

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

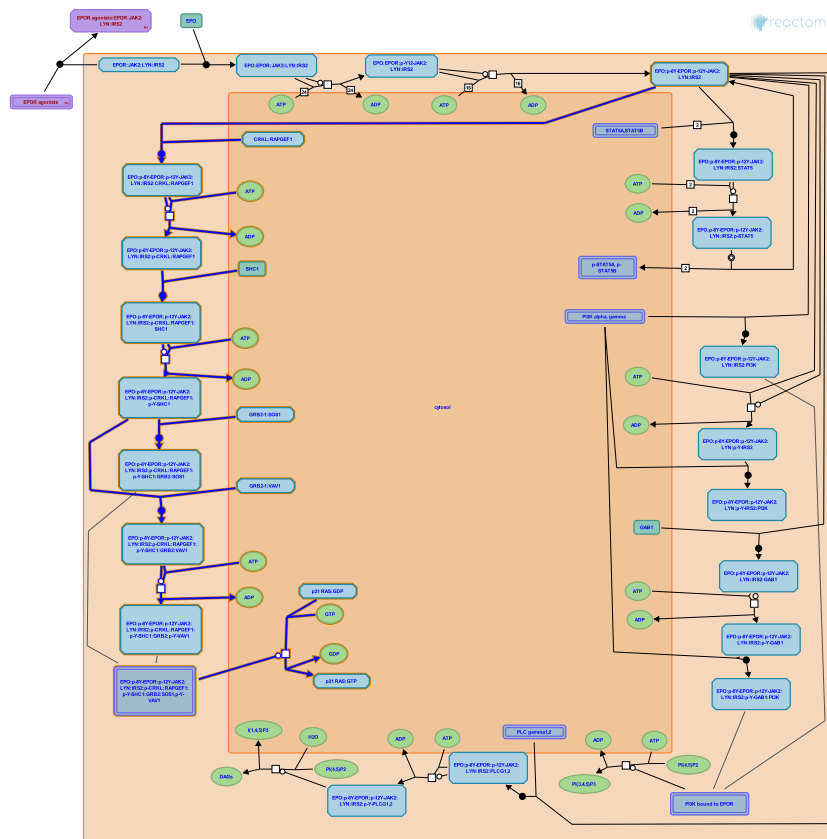
- Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics*, 18, 142. [↗](#)
- Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). 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. [↗](#)

Reactome database release: 88

This document contains 1 pathway and 8 reactions ([see Table of Contents](#))

Erythropoietin activates RAS [↗](#)

Stable identifier: R-HSA-9027284



The RAS guanine nucleotide exchange factors SOS1 and VAV1 bind indirectly to the phosphorylated EPOR via CRKL, SHC1, and GRB2 (Miura et al. 1994, Hanazono et al. 1996, Odai et al. 1997, Arai et al. 2001, reviewed in Kuhrt et al. 2015). The phosphorylated cytoplasmic domain of EPOR binds CRKL, which is then phosphorylated (Arai et al. 2001). Phosphorylated CRKL binds SHC1, which is then phosphorylated and binds either GRB2:SOS1 (Barber et al. 1997) or GRB2:VAV1 (Hanazono et al. 1996). SOS1 and phosphorylated VAV1 catalyze the exchange of GDP for GTP bound to RAS, that is, RAS:GDP is converted to RAS:GTP.

Literature references

Corless, CN., Xia, K., Roberts, TM., D'Andrea, AD., Barber, DL. (1997). Erythropoietin activates Raf1 by an Shc-independent pathway in CTLL-EPO-R cells. *Blood*, 89, 55-64. [↗](#)

Wojchowski, DM., Kuhrt, D. (2015). Emerging EPO and EPO receptor regulators and signal transducers. *Blood*, 125, 3536-41. [↗](#)

Yazaki, Y., Hanazono, Y., Odai, H., Hirai, H., Sasaki, K., Iwamatsu, A. (1996). Proto-oncogene products Vav and c-Cbl are involved in the signal transduction through Grb2/Ash in hematopoietic cells. *Acta Haematol.*, 95, 236-42. [↗](#)

Arai, A., Miura, O., Nosaka, Y., Kanda, E., Miyasaka, N. (2001). CrkL is recruited through its SH2 domain to the erythropoietin receptor and plays a role in Lyn-mediated receptor signaling. *J. Biol. Chem.*, 276, 33282-90. [↗](#)

Yazaki, Y., Hanazono, Y., Odai, H., Iwamatsu, A., Hirai, H., Sasaki, K. (1997). The signal transduction through Grb2/Ash in hematopoietic cells. *Leukemia*, 11, 405-7. [↗](#)

Editions

2017-10-29	Authored, Edited	May, B.
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EPO:p-EPOR:p-JAK2:LYN:IRS2 binds CRKL:RAPGEF1 ↗

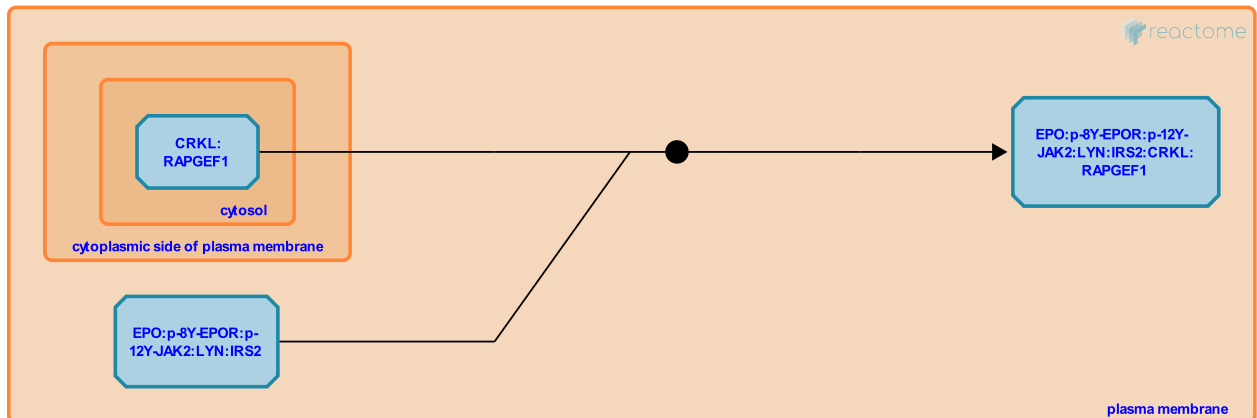
Location: Erythropoietin activates RAS

Stable identifier: R-HSA-9024723

Type: binding

Compartments: plasma membrane

Inferred from: Epo:p-8Y-Epor:p-12Y-Jak2:Lyn:Irs2 binds Crkl:Rapgef1 (Mus musculus)



CRKL, in a constitutive complex with RAPGEF1 (C3G, a nucleotide exchange factor for RAP1), binds the cytoplasmic domain of EPOR in the region of phosphotyrosine-460 (Arai et al. 2001).

Followed by: LYN phosphorylates CRKL in EPO:p-8Y-EPOR:p-12Y-JAK2:LYN:IRS2:CRKL:RAPGEF1

Literature references

Yamamoto, K., Arai, A., Miura, O., Nosaka, Y., Kanda, E., Miyasaka, N. (2001). Rap1 is activated by erythropoietin or interleukin-3 and is involved in regulation of beta1 integrin-mediated hematopoietic cell adhesion. *J. Biol. Chem.*, 276, 10453-62. ↗

Arai, A., Miura, O., Nosaka, Y., Kanda, E., Miyasaka, N. (2001). Crkl is recruited through its SH2 domain to the erythropoietin receptor and plays a role in Lyn-mediated receptor signaling. *J. Biol. Chem.*, 276, 33282-90. ↗

Editions

2017-10-01	Authored, Edited	May, B.
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LYN phosphorylates CRKL in EPO:p-8Y-EPOR:p-12Y-JAK2:LYN:IRS2:CRKL:RAPGEF1



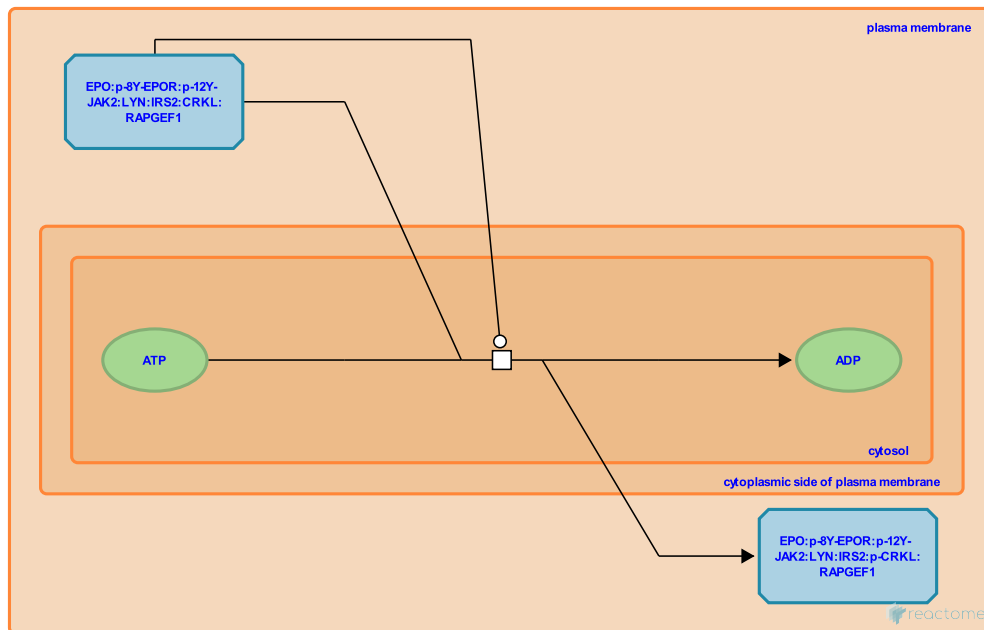
Location: Erythropoietin activates RAS

Stable identifier: R-HSA-9024726

Type: transition

Compartments: cytosol

Inferred from: Lyn phosphorylates Crkl in Epo:p-8Y-Epor:p-12Y-Jak2:Lyn:Irs2:Crkl:Rapgef1 (Mus musculus)



LYN, in a complex with EPOR, phosphorylates CRKL bound to RAPGEF1 (Arai et al. 2001).

Preceded by: EPO:p-EPOR:p-JAK2:LYN:IRS2 binds CRKL:RAPGEF1

Followed by: EPO:p-8Y-EPOR:p-12Y-JAK2:LYN:IRS2:p-CRKL:RAPGEF1 binds SHC1

Literature references

Arai, A., Miura, O., Nosaka, Y., Kanda, E., Miyasaka, N. (2001). CrkL is recruited through its SH2 domain to the erythropoietin receptor and plays a role in Lyn-mediated receptor signaling. *J. Biol. Chem.*, 276, 33282-90. [↗](#)

Editions

2017-10-09	Authored, Edited	May, B.
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EPO:p-8Y-EPOR:p-12Y-JAK2:LYN:IRS2:p-CRKL:RAPGEF1 binds SHC1 ↗

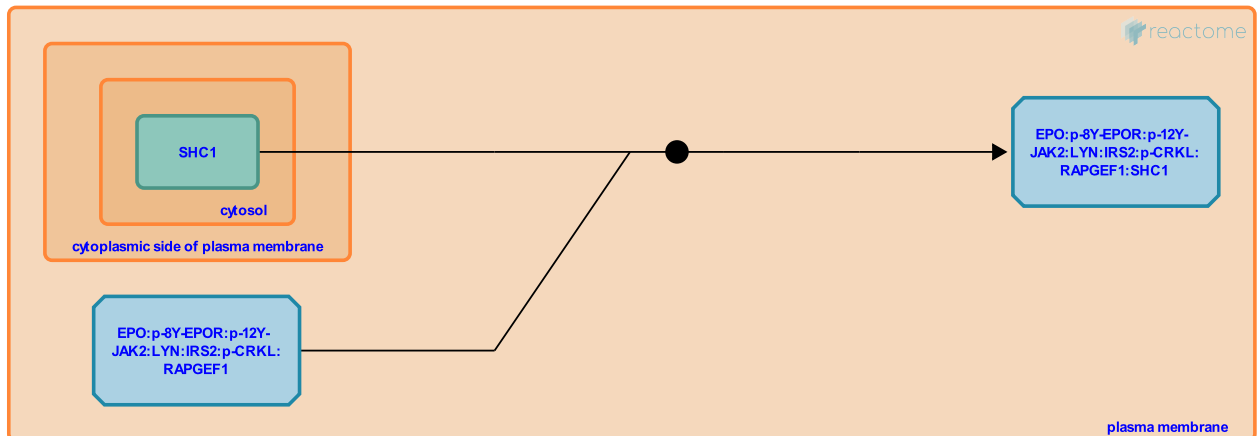
Location: Erythropoietin activates RAS

Stable identifier: R-HSA-9027274

Type: binding

Compartments: plasma membrane

Inferred from: Epo:p-8Y-Epor:p-12Y-Jak2:Lyn:Irs2:p-Crkl:Rapgef1 binds Shc1 (Mus musculus)



After stimulation by EPO, CRKL associates with EPOR, is phosphorylated, and binds SHC1 (inferred from mouse homologs).

Preceded by: LYN phosphorylates CRKL in EPO:p-8Y-EPOR:p-12Y-JAK2:LYN:IRS2:CRKL:RAPGEF1

Followed by: JAK2 phosphorylates SHC1 in EPO:p-8Y-EPOR:p-12Y-JAK2:LYN:p-CRKL:RAPGEF1:SHC1

Editions

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JAK2 phosphorylates SHC1 in EPO:p-8Y-EPOR:p-12Y-JAK2:LYN:p-CRKL:RABGEF1:SHC1 ↗

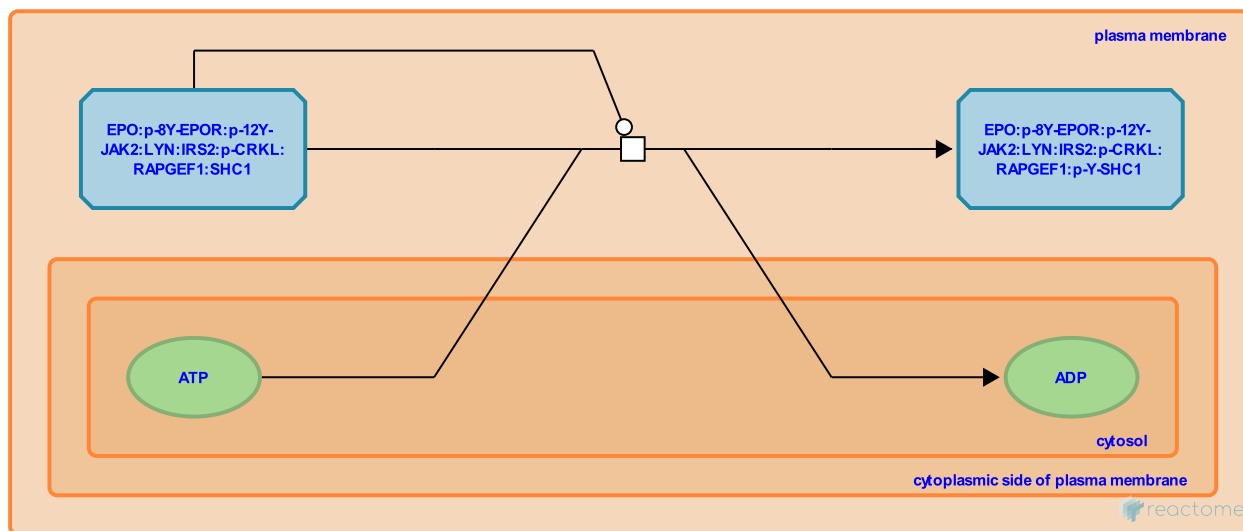
Location: Erythropoietin activates RAS

Stable identifier: R-HSA-9029155

Type: transition

Compartments: plasma membrane

Inferred from: Jak2 phosphorylates Shc1 in Epo:p-8Y-Epor:p-12Y-Jak2:Lyn:Irs2:p-Crkl:Rapgef:Shc1 (Mus musculus)



Phosphorylated JAK2 associated with the EPOR complex phosphorylates SHC1 (Damen et al. 1993, Verma et al. 2014) bound to CRKL in the EPOR complex. The phosphorylated SHC1 serves as a scaffold to bind downstream effectors including GRB2:VAV1 and GRB2:SOS1.

Preceded by: EPO:p-8Y-EPOR:p-12Y-JAK2:LYN:IRS2:p-CRKL:RAPGEF1 binds SHC1

Followed by: EPO:phospho-EPOR:phospho-JAK2:LYN:IRS2:phospho-CRKL:RAPGEF1:phospho-SHC1 binds GRB2:VAV1, EPO:phospho-EPOR:phospho-JAK2:LYN:IRS2:phospho-CRKL:RAPGEF1:phospho-SHC1 binds GRB2:SOS1

Literature references

- Cutler, RL., Liu, L., Krystal, G., Damen, JE. (1993). Erythropoietin stimulates the tyrosine phosphorylation of Shc and its association with Grb2 and a 145-Kd tyrosine phosphorylated protein. *Blood*, 82, 2296-303. ↗
- Stokes, MP., Verma, R., Schatz, PJ., Leu, K., Wojchowski, DM., Young, PR. et al. (2014). RHEX, a novel regulator of human erythroid progenitor cell expansion and erythroblast development. *J. Exp. Med.*, 211, 1715-22. ↗

Editions

2017-11-11	Authored, Edited	May, B.
2018-08-14	Reviewed	McGraw, KL.

EPO:phospho-EPOR:phospho-JAK2:LYN:IRS2:phospho-CRKL:RAPGEF1:phospho-SHC1 binds GRB2:SOS1 ↗

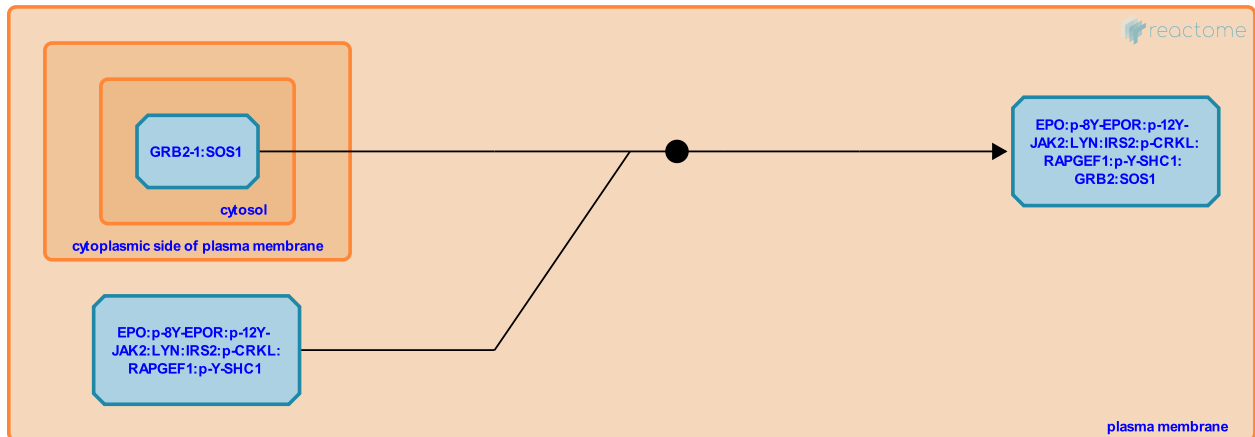
Location: [Erythropoietin activates RAS](#)

Stable identifier: R-HSA-9029149

Type: binding

Compartments: plasma membrane

Inferred from: [Epo:p-8Y-Epor:p-12Y-Jak2:Lyn:Irs2:p-Crkl:Rapgef1:p-Y-Shc1 binds Grb2-1:Sos1 \(Mus musculus\)](#)



Phosphorylated SHC1 in the EPOR complex serves as a scaffold to bind GRB2 bound to SOS1 (Damen et al. 1993, Odai et al. 1997). GRB2 may be pre-associated with VAV1 or SOS1, which are guanine nucleotide exchange factors for RAS, or with CBL, an ubiquitin ligase (Odai et al. 1997).

Preceded by: [JAK2 phosphorylates SHC1 in EPO:p-8Y-EPOR:p-12Y-JAK2:LYN:p-CRKL:RAPGEF1:SHC1](#)

Followed by: [EPO:phospho-EPOR:phospho-JAK2:LYN:IRS2:phospho-CRKL:RAPGEF1:GRB2-1:SOS1,phospho-VAV1 mediates exchange of GTP for GDP bound to RAS](#)

Literature references

Cutler, RL., Liu, L., Krystal, G., Damen, JE. (1993). Erythropoietin stimulates the tyrosine phosphorylation of Shc and its association with Grb2 and a 145-Kd tyrosine phosphorylated protein. *Blood*, 82, 2296-303. ↗

Yazaki, Y., Hanazono, Y., Odai, H., Iwamatu, A., Hirai, H., Sasaki, K. (1997). The signal transduction through Grb2/Ash in hematopoietic cells. *Leukemia*, 11, 405-7. ↗

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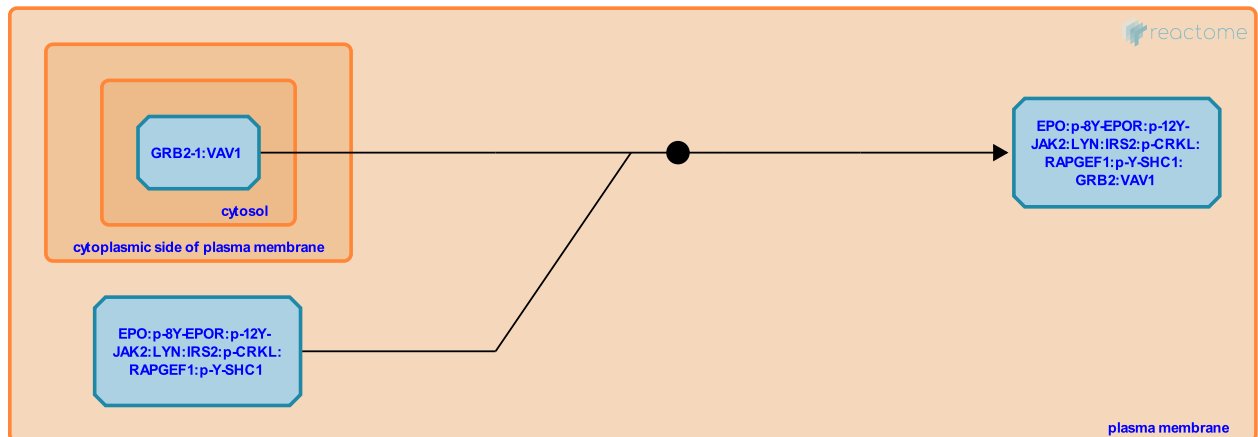
EPO:phospho-EPOR:phospho-JAK2:LYN:IRS2:phospho-CRKL:RAPGEF1:phospho-SHC1 binds GRB2:VAV1 ↗

Location: Erythropoietin activates RAS

Stable identifier: R-HSA-9029150

Type: binding

Compartments: plasma membrane



Phosphorylated SHC1 in a complex with the activated EPOR binds GRB2 bound to VAV1 (Hanazono et al. 1995, Hanazono et al. 1996, Odai et al. 1997). GRB2 exists in pre-assembled complexes with VAV1 (Hanazono et al. 1995), SOS1 (Odai et al. 1997), or CBL (Odai et al. 1997). VAV1 and SOS1 are guanine nucleotide exchange factors that activate the RAS signaling pathway.

Preceded by: JAK2 phosphorylates SHC1 in EPO:p-8Y-EPOR:p-12Y-JAK2:LYN:p-CRKL:RAPGEF1:SHC1

Followed by: JAK2 phosphorylates VAV1 in EPO:p-8Y-EPOR:p-12Y-JAK2:LYN:IRS2:p-Y-CRKL:RAPGEF1:p-Y-SHC1:GRB2:VAV1

Literature references

- Yazaki, Y., Mitani, K., Hanazono, Y., Odai, H., Hirai, H., Sasaki, K. et al. (1995). Tyrosine phosphorylation of the proto-oncogene product Vav and its association with the adapter Grb2/Ash in a human leukemia cell line UT-7. *Jpn. J. Cancer Res.*, 86, 336-41. ↗
- Yazaki, Y., Hanazono, Y., Odai, H., Hirai, H., Sasaki, K., Iwamatsu, A. (1996). Proto-oncogene products Vav and c-Cbl are involved in the signal transduction through Grb2/Ash in hematopoietic cells. *Acta Haematol.*, 95, 236-42. ↗
- Yazaki, Y., Hanazono, Y., Odai, H., Iwamatsu, A., Hirai, H., Sasaki, K. (1997). The signal transduction through Grb2/Ash in hematopoietic cells. *Leukemia*, 11, 405-7. ↗

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JAK2 phosphorylates VAV1 in EPO:p-8Y-EPOR:p-12Y-JAK2:LYN:IRS2:p-Y-CRKL:RASGEF1:p-Y-SHC1:GRB2:VAV1 ↗

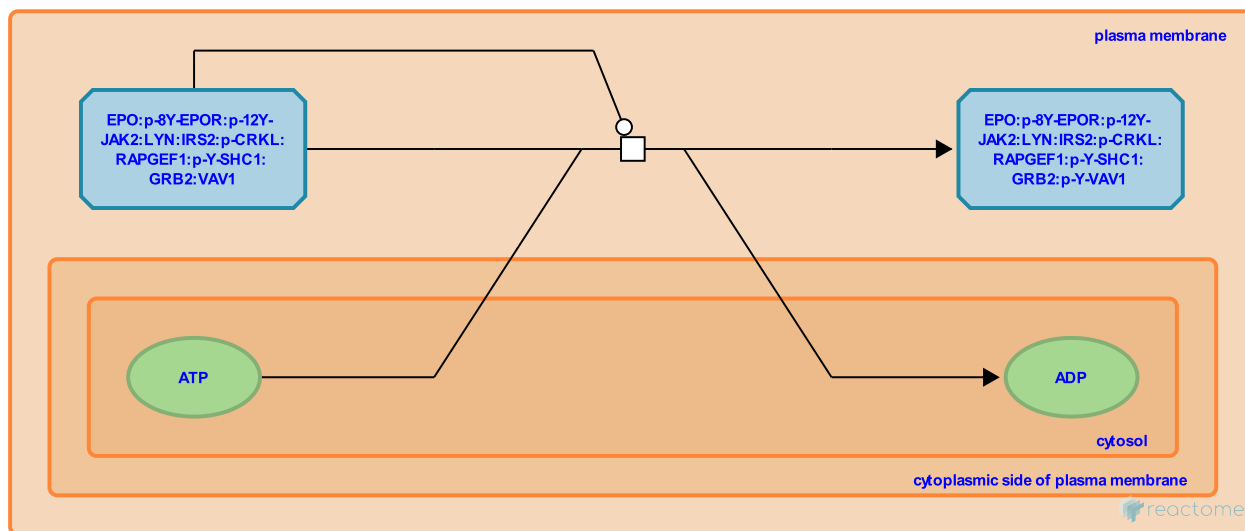
Location: Erythropoietin activates RAS

Stable identifier: R-HSA-9029151

Type: transition

Compartments: plasma membrane

Inferred from: Jak2 phosphorylates Vav1 in Epo:p-8Y-Epor:p-12Y-Jak2:Lyn:Irs2:p-Crkl:Rapgef1:p-Y-Shc1:Grb2-1:Vav1 (Mus musculus)



Phosphorylated JAK2 phosphorylates VAV1 bound to GRB2 in a large complex assembled on the phosphorylated EPOR (Odai et al. 1997, Shigematsu et al. 1997). Phosphorylation of VAV1 activates its guanine nucleotide exchange activity (inferred from the mouse homolog).

Preceded by: EPO:phospho-EPOR:phospho-JAK2:LYN:IRS2:phospho-CRKL:RAPGEF1:phospho-SHC1 binds GRB2:VAV1

Followed by: EPO:phospho-EPOR:phospho-JAK2:LYN:IRS2:phospho-CRKL:RAPGEF1:GRB2-1:SOS1,phospho-VAV1 mediates exchange of GTP for GDP bound to RAS

Literature references

- Yazaki, Y., Hanazono, Y., Odai, H., Iwamatu, A., Hirai, H., Sasaki, K. (1997). The signal transduction through Grb2/Ash in hematopoietic cells. *Leukemia*, 11, 405-7. ↗
- Niho, Y., Ohno, Y., Shigematsu, H., Iwasaki, H., Arima, F., Otsuka, T. (1997). Role of the vav proto-oncogene product (Vav) in erythropoietin-mediated cell proliferation and phosphatidylinositol 3-kinase activity. *J. Biol. Chem.*, 272, 14334-40. ↗

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EPO:phospho-EPOR:phospho-JAK2:LYN:IRS2:phospho-CRKL:RAPGEF1:GRB2-1:SOS1,phospho-VAV1 mediates exchange of GTP for GDP bound to RAS ↗

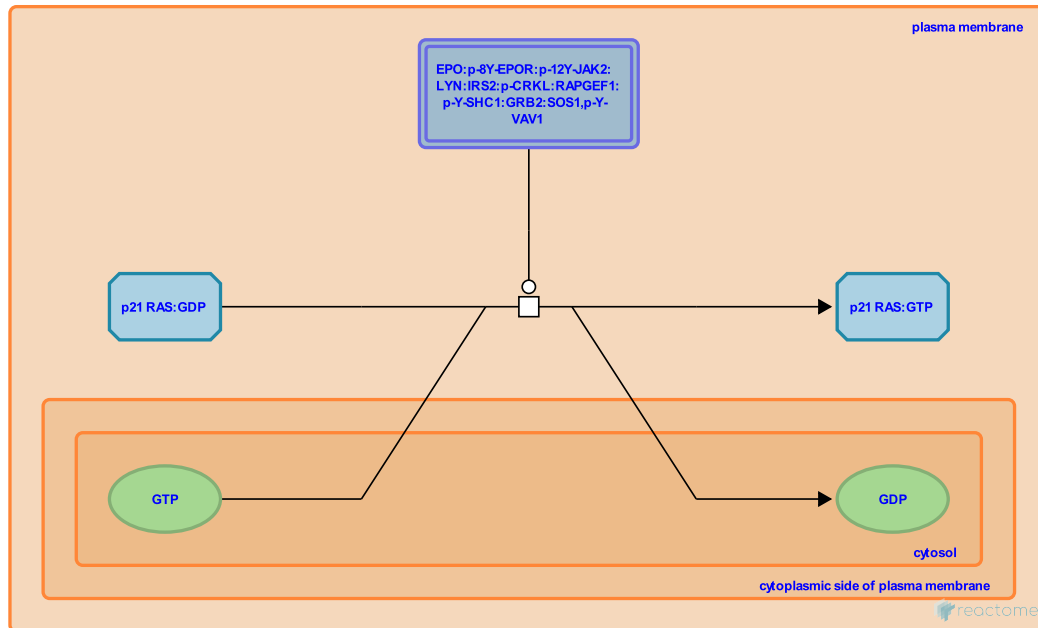
Location: Erythropoietin activates RAS

Stable identifier: R-HSA-9029158

Type: transition

Compartments: plasma membrane

Inferred from: Epo:p-8Y-Epor:p-12Y-Jak2:Lyn:Irs2:p-Y-Crkl:p-Y-Shc1:Grb2-1:Sos1,p-Y-Vav1 mediates exchange of GDP for GTP bound to Ras (Mus musculus)



SOS1 and phospho-VAV1 bound to GRB2 in a complex with the activated EPOR catalyze the exchange of GDP for GTP bound to RAS proteins, yielding RAS:GTP (Komatsu et al. 1992, Torti et al. 1992). RAS:GTP then activates RAF1 and ERK1 and ERK2. EPO is observed to activate HRAS (Komatsu et al. 1992, Torti et al. 1992), KRAS, and NRAS (inferred from mouse homologs). KRAS appears to be particularly important for erythropoiesis since deletion of KRAS causes anemia in mouse.

Preceded by: JAK2 phosphorylates VAV1 in EPO:p-8Y-EPOR:p-12Y-JAK2:LYN:IRS2:p-Y-CRKL:RASGEF1:p-Y-SHC1:GRB2:VAV1, EPO:phospho-EPOR:phospho-JAK2:LYN:IRS2:phospho-CRKL:RAPGEF1:phospho-SHC1 binds GRB2:SOS1

Literature references

Yamamoto, K., Marti, KB., Torti, M., Altschuler, D., Lapetina, EG. (1992). Erythropoietin induces p21ras activation and p120GAP tyrosine phosphorylation in human erythroleukemia cells. *J. Biol. Chem.*, 267, 8293-8. ↗

Yamamoto, K., Torti, M., Adamson, JW., Altschuler, D., Marzocchini, R., Komatsu, N. et al. (1992). Erythropoietin rapidly induces tyrosine phosphorylation in the human erythropoietin-dependent cell line, UT-7. *Blood*, 80, 53-9. ↗

Editions

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