to initiate cytoskeletal events responsible for platelet spreading on fibrinogen.

Preceded by: Activation of Talin

Followed by: Activated integrin alphaIIb beta3 binds SHC1, Interaction of integrin alphaIIb beta3 with Fibrinogen

Literature references

Ruoslahti, E., Giancotti, FG. (1999). Integrin signaling. *Science, 285*, 1028-32. ↗

Calderwood, DA. (2004). Integrin activation. *J Cell Sci, 117*, 657-66. ↗

Liddington, RC., Campbell, ID., Ginsberg, MH., Partridge, AW., Wegener, KL., Pickford, AR. et al. (2007). Structural basis of integrin activation by talin. *Cell, 128*, 171-82. ↗

Lowell, CA., Obergfell, A., Brugge, JS., Mocsai, A., Eto, K., Shattil, SJ. et al. (2002). Coordinate interactions of Csk, Src, and Syk kinases with [alpha]IIb[beta]3 initiate integrin signaling to the cytoskeleton. *J Cell Biol, 157*, 265-75. ↗

Gingras, AR., Critchley, DR. (2008). Talin at a glance. *J Cell Sci, 121*, 1345-7. ↗

Editions

2008-06-16	Authored, Edited	Garapati, P V.
2008-09-16	Reviewed	Shattil, SJ.

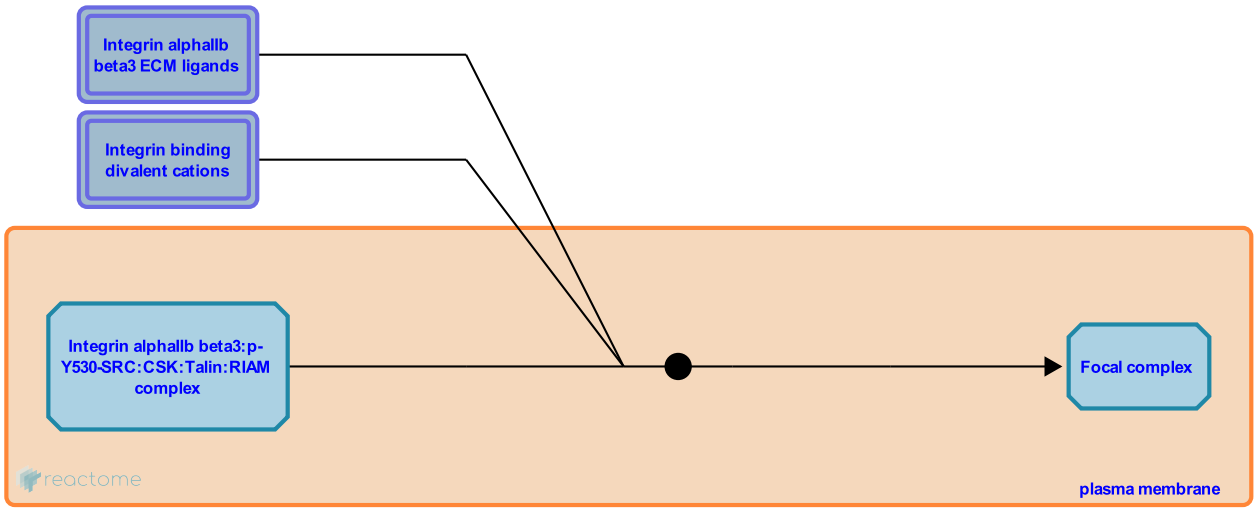
Interaction of integrin alphaIIb beta3 with Fibrinogen ↗

Location: Integrin signaling

Stable identifier: R-HSA-354149

Type: binding

Compartments: plasma membrane, extracellular region



The overall shape of integrins is that of a globular 'head' supported by two rod like legs. The ligand-binding pocket is formed by the combination of A-domain or beta-I domain on the beta3 subunit and the putative beta-propeller fold on the alphaIIb subunit in the head regions. The binding of ligand to integrin is also dependent on divalent cations (usually Mn++ or Mg++or Ca++). A conserved motif, the metal ion-dependant adhesion site (MIDAS) is located in the alpha and the beta chains that coordinate the divalent cation at the top of the domain.
Active integrin alphaIIb beta3 interacts with a variety of plasma proteins such as fibrinogen, vWF, thrombin, thrombospondin, and fibronectin. The ability of alphaIIbbeta3 to bind fibrinogen plays a crucial role in platelet aggregation and hemostasis. Most of these matrix proteins have integrin binding sites of 3-6 amino acids length, of which the best known are the 'RGD' and 'KGD' motifs. The alpha and beta integrin subunits are both required for ligand binding.

Preceded by: Integrin alphaIIb beta3 activation

Followed by: Clustering of Integrin alphaIIb beta3 complexes

Literature references

Litvinov, RI., Shuman, H., Weisel, JW., Bennett, JS. (2005). Multi-step fibrinogen binding to the integrin (alpha)IIb(beta)3 detected using force spectroscopy. *Biophys J, 89*, 2824-34. ↗

Ruoslahti, E., Giancotti, FG. (1999). Integrin signaling. *Science, 285*, 1028-32. ↗

Calderwood, DA. (2004). Integrin activation. *J Cell Sci, 117*, 657-66. ↗

Editions

2008-06-16	Authored, Edited	Garapati, P V.
2008-09-16	Reviewed	Shattil, SJ.

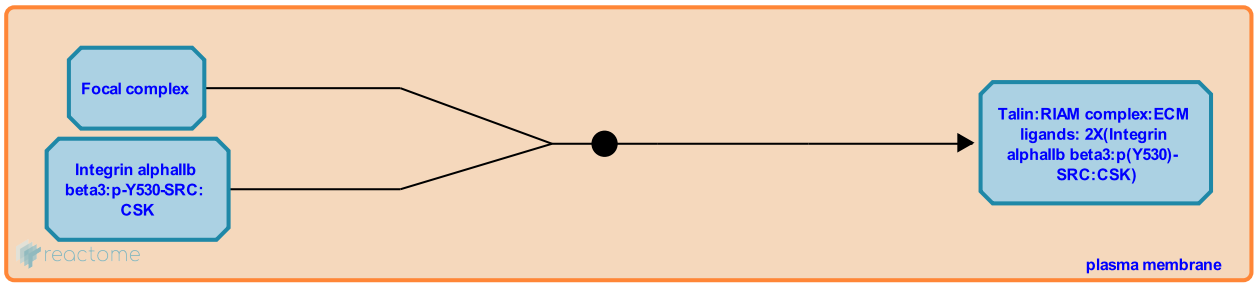
Clustering of Integrin alphaIIb beta3 complexes ↗

Location: Integrin signaling

Stable identifier: R-HSA-377641

Type: binding

Compartments: plasma membrane



The fibrinogen-bound integrin alphaIIb beta3 clusters platelets together to form a platelet plug and generates intracellular signals (outside-in) causing further platelet activation and platelet plug retraction.
Intracellular integrin alphaIIb beta3 clustering brings SRCs bound to integrin beta3 chains into proximity. SRC associates constitutively with integrin alphaIIb beta3. In unstimulated cells this SRC is inactive, auto-inhibited by an internal interaction between phosphorylated Y530 and the SH2 domain. CSK is selective for the Y530 residue and prevents access to SRC of PTP1B, a protein tyrosine phosphatase that is capable of de-phosphorylating Y530.

Preceded by: Interaction of integrin alphaIIb beta3 with Fibrinogen

Followed by: Release of CSK from SRC

Literature references

DeGrado, WF., Li, R., Bennett, JS. (2004). Structural basis for integrin alphaIIbbeta3 clustering. *Biochem Soc Trans, 32*, 412-5. ↗

Shattil, SJ. (2005). Integrins and Src: dynamic duo of adhesion signaling. *Trends Cell Biol, 15*, 399-403. ↗

Editions

2008-06-16	Authored, Edited	Garapati, P V.
2008-09-16	Reviewed	Shattil, SJ.

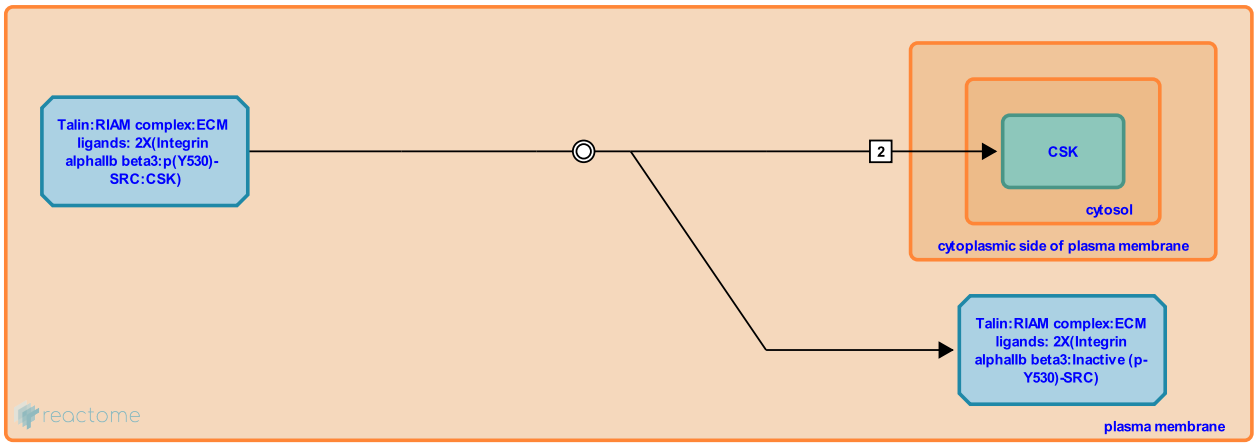
Release of CSK from SRC ↗

Location: Integrin signaling

Stable identifier: R-HSA-377644

Type: dissociation

Compartments: plasma membrane, cytosol



CSK bound to integrin alphaIIb beta3 negatively regulates SRC by phosphorylating the Tyr-530. Platelet adhesion to fibrinogen causes the disassociation of CSK from alphaIIb beta3 complex.

Preceded by: Clustering of Integrin alphaIIb beta3 complexes

Followed by: Dephosphorylation of inactive SRC by PTPB1

Literature references

Nakagawa, H., Yamamoto, T., Okada, M., Yamanashi, Y., Nada, S. (1991). CSK: a protein-tyrosine kinase involved in regulation of src family kinases. *J Biol Chem, 266*, 24249-52. ↗

Shattil, SJ. (2005). Integrins and Src: dynamic duo of adhesion signaling. *Trends Cell Biol, 15*, 399-403. ↗

Editions

2008-06-16	Authored, Edited	Garapati, P V.
2008-09-16	Reviewed	Shattil, SJ.

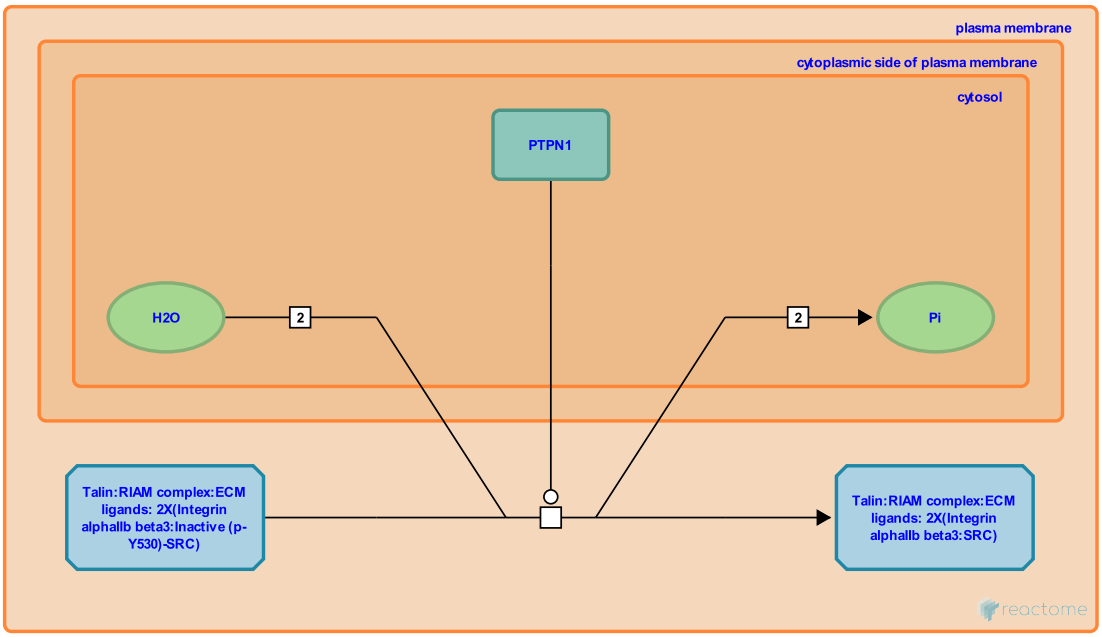
Dephosphorylation of inactive SRC by PTPB1 ↗

Location: Integrin signaling

Stable identifier: R-HSA-377643

Type: transition

Compartments: plasma membrane, cytosol



The integrin alphaIIb beta3:Inactive SRC complex recruits PTP1B protein tyrosine phosphatase resulting in the dephosphorylation of SRC tyrosine 530. The phosphorylated tail of SRC tail interacts with the SH2 domain thereby repressing kinase activity; removal of phosphorylation activates SRC kinase activity.

Preceded by: Release of CSK from SRC

Followed by: Autophosphorylation of SRC

Literature references

Furie, B., Dubois, C., Moran, B., Kasirer-Friede, A., Neel, BG., Arias-Salgado, EG. et al. (2005). PTP-1B is an essential positive regulator of platelet integrin signaling. *J Cell Biol, 170*, 837-45. ↗

Shattil, SJ. (2005). Integrins and Src: dynamic duo of adhesion signaling. *Trends Cell Biol, 15*, 399-403. ↗

Editions

2008-06-16	Authored, Edited	Garapati, P V.
2008-09-16	Reviewed	Shattil, SJ.

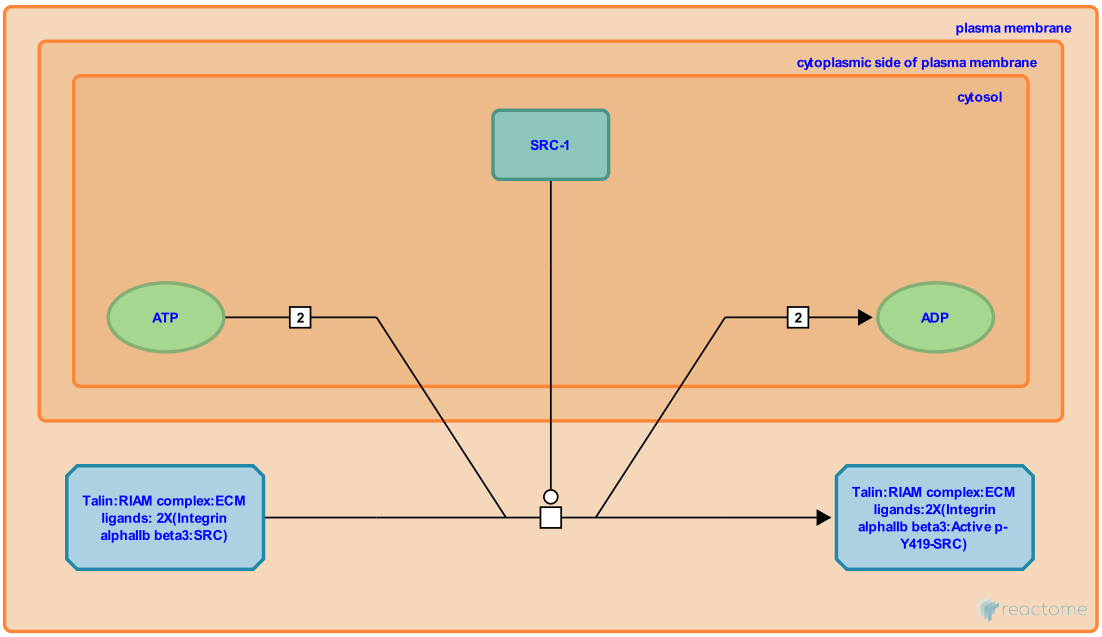
Autophosphorylation of SRC ↗

Location: Integrin signaling

Stable identifier: R-HSA-377640

Type: transition

Compartments: plasma membrane, cytosol



Clustering of Integrin alphaIIb beta3 complexes results in the trans auto-phosphorylation of SRC tyrosine residue 419 (often referred to as 418 in the literature, as the initiating methionine is cleaved in the mature peptide) in SRC's kinase activation loop.

Preceded by: Dephosphorylation of inactive SRC by PTPB1

Followed by: SYK binds to integrin alphaIIb beta3, Translocation of PTK2 to Focal complexes

Literature references

Shattil, SJ. (2005). Integrins and Src: dynamic duo of adhesion signaling. *Trends Cell Biol, 15*, 399-403. ↗

Editions

2008-06-16	Authored, Edited	Garapati, P V.
2008-09-16	Reviewed	Shattil, SJ.

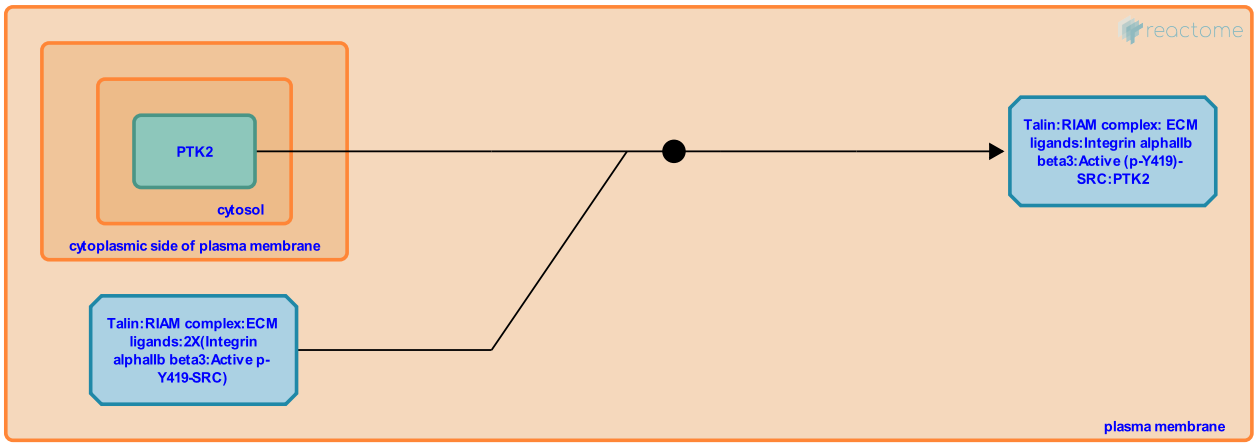
Translocation of PTK2 to Focal complexes ↗

Location: Integrin signaling

Stable identifier: R-HSA-354066

Type: binding

Compartments: plasma membrane, cytosol



As integrins do not have an intrinsic catalytic activity, the signals initiated by the ECM-integrin interactions are transduced into cells through the integrin bound protein-tyrosine kinases. PTK2 (protein-tyrosine kinase 2, also known as Focal adhesion kinase 1; FADK1, FAK) is one of the protein tyrosine kinases that plays a prominent role in integrin signaling. PTK2 has been implicated in controlling cell motility and transmitting a cell survival signal from ECM.

PTK2 is recruited to sites of integrin clustering by directly binding to integrin associated c-Src.

Preceded by: Autophosphorylation of SRC

Followed by: Autophosphorylation of PTK2 at Y397

Literature references

Schaller, MD. (2001). Biochemical signals and biological responses elicited by the focal adhesion kinase. *Biochim Biophys Acta, 1540*, 1-21. ↗

Mitra, SK., Schlaepfer, DD. (2006). Integrin-regulated FAK-Src signaling in normal and cancer cells. *Curr Opin Cell Biol, 18*, 516-23. ↗

Editions

2008-06-16	Authored, Edited	Garapati, P V.
2008-09-16	Reviewed	Shattil, SJ.

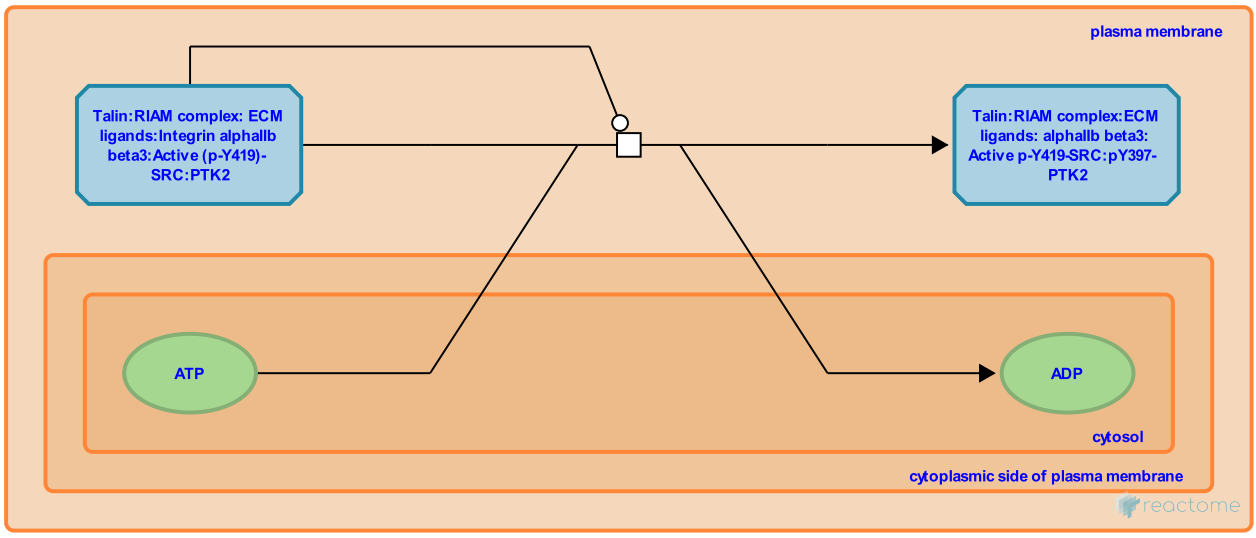
Autophosphorylation of PTK2 at Y397 ↗

Location: Integrin signaling

Stable identifier: R-HSA-354073

Type: transition

Compartments: plasma membrane, cytosol



The co-localization of PTK2/FAK with integrins in focal adhesions and the actin cytoskeleton is essential for the activation and phosphorylation of PTK2/FAK.
PTK2/FAK has six tyrosine phosphorylation sites and tyrosine 397 is the main auto-phosphorylation site present upstream of the kinase domain.

Preceded by: Translocation of PTK2 to Focal complexes

Followed by: Phosphorylation of pPTK2 by SRC

Literature references

Schaller, MD. (2001). Biochemical signals and biological responses elicited by the focal adhesion kinase. *Biochim Biophys Acta, 1540*, 1-21. ↗

Mitra, SK., Schlaepfer, DD. (2006). Integrin-regulated FAK-Src signaling in normal and cancer cells. *Curr Opin Cell Biol, 18*, 516-23. ↗

Editions

2008-06-16	Authored, Edited	Garapati, P V.
2008-09-16	Reviewed	Shattil, SJ.

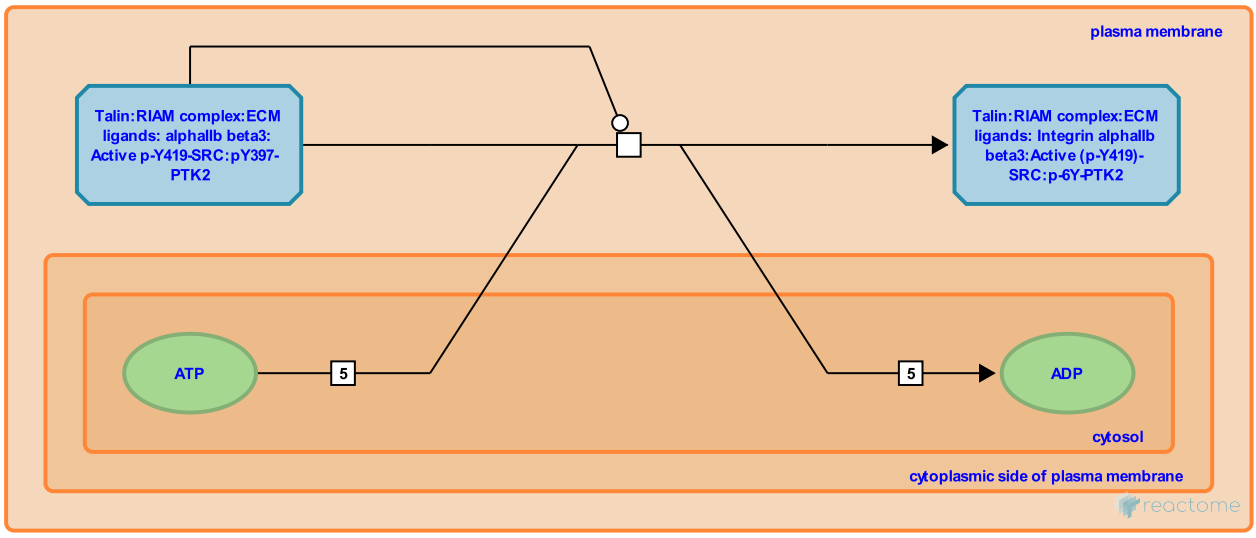
Phosphorylation of pPTK2 by SRC ↗

Location: Integrin signaling

Stable identifier: R-HSA-354124

Type: transition

Compartments: plasma membrane, cytosol



The recruitment of FADK1 to active SRC leads to the efficient tyrosine phosphorylation of multiple additional sites on FADK1. SRC trans-phosphorylates FADK1 within the kinase doman activation loop (Y576 and Y577) and within the FADK1 C-terminal domain (Y861 and Y925).

Preceded by: Autophosphorylation of PTK2 at Y397

Literature references

Schaller, MD. (2001). Biochemical signals and biological responses elicited by the focal adhesion kinase. *Biochim Biophys Acta, 1540*, 1-21. ↗

Mitra, SK., Schlaepfer, DD. (2006). Integrin-regulated FAK-Src signaling in normal and cancer cells. *Curr Opin Cell Biol, 18*, 516-23. ↗

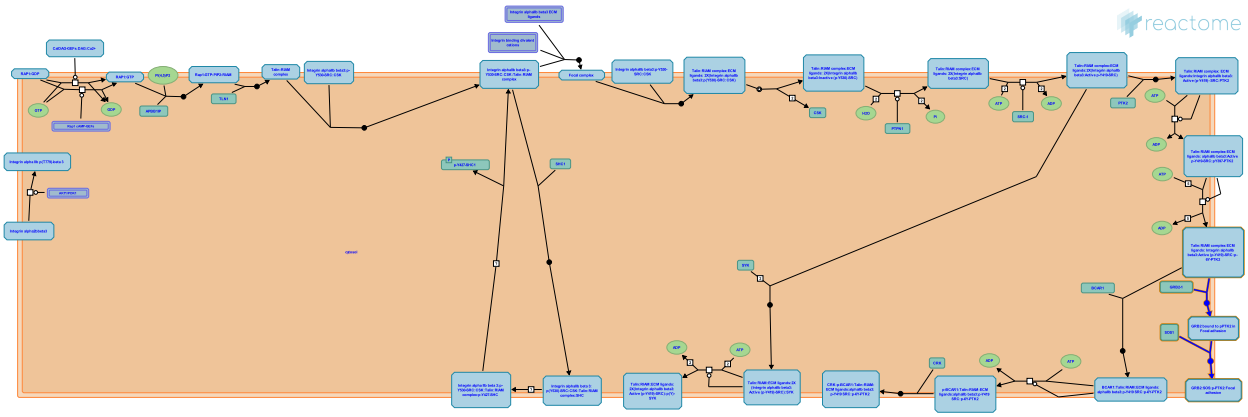
Editions

2008-06-16	Authored, Edited	Garapati, P V.
2008-09-16	Reviewed	Shattil, SJ.

GRB2:SOS provides linkage to MAPK signaling for Integrins ↗

Location: Integrin signaling

Stable identifier: R-HSA-354194



Integrin signaling is linked to the MAP kinase pathway by recruiting Grb2 to the FADK1/SRC activation complex.

Literature references

Schlaepfer, DD., van der Geer, P., Hanks, SK., Hunter, T. (1994). Integrin-mediated signal transduction linked to Ras pathway by GRB2 binding to focal adhesion kinase. *Nature, 372*, 786-91. ↗

Schlaepfer, DD., Jones, KC., Hunter, T. (1998). Multiple Grb2-mediated integrin-stimulated signaling pathways to ERK2/mitogen-activated protein kinase: summation of both c-Src- and focal adhesion kinase-initiated tyrosine phosphorylation events. *Mol Cell Biol, 18*, 2571-85. ↗

Hoellerer, MK., Arold, ST., Noble, ME. (2002). The structural basis of localization and signaling by the focal adhesion targeting domain. *Structure, 10*, 319-27. ↗

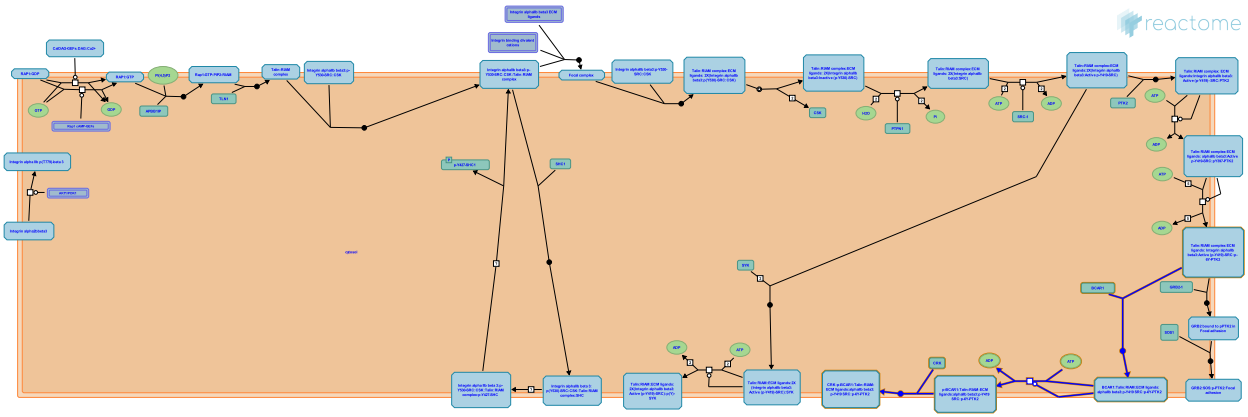
Editions

2008-06-16	Authored, Edited	Garapati, P V.
2008-09-16	Reviewed	Shattil, SJ.

p130Cas linkage to MAPK signaling for integrins ↗

Location: Integrin signaling

Stable identifier: R-HSA-372708



Integrin signaling is linked to the MAP kinase pathway by recruiting p130cas and Crk to the FAK/Src activation complex.

Literature references

Defilippi, P., Di Stefano, P., Cabodi, S. (2006). p130Cas: a versatile scaffold in signaling networks. *Trends Cell Biol, 16*, 257-63. ↗

Editions

2008-06-16	Authored, Edited	Garapati, P V.
2008-09-16	Reviewed	Shattil, SJ.

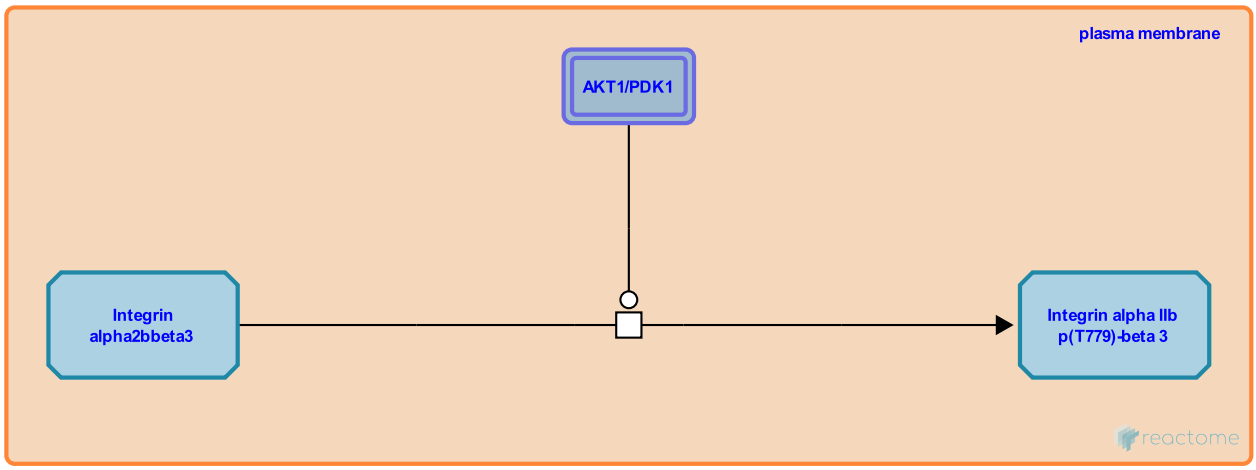
Integrin alpha IIb beta3 T779 phosphorylation blocks SHC binding ↗

Location: Integrin signaling

Stable identifier: R-HSA-432110

Type: transition

Compartments: plasma membrane



The binding of SHC to integrin alpha IIb beta 3 is blocked by phosphorylation of beta 3 at Thr-779, or by substitution of this residue for Asp. PDK1 and Akt1/PKB-alpha both specifically target Thr-779 in in vitro assays.

Followed by: Activated integrin alphaIIb beta3 binds SHC1

Literature references

Kirk, RI., Lerea, KM., Sanderson, MR. (2000). Threonine phosphorylation of the beta 3 integrin cytoplasmic tail, at a site recognized by PDK1 and Akt/PKB in vitro, regulates Shc binding. *J Biol Chem, 275*, 30901-6. ↗

Editions

2009-09-04	Authored	Akkerman, JW.
2010-09-01	Reviewed	Heemskerk, JW.
2010-09-01	Edited	Jupe, S.

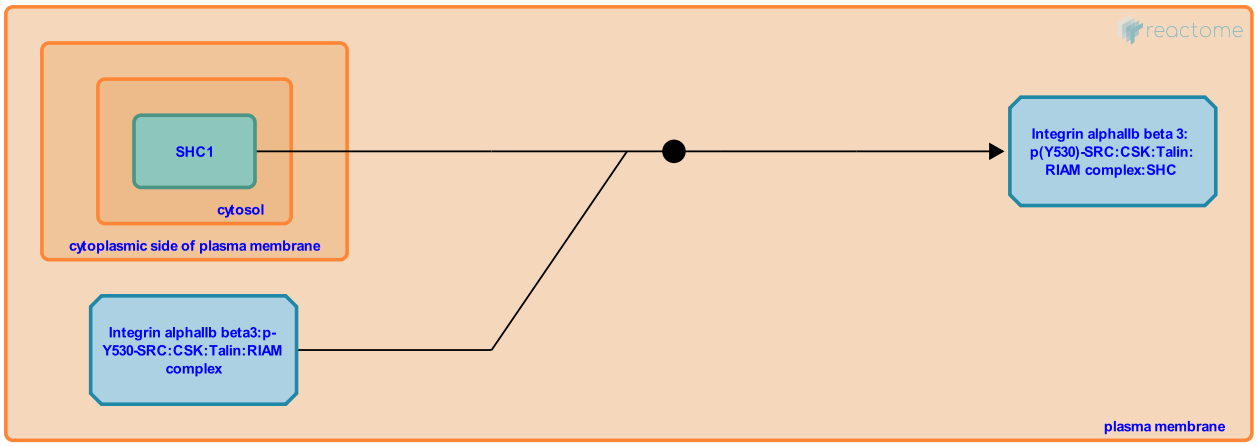
Activated integrin alphaIIb beta3 binds SHC1 ↗

Location: Integrin signaling

Stable identifier: R-HSA-432096

Type: binding

Compartments: plasma membrane, cytosol



The beta 3 integrin cytoplasmic tail binds SH2-containing protein (SHC), an adapter in Ras signaling. Phosphorylation of Y785 may be necessary for binding; phosphorylation of T779 inhibits SHC binding. Mice expressing a mutated beta 3 where Y773 and Y785 have been mutated to F exhibit rebleeding from tail wounds and subtle defects in clot retraction and platelet aggregation.

Preceded by: Integrin alphaIIb beta3 activation, Integrin alpha IIb beta3 T779 phosphorylation blocks SHC binding

Followed by: SHC1 bound to integrin alphaIIb beta3 is phosphorylated somehow

Literature references

Nannizzi-Alaimo, L., Phillips, DR., Law, DA. (1996). Outside-in integrin signal transduction. Alpha IIb beta 3-(GP IIb IIIa) tyrosine phosphorylation induced by platelet aggregation. *J Biol Chem, 271*, 10811-5. ↗

Editions

2009-09-04	Authored	Akkerman, JW.
2010-09-01	Reviewed	Heemskerk, JW.
2010-09-01	Edited	Jupe, S.

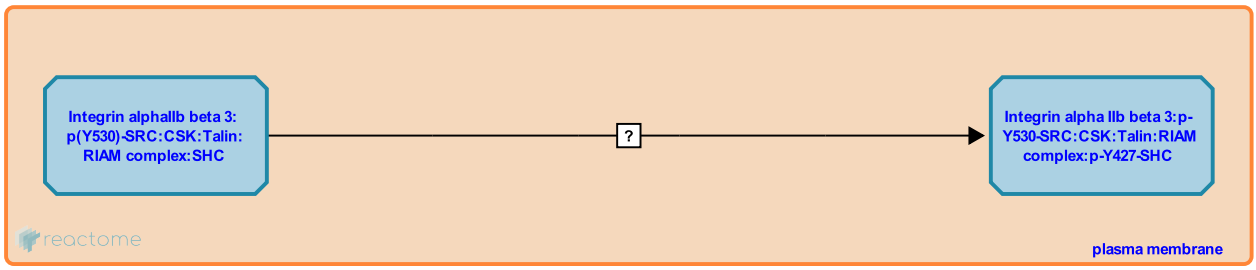
SHC1 bound to integrin alphaIIb beta3 is phosphorylated somehow ↗

Location: Integrin signaling

Stable identifier: R-HSA-443905

Type: uncertain

Compartments: plasma membrane



In a mechanism that is presumed to be analagous to signaling of SHC downstream of the insulin and TrkA receptors, SHC becomes phosphorylated and dissociates from the integrin alphaIIb beta3 complex.

Preceded by: Activated integrin alphaIIb beta3 binds SHC1

Followed by: SHC1 dissociates from integrin alphaIIb beta3

Literature references

Pelicci, G., Bonfini, L., Migliaccio, E., Lanfrancone, L., Pelicci, PG. (1996). Not all Shc's roads lead to Ras. *Trends Biochem Sci, 21*, 257-61. ↗

Phillips, DR., Cowan, KJ., Law, DA. (2000). Identification of shc as the primary protein binding to the tyrosine-phosphorylated beta 3 subunit of alpha IIbbeta 3 during outside-in integrin platelet signaling. *J Biol Chem, 275*, 36423-9 . ↗

Editions

2009-09-04	Authored	Akkerman, JW.
2010-09-01	Reviewed	Heemskerk, JW.
2010-09-01	Edited	Jupe, S.

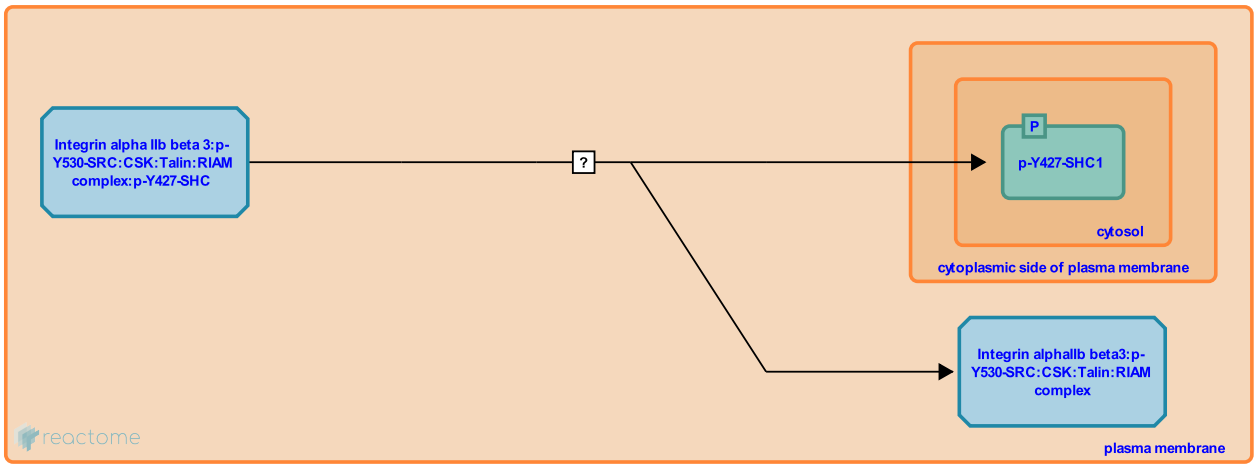
SHC1 dissociates from integrin alphaIIb beta3 ↗

Location: Integrin signaling

Stable identifier: R-HSA-443910

Type: uncertain

Compartments: plasma membrane



In a mechanism that is presumed to be analagous to signaling of SHC downstream of the insulin and TrkA receptors, SHC becomes phosphorylated and dissociates from the integrin alphaIIb beta3 complex.

Preceded by: SHC1 bound to integrin alphaIIb beta3 is phosphorylated somehow

Literature references

Pelicci, G., Bonfini, L., Migliaccio, E., Lanfrancone, L., Pelicci, PG. (1996). Not all Shc's roads lead to Ras. *Trends Biochem Sci, 21*, 257-61. ↗

Phillips, DR., Cowan, KJ., Law, DA. (2000). Identification of shc as the primary protein binding to the tyrosine-phosphorylated beta 3 subunit of alpha IIbbeta 3 during outside-in integrin platelet signaling. *J Biol Chem, 275*, 36423-9 . ↗

Editions

2009-09-04	Authored	Akkerman, JW.
2010-09-01	Reviewed	Heemskerk, JW.
2010-09-01	Edited	Jupe, S.

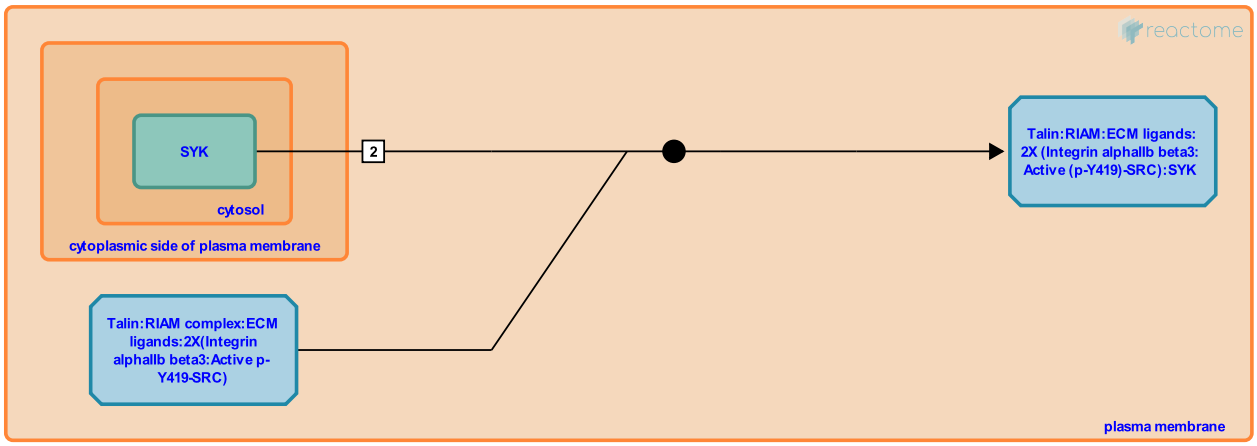
SYK binds to integrin alphaIIb beta3

Location: Integrin signaling

Stable identifier: R-HSA-429415

Type: binding

Compartments: plasma membrane, cytosol



Integrin alphaIIb beta3 'outside-in' signalling involves multiple proteins including SRC, SYK, SLP-76 and PLCgamma2. SRC is constitutively associated with the C-terminal tail of integrin beta 3. SYK is recruited to the beta3 tail and subsequently activated by SRC.

Preceded by: Autophosphorylation of SRC

Followed by: SYK activation by SRC

Literature references

Brugge, JS., Ginsberg, MH., Zoller, KE., Gao, J., Shattil, SJ. (1997). Regulation of the pp72syk protein tyrosine kinase by platelet integrin alpha IIb beta 3. *EMBO J, 16*, 6414-25.

Editions

2009-06-03	Authored	Akkerman, JW.
2010-09-01	Reviewed	Heemskerk, JW.
2010-09-01	Edited	Jupe, S.

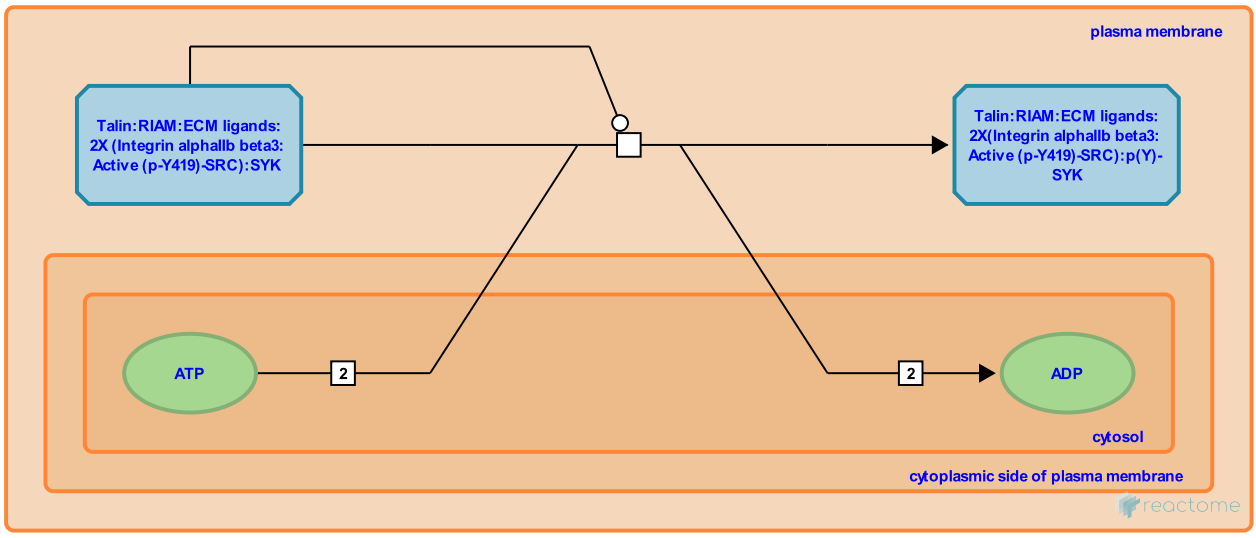
SYK activation by SRC ↗

Location: Integrin signaling

Stable identifier: R-HSA-429441

Type: transition

Compartments: plasma membrane, cytosol



SYK activation in integrin signalling is associated with increased tyrosine phosphorylation. SYK activation and phosphorylation of SYK targets can be blocked by SRC inhibitors or expression of dominant negative SRC mutants.

Preceded by: SYK binds to integrin alphaIIb beta3

Literature references

Yamamoto, T., Taniguchi, T., Yamanashi, Y., Takata, M., Inazu, T., Yamamura, H. et al. (1994). Syk activation by the Src-family tyrosine kinase in the B cell receptor signaling. *J Exp Med, 179*, 1725-9. ↗

Brugge, JS., Ginsberg, MH., Zoller, KE., Gao, J., Shattil, SJ. (1997). Regulation of the pp72syk protein tyrosine kinase by platelet integrin alpha IIb beta 3. *EMBO J, 16*, 6414-25. ↗

Editions

2009-06-03	Authored	Akkerman, JW.
2010-09-01	Reviewed	Heemskerk, JW.
2010-09-01	Edited	Jupe, S.

Table of Contents