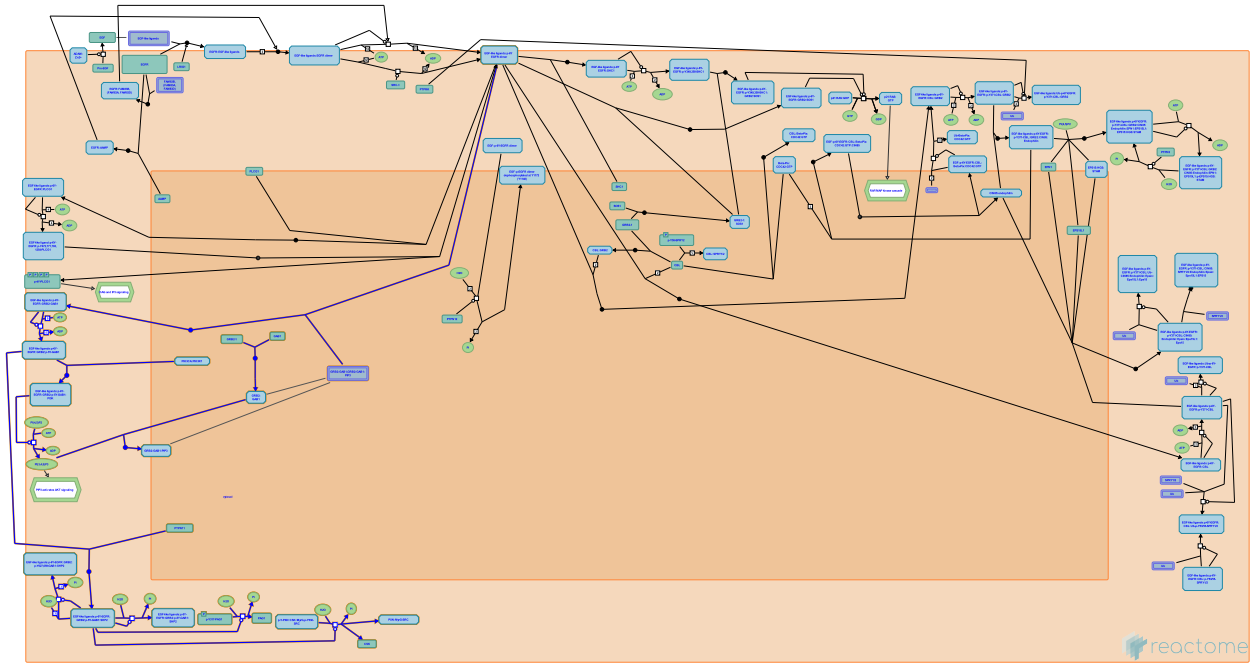
GAB1 signalosome



Castagnoli, L., Heldin, CH., Orlic-Milacic, M.

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.

03/05/2024

Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

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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. ↗

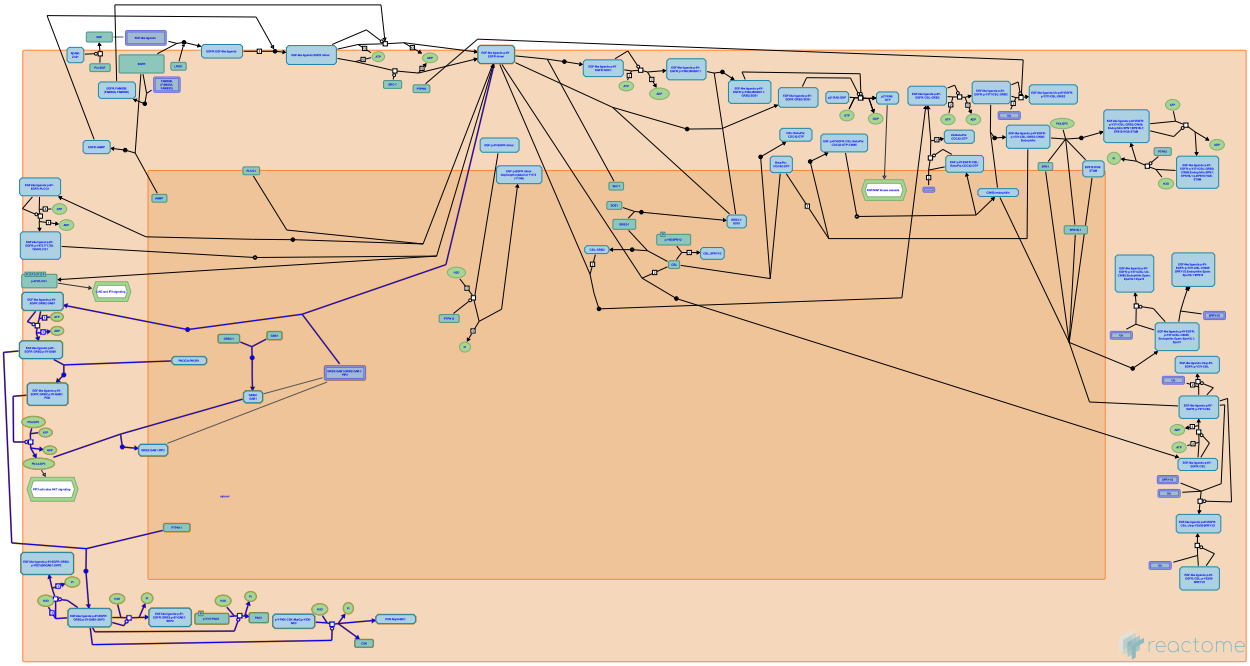
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

GAB1 signalosome ↗

Stable identifier: R-HSA-180292



GAB1 is recruited to the activated EGFR indirectly, through GRB2. GAB1 acts as an adaptor protein that enables formation of an active PIK3, through recruitment of PIK3 regulatory subunit PIK3R1 (also known as PI3Kp85), which subsequently recruits PIK3 catalytic subunit PIK3CA (also known as PI3Kp110). PIK3, in complex with EGFR, GRB2 and GAB1, catalyzes phosphorylation of PIP2 and its conversion to PIP3, which leads to the activation of the AKT signaling.

Literature references

Schlessinger, J., Lax, I., Lamothe, B., Mattoon, DR. (2004). The docking protein Gab1 is the primary mediator of EGF-stimulated activation of the PI-3K/Akt cell survival pathway. *BMC Biol, 2*, 24. ↗

Editions

2006-10-10	Authored	Castagnoli, L.
2008-02-12	Reviewed	Heldin, CH.

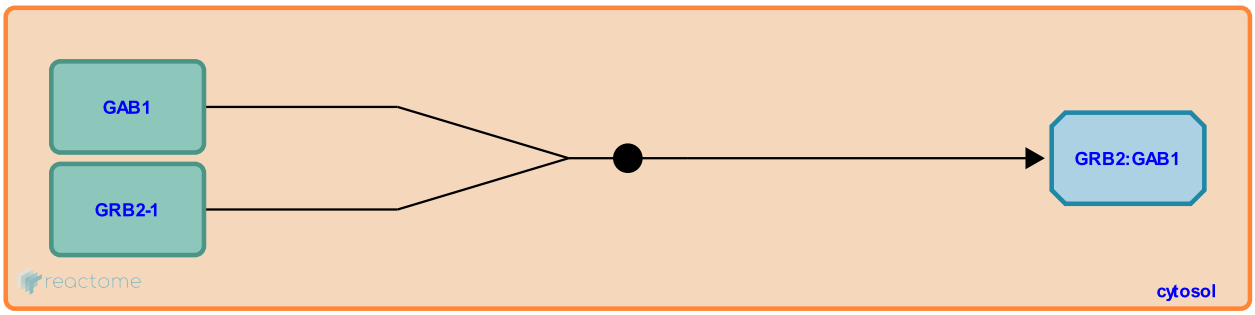
Binding of GRB2 to GAB1 ↗

Location: GAB1 signalosome

Stable identifier: R-HSA-177920

Type: binding

Compartments: cytosol



GRB2 (Growth factor receptor-bound protein 2) binds to GAB1 (GRB2-associated binding protein 1).

Followed by: GRB2:GAB1 binds to phosphorylated EGFR

Literature references

Naujokas, MA., Lock, LS., Park, M., Royal, I. (2000). Identification of an atypical Grb2 carboxyl-terminal SH3 domain binding site in Gab docking proteins reveals Grb2-dependent and -independent recruitment of Gab1 to receptor tyrosine kinases. *J Biol Chem, 275*, 31536-45. ↗

Saucier, C., Lock, LS., Park, M., Frigault, MM. (2003). Grb2-independent recruitment of Gab1 requires the C-terminal lobe and structural integrity of the Met receptor kinase domain. *J Biol Chem, 278*, 30083-90. ↗

Editions

2006-10-10	Authored	Castagnoli, L.
2008-02-12	Reviewed	Heldin, CH.
2011-08-25	Edited	Orlic-Milacic, M.

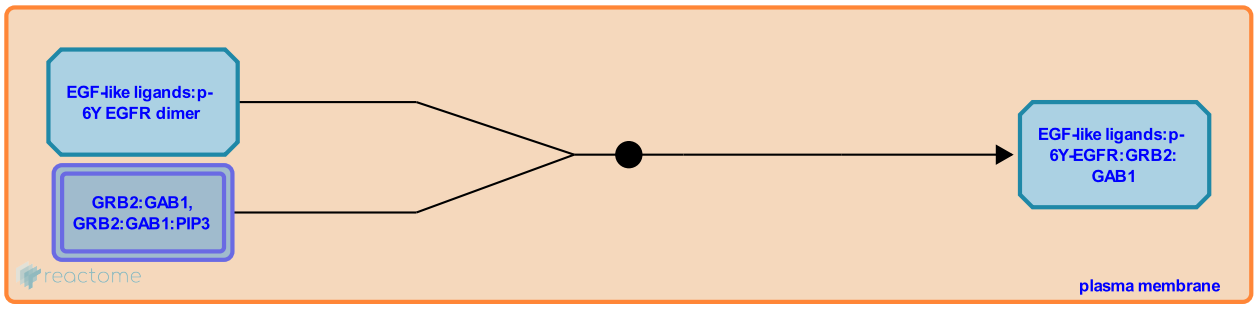
GRB2:GAB1 binds to phosphorylated EGFR ↗

Location: GAB1 signalosome

Stable identifier: R-HSA-177941

Type: binding

Compartments: plasma membrane, extracellular region, cytosol



The regulatory subunit of PIK3 mediates the association of GAB1 and receptor protein-tyrosine kinases such as the EGF receptor, which can phosphorylate GAB1. It appears that the PIK3 regulatory subunit acts as an adaptor protein allowing GAB1 to serve as a substrate for several tyrosine kinases.

Preceded by: GAB1 binds phosphatidylinositol-3,4,5-trisphosphate, Binding of GRB2 to GAB1

Followed by: GAB1 phosphorylation by EGFR kinase

Literature references

Emlet, DR., Holgado-Madruga, M., Wong, AJ., Dieterich, R., Moscatello, DK. (1997). Grb2-associated binder-1 mediates phosphatidylinositol 3-kinase activation and the promotion of cell survival by nerve growth factor. *Proc Natl Acad Sci U S A, 94,* 12419-24. ↗

Editions

2006-10-10	Authored	Castagnoli, L.
2008-02-12	Reviewed	Heldin, CH.
2011-08-25	Edited	Orlic-Milacic, M.

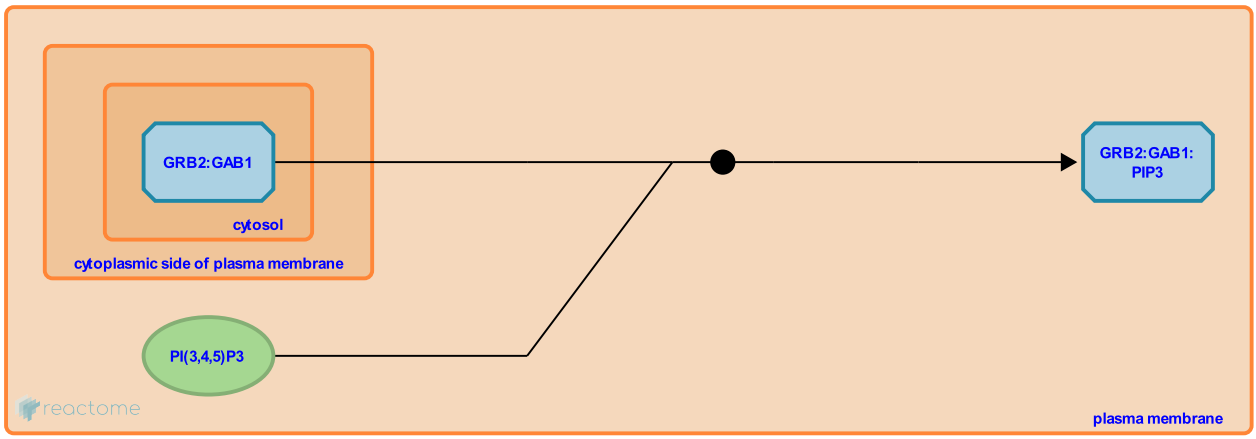
GAB1 binds phosphatidylinositol-3,4,5-trisphosphate ↗

Location: GAB1 signalosome

Stable identifier: R-HSA-179467

Type: binding

Compartments: plasma membrane, cytosol



The pleckstrin homology (PH) domain of GAB1 binds to PIP3 and can target GAB1 to the plasma membrane in response to EGF stimulation. This mechanism provides a positive feedback loop with respect to PI3K activation, to enhance EGFR signalling.

Preceded by: PI3K converts phosphatidylinositol-4,5-bisphosphate (PIP2) to phosphatidylinositol-3,4,5-trisphosphate (PIP3)

Followed by: GRB2:GAB1 binds to phosphorylated EGFR

Literature references

Falasca, M., Rodrigues, GA., Schlessinger, J., Ong, SH., Zhang, Z. (2000). A novel positive feedback loop mediated by the docking protein Gab1 and phosphatidylinositol 3-kinase in epidermal growth factor receptor signaling. *Mol Cell Biol, 20*, 1448-59. ↗

Editions

2006-10-10	Authored	Castagnoli, L.
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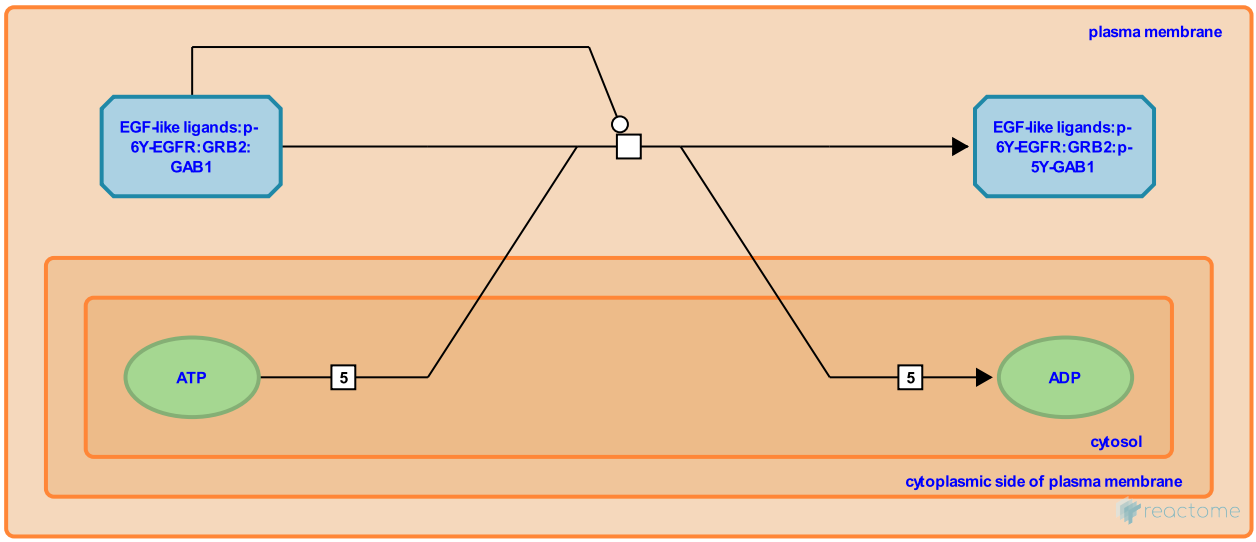
GAB1 phosphorylation by EGFR kinase ↗

Location: GAB1 signalosome

Stable identifier: R-HSA-177930

Type: transition

Compartments: plasma membrane, extracellular region, cytosol



EGFR kinase phosphorylates the phosphorylation sites tyrosine 627 and 659 on GAB1

Preceded by: GRB2:GAB1 binds to phosphorylated EGFR

Followed by: Activation of SHP2 through the binding to phospho-Gab1, PI3K binds to EGF:EGFR:GRB2:GAB1

Literature references

Deb, TB., Wong, L., Johnson, GR., Fan, YX. (2004). Ligand regulates epidermal growth factor receptor kinase specificity: activation increases preference for GAB1 and SHC versus autophosphorylation sites. *J Biol Chem, 279*, 38143-50. ↗

Bruning, JC., Knebel, B., Lehr, S., Siethoff, C., Herkner, A., Muller-Wieland, D. et al. (1999). Identification of tyrosine phosphorylation sites in human Gab-1 protein by EGF receptor kinase in vitro. *Biochemistry, 38*, 151-9. ↗

Editions

2006-10-10	Authored	Castagnoli, L.
2008-02-12	Reviewed	Heldin, CH.

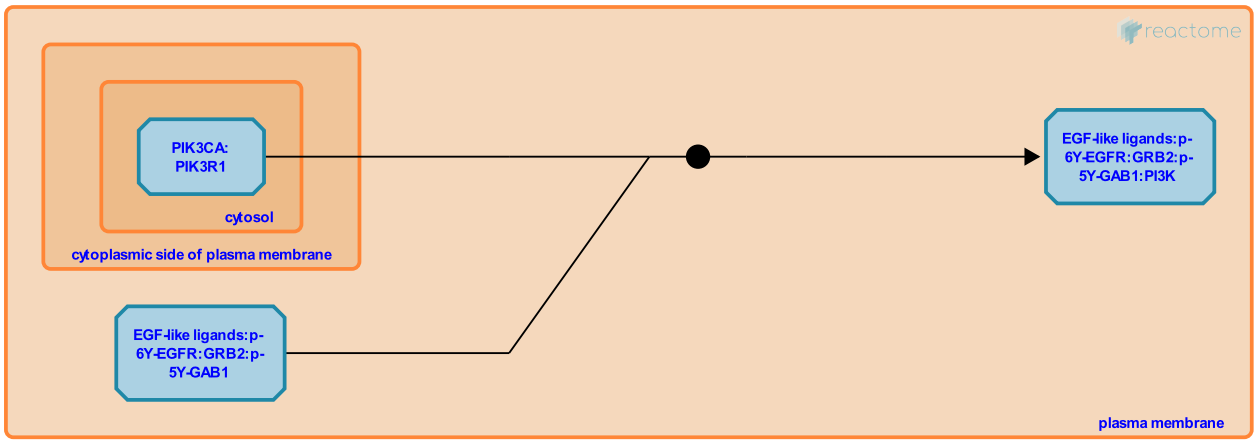
PI3K binds to EGF:EGFR:GRB2:GAB1 ↗

Location: GAB1 signalosome

Stable identifier: R-HSA-177927

Type: binding

Compartments: plasma membrane, extracellular region, cytosol



The Src homology 2 (SH2) domain of the phosphatidylinositol 3-kinase (PIK3) regulatory subunit (PIK3R1, i.e. PI3Kp85) binds to GAB1 in a phosphorylation-independent manner. GAB1 serves as a docking protein which recruits a number of downstream signalling proteins. PIK3R1 can bind to either GAB1 or phosphorylated GAB1(Rodrigues et al. 2000, Onishi-Haraikawa et al. 2001). In unstimulated cells, PI3K class IA exists as an inactive heterodimer of a p85 regulatory subunit (encoded by PIK3R1, PIK3R2 or PIK3R3) and a p110 catalytic subunit (encoded by PIK3CA, PIK3CB or PIK3CD). Binding of the iSH2 domain of the p85 regulatory subunit to the ABD and C2 domains of the p110 catalytic subunit both stabilizes p110 and inhibits its catalytic activity. This inhibition is relieved when the SH2 domains of p85 bind phosphorylated tyrosines on activated RTKs or their adaptor proteins. Binding to membrane-associated receptors brings activated PI3K in proximity to its membrane-localized substrate, PIP2 (Mandelker et al. 2009, Burke et al. 2011).

Preceded by: GAB1 phosphorylation by EGFR kinase

Followed by: PI3K converts phosphatidylinositol-4,5-bisphosphate (PIP2) to phosphatidylinositol-3,4,5-trisphosphate (PIP3)

Literature references

Fukushima, Y., Inukai, K., Kikuchi, M., Ogihara, T., Onishi-Haraikawa, Y., Asano, T. et al. (2001). Unique phosphorylation mechanism of Gab1 using PI 3-kinase as an adaptor protein. *Biochem Biophys Res Commun, 288*, 476-82. ↗

Falasca, M., Rodrigues, GA., Schlessinger, J., Ong, SH., Zhang, Z. (2000). A novel positive feedback loop mediated by the docking protein Gab1 and phosphatidylinositol 3-kinase in epidermal growth factor receptor signaling. *Mol Cell Biol, 20*, 1448-59. ↗

Editions

2006-10-10	Authored	Castagnoli, L.
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2011-08-25	Edited	Orlic-Milacic, M.

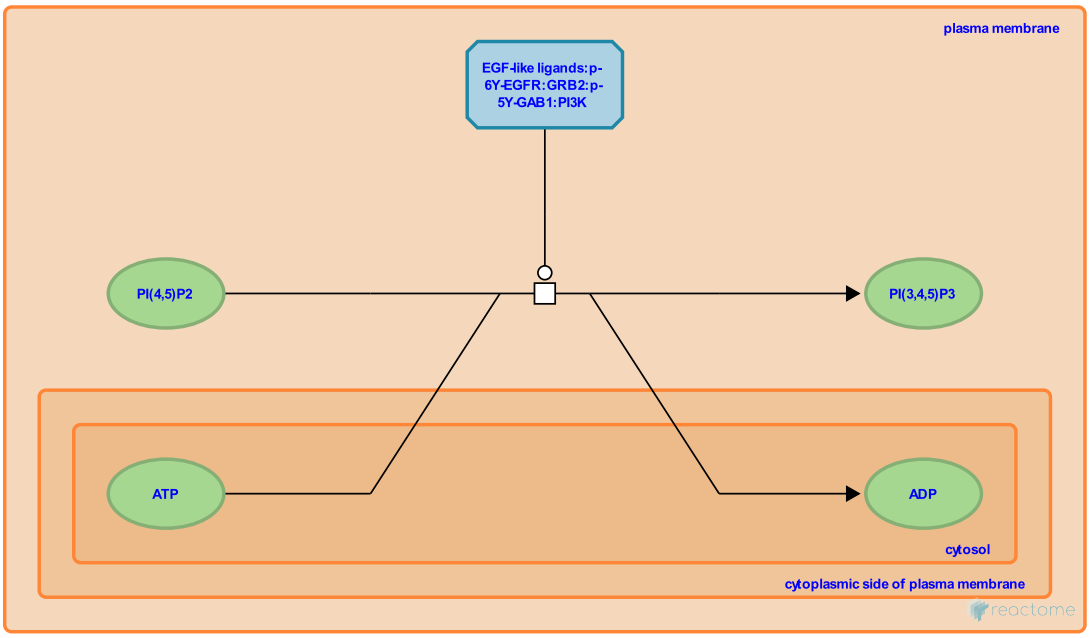
PI3K converts phosphatidylinositol-4,5-bisphosphate (PIP2) to phosphatidylinositol-3,4,5-trisphosphate (PIP3) ↗

Location: GAB1 signalosome

Stable identifier: R-HSA-177939

Type: transition

Compartments: plasma membrane, extracellular region, cytosol



The kinase activity of PIK3 mediates the phosphorylation of PIP2 to form PIP3

Preceded by: PI3K binds to EGF:EGFR:GRB2:GAB1

Followed by: GAB1 binds phosphatidylinositol-3,4,5-trisphosphate

Literature references

Falasca, M., Rodrigues, GA., Schlessinger, J., Ong, SH., Zhang, Z. (2000). A novel positive feedback loop mediated by the docking protein Gab1 and phosphatidylinositol 3-kinase in epidermal growth factor receptor signaling. *Mol Cell Biol, 20*, 1448-59. ↗

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2006-10-10	Authored	Castagnoli, L.
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2011-08-25	Edited	Orlic-Milacic, M.

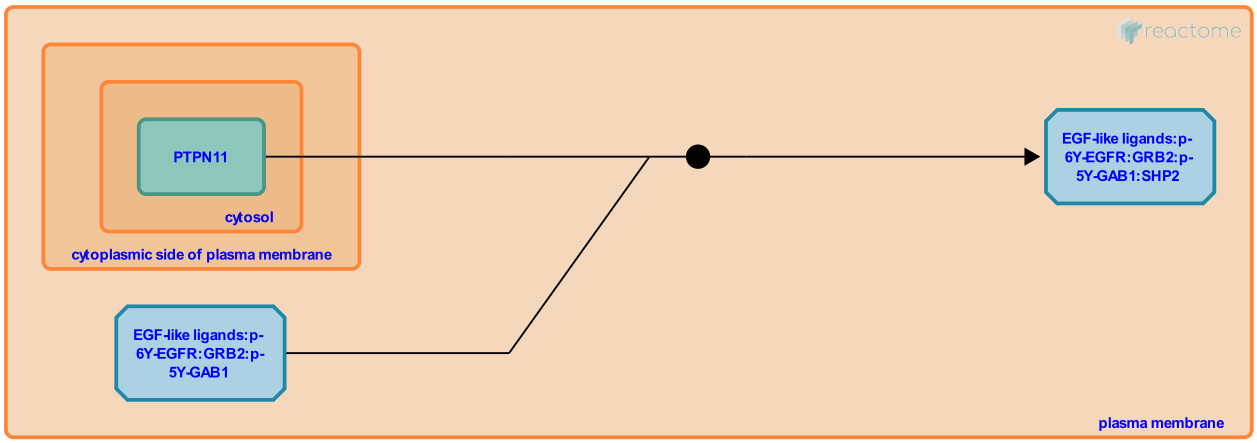
Activation of SHP2 through the binding to phospho-Gab1 ↗

Location: GAB1 signalosome

Stable identifier: R-HSA-177944

Type: binding

Compartments: plasma membrane, cytosol



The SH2 domains repress phosphatase activity of SHP2. Binding of these domains to phosphotyrosine-containing proteins relieves this autoinhibition, possibly by inducing a conformational change in the enzyme.

Preceded by: GAB1 phosphorylation by EGFR kinase

Followed by: SHP2 dephosphorylates Tyr 992 on EGFR, Dephosphorylation of Gab1 by SHP2, Dephosphorylation of PAG by SHP2

Literature references

Doupnik, CA., Mei, L., Wu, J., Cunnick, JM. (2001). Phosphotyrosines 627 and 659 of Gab1 constitute a bisphosphoryl tyrosine-based activation motif (BTAM) conferring binding and activation of SHP2. *J Biol Chem, 276*, 24380-7. ↗

Zhan, Y., Kapoor, GS., O'Rourke, DM., Johnson, GR. (2004). Distinct domains in the SHP-2 phosphatase differentially regulate epidermal growth factor receptor/NF-kappaB activation through Gab1 in glioblastoma cells. *Mol Cell Biol , 24*, 823-36. ↗

Editions

2006-10-10	Authored	Castagnoli, L.
2008-02-12	Reviewed	Heldin, CH.

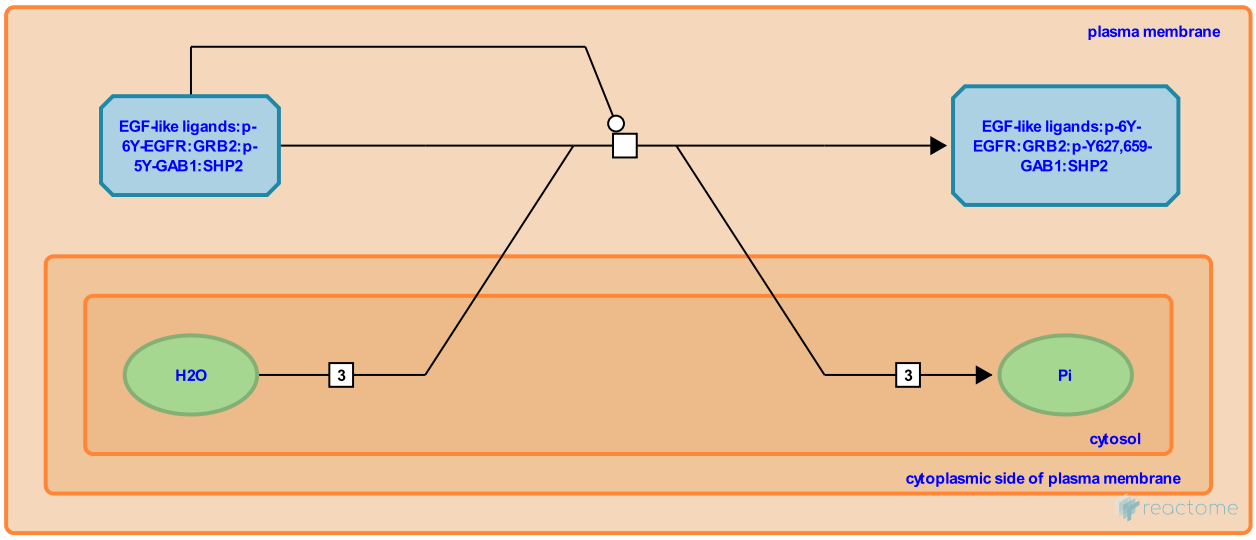
Dephosphorylation of Gab1 by SHP2 ↗

Location: GAB1 signalosome

Stable identifier: R-HSA-177924

Type: transition

Compartments: plasma membrane, cytosol



Phosphorylated GAB1 can bind PI3 kinase by its regulatory alpha subunit. SHP2 dephosphorylation of the tyrosine residues 447, 472 and 589 on GAB1 means PI3 kinase can no longer bind to the complex in the plasma membrane and cannot be activated.

Preceded by: Activation of SHP2 through the binding to phospho-Gab1

Literature references

Williams, TA., Gual, P., Giordano, S., Rocchi, S., Comoglio, PM., Van Obberghen, E. (2000). Sustained recruitment of phospholipase C-gamma to Gab1 is required for HGF-induced branching tubulogenesis. *Oncogene, 19*, 1509-18. ↗

Editions

2006-10-10	Authored	Castagnoli, L.
2008-02-12	Reviewed	Heldin, CH.

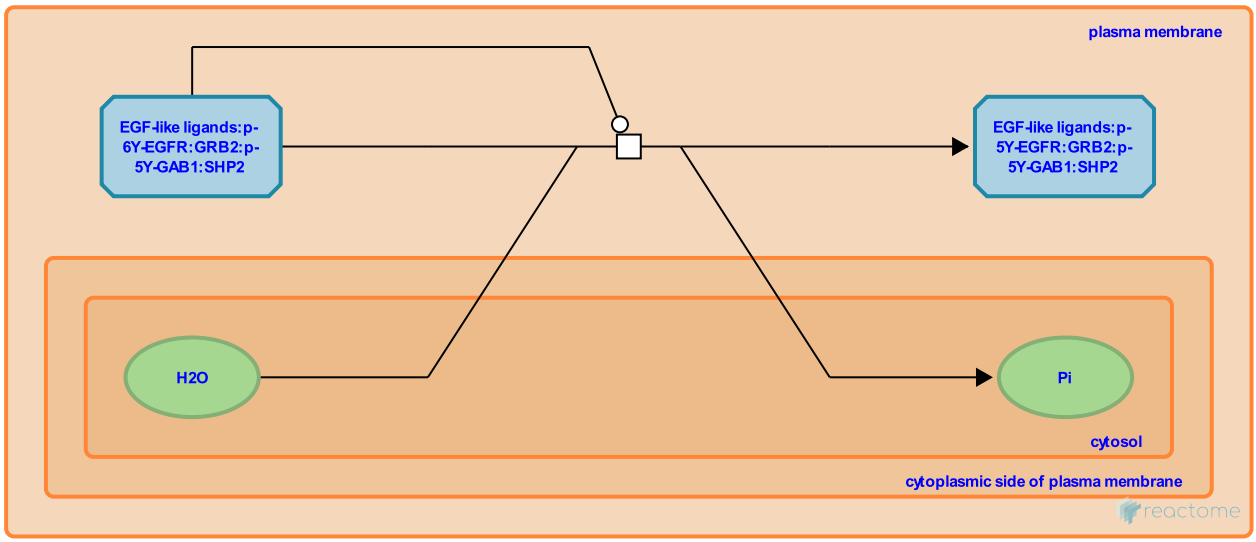
SHP2 dephosphorylates Tyr 992 on EGFR ↗

Location: GAB1 signalosome

Stable identifier: R-HSA-177935

Type: transition

Compartments: plasma membrane, cytosol



The tyrosine-protein phosphatase SHP2 is a positive effector of EGFR signalling. SHP2 inhibits the tyrosine-dependent translocation of RasGAP (catalyses Ras inactivation) to the plasma membrane, thereby keeping it away from Ras-GTP (its substrate). This inhibition is achieved by the dephosphorylation of a RasGAP binding site on the EGF receptor.

Preceded by: Activation of SHP2 through the binding to phospho-Gab1

Literature references

Agazie, YM., Hayman, MJ. (2003). Molecular mechanism for a role of SHP2 in epidermal growth factor receptor signaling. *Mol Cell Biol, 23*, 7875-86. ↗

Editions

2006-10-10	Authored	Castagnoli, L.
2008-02-12	Reviewed	Heldin, CH.

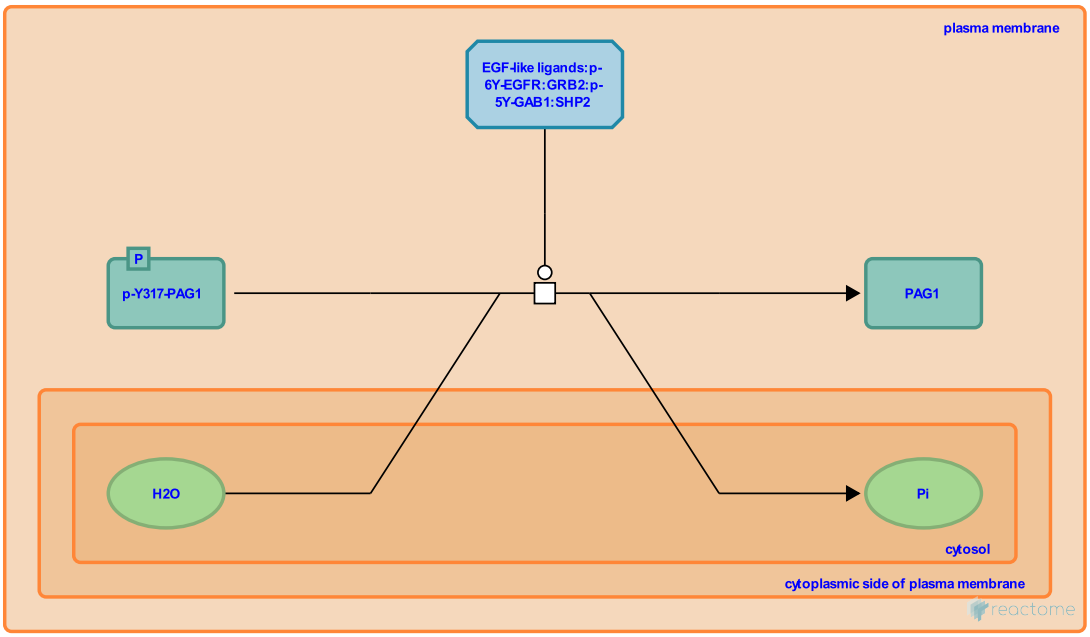
Dephosphorylation of PAG by SHP2

Location: GAB1 signalosome

Stable identifier: R-HSA-177926

Type: transition

Compartments: plasma membrane, cytosol



Dephosphorylation of CBP/PAG negatively regulates the recruitment of the Src inhibiting kinase, Csk. Src is not negatively regulated by phosphorylation by Csk.

Preceded by: Activation of SHP2 through the binding to phospho-Gab1

Followed by: Sustained activation of SRC kinase by SHP2

Literature references

Zhang, SQ., Kontaridis, MI., Wen, G., Araki, T., Philips, MR., Schraven, BL. et al. (2004). Shp2 regulates SRC family kinase activity and Ras/Erk activation by controlling Csk recruitment. *Mol. Cell, 13*, 341-55.

Editions

2006-10-10	Authored	Castagnoli, L.
2008-02-12	Reviewed	Heldin, CH.

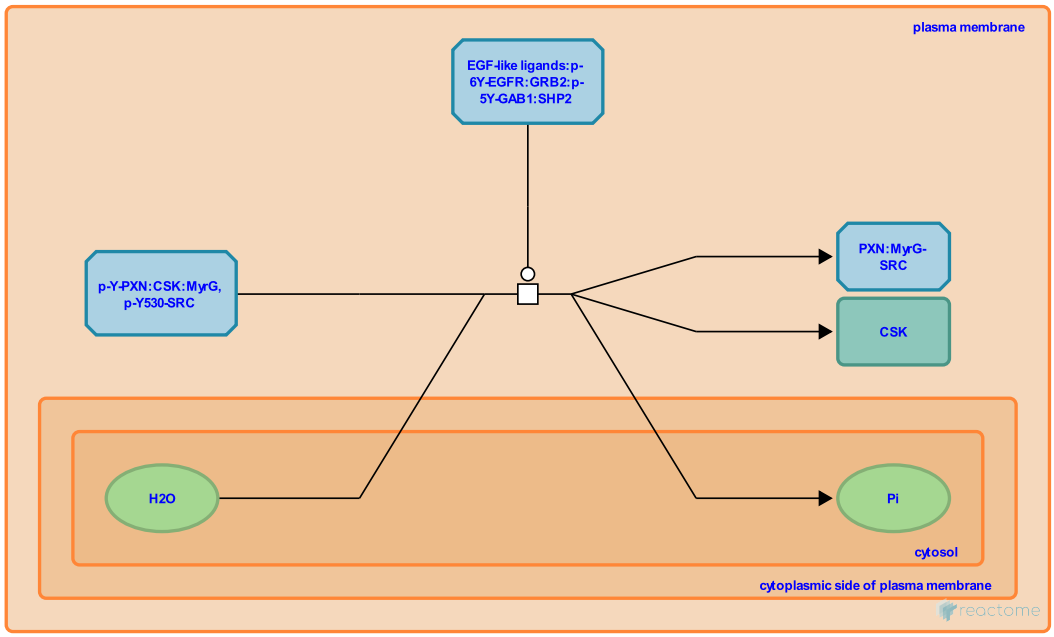
Sustained activation of SRC kinase by SHP2

Location: GAB1 signalosome

Stable identifier: R-HSA-177923

Type: transition

Compartments: plasma membrane, cytosol



SHP2 can dephosphorylate paxillin, which leads to CSK dissociation from the paxillin-SRC complex and SRC activation. SRC is an SHP2 effector in EGF-stimulated ERK activation and cell migration.

Preceded by: Dephosphorylation of PAG by SHP2

Literature references

Meng, S., Mei, L., Zhao, ZJ., Ren, Y., Wu, J., Jove, R. (2004). Roles of Gab1 and SHP2 in paxillin tyrosine dephosphorylation and Src activation in response to epidermal growth factor. *J Biol Chem, 279*, 8497-505.

Salles, JP., Raynal, P., Dance, M., Yart, A., Perret, B., Montagner, A. (2005). A novel role for Gab1 and SHP2 in epidermal growth factor-induced Ras activation. *J Biol Chem, 280*, 5350-60.

Editions

2006-10-10	Authored	Castagnoli, L.
2008-02-12	Reviewed	Heldin, CH.

Table of Contents