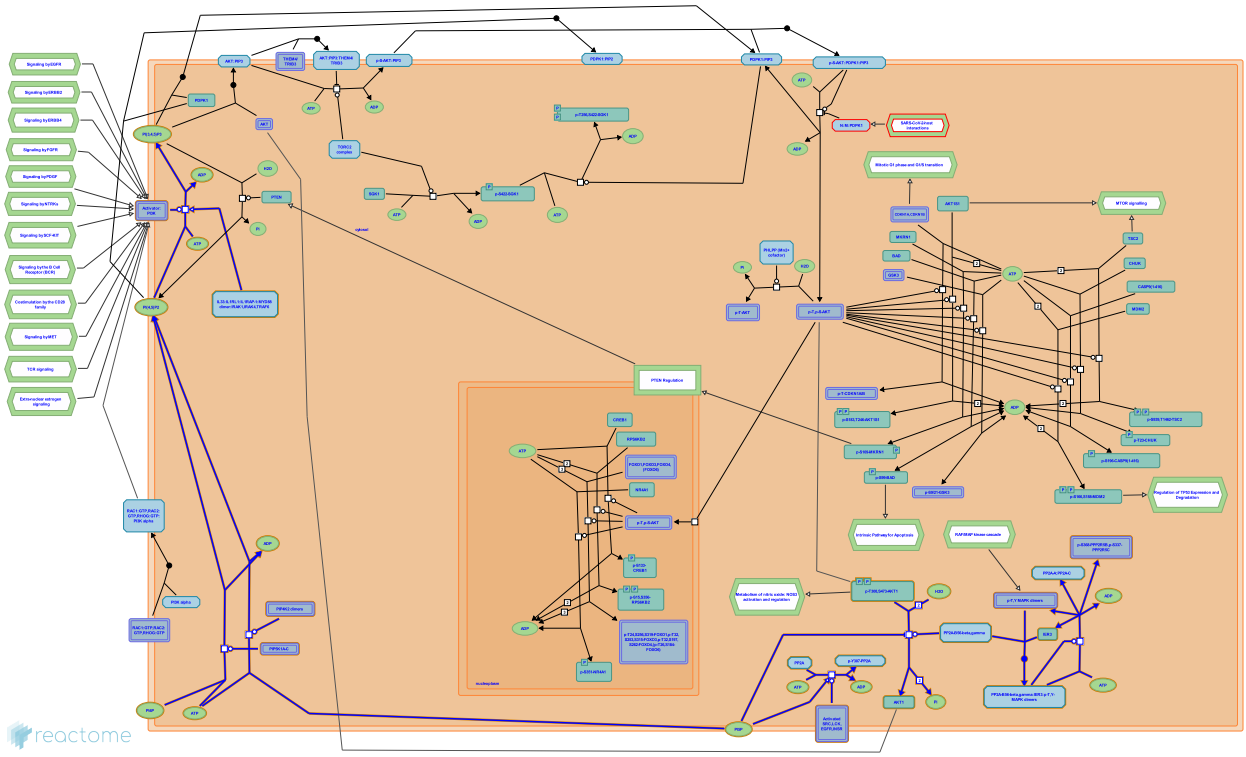
PI5P, PP2A and IER3 Regulate PI3K/AKT Signaling



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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.

19/04/2024

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. ↗

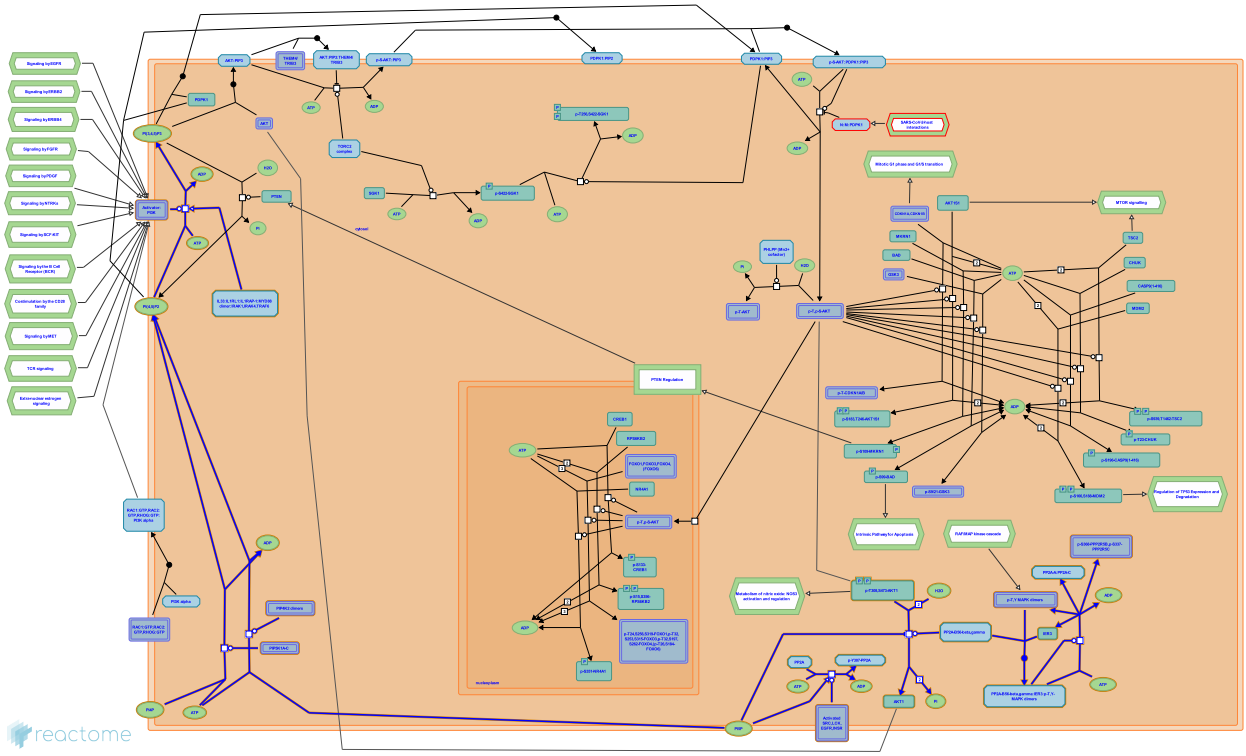
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

PI5P, PP2A and IER3 Regulate PI3K/AKT Signaling ↗

Stable identifier: R-HSA-6811558



Phosphatidylinositol-5-phosphate (PI5P) may modulate PI3K/AKT signaling in several ways. PI5P is used as a substrate for production of phosphatidylinositol-4,5-bisphosphate, PI(4,5)P2 (Rameh et al. 1997, Clarke et al. 2008, Clarke et al. 2010, Clarke and Irvine 2013, Clarke et al. 2015), which serves as a substrate for activated PI3K, resulting in the production of PIP3 (Mandelker et al. 2009, Burke et al. 2011). The majority of PI(4,5)P2 in the cell, however, is produced from the phosphatidylinositol-4-phosphate (PI4P) substrate (Zhang et al. 1997, Di Paolo et al. 2002, Oude Weernink et al. 2004, Halstead et al. 2006, Oude Weernink et al. 2007). PIP3 is necessary for the activating phosphorylation of AKT. AKT1 can be deactivated by the protein phosphatase 2A (PP2A) complex that contains a regulatory subunit B56-beta (PPP2R5B) or B56-gamma (PPP2R5C). PI5P inhibits AKT1 dephosphorylation by PP2A through an unknown mechanism (Ramel et al. 2009). Increased PI5P levels correlate with inhibitory phosphorylation(s) of the PP2A complex. MAPK1 (ERK2) and MAPK3 (ERK1) are involved in inhibitory phosphorylation of PP2A, in a process that involves IER3 (IEX-1) (Letourneux et al. 2006, Rocher et al. 2007). It is uncertain, however, whether PI5P is in any way involved in ERK-mediated phosphorylation of PP2A or if it regulates another PP2A kinase.

Literature references

Rocher, G., Letourneux, C., Porteu, F., Lenormand, P. (2007). Inhibition of B56-containing protein phosphatase 2As by the early response gene IEX-1 leads to control of Akt activity. *J. Biol. Chem., 282*, 5468-77. ↗

Irvine, RF., Clarke, JH., Burke, JE., Giudici, ML., Marugan, J., Maloney, DJ. et al. (2015). The function of phosphatidylinositol 5-phosphate 4-kinase Î³ (PI5P4KÎ³) explored using a specific inhibitor that targets the PI5P-binding site. *Biochem. J., 466*, 359-67. ↗

Wang, M., Irvine, RF., Clarke, JH. (2010). Localization, regulation and function of type II phosphatidylinositol 5-phosphate 4-kinases. *Adv Enzyme Regul, 50*, 12-8. ↗

Schmidt, M., Oude Weernink, PA., López de Jesús, M. (2007). Phospholipase D signaling: orchestration by PIP2 and small GTPases. *Naunyn Schmiedebergs Arch Pharmacol, 374*, 399-411. ↗

Rameh, LE., Cantley, LC., Duckworth, BC., Tolias, KF. (1997). A new pathway for synthesis of phosphatidylinositol-4,5-bisphosphate. *Nature, 390*, 192-6. ↗

Editions

2015-12-22	Authored, Edited	Orlic-Milacic, M.
2016-02-08	Reviewed	Porteu, F.

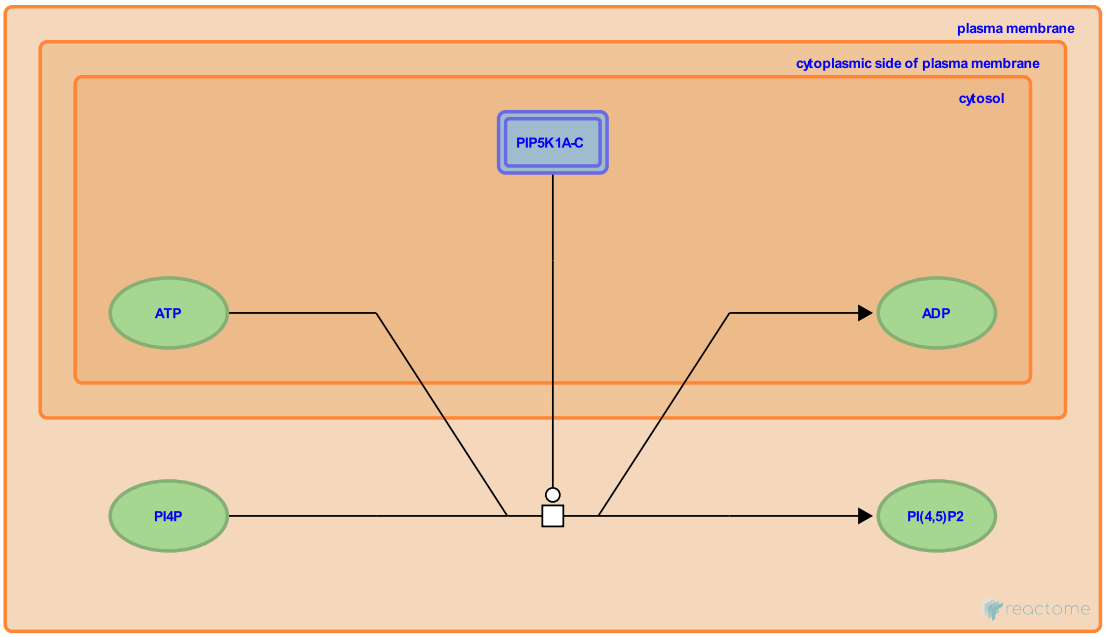
PI4P is phosphorylated to PI(4,5)P2 by PIP5K1A-C at the plasma membrane ↗

Location: PI5P, PP2A and IER3 Regulate PI3K/AKT Signaling

Stable identifier: R-HSA-1676082

Type: transition

Compartments: plasma membrane, cytosol



At the plasma membrane, phosphatidylinositol-4-phosphate 5-kinase type-1 alpha (PIP5K1A), beta (PIP5K1B), and gamma (PIP5K1C) phosphorylate phosphatidylinositol 4-phosphate (PI4P) to produce phosphatidylinositol 4,5-bisphosphate (PI(4,5)P2).

The following lists the above proteins with their corresponding literature references: PIP5K1A (Halstead et al. 2006, Zhang et al. 1997), PIP5K1B (Zhang et al. 1997), and PIP5K1C (Di Paolo et al. 2002).

This reaction is of particular interest because its regulation by small GTPases of the RHO and ARF families, not yet annotated here, ties the process of phosphatidylinositol phosphate biosynthesis to regulation of the actin cytoskeleton and vesicular trafficking, and hence to diverse aspects of cell motility and signalling (Oude Weernink et al. 2004, 2007).

Followed by: PI3K phosphorylates PIP2 to PIP3

Literature references

Schmidt, M., Jakobs, KH., Oude Weernink, PA. (2004). Regulation and cellular roles of phosphoinositide 5-kinases. *Eur J Pharmacol, 500*, 87-99. ↗

Schmidt, M., Oude Weernink, PA., López de Jesús, M. (2007). Phospholipase D signaling: orchestration by PIP2 and small GTPases. *Naunyn Schmiedebergs Arch Pharmacol, 374*, 399-411. ↗

Thum, O., Majerus, PW., Parker, GJ., Boronenkov, IV., Zhang, X., Prestwich, GD. et al. (1997). Phosphatidylinositol-4-phosphate 5-kinase isozymes catalyze the synthesis of 3-phosphate-containing phosphatidylinositol signaling molecules. *J Biol Chem, 272*, 17756-61. ↗

Cestra, G., Pellegrini, L., Di Paolo, G., Zoncu, R., Letinic, K., Wenk, MR. et al. (2002). Recruitment and regulation of phosphatidylinositol phosphate kinase type 1 gamma by the FERM domain of talin. *Nature, 420*, 85-9. ↗

Jalink, K., Heck, AJ., Mohammed, S., Halstead, JR., Meeuws, S., Divecha, N. et al. (2006). A role for PtdIns(4,5)P2 and PIP5Kalpha in regulating stress-induced apoptosis. *Curr Biol, 16*, 1850-6. ↗

Editions

2011-08-12	Edited	Williams, MG.
2011-10-18	Authored	Williams, MG.
2012-05-14	Reviewed	Wakelam, M.
2016-02-08	Reviewed	Porteu, F.

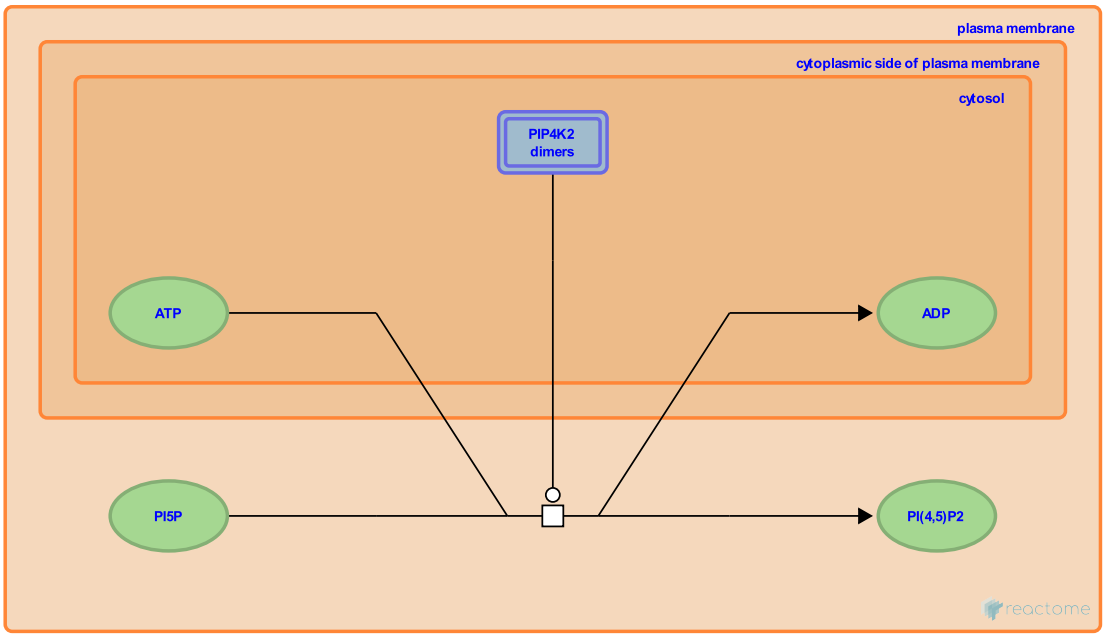
PI5P is phosphorylated to PI(4,5)P2 by PIP4K2 dimers at the plasma membrane ↗

Location: PI5P, PP2A and IER3 Regulate PI3K/AKT Signaling

Stable identifier: R-HSA-1675776

Type: transition

Compartments: plasma membrane, cytosol



At the plasma membrane, phosphatidylinositol-5-phosphate 4-kinase type-2 alpha (PIP4K2A), beta (PIP4K2B) and gamma (PIP4K2C) homodimers and heterodimers (Clarke et al. 2010, Clarke and Irvine 2013, Clarke et al. 2015) phosphorylate phosphatidylinositol 5-phosphate (PI5P) to phosphatidylinositol 4,5-bisphosphate (PI(4,5)P2).

The following lists the above proteins with their corresponding literature references: PIP4K2A (Rameh et al. 1997, Clarke et al. 2008, Clarke and Irvine 2013), PIP4K2B (Rameh et al. 1997, Clarke and Irvine 2013) and PIP4K2C (Clarke and Irvine 2013, Clarke et al. 2015).

Followed by: PI3K phosphorylates PIP2 to PIP3

Literature references

Rameh, LE., Cantley, LC., Duckworth, BC., Tolias, KF. (1997). A new pathway for synthesis of phosphatidylinositol-4,5-bisphosphate. *Nature, 390*, 192-6. ↗

Irvine, RF., Clarke, JH. (2013). Evolutionarily conserved structural changes in phosphatidylinositol 5-phosphate 4-kinase (PI5P4K) isoforms are responsible for differences in enzyme activity and localization. *Biochem. J., 454*, 49-57. ↗

Wang, M., Irvine, RF., Clarke, JH. (2010). Localization, regulation and function of type II phosphatidylinositol 5-phosphate 4-kinases. *Adv Enzyme Regul, 50*, 12-8. ↗

Irvine, RF., Clarke, JH., Burke, JE., Giudici, ML., Marugan, J., Maloney, DJ. et al. (2015). The function of phosphatidylinositol 5-phosphate 4-kinase Î³ (PI5P4KÎ³) explored using a specific inhibitor that targets the PI5P-binding site. *Biochem. J., 466*, 359-67. ↗

Irvine, RF., Emson, PC., Clarke, JH. (2008). Localization of phosphatidylinositol phosphate kinase IIgamma in kidney to a membrane trafficking compartment within specialized cells of the nephron. *Am J Physiol Renal Physiol, 295*, F1422-30. ↗

Editions

2011-08-12	Edited	Williams, MG.
2011-10-18	Authored	Williams, MG.
2012-05-14	Reviewed	Wakelam, M.
2016-02-08	Reviewed	Porteu, F.

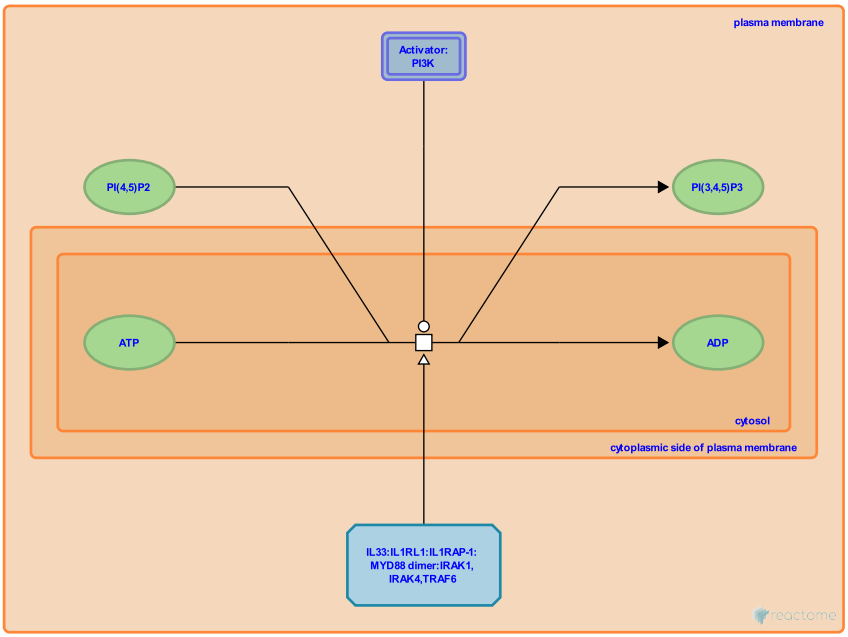
PI3K phosphorylates PIP2 to PIP3 ↗

Location: PI5P, PP2A and IER3 Regulate PI3K/AKT Signaling

Stable identifier: R-HSA-2316434

Type: transition

Compartments: cytosol, plasma membrane



A number of different extracellular signals converge on PI3K activation. PI3K can be activated downstream of receptor tyrosine kinases (RTKs) such as FGFR (Ong et al. 2001, Eswarakumar et al. 2005), KIT (Chian et al. 2001, Ronnstrand 2004, Reber et al. 2006), PDGF (Coughlin et al. 1989, Fantl et al. 1992, Heldin et al. 1998), insulin receptor IGF1R (Hadari et al. 1992, Kooijman et al. 1995), and EGFR and its family members (Rodrigues et al. 2000, Jackson et al. 2004, Kainulainen et al. 2000, Junttila et al. 2009). Other proteins, such as CD28 (Pages et al. 1996, Koyasu 2003, Kane and Weiss, 2003) and TRAT1 (Bruyns et al. 1998, Koyasu 2003, Kolsch et al. 2006), can also trigger PI3K activity.

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: PI4P is phosphorylated to PI(4,5)P2 by PIP5K1A-C at the plasma membrane, PI5P is phosphorylated to PI(4,5)P2 by PIP4K2 dimers at the plasma membrane

Literature references

Cheong, I., Mandelker, D., Zhu, J., Schmidt-Kittler, O., Kinzler, KW., Vogelstein, B. et al. (2009). A frequent kinase domain mutation that changes the interaction between PI3Kalpha and the membrane. *Proc. Natl. Acad. Sci. U.S.A., 106*, 16996-7001. ↗

Vadas, O., Burke, JE., Finegan, T., Williams, RL., Perisic, O., Berndt, A. (2011). Dynamics of the phosphoinositide 3-kinase p110? interaction with p85? and membranes reveals aspects of regulation distinct from p110?. *Structure, 19* , 1127-37. ↗

Editions

2012-07-18	Authored	Orlic-Milacic, M.
2012-08-03	Edited	Matthews, L.
2012-08-13	Reviewed	Zhao, JJ., Yuzugullu, H., Thorpe, L.
2016-02-08	Reviewed	Porteu, F.

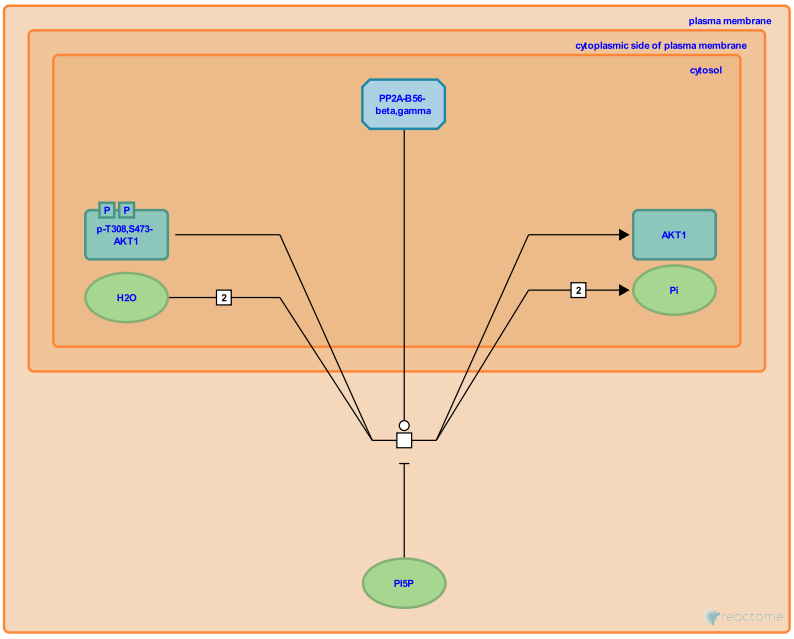
AKT1 dephosphorylation by PP2A-B56-beta,gamma ↗

Location: PI5P, PP2A and IER3 Regulate PI3K/AKT Signaling

Stable identifier: R-HSA-6811504

Type: transition

Compartments: plasma membrane, cytosol



The protein phosphatase 2A (PP2A) complex containing a regulatory subunit B56 beta (PPP2R5B) or B56 gamma (PPP2R5C) dephosphorylates activated AKT1 on threonine residue T308 and serine residue S473, thus halting PI3K/AKT signaling (Rocher et al. 2007). Phosphatidylinositol-5-phosphate (PI5P) negatively regulates PP2A-mediated dephosphorylation of AKT1 by promoting, through an unknown mechanism, an inhibitory phosphorylation on tyrosine residue Y307 (Chen et al. 1992) of the catalytic subunit of PP2A (Ramel et al. 2009).

Literature references

Chen, J., Martin, BL., Brautigan, DL. (1992). Regulation of protein serine-threonine phosphatase type-2A by tyrosine phosphorylation. *Science, 257*, 1261-4. ↗

Leslie, N., Ramel, D., Chicanne, G., Gaits-Iacovoni, F., Lagarrigue, F., Tronchère, H. et al. (2009). PtdIns5P protects Akt from dephosphorylation through PP2A inhibition. *Biochem. Biophys. Res. Commun., 387*, 127-31. ↗

Rocher, G., Letourneux, C., Porteu, F., Lenormand, P. (2007). Inhibition of B56-containing protein phosphatase 2As by the early response gene IEX-1 leads to control of Akt activity. *J. Biol. Chem., 282*, 5468-77. ↗

Editions

2015-12-22	Authored, Edited	Orlic-Milacic, M.
2016-02-08	Reviewed	Porteu, F.

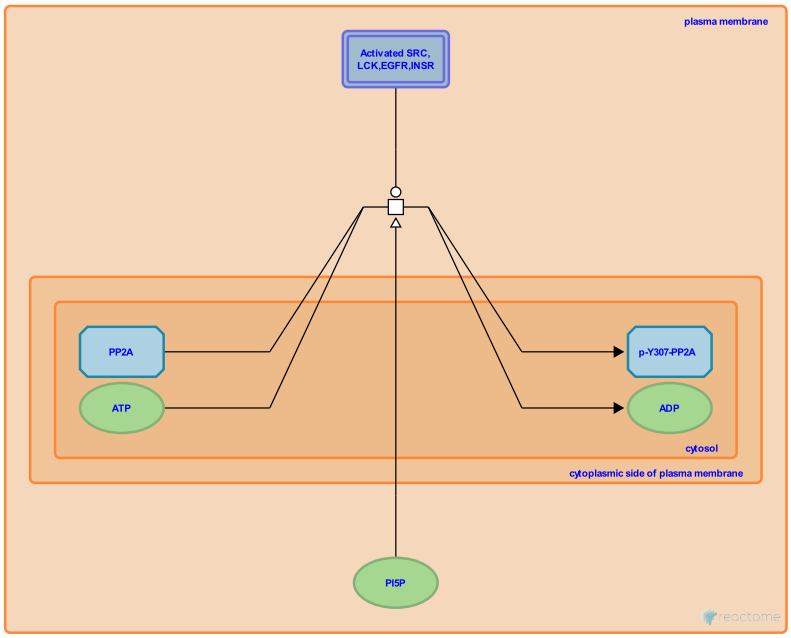
Inhibition of PP2A activity by phosphorylation of the catalytic subunit at tyrosine Y307 ↗

Location: PI5P, PP2A and IER3 Regulate PI3K/AKT Signaling

Stable identifier: R-HSA-8857925

Type: transition

Compartments: plasma membrane, cytosol



SRC family tyrosine kinases, such as SRC and LCK, as well as receptor tyrosine kinases, such as EGFR and insulin receptor, can phosphorylate the catalytic subunit of serine/threonine protein phosphatase PP2A at tyrosine residue Y307. Phosphorylation at Y307 inhibits the catalytic activity of PP2A. Phosphatidylinositol-5-phosphate (PI5P) positively regulates phosphorylation of the catalytic subunit of PP2A at Y307.

Literature references

Chen, J., Martin, BL., Brautigan, DL. (1992). Regulation of protein serine-threonine phosphatase type-2A by tyrosine phosphorylation. *Science, 257*, 1261-4. ↗

Leslie, N., Ramel, D., Chicanne, G., Gaits-Iacovoni, F., Lagarrigue, F., Tronchère, H. et al. (2009). PtdIns5P protects Akt from dephosphorylation through PP2A inhibition. *Biochem. Biophys. Res. Commun., 387*, 127-31. ↗

Editions

2016-02-08	Reviewed	Porteu, F.
2016-02-17	Authored, Edited	Orlic-Milacic, M.

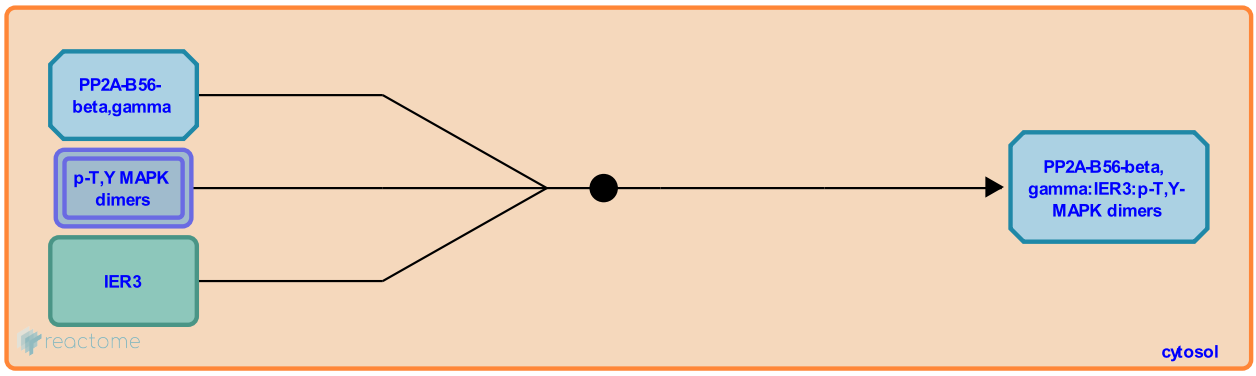
IER3 recruits MAPKs to PP2A-B56-beta,gamma ↗

Location: PI5P, PP2A and IER3 Regulate PI3K/AKT Signaling

Stable identifier: R-HSA-6811472

Type: binding

Compartments: cytosol



IER3 (IEX-1) recruits both an activated MAPK (MAPK1 (ERK2) or MAPK3 (ERK1)) and the protein phosphatase 2A (PP2A) complex containing regulatory subunits B56-beta (PPP2R5B) or B56-gamma (PPP2R5C), through an interaction with the B56 subunit, forming a tripartite complex (Letourneux et al. 2006, Rocher et al. 2007).

Followed by: MAPKs phosphorylate PP2A

Literature references

Rocher, G., Porteu, F., Letourneux, C. (2006). B56-containing PP2A dephosphorylate ERK and their activity is controlled by the early gene IEX-1 and ERK. *EMBO J, 25*, 727-38. ↗

Rocher, G., Letourneux, C., Porteu, F., Lenormand, P. (2007). Inhibition of B56-containing protein phosphatase 2As by the early response gene IEX-1 leads to control of Akt activity. *J. Biol. Chem., 282*, 5468-77. ↗

Editions

2015-12-22	Authored, Edited	Orlic-Milacic, M.
2016-02-08	Reviewed	Porteu, F.

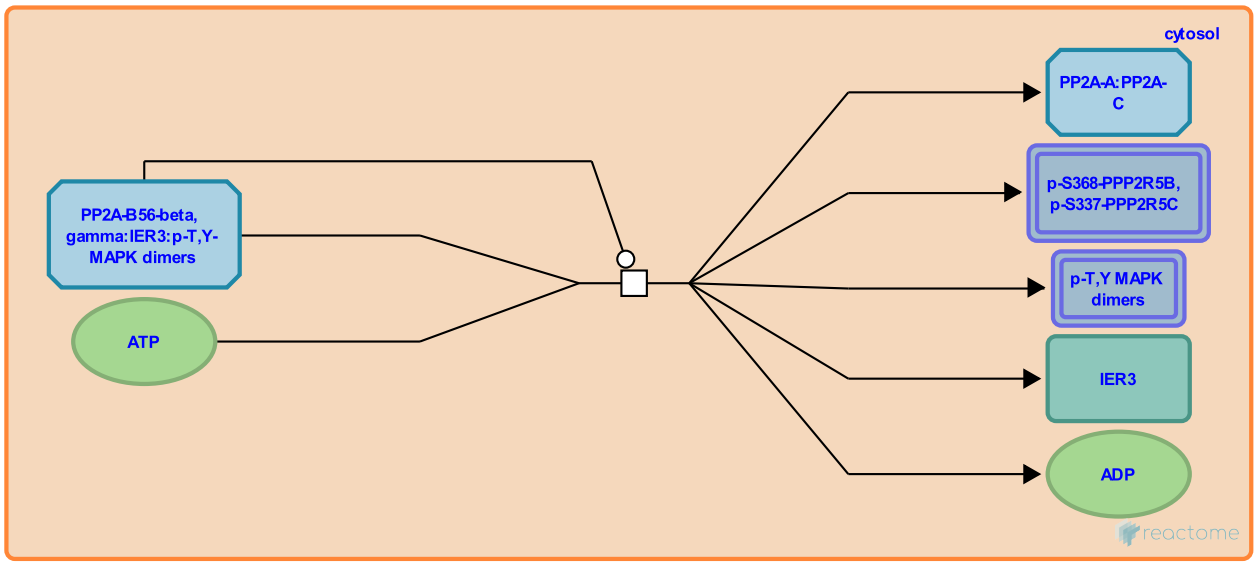
MAPKs phosphorylate PP2A ↗

Location: PI5P, PP2A and IER3 Regulate PI3K/AKT Signaling

Stable identifier: R-HSA-6811454

Type: transition

Compartments: cytosol



Activated MAPK1 (ERK2) or MAPK3 (ERK1), recruited to the PP2A complex through IER3 (IEX-1), phosphorylate the regulatory subunit PPP2R5B (B56-beta) or PPP2R5C (B56-gamma) of the PP2A complex on serine residue S368 or S337, respectively. ERK-mediated phosphorylation of the PP2A regulatory subunits causes dissociation of the PP2A complex and prevents PP2A-mediated dephosphorylation of AKT1 (Letourneux et al. 2006, Rocher et al. 2007).

Preceded by: IER3 recruits MAPKs to PP2A-B56-beta,gamma

Literature references

Rocher, G., Porteu, F., Letourneux, C. (2006). B56-containing PP2A dephosphorylate ERK and their activity is controlled by the early gene IEX-1 and ERK. *EMBO J, 25*, 727-38. ↗

Rocher, G., Letourneux, C., Porteu, F., Lenormand, P. (2007). Inhibition of B56-containing protein phosphatase 2As by the early response gene IEX-1 leads to control of Akt activity. *J. Biol. Chem., 282*, 5468-77. ↗

Editions

2015-12-22	Authored, Edited	Orlic-Milacic, M.
2016-02-08	Reviewed	Porteu, F.

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