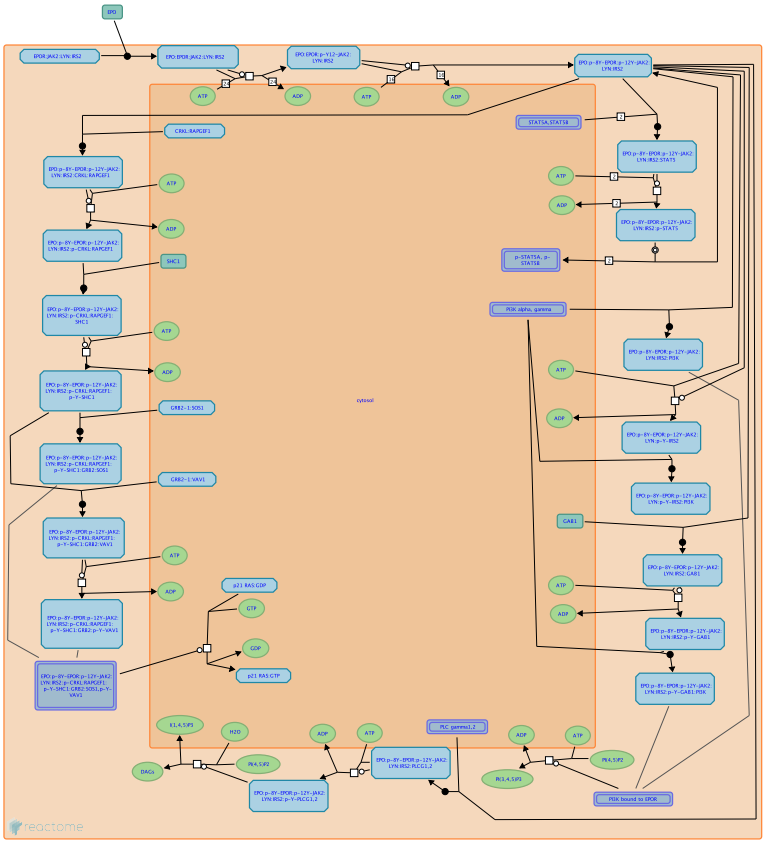
Signaling by Erythropoietin



May, B., McGraw, KL.

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

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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.

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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. ↗

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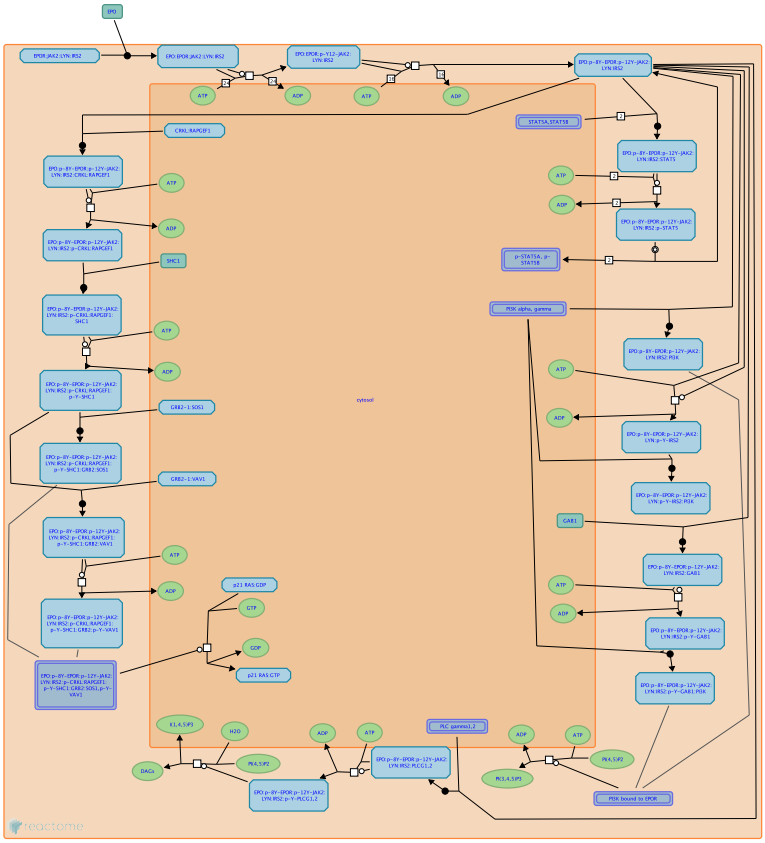
Signaling by Erythropoietin ↗

Stable identifier: R-HSA-9006335



Erythropoietin (EPO) is a cytokine that serves as the primary regulator of erythropoiesis, the differentiation of erythrocytes from stem cells in the liver of the fetus and the bone marrow of adult mammals (reviewed in Ingley 2012, Zhang et al. 2014, Kuhrt and Wojchowski 2015). EPO is produced in the kidneys in response to low oxygen tension and binds a receptor, EPOR, located on progenitor cells: burst forming unit-erythroid (BFU-e) cells and colony forming unit-erythroid (CFU-e) cells.

The erythropoietin receptor (EPOR) exists in lipid rafts (reviewed in McGraw and List 2017) as a dimer pre-associated with proteins involved in downstream signaling: the tyrosine kinase JAK2, the tyrosine kinase LYN, and the scaffold protein IRS2. Binding of EPO to the EPOR dimer causes a change in conformation (reviewed in Watowich et al. 2011, Corbett et al. 2016) that activates JAK2, which then transphosphorylates JAK2 and phosphorylates the cytoplasmic domain of EPOR. The phosphorylated EPOR serves directly or indirectly as a docking site for signaling molecules such as STAT5, phosphatidylinositol 4,5-bisphosphate 3-kinase (PI3K), phospholipase C gamma (PLCG1, PLCG2), and activators of RAS (SHC1, GRB2:SOS1, GRB2:VAV1).

EPO activates 4 major signaling pathways: STAT5-activated transcription, PI3K-AKT, RAS-RAF-ERK, and PLC-PKC. JAK2-STAT5 activates expression of BCL2L1 (Bcl-xL) and therefore appears to be important for anti-apoptosis. PI3K-AKT appears to be important for both anti-apoptosis and proliferation. The roles of other signaling pathways are controversial but both RAS-RAF-MEK-ERK and PLCgamma-PKC have mitogenic effects. Phosphatases such as SHP1 are also recruited and downregulate the EPO signal.

EPO also has effects outside of erythropoiesis. The EPOR is expressed in various tissues such as endothelium where it can act to stimulate growth and promote cell survival (Debeljak et al. 2014, Kimáková et al. 2017). EPO and EPOR in the neurovascular system act via Akt, Wnt1, mTOR, SIRT1, and FOXO proteins to prevent apoptotic cell injury (reviewed in Ostrowski and Heinrich 2018, Maiese 2016) and EPO may have

therapeutic value in the nervous system (Ma et al. 2016).

Literature references

Kimáková, P., Solár, P., Solárová, Z., Komel, R., Debeljak, N. (2017). Erythropoietin and Its Angiogenic Activity. *Int J Mol Sci, 18*.

Watowich, SS. (2011). The erythropoietin receptor: molecular structure and hematopoietic signaling pathways. *J. Investig. Med., 59*, 1067-72.

Ingley, E. (2012). Integrating novel signaling pathways involved in erythropoiesis. *IUBMB Life, 64*, 402-10.

Corbett, MS., Poger, D., Mark, AE. (2016). Revisiting the scissor-like mechanism of activation for the erythropoietin receptor. *FEBS Lett., 590*, 3083-8.

Debeljak, N., Solár, P., Sytkowski, AJ. (2014). Erythropoietin and cancer: the unintended consequences of anemia correction. *Front Immunol, 5*, 563.

Editions

2017-04-22	Authored, Edited	May, B.
2018-08-14	Reviewed	McGraw, KL.

EPO binds EPOR:JAK2:LYN:IRS2 ↗

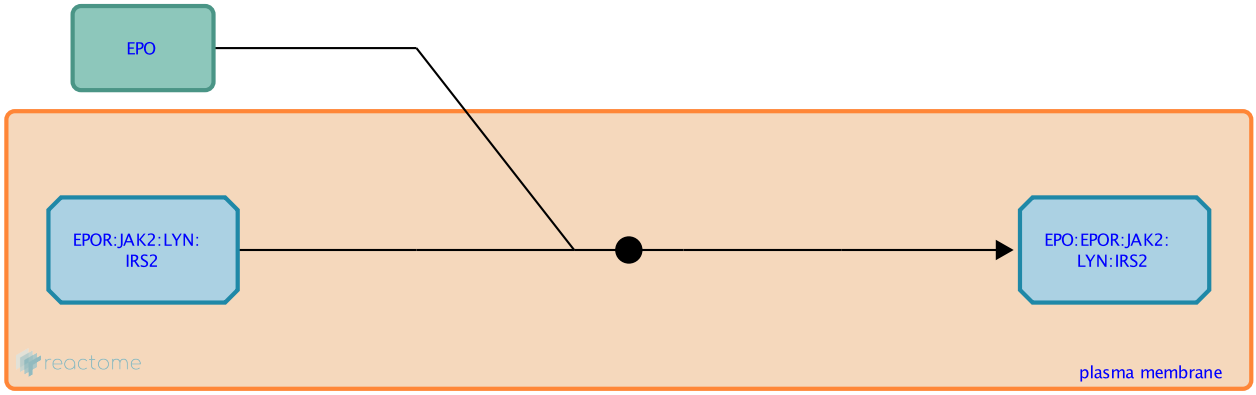
Location: Signaling by Erythropoietin

Stable identifier: R-HSA-9006325

Type: binding

Compartments: plasma membrane

Inferred from: Epo binds Epor:Jak2:Lyn:Irs2 (Mus musculus)



Extracellular Erythropoietin (EPO) binds the EPO receptor (EPOR) located in the plasma membrane of the target cell (Jones et al. 1990, Syed et al. 1998, Remy et al. 1999, and inferred from mouse homologs). EPOR is a dimer that appears to be preassociated with downstream signaling proteins JAK2 (inferred from mouse homologs) and LYN (Chin et al. 1998, and inferred from mouse homologs) and the scaffold protein IRS2 (Verdier et al. 1997). Binding of EPO to EPOR causes a change in the conformation of the dimer which activates JAK2 (Syed et al. 1998, Remy et al. 1999, Kubatzky et al. 2001).

Followed by: JAK2 transphosphorylates and is activated in response to Erythropoietin

Literature references

Jones, SS., D'Andrea, AD., Haines, LL., Wong, GG. (1990). Human erythropoietin receptor: cloning, expression, and biologic characterization. *Blood, 76*, 31-5. ↗

Remy, I., Wilson, IA., Michnick, SW. (1999). Erythropoietin receptor activation by a ligand-induced conformation change. *Science, 283*, 990-3. ↗

Syed, RS., Reid, SW., Li, C., Cheetham, JC., Aoki, KH., Liu, B. et al. (1998). Efficiency of signalling through cytokine receptors depends critically on receptor orientation. *Nature, 395*, 511-6. ↗

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Chin, H., Arai, A., Wakao, H., Kamiyama, R., Miyasaka, N., Miura, O. (1998). Lyn physically associates with the erythropoietin receptor and may play a role in activation of the Stat5 pathway. *Blood, 91*, 3734-45. ↗

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JAK2 transphosphorylates and is activated in response to Erythropoietin ↗

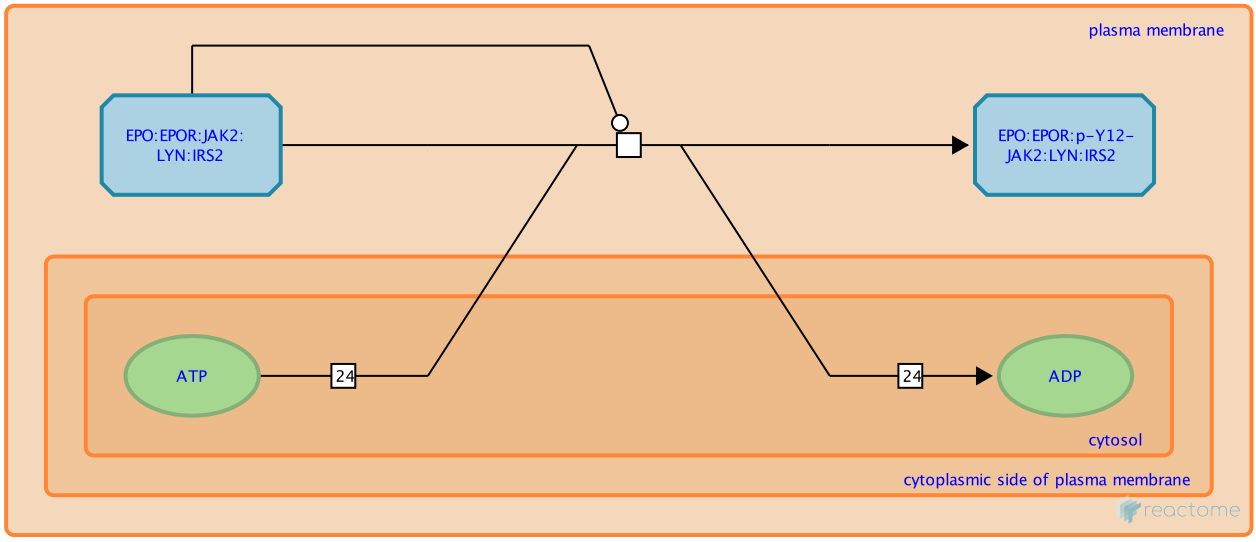
Location: Signaling by Erythropoietin

Stable identifier: R-HSA-9006332

Type: transition

Compartments: plasma membrane

Inferred from: Jak2 transphosphorylates and is activated in response to Erythropoietin (Mus musculus)



Upon binding EPO, the EPOR dimer changes conformation, resulting in activation of JAK2 associated with box 1 and box 2 of the cytoplasmic domain of each EPOR (inferred from mouse homologs). One JAK2 transphosphorylates 12 tyrosine residues of the other JAK2 thereby activating JAK2 to phosphorylate EPOR and other substrates (Arcasoy et al. 1999, Watowich et al. 1999, Erickson-Miller et al. 2000, and inferred from mouse homologs).

Preceded by: EPO binds EPOR:JAK2:LYN:IRS2

Followed by: Phospho-JAK2 phosphorylates EPOR

Literature references

Arcasoy, MO., Harris, KW., Forget, BG. (1999). A human erythropoietin receptor gene mutant causing familial erythrocytosis is associated with deregulation of the rates of Jak2 and Stat5 inactivation. *Exp. Hematol., 27*, 63-74. ↗

Erickson-Miller, CL., Pelus, LM., Lord, KA. (2000). Signaling induced by erythropoietin and stem cell factor in UT-7/Epo cells: transient versus sustained proliferation. *Stem Cells, 18*, 366-73. ↗

Watowich, SS., Xie, X., Klingmüller, U., Kere, J., Lindlof, M., Berglund, S. et al. (1999). Erythropoietin receptor mutations associated with familial erythrocytosis cause hypersensitivity to erythropoietin in the heterozygous state. *Blood, 94*, 2530-2. ↗

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Phospho-JAK2 phosphorylates EPOR ↗

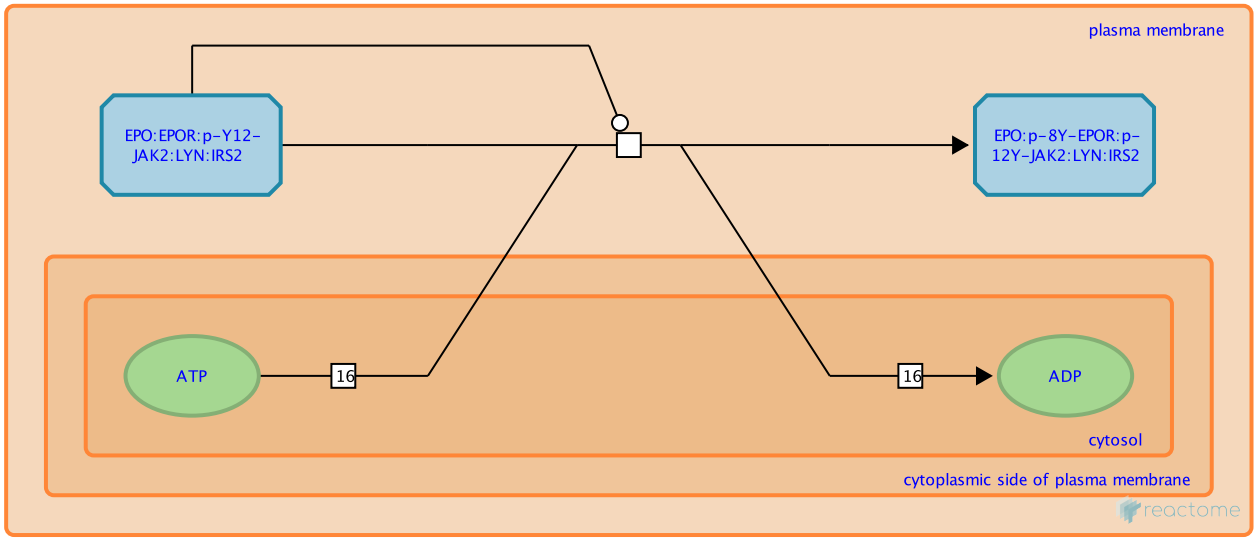
Location: Signaling by Erythropoietin

Stable identifier: R-HSA-9006323

Type: transition

Compartments: plasma membrane

Inferred from: Phospho-Jak2 phosphorylates Epor (Mus musculus)



Phosphorylated JAK2 phosphorylates 8 tyrosine residues in the cytoplasmic tail of EPOR (Dusanter-Fourt et al. 1992, McGraw et al. 2012, and inferred from mouse homologs). The phosphorylated residues then serve as binding sites for scaffold proteins such as CRKL and GAB1 and downstream signaling proteins such as STAT5, phospholipase C, and phosphatidylinositol 3-kinase.

Preceded by: JAK2 transphosphorylates and is activated in response to Erythropoietin

Literature references

Dusanter-Fourt, I., Casadevall, N., Lacombe, C., Muller, O., Billat, C., Fischer, S. et al. (1992). Erythropoietin induces the tyrosine phosphorylation of its own receptor in human erythropoietin-responsive cells. *J. Biol. Chem., 267*, 10670-5. ↗

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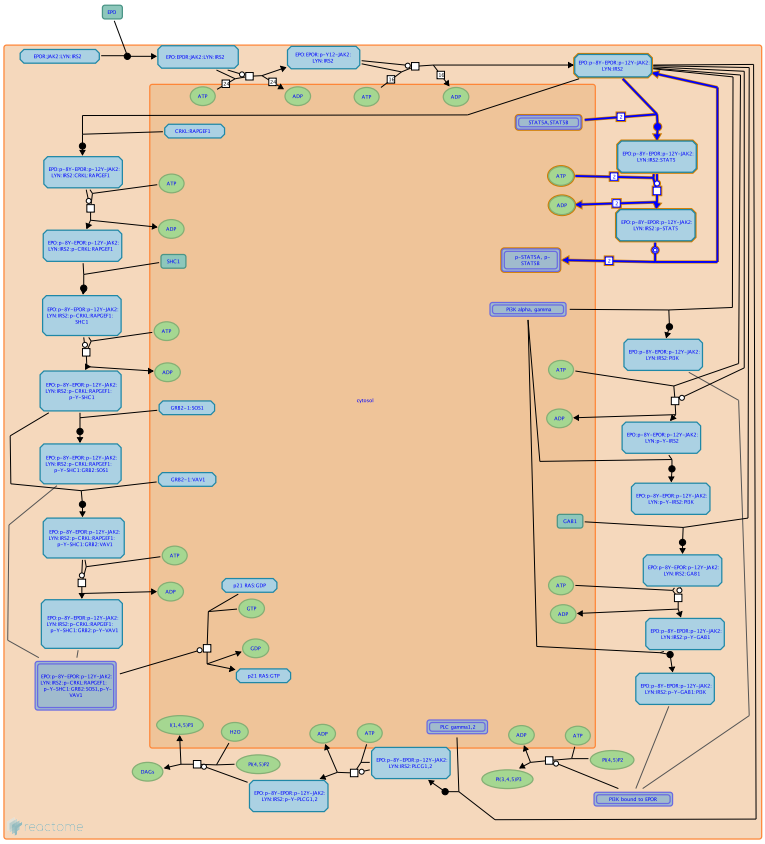
Erythropoietin activates STAT5 ↗

Location: Signaling by Erythropoietin

Stable identifier: R-HSA-9027283



STAT5 (STAT5A or STAT5B) directly binds the phosphorylated cytoplasmic domain of EPOR, where it is phosphorylated by JAK2 and LYN (Oda et al. 1998, inferred from mouse homologs, reviewed in Kuhrt and Wojchowski 2015). Phosphorylated STAT5 then dissociates from EPOR, dimerizes, and transits to the nucleus where it activates gene expression.

Literature references

Oda, A., Sawada, K., Druker, BJ., Ozaki, K., Takano, H., Koizumi, K. et al. (1998). Erythropoietin induces tyrosine phosphorylation of Jak2, STAT5A, and STAT5B in primary cultured human erythroid precursors. *Blood, 92*, 443-51. ↗

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

Editions

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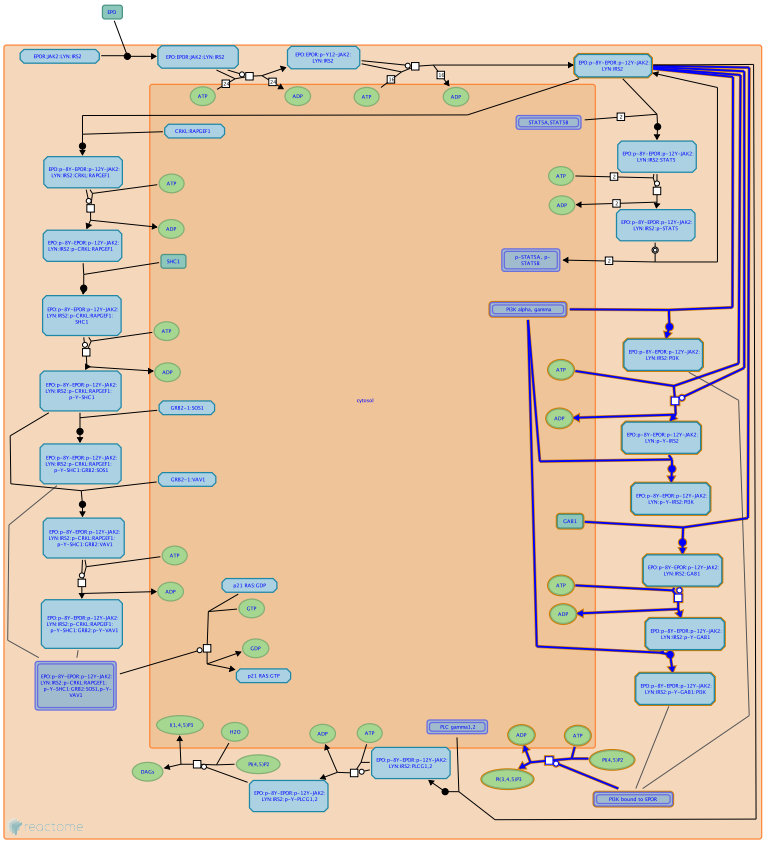
Erythropoietin activates Phosphoinositide-3-kinase (PI3K) ↗

Location: Signaling by Erythropoietin

Stable identifier: R-HSA-9027276



PI3K can bind the activated EPO receptor (EPOR) by three different mechanisms: direct binding to phospho-Y479 of the EPOR, indirect binding via phosphorylated IRS2 bound to the EPOR, and indirect binding via phosphorylated GAB1 bound to the EPOR (Bouscary et al. 2003, Schmidt et al. 2004, reviewed in Kuhrt and Wojchowski 2015). PI3K phosphorylates phosphatidylinositol 4,5-bisphosphate to yield phosphatidylinositol 3,4,5-trisphosphate which recruits AKT1 to the membrane.

Literature references

Bouscary, D., Pene, F., Claessens, YE., Muller, O., Chrétien, S., Fontenay-Roupie, M. et al. (2003). Critical role for PI 3-kinase in the control of erythropoietin-induced erythroid progenitor proliferation. *Blood, 101*, 3436-43. ↗

Schmidt, EK., Fichelson, S., Feller, SM. (2004). PI3 kinase is important for Ras, MEK and Erk activation of Epo-stimulated human erythroid progenitors. *BMC Biol., 2*, 7. ↗

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

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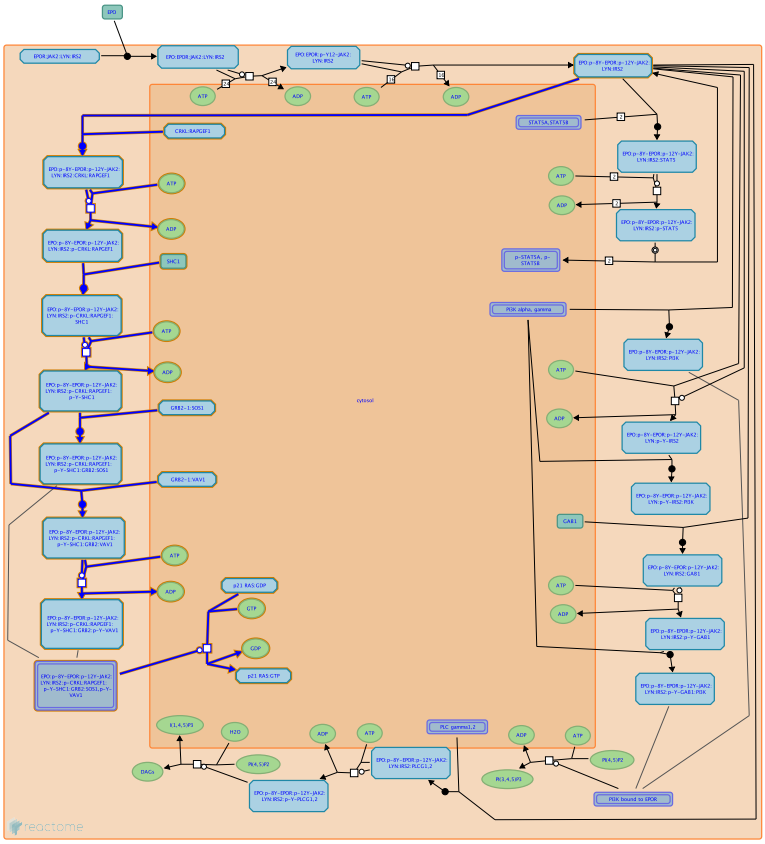
Erythropoietin activates RAS ↗

Location: Signaling by Erythropoietin

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

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

Arai, A., Kanda, E., Nosaka, Y., Miyasaka, N., Miura, O. (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. ↗

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

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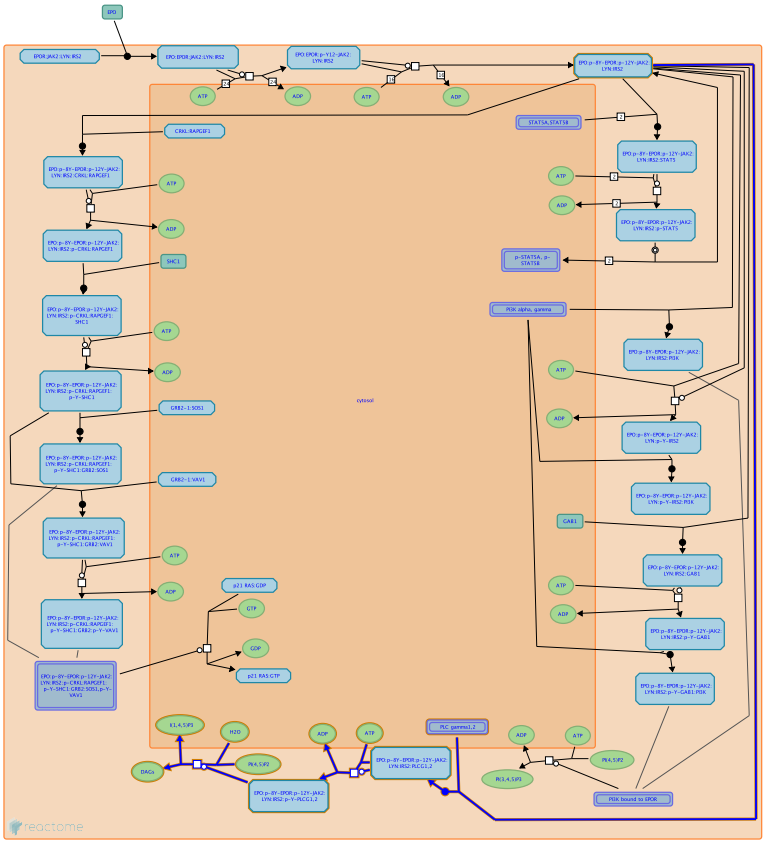
Erythropoietin activates Phospholipase C gamma (PLCG) ↗

Location: Signaling by Erythropoietin

Stable identifier: R-HSA-9027277



PLCG1 (Phospholipase C gamma1) or PLCG2 bound to the activated EPOR is phosphorylated on tyrosine residues by the kinase LYN (Ren et al. 1994, and inferred from mouse homologs). PLCG1 and PLCG2 produce inositol 1,4,5-trisphosphate which then activates calcium signaling, and diacylglycerol (DAG) which then activates protein kinase C (PKC).

Literature references

Ren, HY., Komatsu, N., Shimizu, R., Okada, K., Miura, Y. (1994). Erythropoietin induces tyrosine phosphorylation and activation of phospholipase C-gamma 1 in a human erythropoietin-dependent cell line. *J. Biol. Chem., 269*, 19633-8. ↗

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