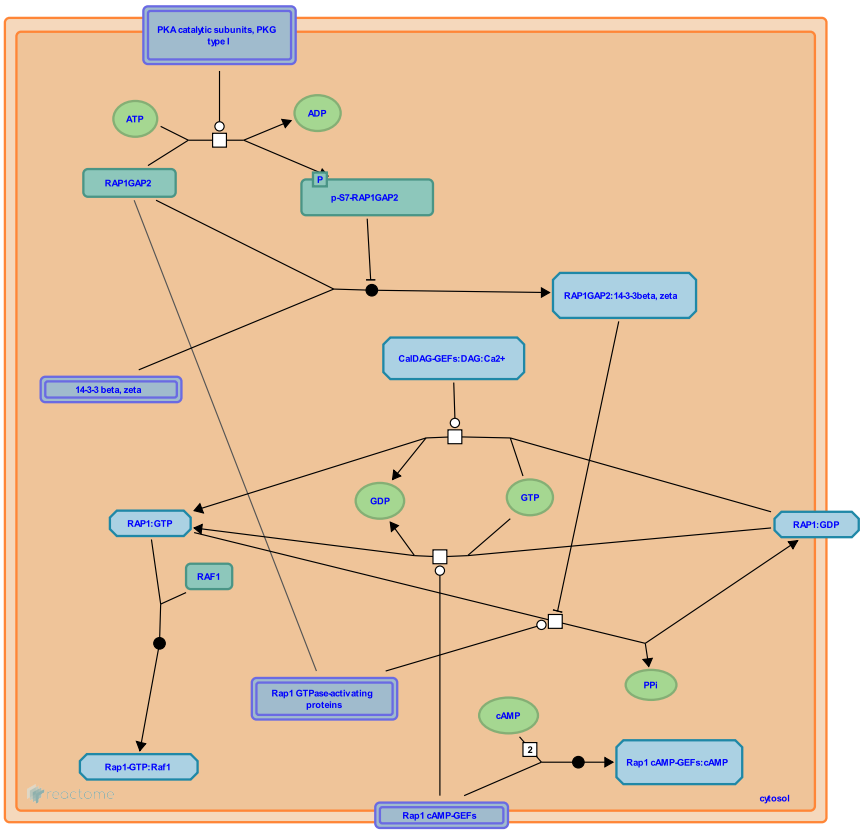
Rap1 signalling



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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. ↗

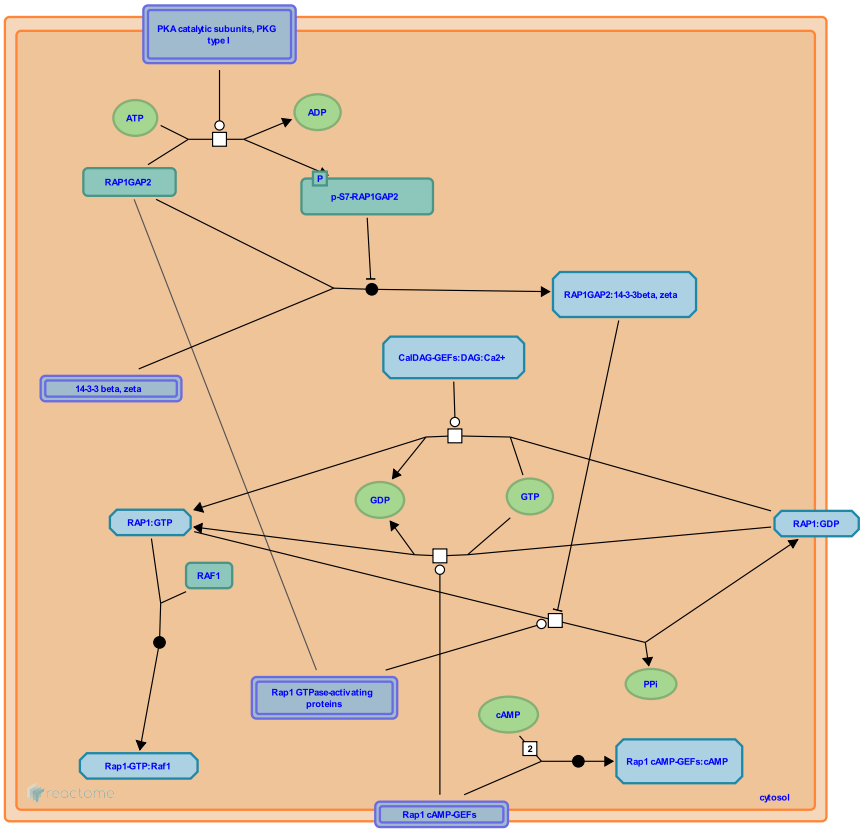
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

Rap1 signalling ↗

Stable identifier: R-HSA-392517

Compartments: plasma membrane



Rap1 (Ras-proximate-1) is a small G protein in the Ras superfamily. Like all G proteins, Rap1 is activated when bound GDP is exchanged for GTP. Rap1 is targeted to lipid membranes by the covalent attachment of lipid moieties to its carboxyl terminus. Movement of Rap1 from endosomal membranes to the plasma membrane upon activation has been reported in several cell types including Jurkat T cells and megakaryocytes. On activation, Rap1 undergoes conformational changes that facilitate recruitment of a variety of effectors, triggering it's participation in integrin signaling, ERK activation, and others.

Literature references

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

Editions

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

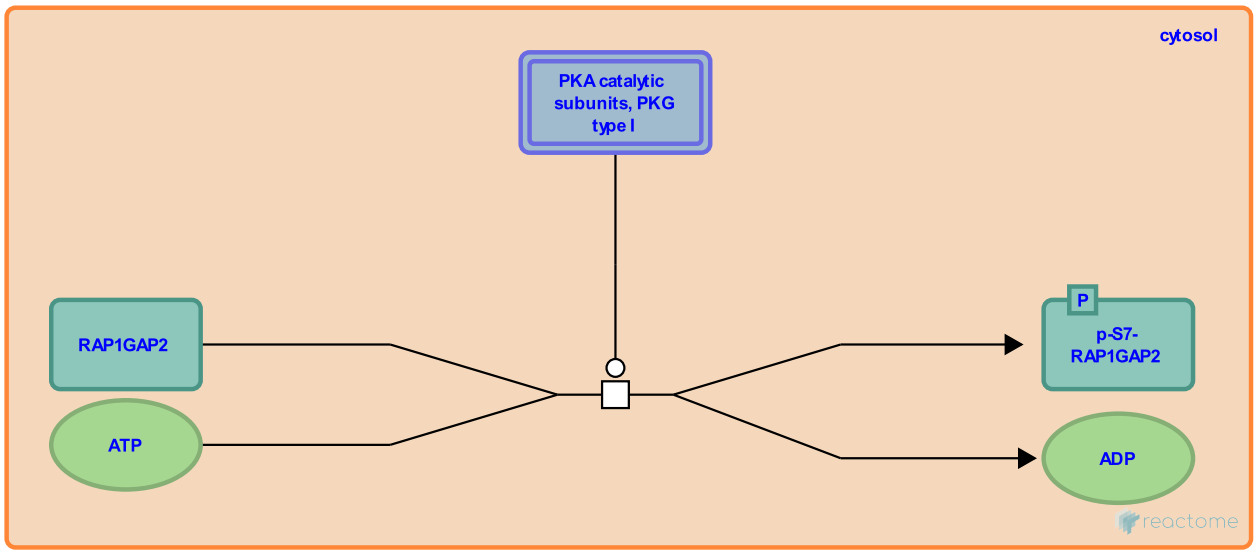
PKA/PKG phosphorylate Rap1GAP2 ↗

Location: Rap1 signalling

Stable identifier: R-HSA-913996

Type: transition

Compartments: cytosol



cGMP and cAMP dependent protein kinases (PKG and PKA respectively) phosphorylate the Rap1 GTPase activating RAP1GAP2 at serine 7 (Schultess et al. 2007). This reduces the binding of inhibitory 14-3-3 proteins to RAP1GAP2.

Followed by: 14-3-3 proteins beta and zeta bind and inhibit Rap1Gap2

Literature references

Schultess, J., Danielewski, O., Smolenski, AP. (2005). Rap1GAP2 is a new GTPase-activating protein of Rap1 expressed in human platelets. *Blood, 105*, 3185-92. ↗

Editions

2009-06-03	Authored	Akkerman, JW.
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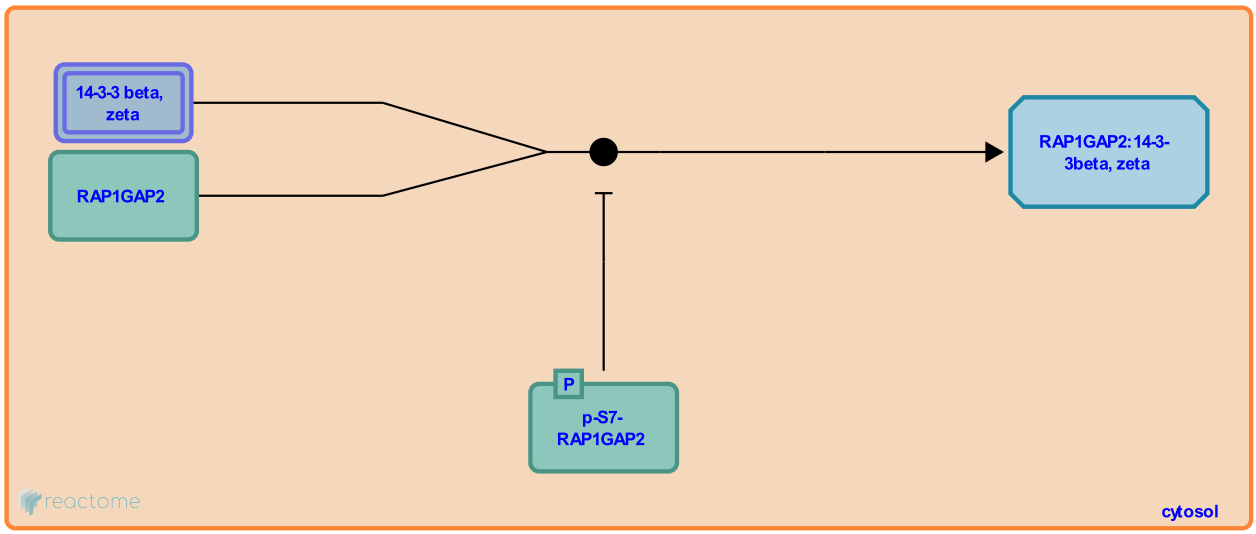
14-3-3 proteins beta and zeta bind and inhibit Rap1Gap2 ↗

Location: Rap1 signalling

Stable identifier: R-HSA-913993

Type: binding

Compartments: cytosol



RAP1GAP2 binds 14-3-3 proteins beta and zeta, inhibiting its GAP activity for Rap1. This effect is diminished by Ser-7 phosphorylation of RAP1GAP2 by cGMP- and cAMP-dependent protein kinases (PKG and PKA respectively), which inhibits the binding of 14-3-3 proteins beta and zeta to Rap1GAP2. 14-3-3 binding does not appear to alter the GTPase-activating function of Rap1GAP2 in vitro, but attenuates Rap1GAP2 mediated inhibition of cell adhesion (Hoffmeister et al. 2008).

Preceded by: PKA/PKG phosphorylate Rap1GAP2

Followed by: Rap1 signal termination by Rap1GAPs

Literature references

Neumüller, O., Riha, P., Schultess, J., Danielewski, O., Smolenski, AP., Hoffmeister, M. (2008). Cyclic nucleotide-dependent protein kinases inhibit binding of 14-3-3 to the GTPase-activating protein Rap1GAP2 in platelets. *J Biol Chem, 283*, 2297-306. ↗

Editions

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

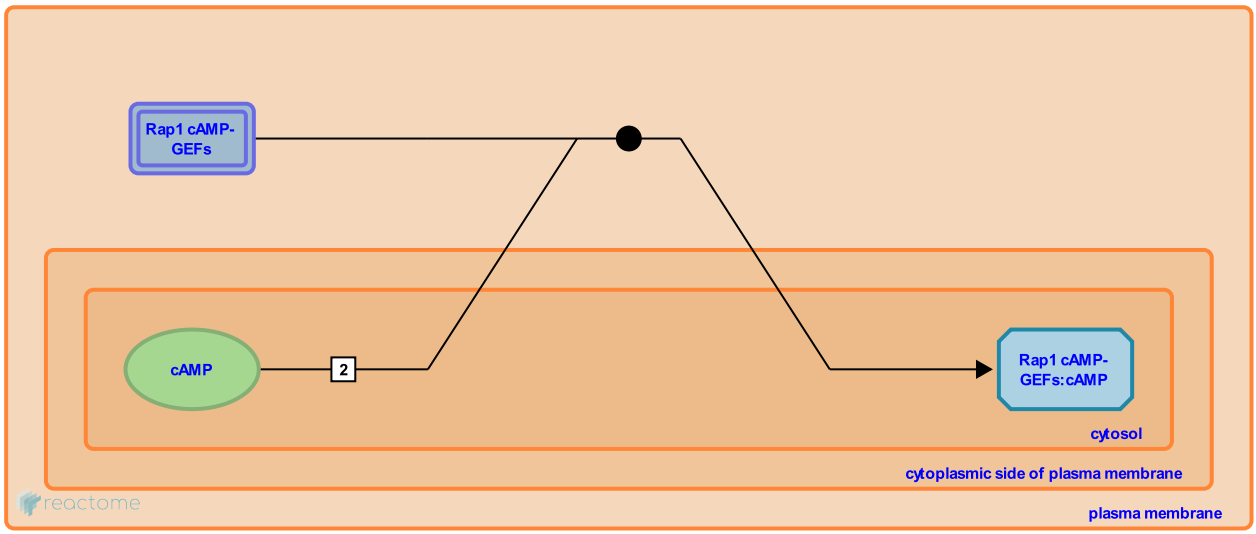
Activation of EPACs by cAMP ↗

Location: Rap1 signalling

Stable identifier: R-HSA-392834

Type: binding

Compartments: plasma membrane, cytosol



EPACs (exchange proteins directly activated by cAMP) are Rap1 GEFs that are activated by direct binding of cAMP (cyclic adenosine monophosphate). cAMP-GEFI (EPAC1) is widely expressed, while cAMP-GEFII (EPAC2) is enriched in brain and adrenal tissue. Both are selective for Rap1. A role of EPACs has been proposed for Rap1-dependent cell adhesion to laminin in both epithelial and red blood cells, and in the regulation of vascular endothelial barrier function.

Followed by: Activation of Rap1 by membrane-associated GEFs

Literature references

Mochizuki, N., Graybiel, AM., Housman, DE., Canales, JJ., Matsuda, M., Blumenstiel, JP. et al. (1998). A Rap guanine nucleotide exchange factor enriched highly in the basal ganglia. *Proc Natl Acad Sci U S A, 95*, 13278-83. ↗

Editions

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

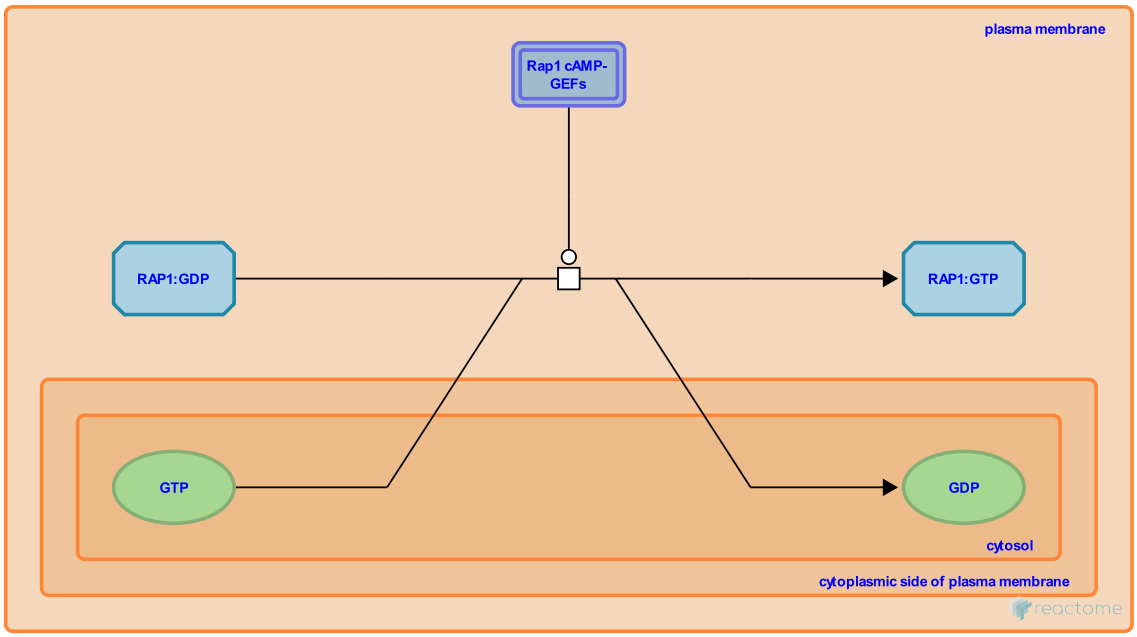
Activation of Rap1 by membrane-associated GEFs ↗

Location: Rap1 signalling

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.

Preceded by: Activation of EPACs by cAMP

Followed by: Rap1 sequesters Raf1 to inhibit ERK cascade, Rap1 signal termination by Rap1GAPs

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.

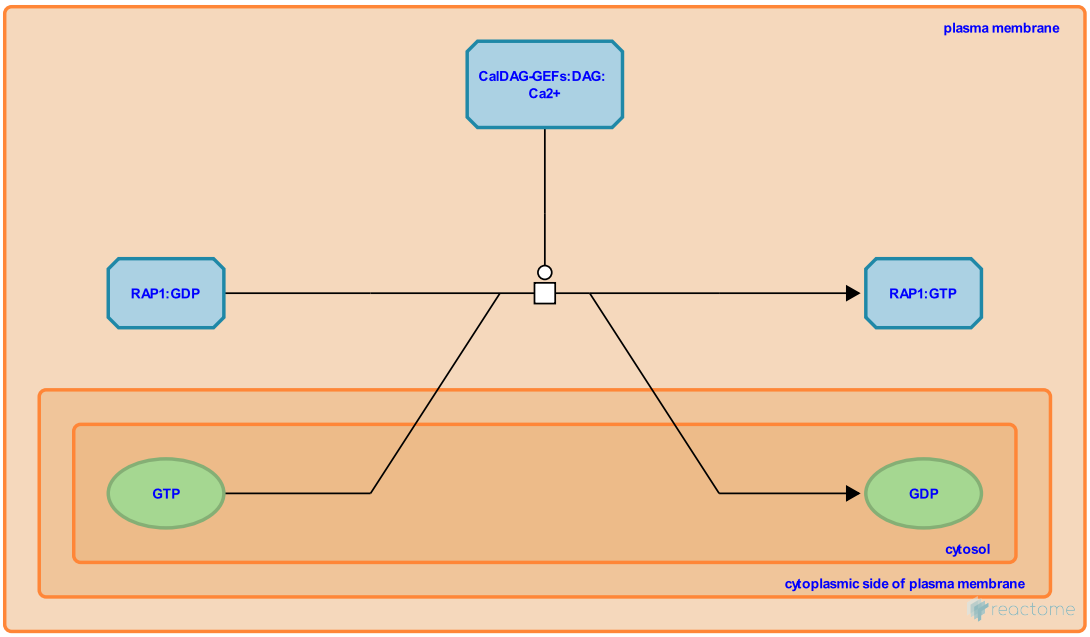
Activation of Rap1 by cytosolic GEFs ↗

Location: Rap1 signalling

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: Rap1 sequesters Raf1 to inhibit ERK cascade, Rap1 signal termination by Rap1GAPs

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.

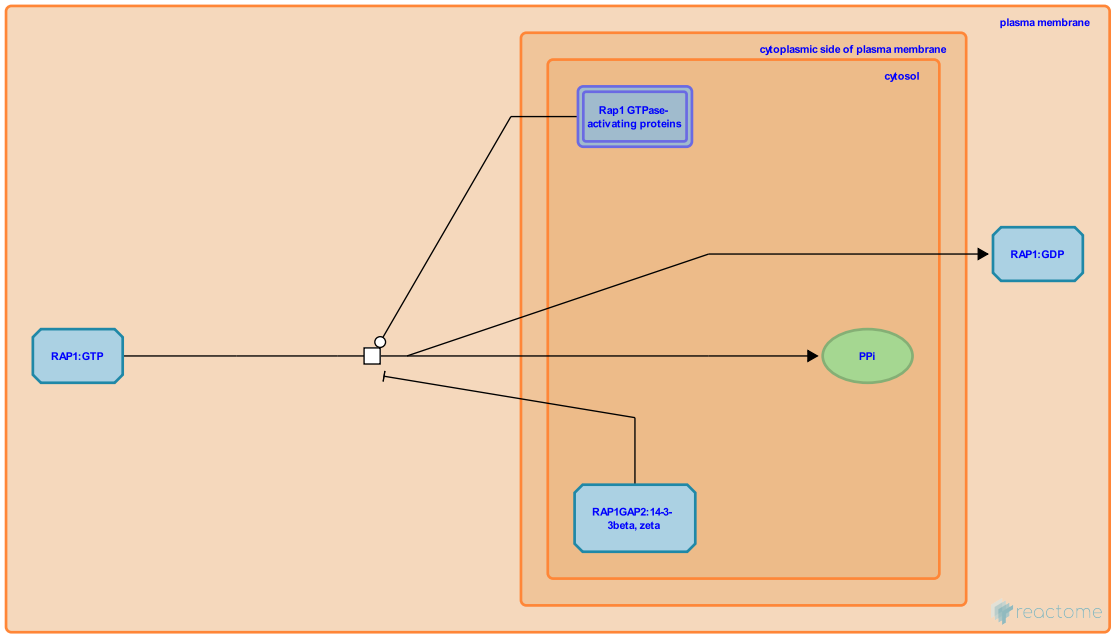
Rap1 signal termination by Rap1GAPs ↗

Location: Rap1 signalling

Stable identifier: R-HSA-392513

Type: transition

Compartments: plasma membrane, cytosol



Rap1 signalling is terminated by the hydrolysis of bound GTP to GDP. The intrinsic GTPase activity of Rap1 is greatly enhanced by GTP-ase activating proteins (GAPs).

Preceded by: Activation of Rap1 by membrane-associated GEFs, Activation of Rap1 by cytosolic GEFs, 14-3-3 proteins beta and zeta bind and inhibit Rap1Gap2

Literature references

McCormick, F., Polakis, PG., Evans, T., Rubinfeld, B. (1991). Purification of a plasma membrane-associated GTPase-activating protein specific for rap1/Krev-1 from HL60 cells. *Proc Natl Acad Sci U S A, 88*, 239-43. ↗

Tsukamoto, N., Kurachi, H., Kubota, H., Wada, Y., Hattori, M., Minato, N. et al. (1997). Human SPA-1 gene product selectively expressed in lymphoid tissues is a specific GTPase-activating protein for Rap1 and Rap2. Segregate expression profiles from a rap1GAP gene product. *J Biol Chem, 272*, 28081-8. ↗

Schultess, J., Danielewski, O., Smolenski, AP. (2005). Rap1GAP2 is a new GTPase-activating protein of Rap1 expressed in human platelets. *Blood, 105*, 3185-92. ↗

Editions

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

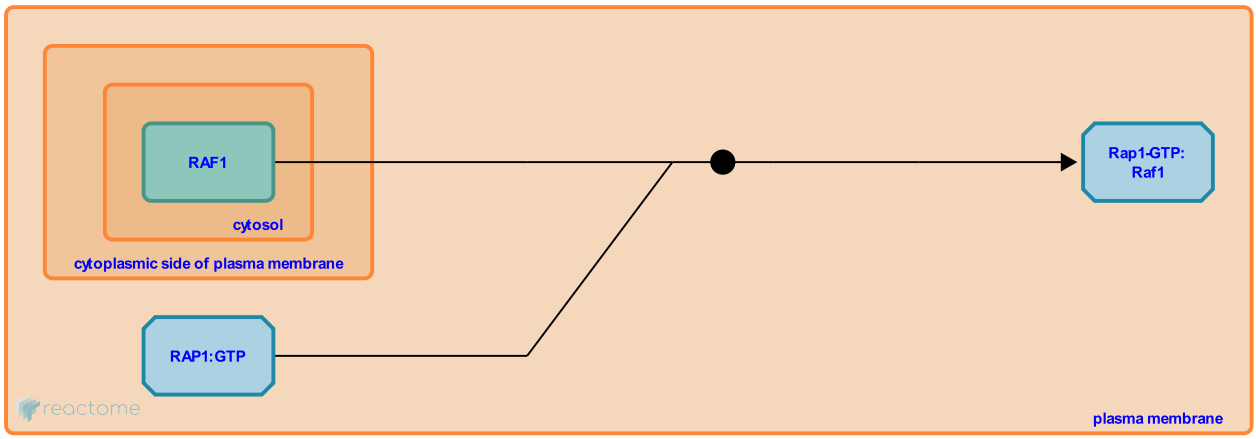
Rap1 sequesters Raf1 to inhibit ERK cascade ↗

Location: Rap1 signalling

Stable identifier: R-HSA-392835

Type: binding

Compartments: plasma membrane, cytosol



Active Rap1 binds but does not activate Raf-1, preventing Raf-1 from participating in the Ras/ERK pathway.

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

Literature references

McCormick, F., Albert, I., Cook, SJ., Rubinfeld, B. (1993). RapV12 antagonizes Ras-dependent activation of ERK1 and ERK2 by LPA and EGF in Rat-1 fibroblasts. *EMBO J, 12*, 3475-85. ↗

Kotani, G., Hu, CD., Yokoyama, S., Shirouzu, M., Kariya, K., Kataoka, T. (1997). Coassociation of Rap1A and Ha-Ras with Raf-1 N-terminal region interferes with ras-dependent activation of Raf-1. *J Biol Chem, 272*, 11702-5. ↗

Editions

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

Table of Contents