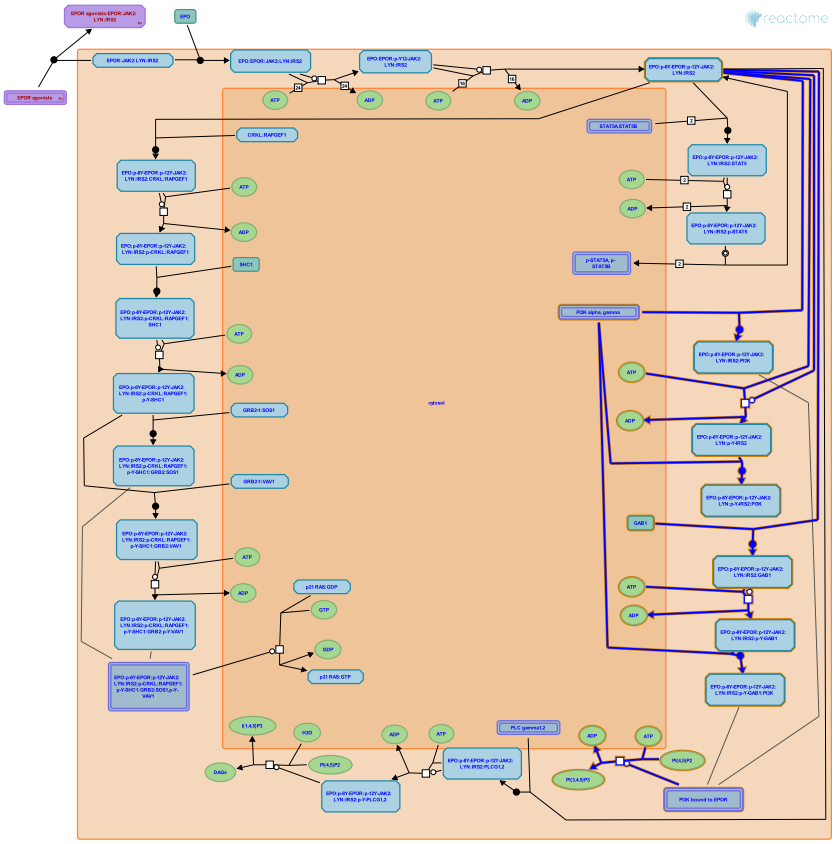
Erythropoietin activates Phosphoinositide-3-kinase (PI3K)



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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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.

28/04/2024

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. ↗

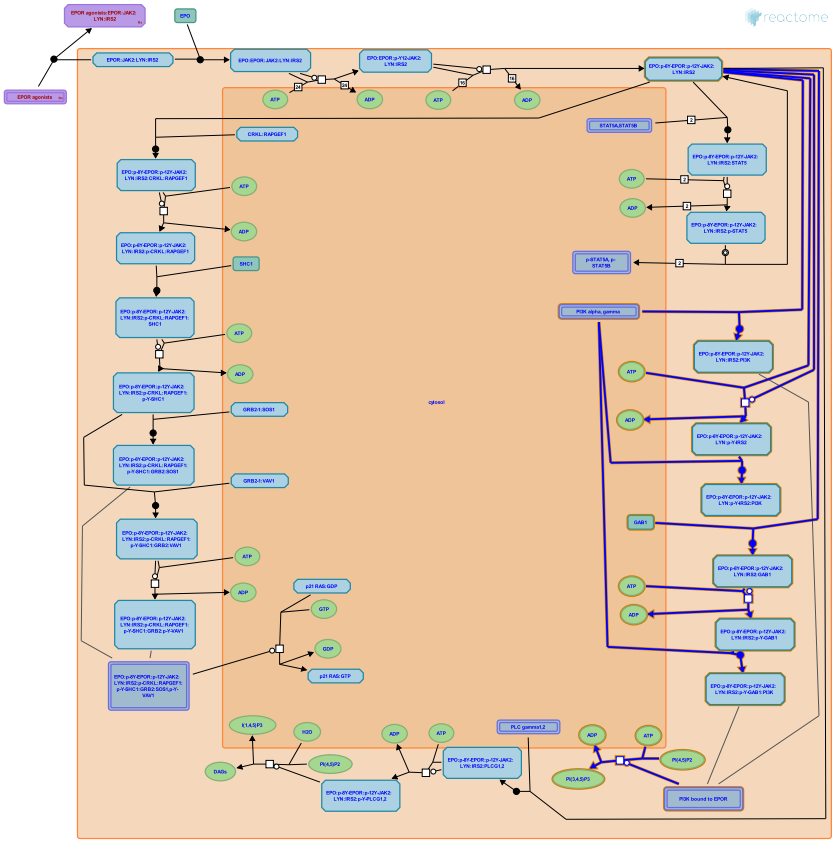
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

Erythropoietin activates Phosphoinositide-3-kinase (PI3K) ↗

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

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

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

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

Editions

2017-10-29	Authored, Edited	May, B.
2018-08-14	Reviewed	McGraw, KL.

EPO:phospho-EPOR:phospho-JAK2:LYN:IRS2 binds PI3K ↗

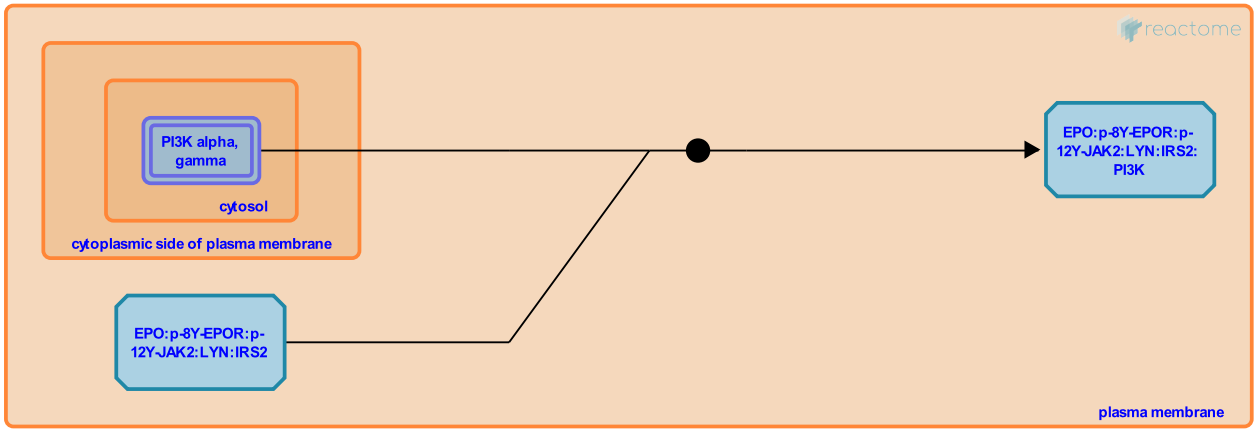
Location: Erythropoietin activates Phosphoinositide-3-kinase (PI3K)

Stable identifier: R-HSA-9027280

Type: binding

Compartments: plasma membrane

Inferred from: Epo:p-8Y-Epor:p-12Y-Jak2:Lyn:Irs2 binds Pi3k (Mus musculus)



Phosphatidylinositol 4,5-bisphosphate 3-kinase (PI3K) can directly bind phosphotyrosine-479 in the cytosolic domain of EPOR (Kubota et al. 2001, Bouscary et al. 2003, and inferred from mouse homologs).

Followed by: EPOR-associated PI3K phosphorylates PIP2 to PIP3

Literature references

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

Kubota, Y., Kitanaka, A., Ishida, T., Kamano, H., Ohnishi, H., Waki, M. et al. (2001). Src transduces erythropoietin-induced differentiation signals through phosphatidylinositol 3-kinase. *EMBO J., 20*, 5666-77. ↗

Editions

2017-10-29	Authored, Edited	May, B.
2018-08-14	Reviewed	McGraw, KL.

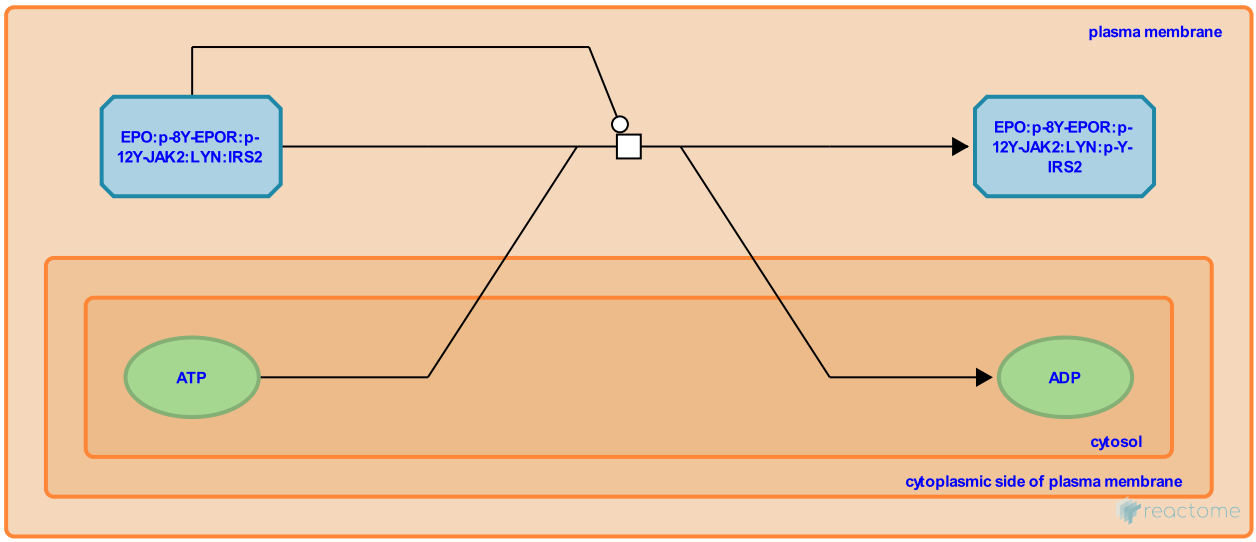
EPO:phospho-EPOR:phospho-JAK2:LYN:IRS2 phosphorylates IRS2 ↗

Location: Erythropoietin activates Phosphoinositide-3-kinase (PI3K)

Stable identifier: R-HSA-9027272

Type: transition

Compartments: plasma membrane



IRS2 is constitutively associated with EPOR and is phosphorylated on tyrosine residues in response to EPO (Verdier et al. 1997, Bouscary et al. 2003). The phosphorylated IRS2 serves as a docking site for downstream signaling proteins, notably phosphatidylinositol 4,5-bisphosphate 3-kinase (PI3K) (Bouscary et al. 2003).

Followed by: EPO:phospho-EPOR:phospho-JAK2:LYN:phospho-IRS2 binds PI3K

Literature references

Mayeux, P., Lacombe, C., Billat, C., Verdier, F., Gisselbrecht, S., Chrétien, S. (1997). Erythropoietin induces the tyrosine phosphorylation of insulin receptor substrate-2. An alternate pathway for erythropoietin-induced phosphatidylinositol 3-kinase activation. *J. Biol. Chem., 272*, 26173-8. ↗

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

Editions

2017-10-21	Authored, Edited	May, B.
2018-08-14	Reviewed	McGraw, KL.

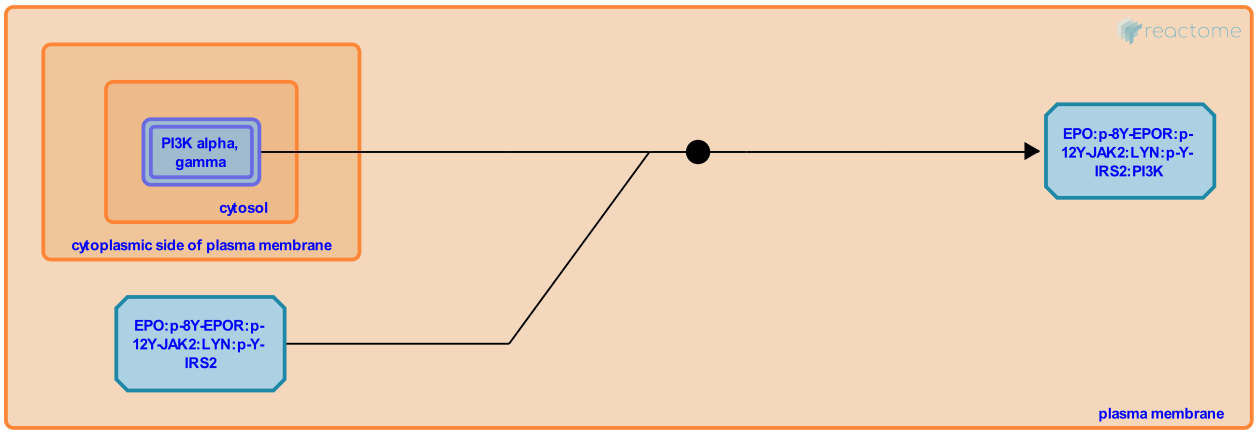
EPO:phospho-EPOR:phospho-JAK2:LYN:phospho-IRS2 binds PI3K ↗

Location: Erythropoietin activates Phosphoinositide-3-kinase (PI3K)

Stable identifier: R-HSA-9012657

Type: binding

Compartments: plasma membrane



Phosphatidylinositol 4,5-bisphosphate 3-kinase (PI3K) binds phosphorylated IRS2 associated with the phosphorylated EPOR (Bouscary et al. 2003).

Preceded by: EPO:phospho-EPOR:phospho-JAK2:LYN:IRS2 phosphorylates IRS2

Followed by: EPOR-associated PI3K phosphorylates PIP2 to PIP3

Literature references

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

Kubota, Y., Kitanaka, A., Ishida, T., Kamano, H., Ohnishi, H., Waki, M. et al. (2001). Src transduces erythropoietin-induced differentiation signals through phosphatidylinositol 3-kinase. *EMBO J., 20*, 5666-77. ↗

Editions

2017-06-17	Authored, Edited	May, B.
2018-08-14	Reviewed	McGraw, KL.

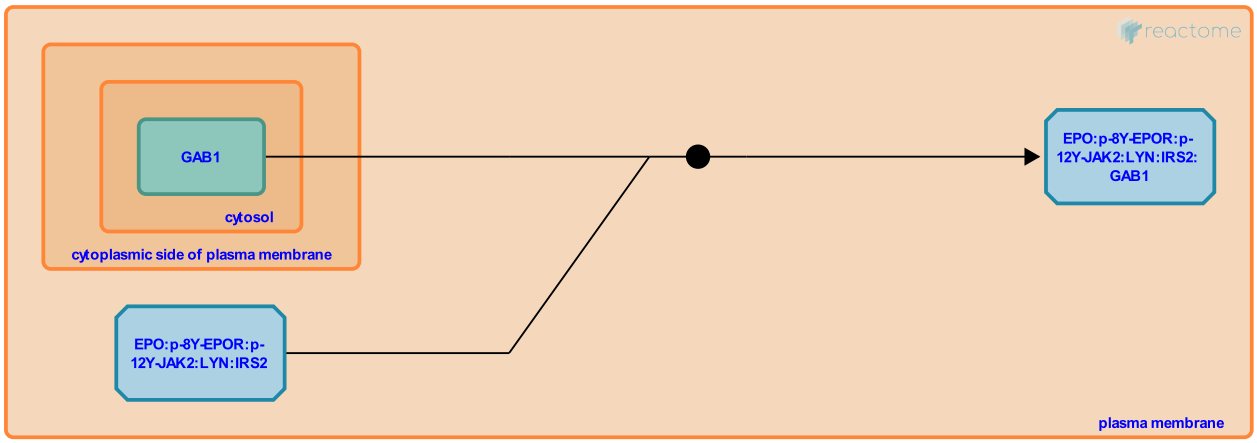
EPO:phospho-EPOR:phospho-JAK2:LYN:IRS2 binds GAB1

Location: Erythropoietin activates Phosphoinositide-3-kinase (PI3K)

Stable identifier: R-HSA-9027281

Type: binding

Compartments: plasma membrane



GAB1 binds directly to phosphotyrosines 344 and 402 of the EPOR (Bouscary et al. 2003, Montoye et al. 2005). GAB1 can also indirectly bind the EPOR via SHC1 or GRB2. GAB2 is absent from human erythroid progenitors but present in mouse erythroid progenitors (Wickrema et al. 1999).

Literature references

Krystal, G., Ahmad, S., Chen, F., Sharma, A., Sawyer, ST., Platanias, LC. et al. (1999). Engagement of Gab1 and Gab2 in erythropoietin signaling. *J Biol Chem, 274*, 24469-74.

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

Lemmens, I., Eyckerman, S., Catteeuw, D., Tavernier, J., Montoye, T. (2005). A systematic scan of interactions with tyrosine motifs in the erythropoietin receptor using a mammalian 2-hybrid approach. *Blood, 105*, 4264-71.

Editions

2017-10-29	Authored, Edited	May, B.
2018-08-14	Reviewed	McGraw, KL.

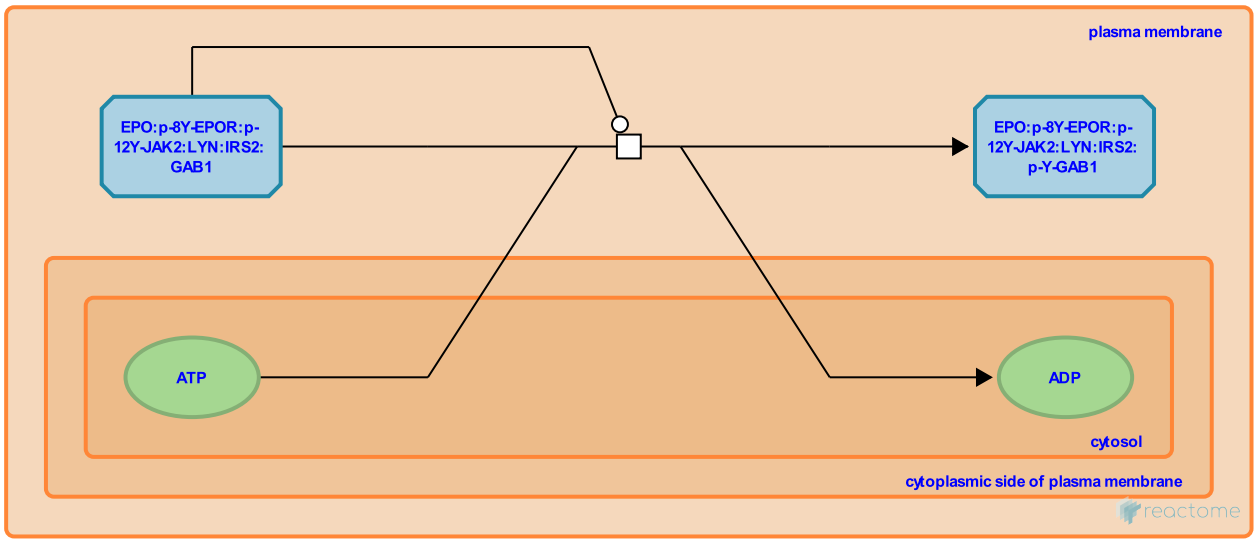
JAK2 phosphorylates GAB1 in EPO:phospho-EPOR:phospho-JAK2:LYN:IRS2:GAB1 ↗

Location: Erythropoietin activates Phosphoinositide-3-kinase (PI3K)

Stable identifier: R-HSA-9027273

Type: transition

Compartments: plasma membrane



Phosphorylated JAK2 in a complex with EPOR and GAB1 phosphorylates GAB1 on unknown tyrosine residues (Lecoq-Lafon et al. 1999, Wickrema et al. 1999, Bouscary et al. 2003, Fukumoto et al. 2009). Phosphorylated GAB1 serves as a scaffold for binding downstream signaling molecules including phosphatidylinositol 4,5-bisphosphate 3-kinase (PI3K) (Bouscary et al. 2003).

Followed by: EPO:phospho-EPOR:phospho-JAK2:LYN:IRS2:phospho-GAB1 binds PI3K

Literature references

Mayeux, P., Lecoq-Lafon, C., Lacombe, C., Verdier, F., Gisselbrecht, S., Chrétien, S. et al. (1999). Erythropoietin induces the tyrosine phosphorylation of GAB1 and its association with SHC, SHP2, SHIP, and phosphatidylinositol 3-kinase. *Blood, 93*, 2578-85. ↗

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

Krystal, G., Ahmad, S., Chen, F., Sharma, A., Sawyer, ST., Platanias, LC. et al. (1999). Engagement of Gab1 and Gab2 in erythropoietin signaling. *J Biol Chem, 274*, 24469-74. ↗

Ishida, T., Tanaka, T., Yamaoka, G., Fukumoto, T., Ohara-Waki, F., Kitanaka, A. et al. (2009). Gab1 transduces PI3K-mediated erythropoietin signals to the Erk pathway and regulates erythropoietin-dependent proliferation and survival of erythroid cells. *Cell. Signal., 21*, 1775-83. ↗

Editions

2017-10-29	Authored, Edited	May, B.
2018-08-14	Reviewed	McGraw, KL.

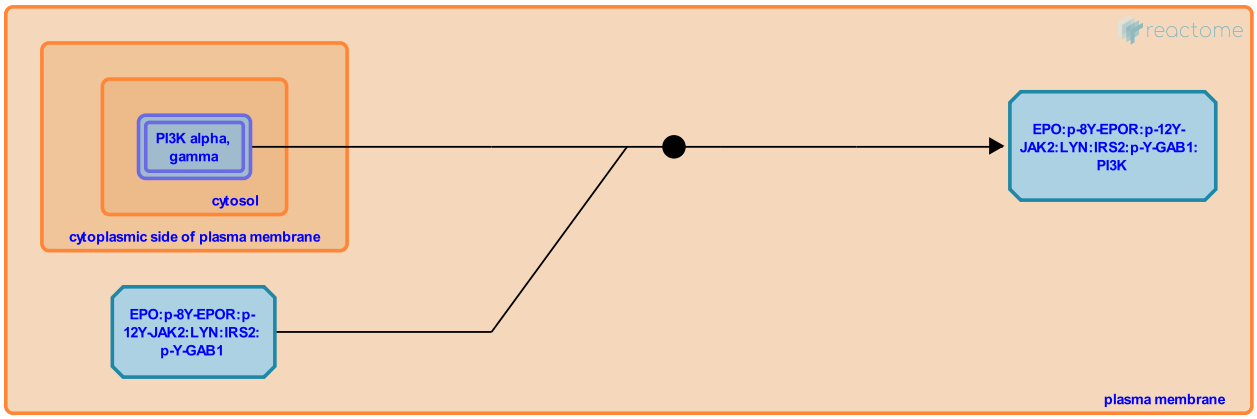
EPO:phospho-EPOR:phospho-JAK2:LYN:IRS2:phospho-GAB1 binds PI3K ↗

Location: Erythropoietin activates Phosphoinositide-3-kinase (PI3K)

Stable identifier: R-HSA-9027275

Type: binding

Compartments: plasma membrane



Phosphorylated GAB1 in a complex with EPOR binds the p85 subunit of phosphatidylinositol 4,5-bisphosphate 3-kinase (PI3K) (Lecoq-Lafon et al. 1999, Wickrema et al. 1999, Bouscary et al. 2003).

Preceded by: JAK2 phosphorylates GAB1 in EPO:phospho-EPOR:phospho-JAK2:LYN:IRS2:GAB1

Followed by: EPOR-associated PI3K phosphorylates PIP2 to PIP3

Literature references

Mayeux, P., Lecoq-Lafon, C., Lacombe, C., Verdier, F., Gisselbrecht, S., Chrétien, S. et al. (1999). Erythropoietin induces the tyrosine phosphorylation of GAB1 and its association with SHC, SHP2, SHIP, and phosphatidylinositol 3-kinase. *Blood, 93*, 2578-85. ↗

Krystal, G., Ahmad, S., Chen, F., Sharma, A., Sawyer, ST., Platanias, LC. et al. (1999). Engagement of Gab1 and Gab2 in erythropoietin signaling. *J Biol Chem, 274*, 24469-74. ↗

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

Editions

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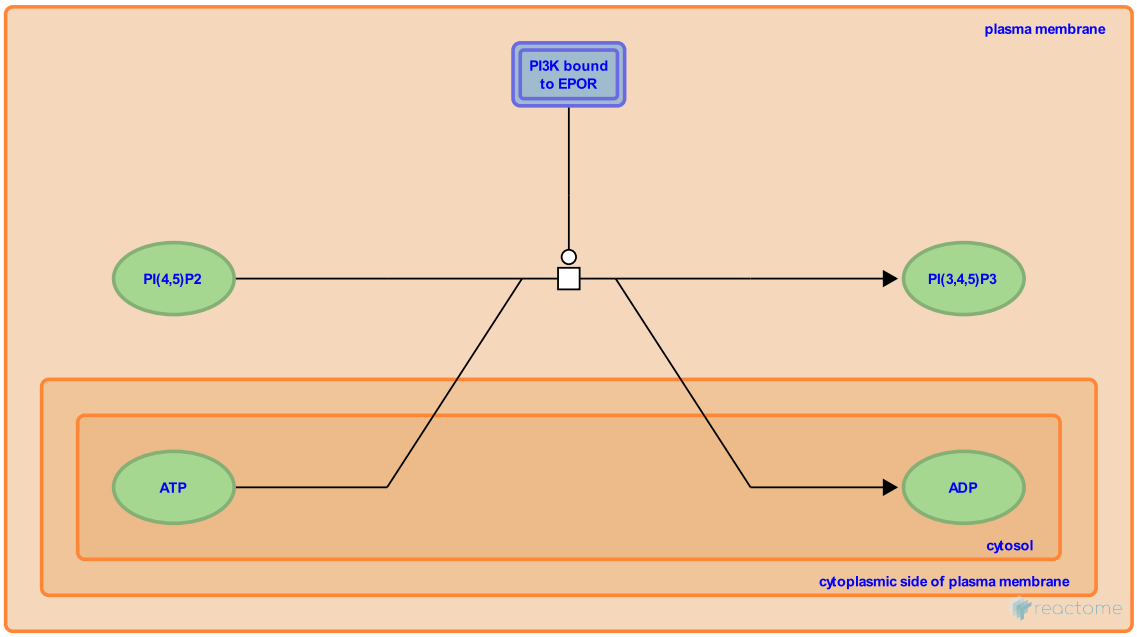
EPOR-associated PI3K phosphorylates PIP2 to PIP3 ↗

Location: Erythropoietin activates Phosphoinositide-3-kinase (PI3K)

Stable identifier: R-HSA-9021627

Type: transition

Compartments: plasma membrane



Phosphatidylinositol 4,5-bisphosphate 3-kinase (PI3K) associated with EPOR phosphorylates phosphatidylinositol 4,5-bisphosphate to yield phosphatidyl 3,4,5-trisphosphate (Kubota et al. 2001, Schmidt et al. 2004). PI3K binds the phosphorylated EPOR directly or indirectly via phosphorylated IRS2 or phosphorylated GAB1 (Bouscary et al. 2003).

Preceded by: EPO:phospho-EPOR:phospho-JAK2:LYN:IRS2 binds PI3K, EPO:phospho-EPOR:phospho-JAK2:LYN:phospho-IRS2 binds PI3K, EPO:phospho-EPOR:phospho-JAK2:LYN:IRS2:phospho-GAB1 binds PI3K

Literature references

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

Kubota, Y., Kitanaka, A., Ishida, T., Kamano, H., Ohnishi, H., Waki, M. et al. (2001). Src transduces erythropoietin-induced differentiation signals through phosphatidylinositol 3-kinase. *EMBO J., 20,* 5666-77. ↗

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

Editions

2017-08-30	Authored, Edited	May, B.
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