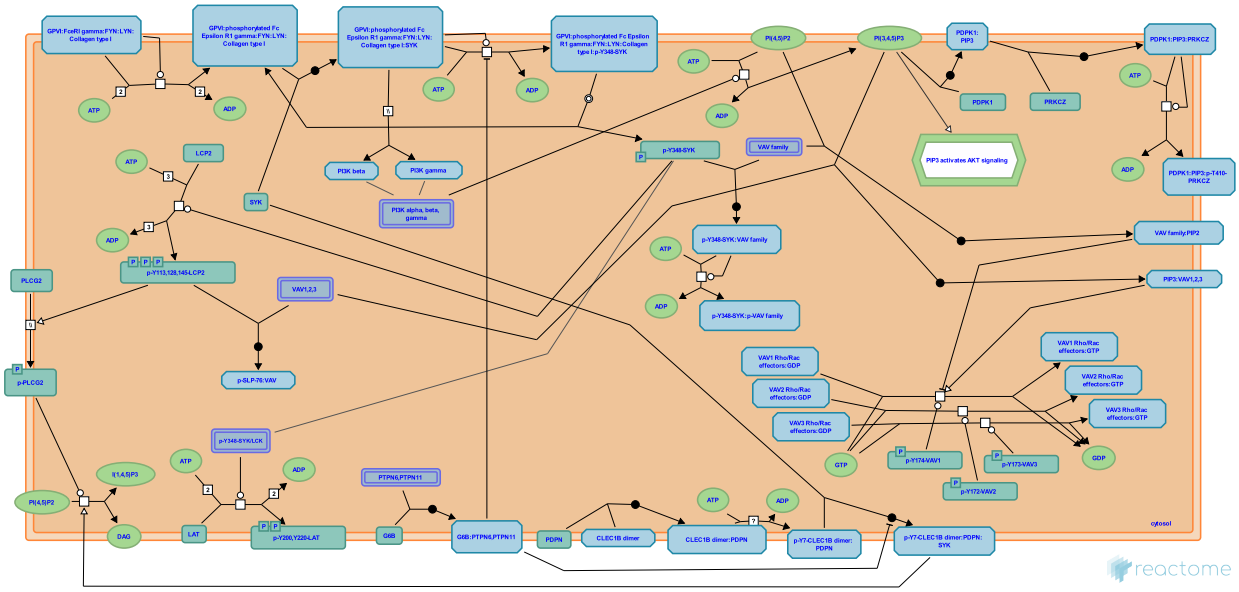
GPVI-mediated activation cascade



Akkerman, JW., Annibali, D., Greene, LA., Harper, MT., Jones, ML., Jupe, S., Kunapuli, SP., Matthews, L., Nasi, S., Orlic-Milacic, M., Poole, AW., Thorpe, L., Yuzugullu, H., Zhao, JJ.

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

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

01/04/2024

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. ↗

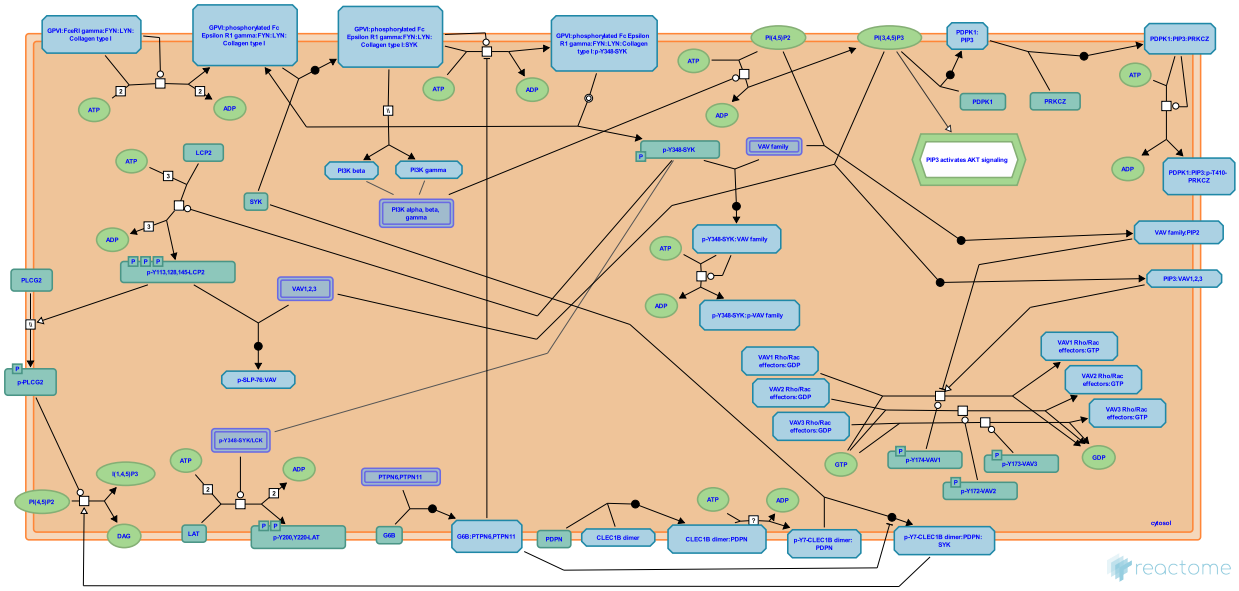
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

GPVI-mediated activation cascade ↗

Stable identifier: R-HSA-114604



The GPVI receptor is a complex of the GPVI protein with Fc epsilon R1 gamma (FcR). The Src family kinases Fyn and Lyn constitutively associate with the GPVI-FcR complex in platelets and initiate platelet activation through phosphorylation of the immunoreceptor tyrosine-based activation motif (ITAM) in the FcR gamma 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.

The GPVI receptor signaling cascade is similar to that of T- and B-cell immune receptors, involving the formation of a signalosome composed of adapter and effector proteins. At the core of the T-cell receptor signalosome is the transmembrane adapter LAT and two cytosolic adapters SLP-76 and Gads. While LAT is essential for signalling to PLCgamma1 downstream of the T-cell receptor, the absence of LAT in platelets only impairs the activation of PLCgamma2, the response to collagen and GPVI receptor ligands remains sufficient to elicit a full aggregation response. In contrast, GPVI signalling is almost entirely abolished in the absence of SLP-76.

Literature references

Suzuki-Inoue, K., Moroi, M., Bori-Sanz, T., Inoue, O., Berndt, MC., Watson, SP. et al. (2002). Association of Fyn and Lyn with the proline-rich domain of glycoprotein VI regulates intracellular signaling. *J Biol Chem, 277*, 21561-6. ↗

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

Editions

2009-11-03	Edited	Jupe, S.
2017-12-06	Edited	Orlic-Milacic, M.

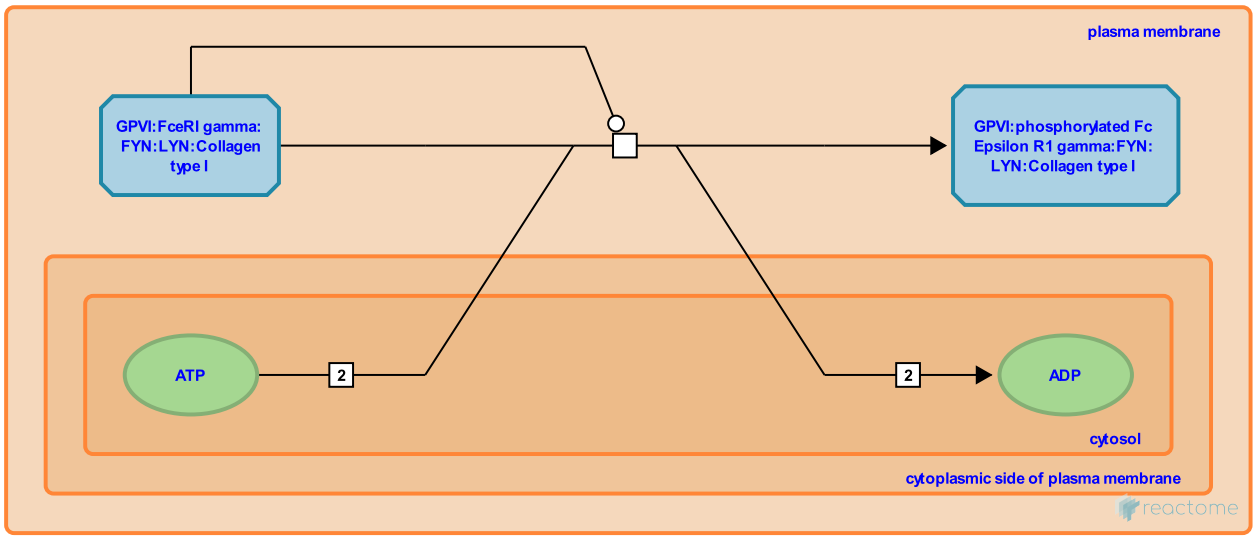
Fyn/Lyn-mediated phosphorylation of FcR1 gamma ↗

Location: GPVI-mediated activation cascade

Stable identifier: R-HSA-114600

Type: transition

Compartments: plasma membrane, cytosol



At the beginning of this reaction, 1 molecule of 'GP VI:Fc Epsilon R1 gamma:Collagen IV complex', and 1 molecule of 'ATP' are present. At the end of this reaction, 1 molecule of 'ADP', and 1 molecule of 'GP VI:phosphorylated Fc Epsilon R1 gamma:Collagen IV complex' are present.

This reaction is mediated by the 'protein-tyrosine kinase activity' of 'GP VI: Fc Epsilon R1 gamma: Collagen IV: SRC'.

Followed by: Binding of Syk tyrosine kinase

Literature references

Farndale, RW., Morton, LF., Watson, SP., Barnes, MJ., Gibbins, JM., Asselin, J. et al. (1997). A collagen-like peptide stimulates tyrosine phosphorylation of syk and phospholipase C gamma2 in platelets independent of the integrin alpha2beta1. *Blood, 89*, 1235-42. ↗

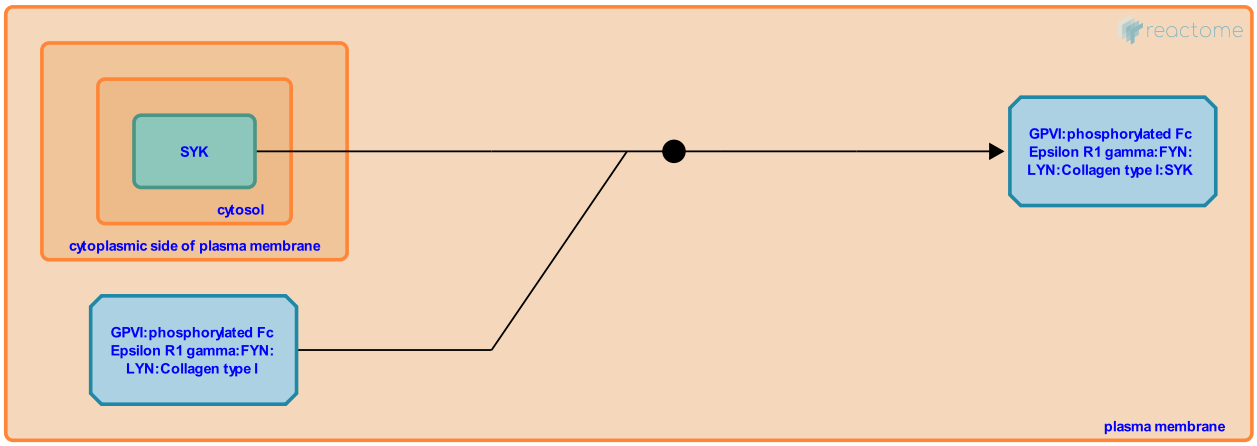
Binding of Syk tyrosine kinase ↗

Location: GPVI-mediated activation cascade

Stable identifier: R-HSA-139842

Type: binding

Compartments: plasma membrane, cytosol



Syk binds to the phosphorylated ITAM motif of Fc epsilon R1 gamma chain, each SH2 domain binding a phosphorylated tyrosine. Unlike Zap70, Syk appears to autophosphorylate, so does not require Src family kinases for activation.

Preceded by: Fyn/Lyn-mediated phosphorylation of FcR1 gamma

Followed by: GPVI stimulates PI3K beta, gamma, SYK autophosphorylates

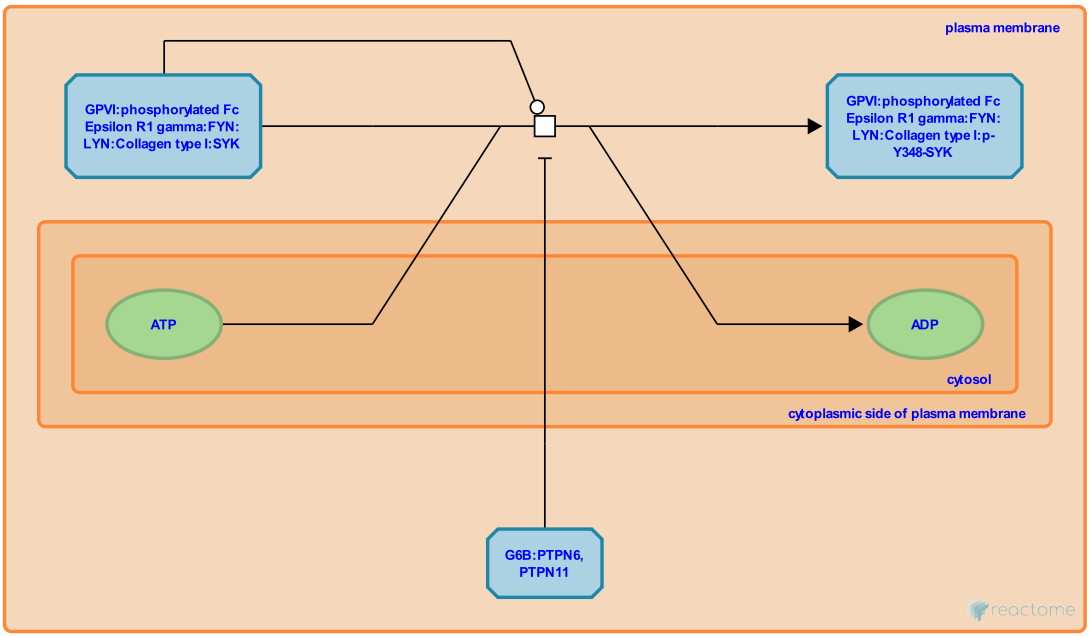
SYK autophosphorylates ↗

Location: GPVI-mediated activation cascade

Stable identifier: R-HSA-453200

Type: transition

Compartments: plasma membrane, cytosol



Binding of Syk causes conformational changes that lead to Syk activation by autophosphorylation. Syk can be activated by a number of phosphorylation events, and it has been proposed that Syk may function as a switch whereby any of several possible stimuli trigger the acquisition of similar activated conformations. (Tsang et al. 2008). These phosphorylations both modulate Syk's catalytic activity (Keshvara et al. 1997) and generate docking sites for SH2 domain-containing proteins, such as c-Cbl, PLC, and Vav1. Syk tyrosine phosphorylation is reduced in the presence of the ITIM-containing immunoglobulin superfamily transmembrane protein G6B (Mori et al. 2008).

Preceded by: Binding of Syk tyrosine kinase

Followed by: p-Y348-SYK dissociates

Literature references

Nagai, K., Suzuki, J., Kobayashi, T., Taniguchi, T., Yamada, T., Nakamura, H. et al. (1991). Molecular cloning of a porcine gene syk that encodes a 72-kDa protein-tyrosine kinase showing high susceptibility to proteolysis. *J Biol Chem, 266*, 15790-6. ↗

Yamamura, H., Sada, K., Yanagi, S., Takano, T. (2001). Structure and function of Syk protein-tyrosine kinase. *J Biochem, 130*, 177-86. ↗

Recuero-Checa, MA., Llorca, O., Bustelo, XR., Arias-Palomo, E. (2009). Conformational rearrangements upon Syk auto-phosphorylation. *Biochim Biophys Acta, 1794*, 1211-7. ↗

Editions

2009-09-04	Authored	Akkerman, JW.
2010-06-07	Edited	Jupe, S.
2010-06-07	Reviewed	Kunapuli, SP.

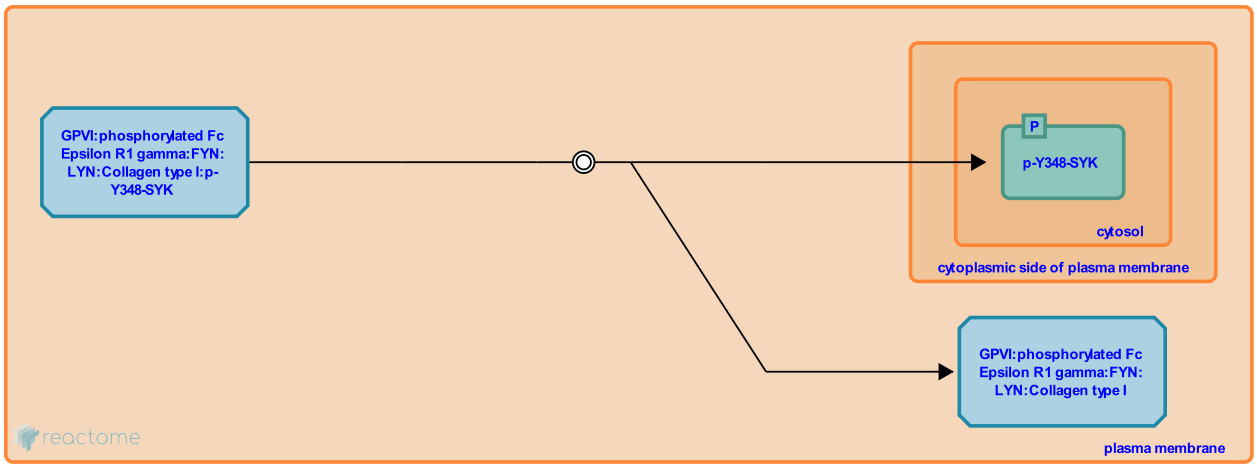
p-Y348-SYK dissociates ↗

Location: GPVI-mediated activation cascade

Stable identifier: R-HSA-453183

Type: dissociation

Compartments: plasma membrane, cytosol



Structural and biophysical studies indicate that the adaptability of the Syk tandem SH2 domains is made possible by relatively weak interactions between the two SH2 domains and the flexibility of interdomain A (Zhang et al. 2008). A large proportion of phosphorylated Syk is released into the cytosol. One factor that has been proposed for modulating the interactions of Syk with the receptor ITAM is the phosphorylation of Syk on Y130 (Keshvara et al. 1997).

Preceded by: SYK autophosphorylates

Followed by: Syk/Lck phosphorylate LAT, p-Y348-SYK binds VAV family, Syk activation leads to SLP-76 activation

Literature references

Peters, JD., Asai, DJ., Furlong, MT., Geahlen, RL., Harrison, ML. (1996). Syk, activated by cross-linking the B-cell antigen receptor, localizes to the cytosol where it interacts with and phosphorylates alpha-tubulin on tyrosine. *J Biol Chem, 271*, 4755-62. ↗

Editions

2009-09-04	Authored	Akkerman, JW.
2010-06-07	Edited	Jupe, S.
2010-06-07	Reviewed	Kunapuli, SP.

p-Y348-SYK binds VAV family ↗

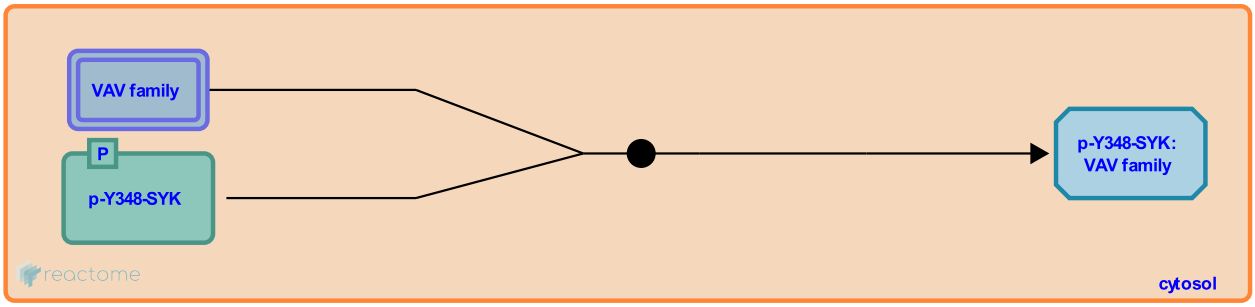
Location: GPVI-mediated activation cascade

Stable identifier: R-HSA-437932

Type: binding

Compartments: cytosol

Inferred from: Pig Syk binds human Vav1 (Sus scrofa), Syk binds Vav2 (Mus musculus)



The SH2 region of Vav1 binds to Syk at a site including phosphorylated tyrosine Y348. Mutation of this residue to F abolishes binding and subsequent Vav1 phosphorylation. Vav2 has also been shown to bind Syk.

Preceded by: p-Y348-SYK dissociates

Followed by: p-Y348-SYK phosphorylates VAV family

Editions

2009-09-04	Authored	Akkerman, JW.
2010-06-07	Edited	Jupe, S.
2010-06-07	Reviewed	Kunapuli, SP.

p-Y348-SYK phosphorylates VAV family ↗

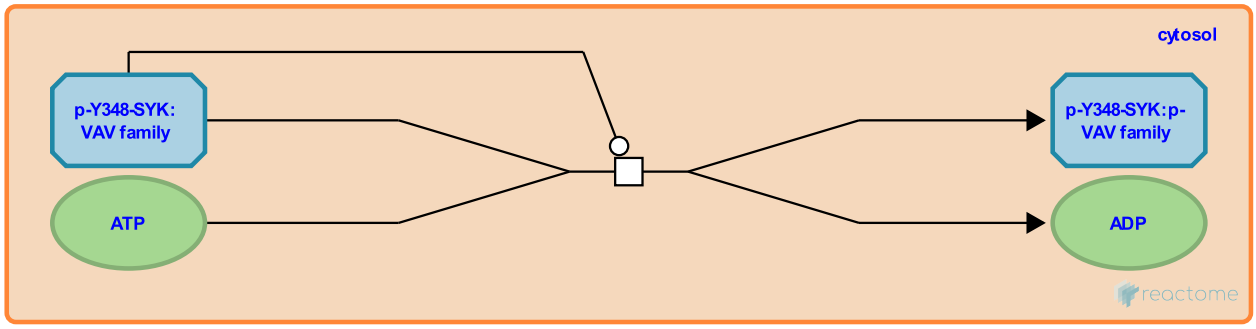
Location: GPVI-mediated activation cascade

Stable identifier: R-HSA-437936

Type: transition

Compartments: cytosol

Inferred from: Syk phosphorylates VAV1 (Homo sapiens)



Tyrosine phosphorylateion is believed to be a general activation mechansim for the Vav family. VAV1 Tyr-174 binds to the Dbl homology region, inhibiting GEF activity. Phosphorylation of this residue by Syk relieves inhibition, activating Vav1. In Jurkat cells T-cell receptor activation leads to increased Vav2 tyrosine phosphorylation; the expression of Lck, Fyn, Zap70, or Syk stimulated this phosphorylation. Vav is regulated downstream of the thrombin and thrombopoietin receptors (Miyakawa et al. 1997) and integrins, including the major platelet integrin alphaIIbbeta3. Vav family proteins are involved in filopodia and lamellipodia formation; mouse platelets deficient in Vav1 and Vav3 exhibit reduced filopodia and lamellipodia formation during spreading on fibrinogen. This is accompanied by reduced alphaIIbbeta3-mediated PLCgamma2 tyrosine phosphorylation and reduced Ca(2+) mobilization (Pearce et al. 2007).

Preceded by: p-Y348-SYK binds VAV family

Followed by: VAV1 is a GEF for Rho/Rac family GTPases, PIP2 binds inhibiting VAV, PI(3,4,5)P3 binds VAV1,2,3, VAV3 is a GEF for Rho/Rac family kinases, VAV2 is a GEF for Rho/Rac family kinases

Literature references

Tartare-Deckert, S., Deckert, M., Altman, A., Mustelin, T., Couture, C. (1996). Functional and physical interactions of Syk family kinases with the Vav proto-oncogene product. *Immunity, 5*, 591-604. ↗

Editions

2009-09-04	Authored	Akkerman, JW.
2010-06-07	Edited	Jupe, S.
2010-06-07	Reviewed	Kunapuli, SP.

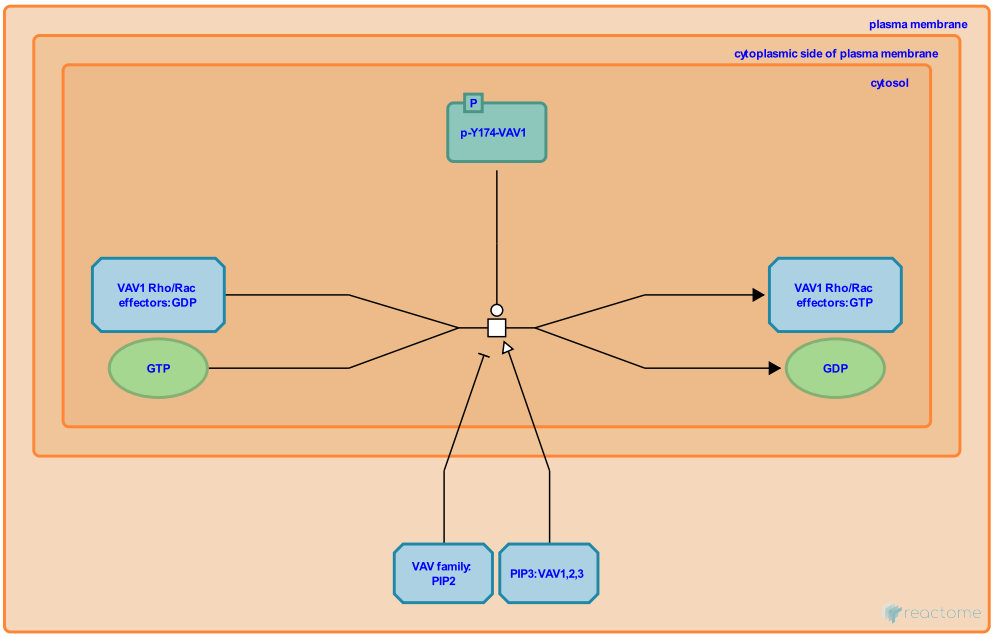
VAV1 is a GEF for Rho/Rac family GTPases ↗

Location: GPVI-mediated activation cascade

Stable identifier: R-HSA-442273

Type: transition

Compartments: cytosol



Vav family members are guanine nucleotide exchange factors (GEFs) for Rho-family GTPases. Vav1 is a GEF for Rac1, Rac2 and RhoG, and possibly RhoA and Cdc42

Preceded by: PI(3,4,5)P3 binds VAV1,2,3, p-Y348-SYK phosphorylates VAV family

Literature references

Ostrom, AA., Bustelo, XR., Gutkind, JS., Crespo, P., Schuebel, KE. (1997). Phosphotyrosine-dependent activation of Rac-1 GDP/GTP exchange by the vav proto-oncogene product. *Nature, 385*, 169-72. ↗

Kuhn, P., Tainer, JA., Streiff, M., Zhang, H., Widmer, H., Hura, GL. et al. (2008). Structural basis of guanine nucleotide exchange mediated by the T-cell essential Vav1. *J Mol Biol, 380*, 828-43. ↗

Editions

2009-09-04	Authored	Akkerman, JW.
2009-09-09	Edited	Jupe, S.
2010-06-07	Reviewed	Kunapuli, SP.

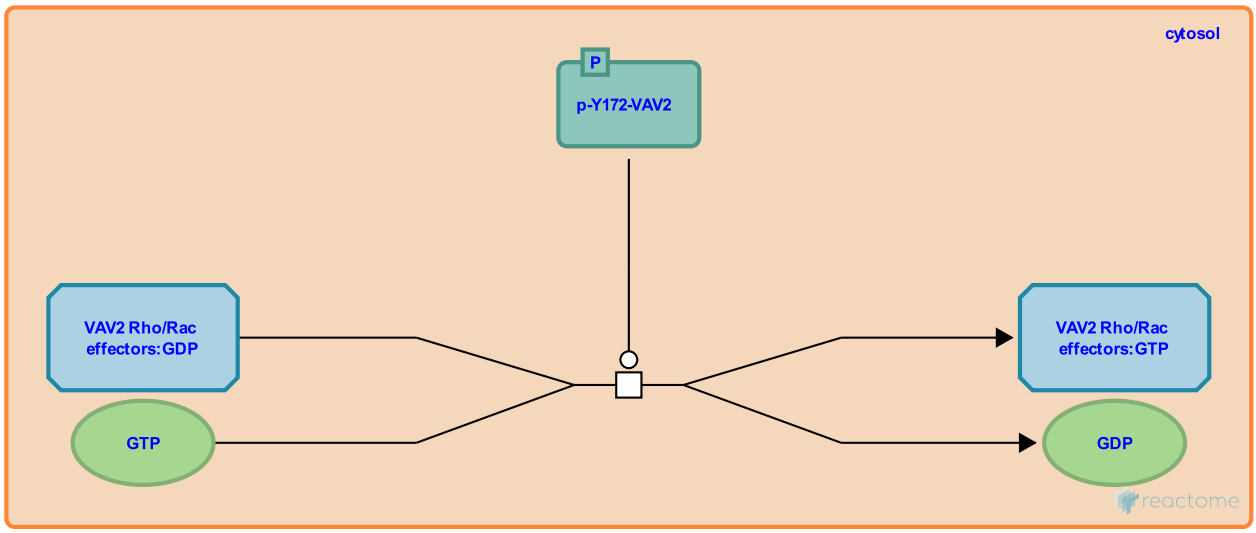
VAV2 is a GEF for Rho/Rac family kinases ↗

Location: GPVI-mediated activation cascade

Stable identifier: R-HSA-442291

Type: transition

Compartments: cytosol



Members of the Vav family are guanine nucleotide exchange factors (GEFs) for Rho-family GTPases. Vav2 is a GEF for RhoA, RhoB and RhoG, and possibly Rac1 and Cdc42

Preceded by: p-Y348-SYK phosphorylates VAV family

Literature references

Ostrom, AA., Bustelo, XR., Gutkind, JS., Crespo, P., Schuebel, KE. (1997). Phosphotyrosine-dependent activation of Rac-1 GDP/GTP exchange by the vav proto-oncogene product. *Nature, 385*, 169-72. ↗

Kuhn, P., Tainer, JA., Streiff, M., Zhang, H., Widmer, H., Hura, GL. et al. (2008). Structural basis of guanine nucleotide exchange mediated by the T-cell essential Vav1. *J Mol Biol, 380*, 828-43. ↗

Editions

2009-09-04	Authored	Akkerman, JW.
2009-09-09	Edited	Jupe, S.
2010-06-07	Reviewed	Kunapuli, SP.

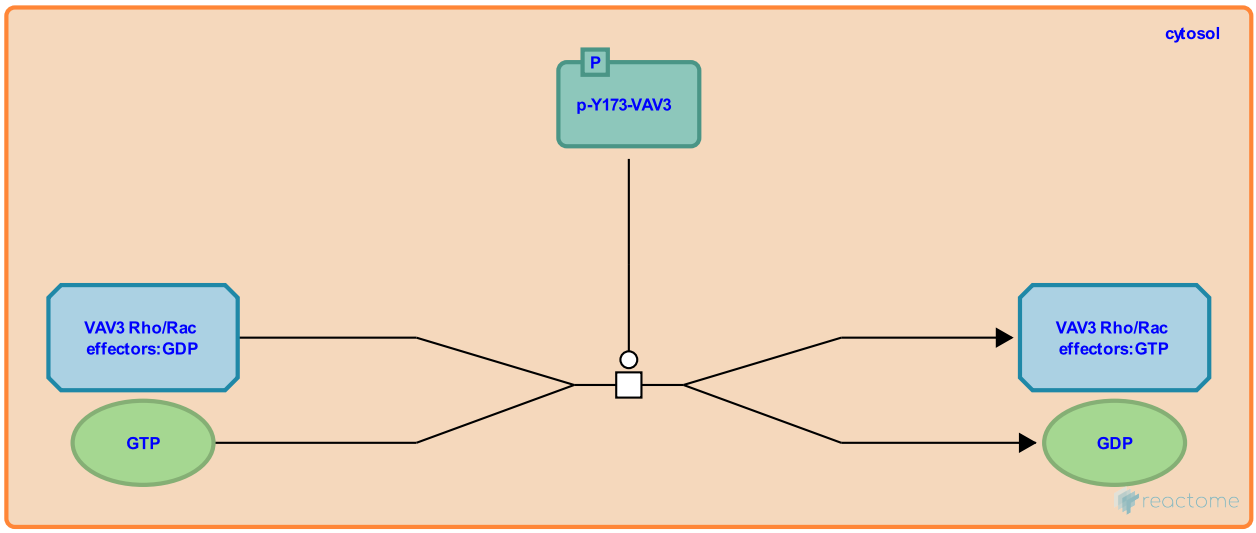
VAV3 is a GEF for Rho/Rac family kinases ↗

Location: GPVI-mediated activation cascade

Stable identifier: R-HSA-442314

Type: transition

Compartments: cytosol



Vav3 is a guanine nucleotide exchange factors (GEF) for RhoA, RhoB and to a lesser extent Rac1.

Preceded by: p-Y348-SYK phosphorylates VAV family

Literature references

Ostrom, AA., Bustelo, XR., Gutkind, JS., Crespo, P., Schuebel, KE. (1997). Phosphotyrosine-dependent activation of Rac-1 GDP/GTP exchange by the vav proto-oncogene product. *Nature, 385*, 169-72. ↗

Kuhn, P., Tainer, JA., Streiff, M., Zhang, H., Widmer, H., Hura, GL. et al. (2008). Structural basis of guanine nucleotide exchange mediated by the T-cell essential Vav1. *J Mol Biol, 380*, 828-43. ↗

Editions

2009-09-04	Authored	Akkerman, JW.
2010-06-07	Edited	Jupe, S.
2010-06-07	Reviewed	Kunapuli, SP.

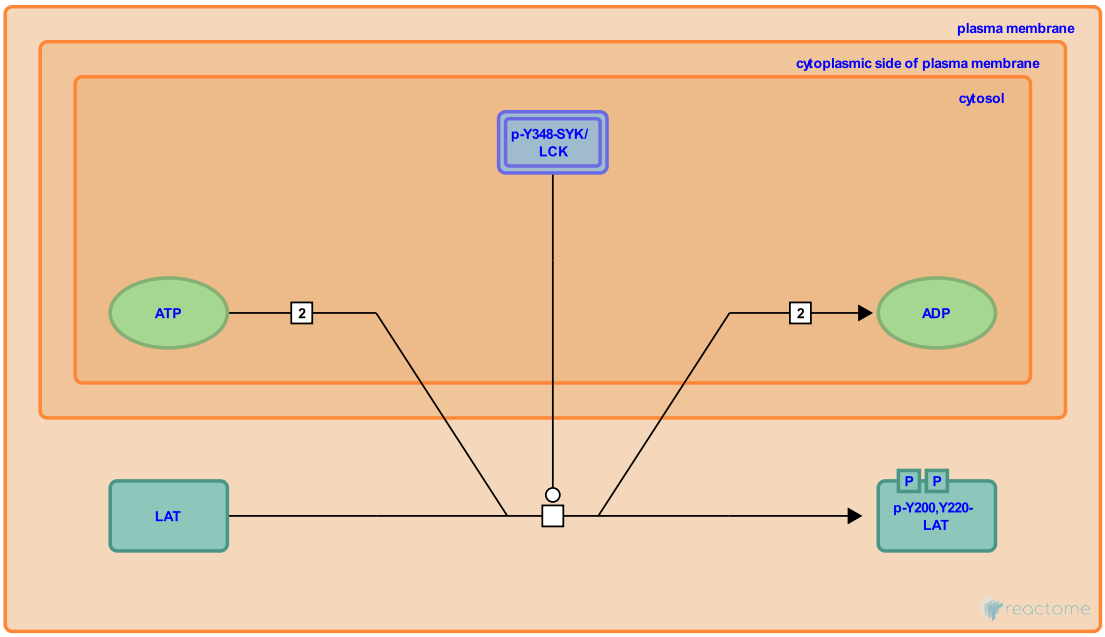
Syk/Lck phosphorylate LAT ↗

Location: GPVI-mediated activation cascade

Stable identifier: R-HSA-434836

Type: transition

Compartments: plasma membrane, cytosol



Activated Syk (or possibly the related kinase Lck) phosphorylates two key tyrosine residues of LAT.

Preceded by: p-Y348-SYK dissociates

Literature references

Jiang, Y., Cheng, H. (2007). Evidence of LAT as a dual substrate for Lck and Syk in T lymphocytes. *Leuk Res, 31*, 541-5. ↗

Editions

2009-09-04	Authored	Akkerman, JW.
2009-11-02	Reviewed	Poole, AW., Jones, ML., Harper, MT.
2010-06-07	Edited	Jupe, S.

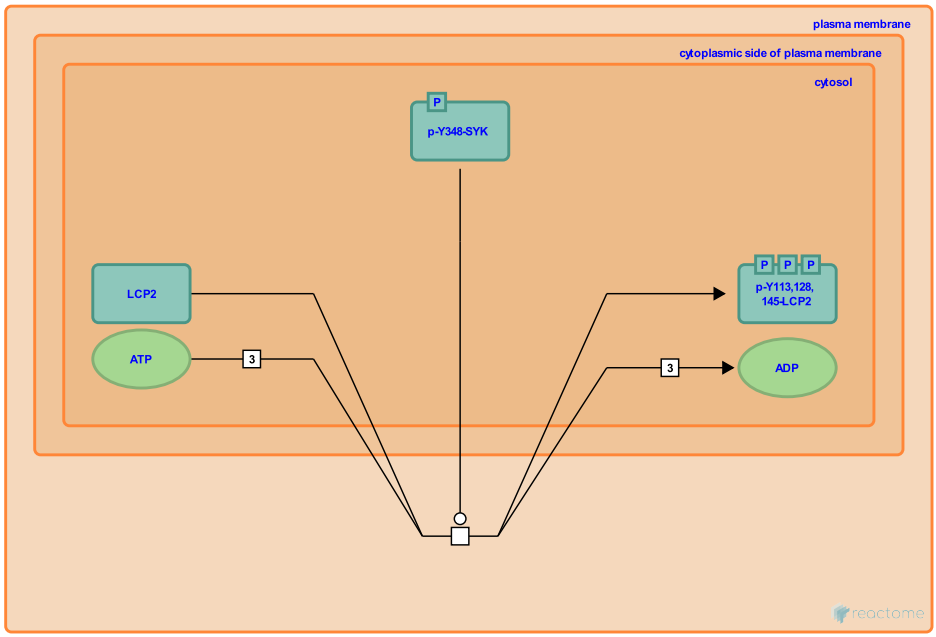
Syk activation leads to SLP-76 activation ↗

Location: GPVI-mediated activation cascade

Stable identifier: R-HSA-429449

Type: transition

Compartments: plasma membrane



Stimulation of platelets with collagen-related peptide leads to tyrosine phosphorylation of SLP-76, an adaptor protein with multiple binding domains (Gross et al. 1999). Phosphorylation of SLP-76 is mediated by Syk, analogous to the role of ZAP-70 in phosphorylating T-cell SLP-76 (Bubeck-Wardenberg et al. 1996, Hussain et al. 1999, Fasbender et al. 2017). SLP-76 was shown to bind to tyrosine-phosphorylated C-terminal tail of SYK (de Castro et al. 2012). The phosphorylated tyrosine residues provide a binding site for the SH2 domains of downstream signalling proteins like Vav, Itk and ADAP (Jordan et al. 2003). Platelets from mice defective in SLP76 do not connect GPVI engagement with downstream signaling (Clements et al. 1999, Judd et al. 2000). GPVI signaling via SLP-76 does not appear to require LAT or GADS (Judd et al. 2002) suggesting that the mechanism is not identical to that of T-cells. LAT and SLP-76 are both required for P-selectin expression and degranulation but may function independently, or rely on proteins not required by T-cells (Jordan et al. 2003).

Preceded by: p-Y348-SYK dissociates

Followed by: p-SLP-76 binds VAV, SLP-76 stimulates PLC gamma 2

Literature references

Sandusky, M., Fasbender, F., Watzl, C., Claus, M., Wingert, S. (2017). Differential Requirements for Src-Family Kinases in SYK or ZAP70-Mediated SLP-76 Phosphorylation in Lymphocytes. *Front Immunol, 8*, 789. ↗

Watson, SP., Turner, M., Tybulewicz, VL., Lee, JR., Gross, BS., Clements, JL. et al. (1999). Tyrosine phosphorylation of SLP-76 is downstream of Syk following stimulation of the collagen receptor in platelets. *J Biol Chem, 274*, 5963-71. ↗

Nore, BF., Faryal, R., Mohamed, AJ., Smith, CI., Hussain, A. (2009). Phosphatidylinositol-3-kinase-dependent phosphorylation of SLP-76 by the lymphoma-associated ITK-SYK fusion-protein. *Biochem. Biophys. Res. Commun., 390*, 892-6. ↗

Siraganian, RP., Barbu, EA., de Castro, RO., Groves, JR., Zhang, J. (2012). Once phosphorylated, tyrosines in carboxyl terminus of protein-tyrosine kinase Syk interact with signaling proteins, including TULA-2, a negative regulator of mast cell degranulation. *J. Biol. Chem., 287*, 8194-204. ↗

Editions

2009-06-03	Authored	Akkerman, JW.
2009-11-02	Reviewed	Poole, AW., Jones, ML., Harper, MT.
2009-11-03	Edited	Jupe, S.
2017-12-06	Edited, Revised	Orlic-Milacic, M.

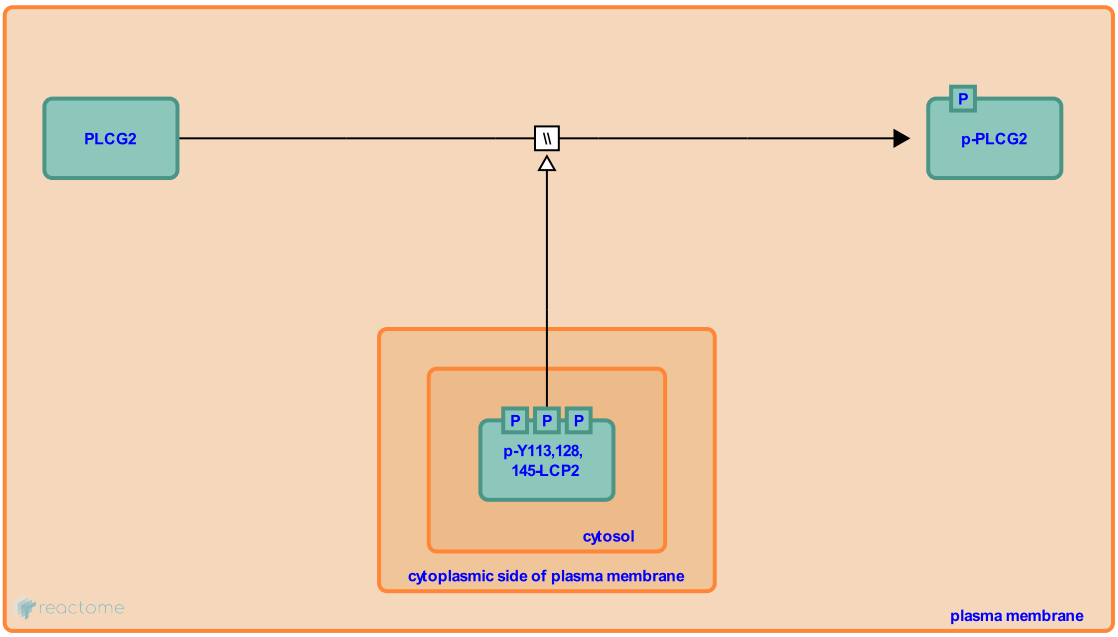
SLP-76 stimulates PLC gamma 2 ↗

Location: GPVI-mediated activation cascade

Stable identifier: R-HSA-429497

Type: omitted

Compartments: plasma membrane



SLP-76 has a well-established role in recruitment of PLC gamma 1 in immunoreceptor signalling; its role in the recruitment of PLC gamma 2 in integrin signalling is less clear. Results from SLP-76 null mice imply a functional role in GPVI signalling. Platelets from SLP-76 null mice exhibit a marked reduction in spreading and a decrease in whole cell phosphotyrosine levels when adhered to a fibrinogen-coated surface. In vivo reconstitution of SLP-76 by retroviral gene transfer corrects bleeding diathesis and restores normal responses to both collagen and fibrinogen (Judd et al., 2000).

Preceded by: Syk activation leads to SLP-76 activation

Followed by: PLC gamma 2-mediated PIP2 hydrolysis

Literature references

Watson, SP., Gross, BS., Melford, SK. (1999). Evidence that phospholipase C-gamma2 interacts with SLP-76, Syk, Lyn, LAT and the Fc receptor gamma-chain after stimulation of the collagen receptor glycoprotein VI in human platelets. *Eur J Biochem, 263*, 612-23. ↗

Eckly, A., Lanza, F., Goncalves, I., Jackson, SP., Freund, M., Gachet, C. et al. (2003). Signaling role for phospholipase C gamma 2 in platelet glycoprotein Ib alpha calcium flux and cytoskeletal reorganization. Involvement of a pathway distinct from FcR gamma chain and Fc gamma RIIA. *J Biol Chem, 278*, 32880-91. ↗

Yap, CL., Hughan, SC., Goncalves, I., Jackson, SP., Schoenwaelder, SM., Yuan, Y. (2003). Integrin alpha IIb beta 3-dependent calcium signals regulate platelet-fibrinogen interactions under flow. Involvement of phospholipase C gamma 2. *J Biol Chem, 278*, 34812-22. ↗

Editions

2009-06-03	Authored	Akkerman, JW.
2009-11-02	Reviewed	Poole, AW., Jones, ML., Harper, MT.
2009-11-03	Edited	Jupe, S.

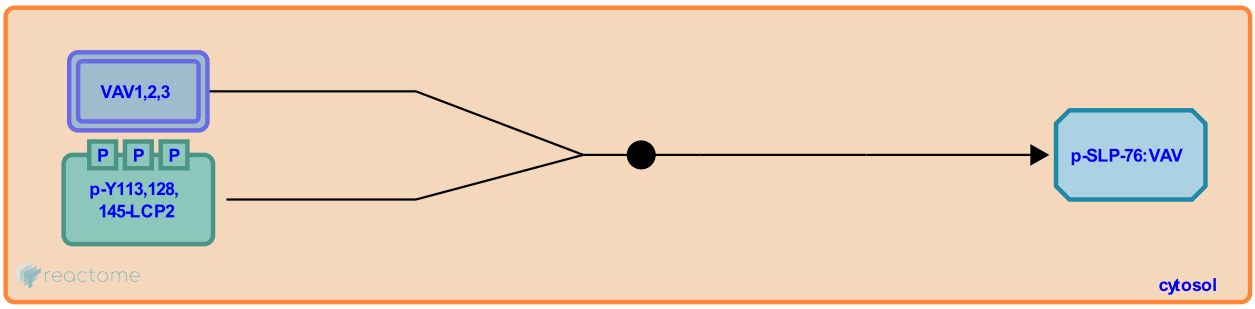
p-SLP-76 binds VAV ↗

Location: GPVI-mediated activation cascade

Stable identifier: R-HSA-430158

Type: binding

Compartments: cytosol



SLP-76 is a hematopoietic cell-specific adapter protein. Studies indicate that three phosphotyrosines in SLP-76 (Y113, Y128, and Y145) are required for interactions with the SH2 domains of Vav1 (and Nck and Itk). This interaction is essential for membrane recruitment of Vav1. Similarly, association of Vav3 with SLP-76 was found to be essential for membrane recruitment. Vav2 has been shown to interact with SLP-76 in resting Jurkat cells.

Preceded by: Syk activation leads to SLP-76 activation

Literature references

Charvet, C., Tartare-Deckert, S., Monthouel, MN., Deckert, M., Altman, A., Bernard, A. et al. (2001). Vav2 activates c-fos serum response element and CD69 expression but negatively regulates nuclear factor of activated T cells and interleukin-2 gene activation in T lymphocyte. *J Biol Chem, 276*, 20849-57. ↗

Billadeau, DD., Charvet, C., Altman, A., Canonigo, AJ. (2005). Membrane localization and function of Vav3 in T cells depend on its association with the adapter SLP-76. *J Biol Chem, 280*, 15289-99. ↗

Motto, DG., Weiss, A., Koretzky, GA., Wu, J. (1996). Vav and SLP-76 interact and functionally cooperate in IL-2 gene activation. *Immunity, 4*, 593-602. ↗

Editions

2009-06-03	Authored	Akkerman, JW.
2009-11-02	Reviewed	Poole, AW., Jones, ML., Harper, MT.
2009-11-03	Edited	Jupe, S.

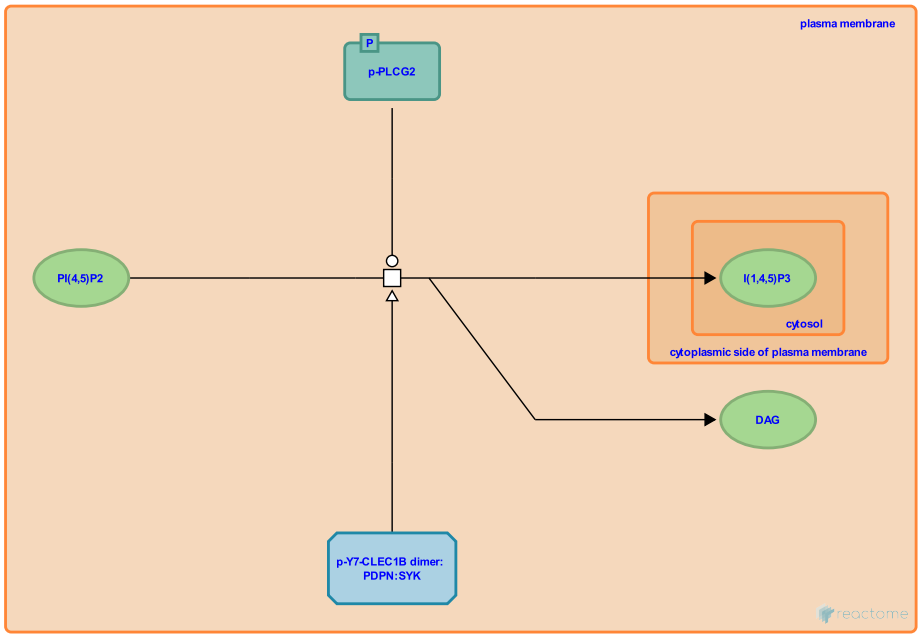
PLC gamma 2-mediated PIP2 hydrolysis ↗

Location: GPVI-mediated activation cascade

Stable identifier: R-HSA-114689

Type: transition

Compartments: plasma membrane, cytosol



At the beginning of this reaction, 1 molecule of '1-Phosphatidyl-D-myo-inositol 4,5-bisphosphate' is present. At the end of this reaction, 1 molecule of '1D-myo-Inositol 1,4,5-trisphosphate', and 1 molecule of '1,2-Diacylglycerol' are present.

This reaction is mediated by the 'phospholipase C activity' of 'Phosphorylated phospholipase C gamma 2'.

Preceded by: SLP-76 stimulates PLC gamma 2

Literature references

Nozawa, Y., Yada, Y., Banno, Y. (1988). Purification and characterization of membrane-bound phospholipase C specific for phosphoinositides from human platelets. *J Biol Chem, 263*, 11459-65. ↗

Editions

2009-09-09	Edited	Jupe, S.

PI(3,4,5)P3 binds VAV1,2,3

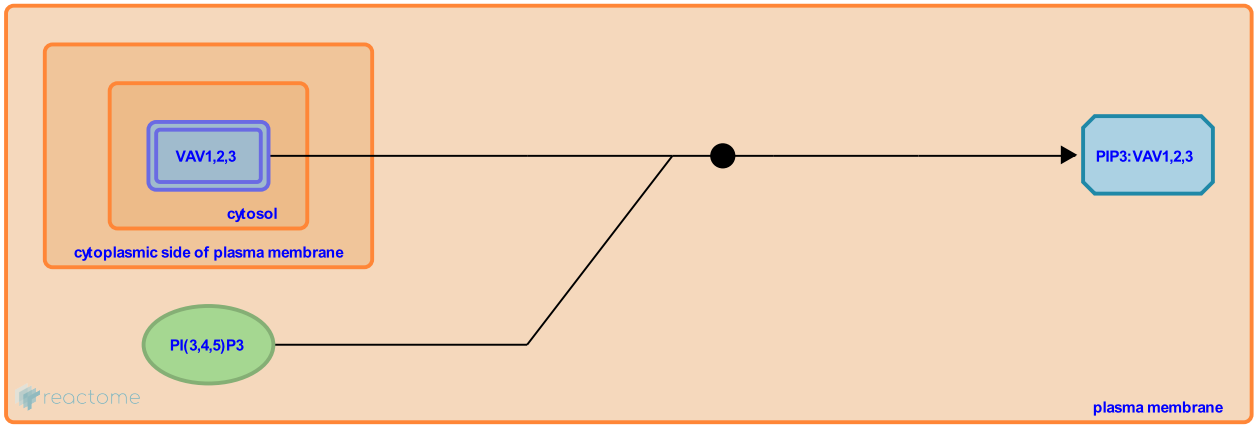
Location: GPVI-mediated activation cascade

Stable identifier: R-HSA-434637

Type: binding

Compartments: plasma membrane, cytosol

Inferred from: PIP3 stimulates Vav1 (Mus musculus)



Vav interacts directly with PIP2 and PIP3, with a fivefold selectivity for PIP3 over PIP2. PIP3 gives a twofold stimulation of Vav1 GEF activity while PIP2 leads to 90% inhibition. Binding probably occurs through the PH domain, known to bind phosphoinositides.

Preceded by: PI3K alpha, beta, gamma convert PIP2 to PIP3, p-Y348-SYK phosphorylates VAV family

Followed by: VAV1 is a GEF for Rho/Rac family GTPases

Literature references

White, MA., Falck, JR., Mosteller, RD., Xia, Y., Han, J., Shu, X. et al. (1998). Role of substrates and products of PI 3-kinase in regulating activation of Rac-related guanosine triphosphatases by Vav. *Science, 279*, 558-60.

Editions

2009-09-02	Authored	Jupe, S.
2009-11-02	Reviewed	Poole, AW., Jones, ML., Harper, MT.
2009-11-03	Edited	Jupe, S.

PIP2 binds inhibiting VAV ↗

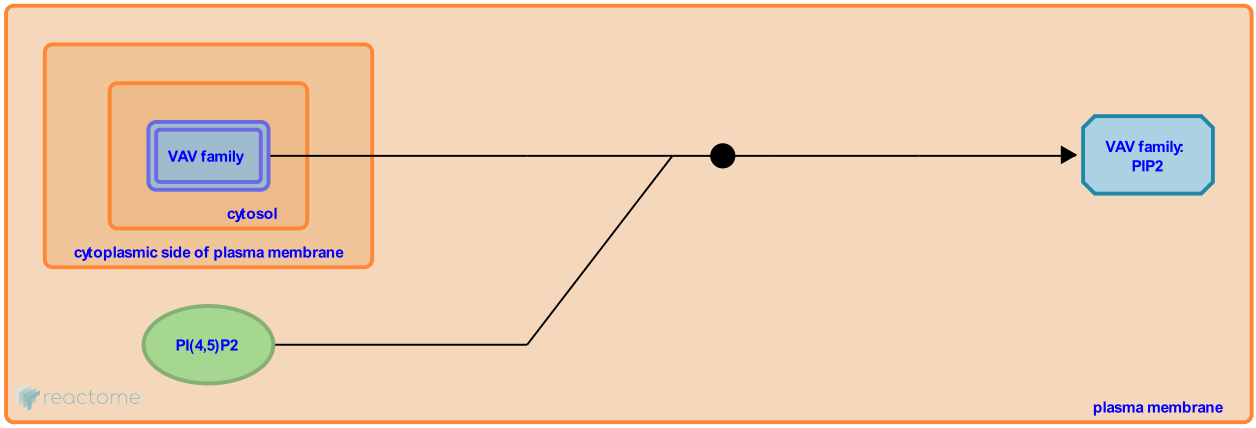
Location: GPVI-mediated activation cascade

Stable identifier: R-HSA-434633

Type: binding

Compartments: plasma membrane, cytosol

Inferred from: PIP2 inhibits Vav1 (Mus musculus)



Vav interacts directly with PIP2 and PIP3, with a fivefold selectivity for PIP3 over PIP2. PIP3 gives a twofold stimulation of Vav1 GEF activity while PIP2 leads to 90% inhibition. Binding probably occurs through the PH domain, known to bind phosphoinositides.

Preceded by: PI3K alpha, beta, gamma convert PIP2 to PIP3, p-Y348-SYK phosphorylates VAV family

Literature references

White, MA., Falck, JR., Mosteller, RD., Xia, Y., Han, J., Shu, X. et al. (1998). Role of substrates and products of PI 3-kinase in regulating activation of Rac-related guanosine triphosphatases by Vav. *Science, 279*, 558-60. ↗

Editions

2009-09-04	Authored	Akkerman, JW.
2009-11-02	Reviewed	Poole, AW., Jones, ML., Harper, MT.
2009-11-03	Edited	Jupe, S.

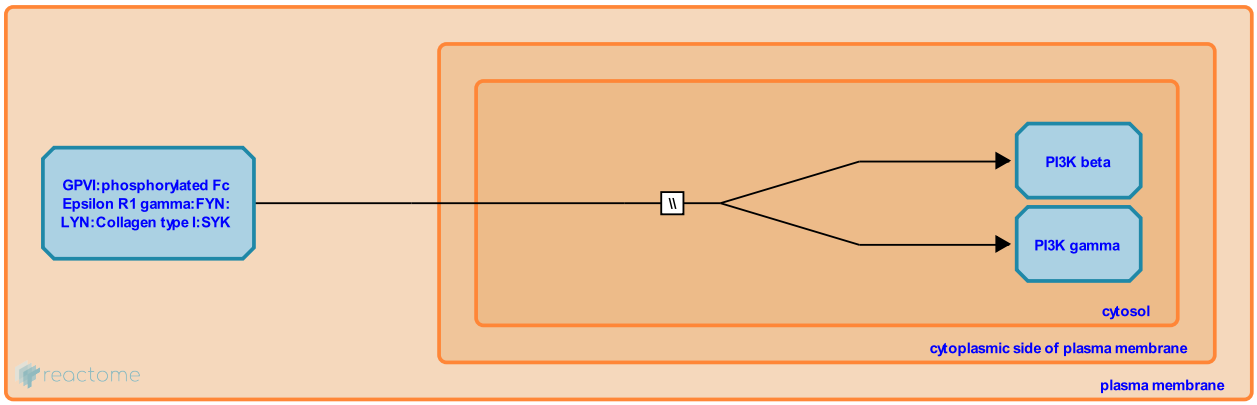
GPVI stimulates PI3K beta, gamma ↗

Location: GPVI-mediated activation cascade

Stable identifier: R-HSA-437118

Type: omitted

Compartments: cytosol



GPVI downstream signaling involves PI3K. Mouse knockouts of PI3Kbeta/PI3Kgamma suggest that though both isoforms are required for a full platelet response, only beta is absolutely required for Akt phosphorylation, Rap1 activation, and platelet aggregation downstream. The pathway connecting GPVI to PI3K is unclear. Two possible routes are suggested by interactions of the PI3K p85 regulatory subunit with LAT and with peptides representing the ITAM motif of Fc Epsilon R1 gamma.

Preceded by: Binding of Syk tyrosine kinase

Followed by: PI3K alpha, beta, gamma convert PIP2 to PIP3

Literature references

Kim, S., Jackson, SP., Lillian, R., Dangelmaier, C., Mangin, P., Kunapuli, SP. et al. (2009). The role of PI 3-K{beta} in glycoprotein VI-mediated akt activation in platelets. *J Biol Chem.* ↗

Editions

2009-09-04	Authored	Akkerman, JW.
2009-11-02	Reviewed	Poole, AW., Jones, ML., Harper, MT.
2009-11-03	Edited	Jupe, S.

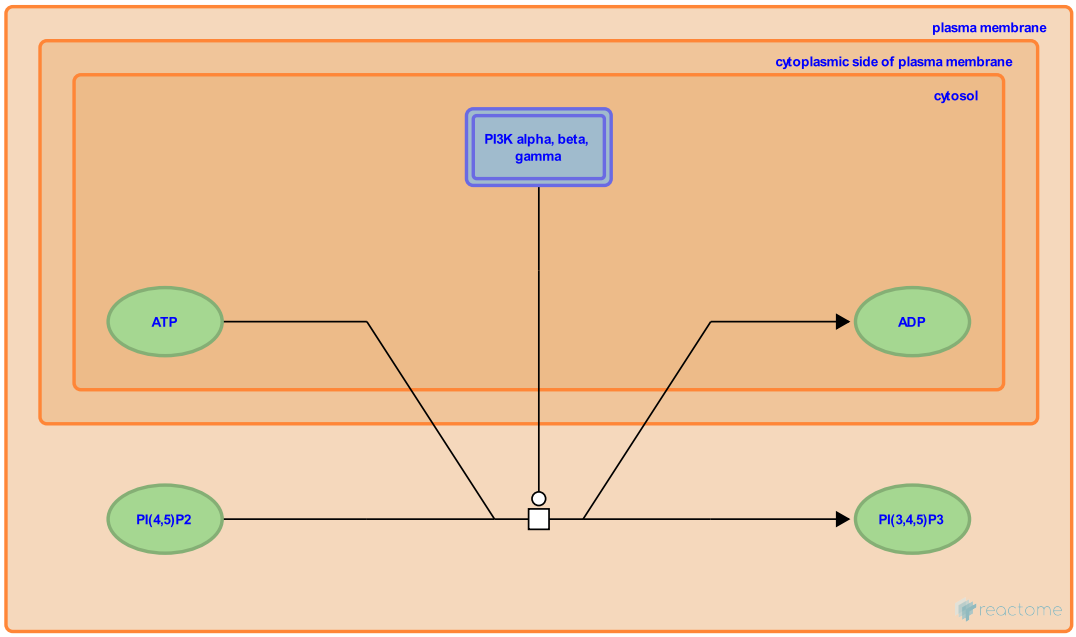
PI3K alpha, beta, gamma convert PIP2 to PIP3 ↗

Location: GPVI-mediated activation cascade

Stable identifier: R-HSA-437162

Type: transition

Compartments: plasma membrane, cytosol



Class I Phosphoinositide 3-kinases (PI3Ks) are heterodimeric proteins, each having a catalytic subunit of 110-120 kDa and an associated regulatory subunit. PI3Ks alpha, beta and delta share a common regulatory p85 subunit, PI3K gamma has a p101 regulatory subunit. All the class I PI3Ks are able to phosphorylate PtdIns, PtdIns-4-P, or PtdIns-4,5-P2 (PIP2) on the free 3-position, and have a strong preference for PIP2.They are activated by receptor tyrosine kinases and by Ras and Rho family GTPases.

Preceded by: GPVI stimulates PI3K beta, gamma

Followed by: PIP2 binds inhibiting VAV, PI(3,4,5)P3 binds VAV1,2,3, PIP3 recruits PDPK1 to the membrane

Literature references

Schlessinger, J., Mondino, A., Hu, P., Skolnik, EY. (1993). Cloning of a novel, ubiquitously expressed human phosphatidylinositol 3-kinase and identification of its binding site on p85. *Mol Cell Biol, 13*, 7677-88. ↗

Malek, D., Nurnberg, B., Dhand, R., Vanhaesebroeck, B., Volinia, S., Loubtchenkov, M. et al. (1995). Cloning and characterization of a G protein-activated human phosphoinositide-3 kinase. *Science, 269*, 690-3. ↗

Editions

2009-09-04	Authored	Akkerman, JW.
2009-11-02	Reviewed	Poole, AW., Jones, ML., Harper, MT.
2009-11-03	Edited	Jupe, S.

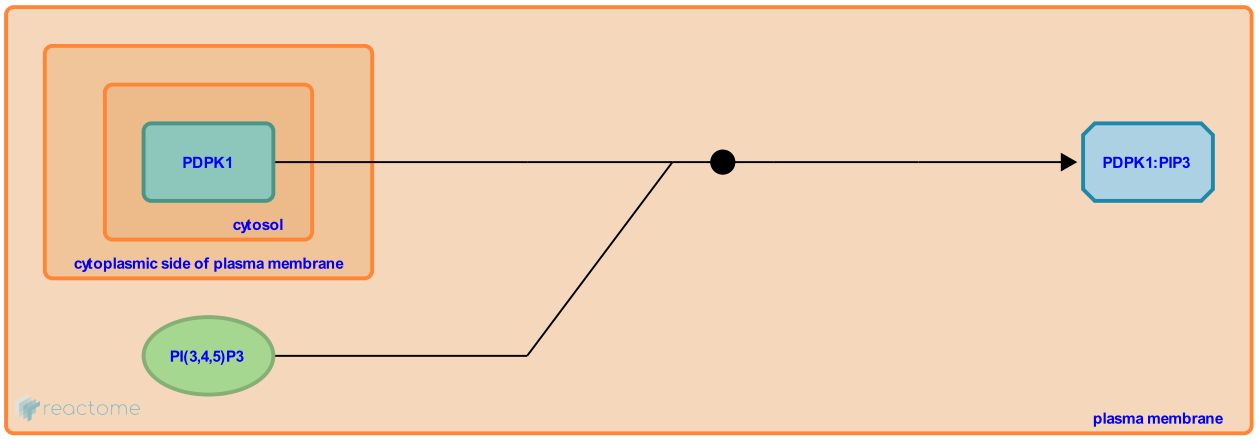
PIP3 recruits PDPK1 to the membrane ↗

Location: GPVI-mediated activation cascade

Stable identifier: R-HSA-2316429

Type: binding

Compartments: plasma membrane, cytosol



PIP3 generated by PI3K recruits phosphatidylinositide-dependent protein kinase 1 (PDPK1 i.e. PDK1) to the membrane, through its PH (pleckstrin-homology) domain. PDPK1 binds PIP3 with high affinity, and also shows low affinity for PIP2 (Currie et al. 1999).

Preceded by: PI3K alpha, beta, gamma convert PIP2 to PIP3

Followed by: PDPK1 binds PRKCZ

Literature references

Alessi, DR., Cohen, P., Downes, CP., Casamayor, A., Lucocq, J., Currie, RA. et al. (1999). Role of phosphatidylinositol 3,4,5-trisphosphate in regulating the activity and localization of 3-phosphoinositide-dependent protein kinase-1. *Biochem J, 337*, 575-83. ↗

Editions

2006-10-10	Authored	Annibali, D., Nasi, S.
2007-11-08	Reviewed	Greene, LA.
2012-07-18	Revised	Orlic-Milacic, M.
2012-08-03	Edited	Matthews, L.
2012-08-13	Reviewed	Zhao, JJ., Yuzugullu, H., Thorpe, L.

PDPK1 binds PRKCZ ↗

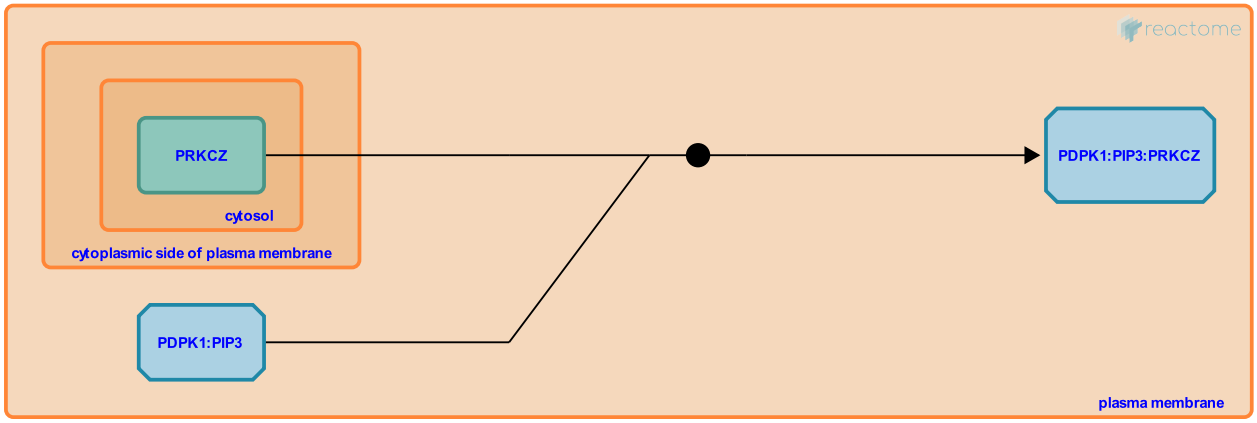
Location: GPVI-mediated activation cascade

Stable identifier: R-HSA-437192

Type: binding

Compartments: plasma membrane, cytosol

Inferred from: PDK1 binds PKC zeta (Rattus norvegicus)



3-phosphoinositide dependent protein kinase-1 (PDPK1, also known as PDK1) and Protein kinase C zeta type (PRKCZ, also known as PKC zeta) are associated in fibroblasts.

Preceded by: PIP3 recruits PDPK1 to the membrane

Followed by: PDPK1 activates PRKCZ

Literature references

Lee, MH., Chen, CS., Chou, MM., Johnson, J., Toker, A., Graham, LK. et al. (1998). Regulation of protein kinase C zeta by PI 3-kinase and PDK-1. *Curr Biol, 8*, 1069-77. ↗

Editions

2009-09-04	Authored	Akkerman, JW.
2009-11-02	Reviewed	Poole, AW., Jones, ML., Harper, MT.
2009-11-03	Edited	Jupe, S.

PDPK1 activates PRKCZ ↗

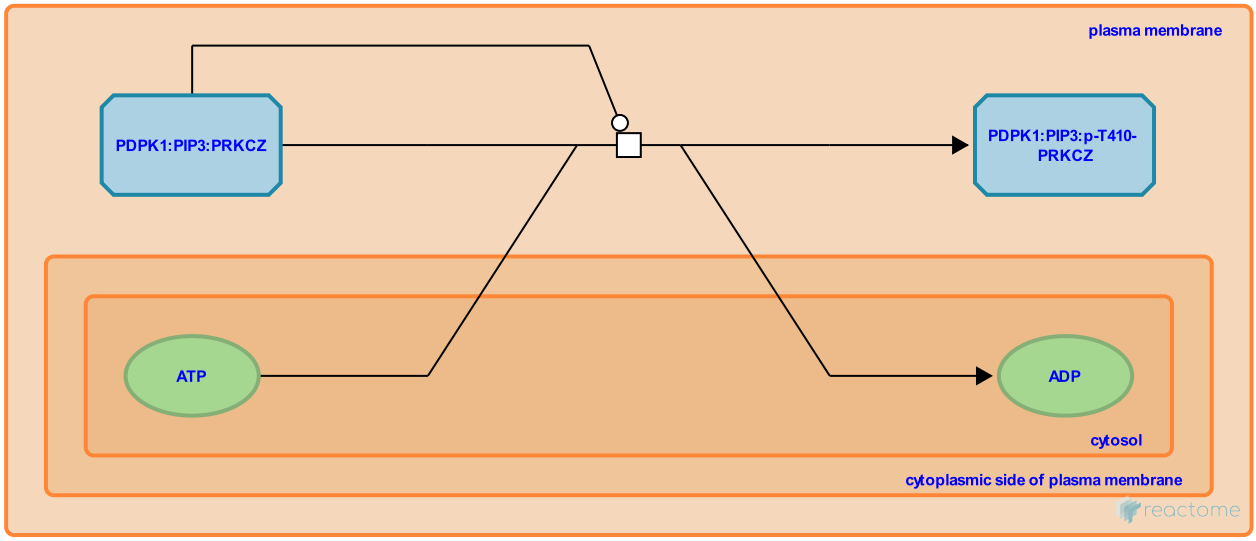
Location: GPVI-mediated activation cascade

Stable identifier: R-HSA-437195

Type: transition

Compartments: plasma membrane, cytosol

Inferred from: PDK1 activates PKC zeta (Rattus norvegicus)



3-phosphoinositide dependent protein kinase-1 (Pdpk1, also known as Pdk1 and PKB kinase because of its activity at Protein kinase B) phosphorylates T410 of protein kinase C zeta type (Prkcz, also known as PKC zeta), leading to activation. The motif surrounding T410 is highly conserved in other PKC family members suggesting that Pdpk1 might activate other PKCs.

Preceded by: PDPK1 binds PRKCZ

Literature references

Lee, MH., Chen, CS., Chou, MM., Johnson, J., Toker, A., Graham, LK. et al. (1998). Regulation of protein kinase C zeta by PI 3-kinase and PDK-1. *Curr Biol, 8*, 1069-77. ↗

Editions

2009-09-04	Authored	Akkerman, JW.
2009-11-02	Reviewed	Poole, AW., Jones, ML., Harper, MT.
2009-11-03	Edited	Jupe, S.

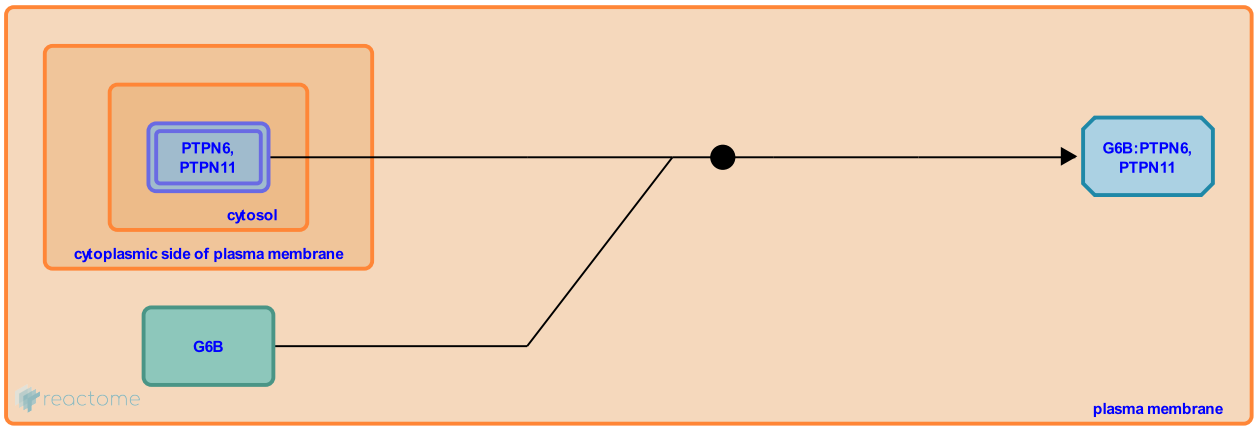
G6B binds PTPN6,PTPN11 ↗

Location: GPVI-mediated activation cascade

Stable identifier: R-HSA-5684169

Type: binding

Compartments: plasma membrane, cytosol



G6B is a member of the immunoglobulin superfamily. The G6B-B variant is the only variant to contain both a transmembrane region and two immunoreceptor tyrosine-based inhibitory motifs (ITIMs) that support binding to the SH2 domain-containing protein tyrosine phosphatases PTPN6 (SHP1) and PTPN11 (SHP2) (de Vet et al. 2001, Senis et al. 2007). ITIMs are defined by the consensus sequence (L/I/V/S)-X-Y-X-X-(L/V) and are commonly present in pairs separated by 15 to 30 amino acid residues. ITIM-containing receptors were originally identified by their ability to inhibit signaling by ITAM receptors (Bijsterbosch & Klaus 1985). Expression of the GPVI-FcR gamma-chain complex orC-type lectin domain family 1 member B (CLEC1B, CLEC2) in DT40 (chicken) B cells leads to the generation of both constitutive and agonist-induced signals that are inhibited by G6B. This effect is dependent on the two ITIMs in the cytosolic tail of G6B, but is reported to be independent of the two SH2 domain-containing tyrosine phosphatases PTPN6 and PTPN11, and the inositol lipid 5”²-phosphatase SHIP1 (Mori et al. 2008). A more recent study (Coxon et al. 2011) found that other SH2 domain-containing proteins including SYK and PLCgamma2 also recognize G6B phosphomotifs, which may explain why G6B remains inhibitory in the absence of both PTPN6 and PTPN11.

The tandem SH2 domains of PTPN11 have a 100-fold higher binding affinity for G6B than that of PTPN6. PTPN6 has an absolute binding requirement for phosphorylation at both ITAM motifs, while PTPN11 can associate with G6B when only one motif is phosphorylated. The presence of dual phosphorylated G6B in washed human platelets reduced the EC(50) for both CRP and collagen-induced aggregation (Coxon et al. 2011). G6B is proposed to inhibit sustained constitutive signaling from GPVI-FcRgamma and CLEC1B (Mori et al. 2008).

Literature references

Watson, SP., Tomlinson, MG., Mori, J., Grygielska, B., Eble, JA., Senis, YA. et al. (2008). G6b-B inhibits constitutive and agonist-induced signaling by glycoprotein VI and CLEC-2. *J. Biol. Chem., 283*, 35419-27. ↗

Editions

2015-03-20	Authored	Jupe, S.
2015-11-09	Reviewed	Akkerman, JW.
2015-11-09	Edited	Jupe, S.

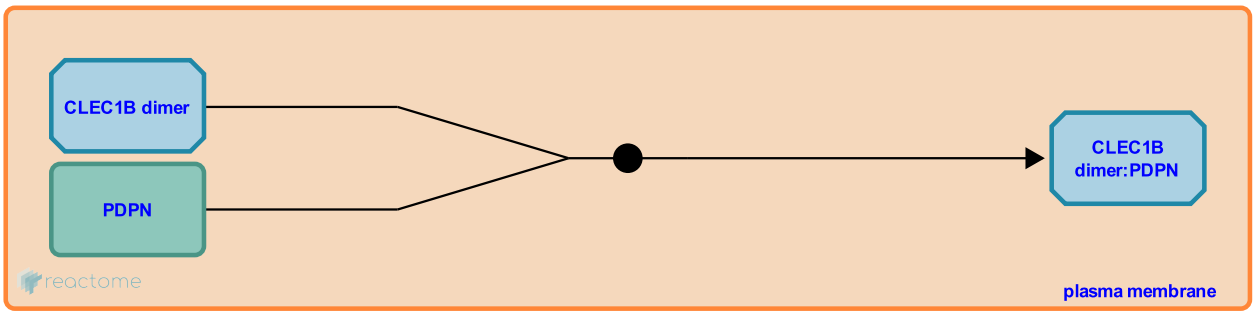
CLEC1B dimer binds PDPN ↗

Location: GPVI-mediated activation cascade

Stable identifier: R-HSA-5684836

Type: binding

Compartments: plasma membrane



C-type lectin domain family 1 member B (CLEC1B, CLEC2) is a 32-kDa C-type lectin-like receptor that dimerizes to form the platelet receptor for the snake venom toxin rhodocytin and the endogenous lymphatic endothelial marker, podoplanin (PDPN) (Suzuki-Inoue et al. 2006, 2007, Christou et al. 2008, Watson et al. 2009). PDPN is a sialomucin-like glycoprotein with a wide tissue distribution. It is found at a high level in lung type I alveolar cells, kidney podocytes, choroid plexus epithelium, lymphatic endothelial cells and fibroblastic reticular cells within secondary lymphoid organs. PDPN is not found on vascular endothelial cells. It is up-regulated in a variety of tumors and on macrophages following lipopolysaccharide stimulation. Cells expressing PDPN or recombinant forms of its extracellular domain have been shown to induce platelet activation (Pollitt et al. 2014).

Followed by: Unknown kinase phosphorylates CLEC1B dimer:PDPN

Literature references

Mishima, K., Inoue, O., Suzuki-Inoue, K., Ozaki, Y., Kato, Y., Narimatsu, H. et al. (2007). Involvement of the snake toxin receptor CLEC-2, in podoplanin-mediated platelet activation, by cancer cells. *J. Biol. Chem., 282*, 25993-6001 . ↗

Editions

2015-03-20	Authored	Jupe, S.
2015-11-09	Reviewed	Akkerman, JW.
2015-11-09	Edited	Jupe, S.

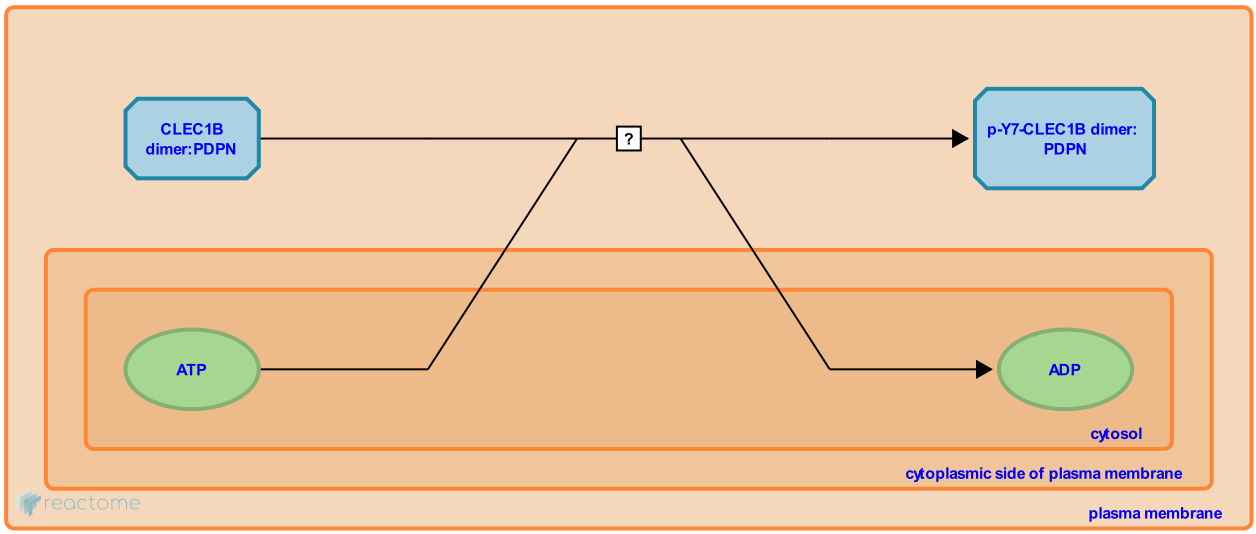
Unknown kinase phosphorylates CLEC1B dimer:PDPN ↗

Location: GPVI-mediated activation cascade

Stable identifier: R-HSA-5684806

Type: uncertain

Compartments: plasma membrane, cytosol



Following stimulation by rhodocytin CLEC1B is phosphorylated on the YxxL or hemi-ITAM motif. The kinase responsible for this is not clear. Phosphorylation is suggested to allow the tandem SH2 domains of SYK to bind phosphorylated CLEC1B hemi-ITAM sites (Suzuki-Inoue et al. 2006). GPVI ITAMs are phosphorylated by the Src family kinases FYN and LYN, which results in SYK binding, but CLEC1B appears to be phosphorylated mainly by SYK. The SYK-specific inhibitor R406 inhibits CLEC1B phosphorylation in response to rhodocytin, suggesting SYK is responsible for hemi-ITAM phosphorylation in human platelets (Spalton et al. 2009). However the Src family-specific kinase inhibitor PP2 also inhibits CLEC1B tyrosine phosphorylation (Suzuki-Inoue et al. 2006), suggesting that CLEC1B is phosphorylated by Syk and Src family kinases in human platelets (Suzuki-Inoue et al. 2006, Suzuki-Inoue 2011). Severin et al. (2011) reported that phosphorylation of CLEC1B by rhodocytin is abolished in Syk-deficient mice, while phosphorylation is not altered in mice deficient in the major platelet Src family kinases Fyn, Lyn, Src, or the tyrosine phosphatase CD148, which regulates the basal activity of Src family kinases. The same group also reported that PP2 does not inhibit phosphorylation of mouse Clec1b by rhodocytin, in contrast to the reported effect in human platelets (Suzuki-Inoue et al. 2006), suggesting that Syk phosphorylates Clec1b independently of the Src family kinases in mice.

Preceded by: CLEC1B dimer binds PDPN

Followed by: p-Y7-CLEC1B dimer:PDPN binds SYK

Literature references

Theakston, RD., Watson, SP., Suzuki-Inoue, K., Eble, JA., Ozaki, Y., Morita, T. et al. (2006). A novel Syk-dependent mechanism of platelet activation by the C-type lectin receptor CLEC-2. *Blood, 107*, 542-9. ↗

Editions

2015-03-20	Authored	Jupe, S.
2015-11-09	Reviewed	Akkerman, JW.
2015-11-09	Edited	Jupe, S.

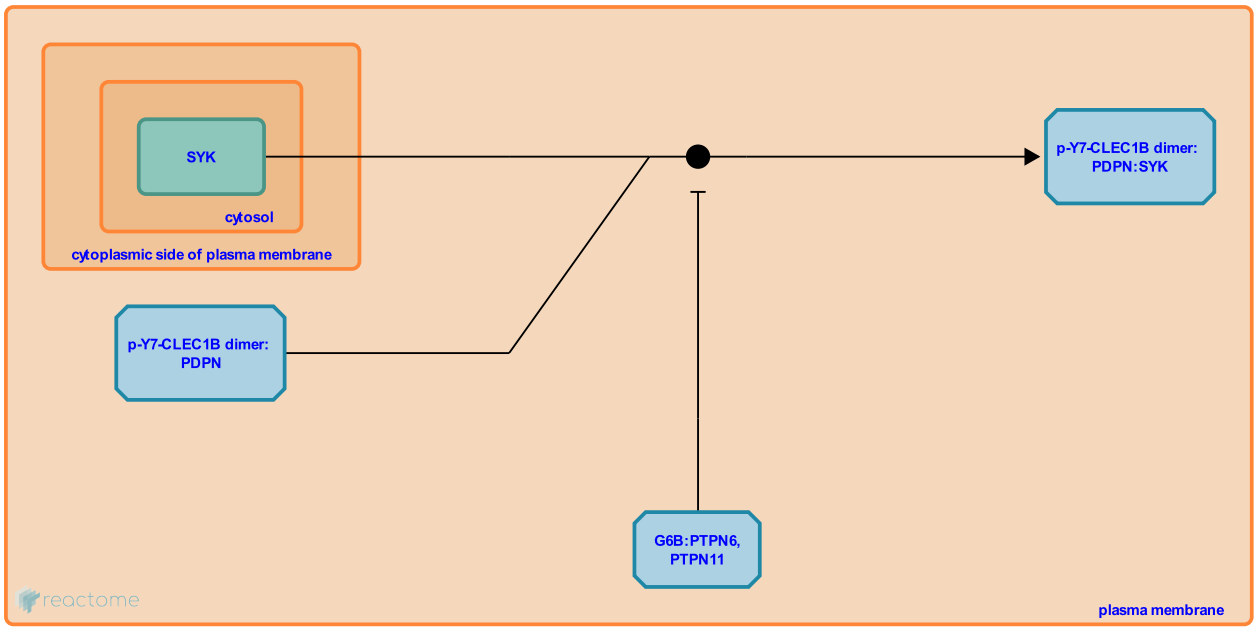
p-Y7-CLEC1B dimer:PDPN binds SYK ↗

Location: GPVI-mediated activation cascade

Stable identifier: R-HSA-5684801

Type: binding

Compartments: plasma membrane, cytosol



Following the phosphorylation of CLEC1B on its hemi-ITAM motif it can bind the kinase SYK (Suzuki-Inoue et al. 2006, 2007, Spalton et al. 2009, Severin et al. 2011). Beyond SYK, CLEC1B signalling is similar to that of GPVI:FcR1 gamma. Murine platelets deficient in Syk or PLC gamma 2 fail to respond to rhodocytin, suggesting they are crucial for Clec1b signal transduction. Mice deficient in the adaptor proteins Linker for activation of T-cells family member 1 (LAT), LCP2 (SLP-76) or the guanine nucleotide exchange factors Vav1-3 are able to respond to high concentrations of rhodocytin, suggesting that these molecules participate in Clec1b signaling but do not prevent signaling when absent (Suzuki-Inoue et al. 2006, Finney et al. 2011).

Clec1b signaling is reduced in the presence of the ITIM-containing immunoglobulin superfamily transmembrane protein G6B (Mori et al. 2008). G6B is thought to act by reducing Syk tyrosine phosphorylation (Mori et al. 2008) but it is possible that the target of inhibition is elsewhere in the CLEC1B signaling cascade.

Preceded by: Unknown kinase phosphorylates CLEC1B dimer:PDPN

Literature references

Theakston, RD., Watson, SP., Suzuki-Inoue, K., Eble, JA., Ozaki, Y., Morita, T. et al. (2006). A novel Syk-dependent mechanism of platelet activation by the C-type lectin receptor CLEC-2. *Blood, 107*, 542-9. ↗

Editions

2015-03-20	Authored	Jupe, S.
2015-11-09	Reviewed	Akkerman, JW.
2015-11-09	Edited	Jupe, S.

Table of Contents