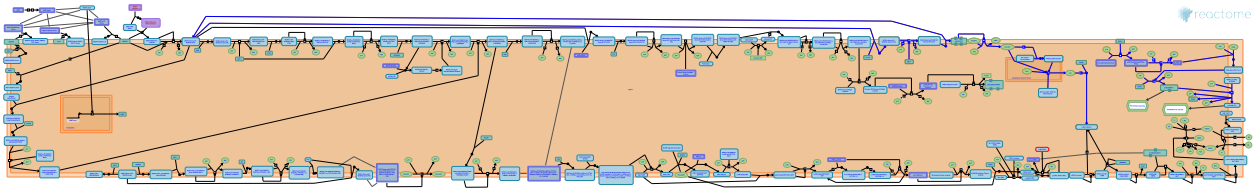
VEGFR2 mediated cell proliferation



Annibali, D., Ballmer-Hofer, K., Berger, P., Garapati, P V., Gillespie, ME., Greene, LA., Jassal, B., Le Novere, N., Nasi, S., Rush, MG., Welsh, M.

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

20/11/2024

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. ↗

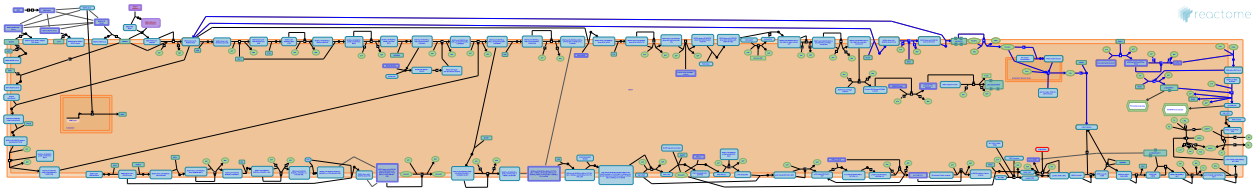
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

VEGFR2 mediated cell proliferation ↗

Stable identifier: R-HSA-5218921

Compartments: cytosol, plasma membrane, extracellular region



VEGFR2 stimulates ERK not via GRB2-SOS-RAS, but via pY1175-dependent phosphorylation of PLC gamma and subsequent activation of PKCs. PKC plays an important mediatory role in the proliferative Ras/Raf/MEK/ERK pathway. PKC alpha can intersect the Ras/Raf/MEK/ERK cascade at the level of Ras (Clark et al. 2004) or downstream of Ras through direct phosphorylation of Raf (Kolch et al. 1993). VEGF stimulation leads to Ras activation in a Ras-guanine nucleotide exchange factor (GEF) independent mechanism. It rather relies on modulating the regulation of Ras-GTPase activating protein (GAP) than regulation of Ras-GEFS (Wu et al. 2003).

Literature references

Shibuya, M. (2011). Vascular Endothelial Growth Factor (VEGF) and Its Receptor (VEGFR) Signaling in Angiogenesis: A Crucial Target for Anti- and Pro-Angiogenic Therapies. *Genes Cancer, 2*, 1097-105. ↗

Berger, P., Ballmer-Hofer, K. (2011). The reception and the party after: how vascular endothelial growth factor receptor 2 explores cytoplasmic space. *Swiss Med Wkly, 141*, w13318. ↗

Koch, S., Claesson-Welsh, L. (2012). Signal transduction by vascular endothelial growth factor receptors. *Cold Spring Harb Perspect Med, 2*, a006502. ↗

Editions

2013-08-30	Authored, Edited	Garapati, P V.
2014-05-12	Reviewed	Welsh, M., Ballmer-Hofer, K., Berger, P.

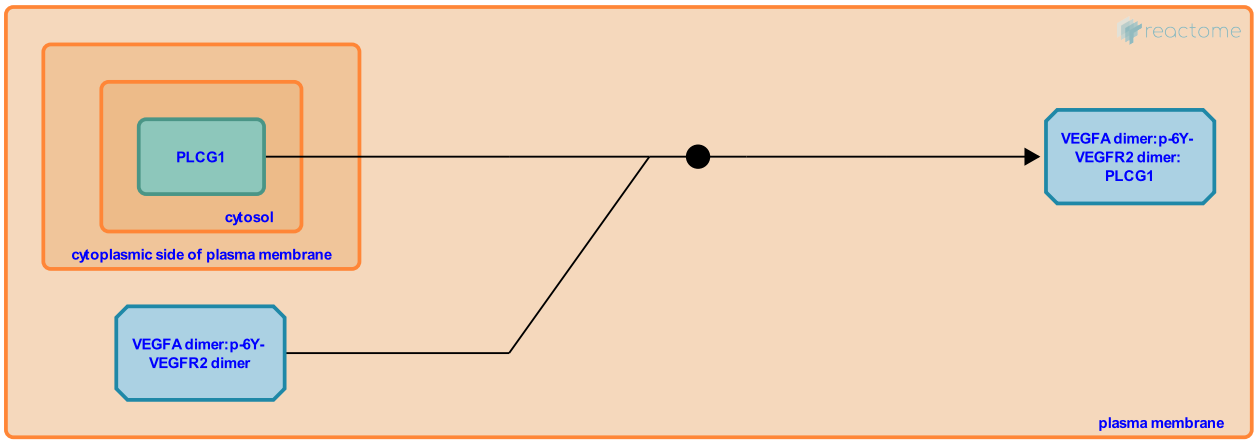
p-6Y-VEGFR2 binds PLCG1 ↗

Location: VEGFR2 mediated cell proliferation

Stable identifier: R-HSA-4420153

Type: binding

Compartments: plasma membrane, cytosol



Phospholipase C-gamma 1 (PLCG1) plays a pivotal role in angiogenesis and VEGFR2 signal transduction. VEGFR2-mediated activation of PLCG1 in certain endothelial cellular backgrounds is suggested to stimulate cell proliferation and in other endothelial cells to stimulate differentiation and tubulogenesis (Rahimi 2006). Phosphorylated tyrosine 1175 of VEGFR2 provides the binding site for PLCG1, SHC-transforming protein 2 (SHC2/SCK) and SH2 domain-containing adapter protein B (SHB) (Takahashi et al. 2001). Binding of PLCG1 activates protein kinase C (PKC) and this in-turn stimulates mitogen-activated protein (MAP) kinase (MAPK)-dependent pathway and cell proliferation (McLaughlin & Vries 2001).

Followed by: SFKs phosphorylate PLCG1

Literature references

Chida, K., Shibuya, M., Takahashi, T., Yamaguchi, S. (2001). A single autophosphorylation site on KDR/Flk-1 is essential for VEGF-A-dependent activation of PLC-gamma and DNA synthesis in vascular endothelial cells. *EMBO J, 20*, 2768-78. ↗

McLaughlin, AP., De Vries, GW. (2001). Role of PLCgamma and Ca(2+) in VEGF- and FGF-induced choroidal endothelial cell proliferation. *Am. J. Physiol., Cell Physiol., 281*, C1448-56. ↗

Editions

2013-08-30	Authored, Edited	Garapati, P V.
2014-05-12	Reviewed	Welsh, M., Ballmer-Hofer, K., Berger, P.

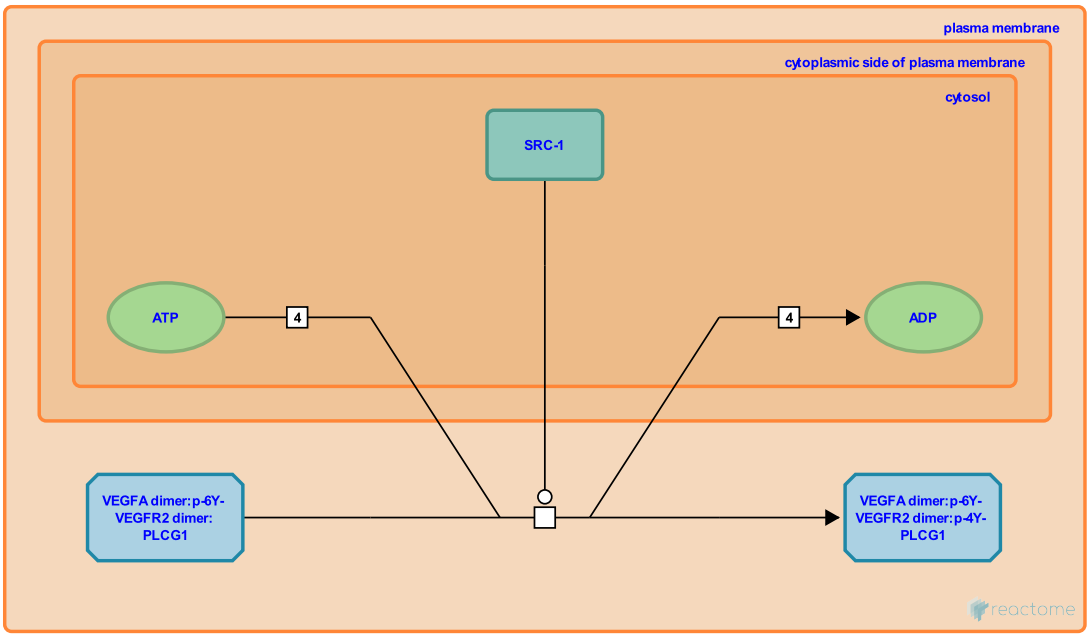
SFKs phosphorylate PLCG1 ↗

Location: VEGFR2 mediated cell proliferation

Stable identifier: R-HSA-4420121

Type: transition

Compartments: plasma membrane, cytosol



Activation of VEGFR2 has been shown to lead to direct binding and phosphorylation of PLC-gamma 1 (McLaughlin & Vries 2001). PLCG1 is tyrosine phosphorylated directly by VEGFR2 or through the Src kinases on four tyrosine residues, enhancing the activity of PLCG1.

Preceded by: p-6Y-VEGFR2 binds PLCG1

Followed by: PLCG1 disassociates from VEGFR2 and translocate to PM

Literature references

Reischl, IG., Graham, L., DeBell, K., Rellahan, BL., Rawat, R., Serrano, CJ. et al. (2005). A new tyrosine phosphorylation site in PLC gamma 1: the role of tyrosine 775 in immune receptor signaling. *J. Immunol., 174*, 6233-7. ↗

McLaughlin, AP., De Vries, GW. (2001). Role of PLCgamma and Ca(2+) in VEGF- and FGF-induced choroidal endothelial cell proliferation. *Am. J. Physiol., Cell Physiol., 281*, C1448-56. ↗

Hicks, SN., Sondek, J., Harden, TK., Gresset, A. (2010). Mechanism of phosphorylation-induced activation of phospholipase C-gamma isozymes. *J. Biol. Chem., 285*, 35836-47. ↗

Editions

2013-08-30	Authored, Edited	Garapati, P V.
2014-05-12	Reviewed	Welsh, M., Ballmer-Hofer, K., Berger, P.

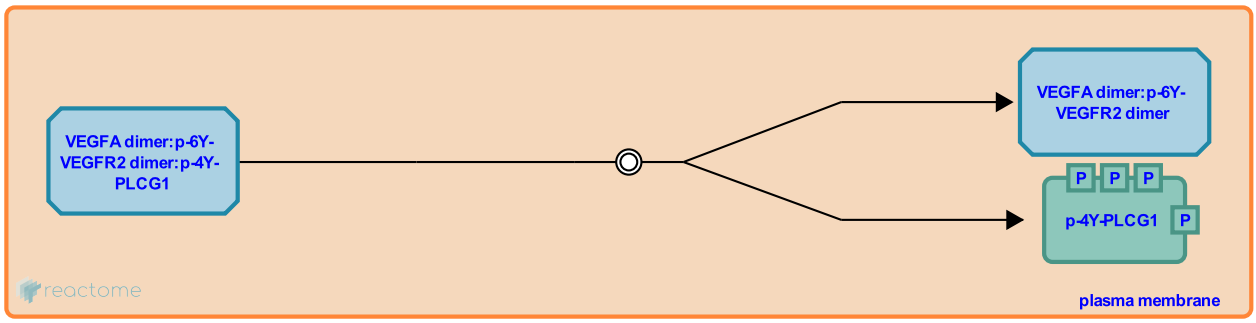
PLCG1 disassociates from VEGFR2 and translocate to PM ↗

Location: VEGFR2 mediated cell proliferation

Stable identifier: R-HSA-4420202

Type: dissociation

Compartments: plasma membrane



Following tyrosine phosphorylation and activation, PLCG1 dissociates from the VEGFR2 receptor and associates with its substrate phosphatidylinositol (4,5)-bisphosphate (PIP2) in the plasma membrane. PLCG1 hydrolyses PIP2 resulting in the generation of diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP3). DAG is an activator of PKC which leads to subsequent activation of MAP kinase, resulting in increased endothelial cell proliferation. IP3 acts upon receptors in the endoplasmic reticulum causing release of intracellular calcium. Elevation of cytosolic Ca2+ stimulates eNOS to produce nitric oxide (NO) causing vascular dilation. Entry of extracellular calcium through specific channels is important for the activation of certain proteins (Takahashi et al. 2001, Takahashi et al. 1999, Xia et al. 1996).

Preceded by: SFKs phosphorylate PLCG1

Followed by: Active PLCG1 hydrolyses PIP2

Literature references

Chida, K., Shibuya, M., Takahashi, T., Yamaguchi, S. (2001). A single autophosphorylation site on KDR/Flk-1 is essential for VEGF-A-dependent activation of PLC-gamma and DNA synthesis in vascular endothelial cells. *EMBO J, 20*, 2768-78. ↗

McLaughlin, AP., De Vries, GW. (2001). Role of PLCgamma and Ca(2+) in VEGF- and FGF-induced choroidal endothelial cell proliferation. *Am. J. Physiol., Cell Physiol., 281*, C1448-56. ↗

Editions

2013-08-30	Authored, Edited	Garapati, P V.
2014-05-12	Reviewed	Welsh, M., Ballmer-Hofer, K., Berger, P.

Active PLCG1 hydrolyses PIP2 ↗

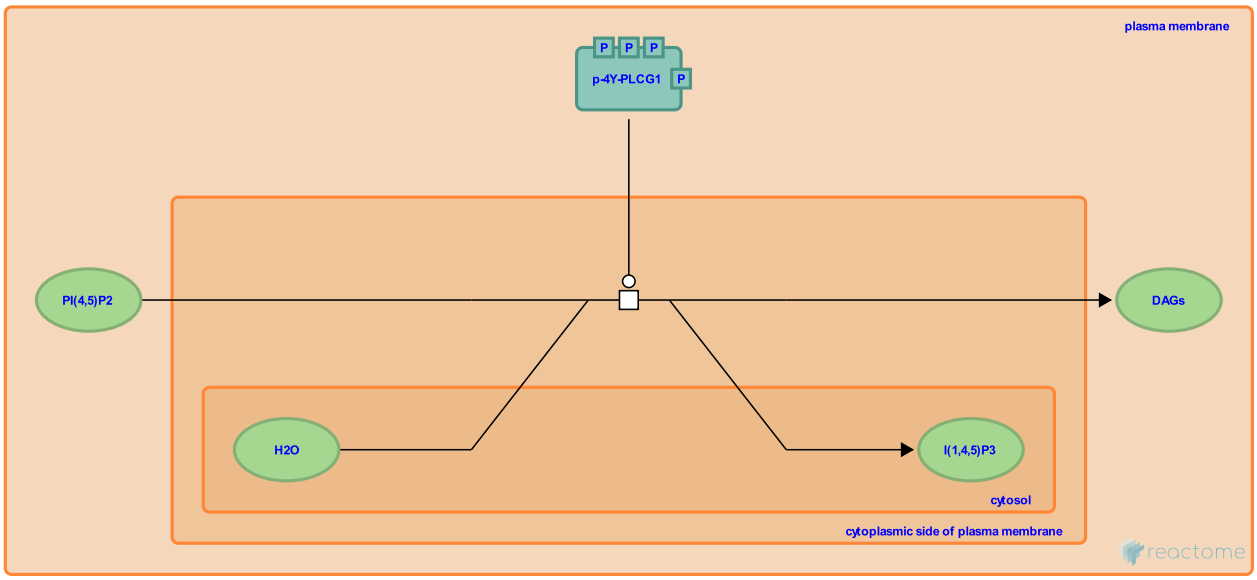
Location: VEGFR2 mediated cell proliferation

Stable identifier: R-HSA-167686

Type: transition

Compartments: cytoplasmic side of plasma membrane, plasma membrane, cytosol

Inferred from: Active Plcg1 hydrolyses PIP2 (Rattus norvegicus)



Inositol 1,4,5-triphosphate (IP3) is a second messenger produced by phospholipase C (PLC) metabolism of phosphoinositol 4,5-bisphosphate (PIP2) (Canossa et al. 2001).

Preceded by: PLCG1 disassociates from VEGFR2 and translocate to PM

Followed by: DAG and Ca+2 bind to PKC and tether it to membrane, IP3R:I(1,4,5)P3 tetramer transports Ca2+ from ER lumen to cytosol, IP3 binds to the IP3 receptor, opening the endoplasmic reticulum Ca2+ channel

Editions

2006-10-10	Edited	Jassal, B.
2006-10-10	Authored	Annibali, D., Nasi, S.
2007-11-08	Reviewed	Greene, LA.

IP3 binds to the IP3 receptor, opening the endoplasmic reticulum Ca2+ channel ↗

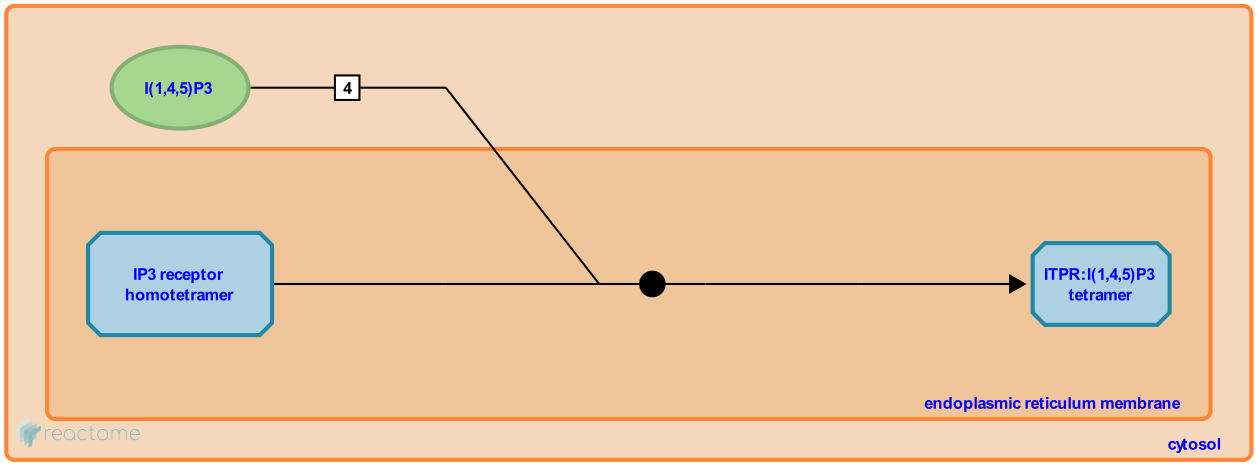
Location: VEGFR2 mediated cell proliferation

Stable identifier: R-HSA-169680

Type: binding

Compartments: endoplasmic reticulum membrane, cytosol

Inferred from: IP3 binds to the IP3 receptor, opening the Ca2+ channel (Rattus norvegicus)



The IP3 receptor (IP3R) is an IP3-gated calcium channel. It is a large, homotetrameric protein, similar to other calcium channel proteins such as ryanodine. The four subunits form a 'four-leafed clover' structure arranged around the central calcium channel. Binding of ligands such as IP3 results in conformational changes in the receptor's structure that leads to channel opening.

Preceded by: Active PLCG1 hydrolyses PIP2

Followed by: IP3R:I(1,4,5)P3 tetramer transports Ca2+ from ER lumen to cytosol

Editions

2004-03-31	Authored	Jassal, B., Le Novere, N.
2006-10-10	Edited	Jassal, B.
2009-06-02	Reviewed	Gillespie, ME.

IP3R:I(1,4,5)P3 tetramer transports Ca2+ from ER lumen to cytosol ↗

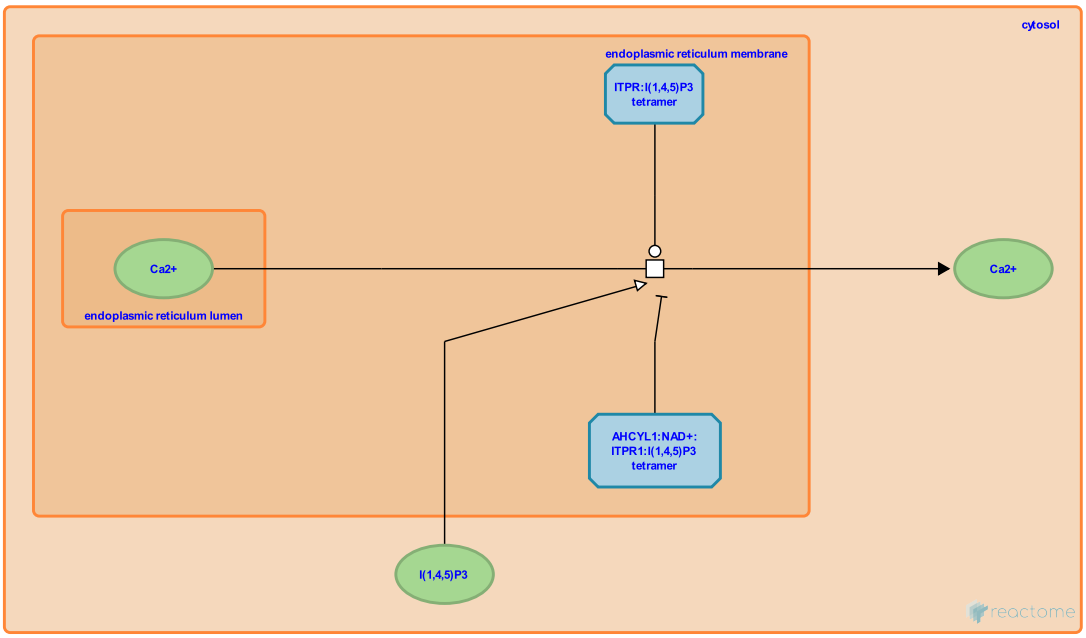
Location: VEGFR2 mediated cell proliferation

Stable identifier: R-HSA-169683

Type: transition

Compartments: endoplasmic reticulum membrane

Inferred from: Calcium release from intracellular stores by IP3 receptor activation (Rattus norvegicus)



IP3 promotes the release of intracellular calcium.

Preceded by: Active PLCG1 hydrolyses PIP2, IP3 binds to the IP3 receptor, opening the endoplasmic reticulum Ca2+ channel

Followed by: DAG and Ca+2 bind to PKC and tether it to membrane, Calcium binds calmodulin

Editions

2004-03-31	Authored	Jassal, B., Le Novere, N.
2006-10-10	Edited	Jassal, B.
2009-06-02	Reviewed	Gillespie, ME.

Calcium binds calmodulin ↗

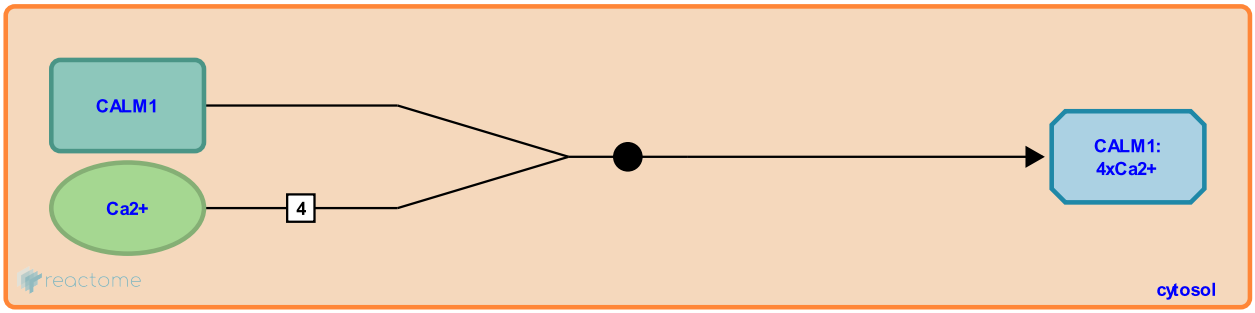
Location: VEGFR2 mediated cell proliferation

Stable identifier: R-HSA-74448

Type: binding

Compartments: cytosol

Inferred from: Calcium binds calmodulin (Bos taurus)



Upon increase in calcium concentration, calmodulin (CaM) is activated by binding to four calcium ions (Crouch and Klee 1980).

Preceded by: IP3R:I(1,4,5)P3 tetramer transports Ca2+ from ER lumen to cytosol

Editions

2004-03-31	Authored	Jassal, B., Le Novere, N.
2008-01-11	Reviewed	Rush, MG.
2008-11-06	Edited	Jassal, B.

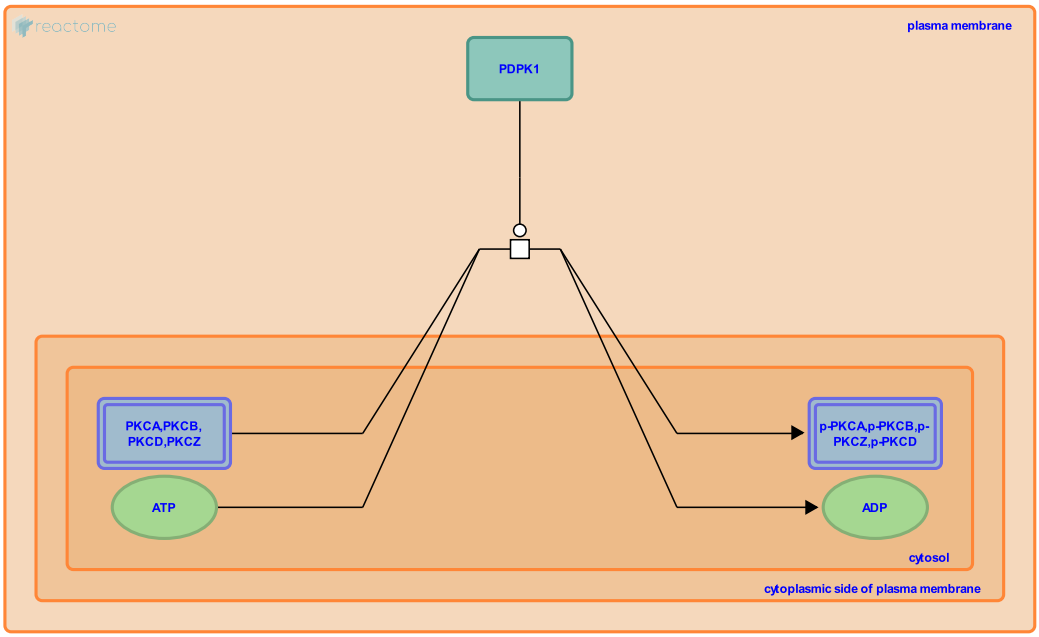
PDK1 phosphorylates PKC ↗

Location: VEGFR2 mediated cell proliferation

Stable identifier: R-HSA-5218821

Type: transition

Compartments: plasma membrane, cytosol



Protein kinase C (PKC) activation enhances angiogenesis by participating in the intracellular signaling of vascular endothelial growth factor (VEGF) in endothelial cells. VEGF can activate several PKC isoforms including alpha, beta, delta and zeta isoforms. Their activation is preceded by the activation of PLC gamma (Suzuma et al. 2002, Xia et al. 1996, Takahashi et al. 1999, Wellner et al. 1999). Before Protein kinase C (PKC) is competent to respond to second messengers it must first be phosphorylated at three conserved positions: the activation loop and two positions at the carboxyl terminus of the protein (Dutil et al. 1998). The phosphorylation of the activation loop appears to occur first and is mediated by phosphoinositide dependent protein kinases (PDKs). PDK1 phosphorylates PKCs at a critical Thr (T) residue in the activation loop, a requirement for PKC to gain catalytic competency (Toker 2003).

Followed by: PKC autophosphorylates

Literature references

Toker, A. (2003). PDK-1 and protein kinase C phosphorylation. *Methods Mol. Biol., 233*, 171-89. ↗

Dutil, EM., Newton, AC., Toker, A. (1998). Regulation of conventional protein kinase C isozymes by phosphoinositide-dependent kinase 1 (PDK-1). *Curr. Biol., 8*, 1366-75. ↗

Editions

2013-08-30	Authored, Edited	Garapati, P V.
2014-05-12	Reviewed	Welsh, M., Ballmer-Hofer, K., Berger, P.

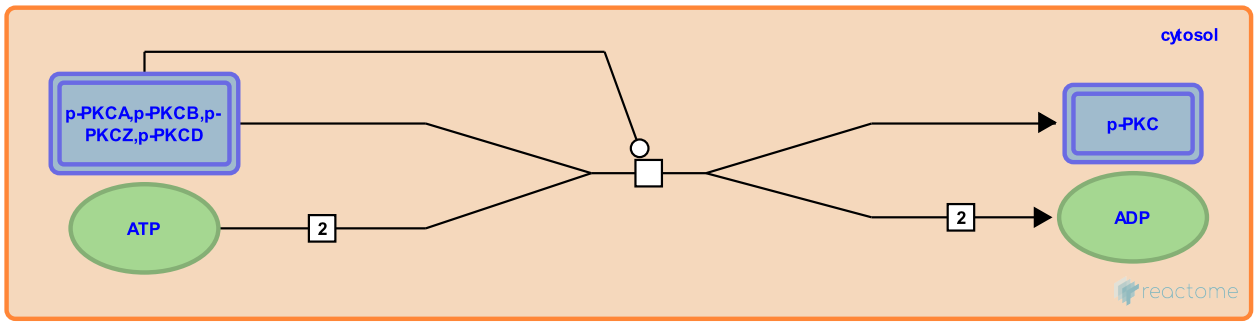
PKC autophosphorylates ↗

Location: VEGFR2 mediated cell proliferation

Stable identifier: R-HSA-5218805

Type: transition

Compartments: cytosol



After phosphorylation by PDK1, PKC undergoes autophosphorylation at two sites important for PKC activity, one in the turn motif (Thr-642 in PKCB) and the second in the hydrophobic phosphorylation motif (Ser-661 in PKCB). These phosphorylations render the enzyme catalytically competent but still inactive; diacylglycerol (DAG) and calcium are required for full activation.

Preceded by: PDK1 phosphorylates PKC

Followed by: DAG and Ca+2 bind to PKC and tether it to membrane

Literature references

Newton, AC., Edwards, AS. (1997). Phosphorylation at conserved carboxyl-terminal hydrophobic motif regulates the catalytic and regulatory domains of protein kinase C. *J. Biol. Chem., 272*, 18382-90. ↗

Newton, AC., Behn-Krappa, A. (1999). The hydrophobic phosphorylation motif of conventional protein kinase C is regulated by autophosphorylation. *Curr. Biol., 9*, 728-37. ↗

Editions

2013-08-30	Authored, Edited	Garapati, P V.
2014-05-12	Reviewed	Welsh, M., Ballmer-Hofer, K., Berger, P.

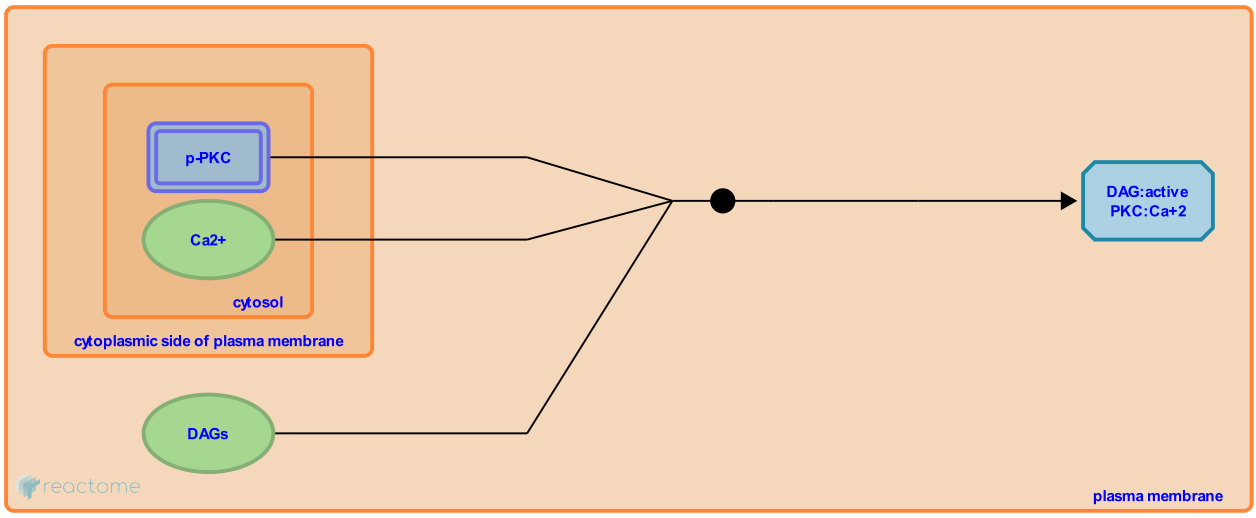
DAG and Ca+2 bind to PKC and tether it to membrane ↗

Location: VEGFR2 mediated cell proliferation

Stable identifier: R-HSA-5218813

Type: binding

Compartments: plasma membrane, cytosol



PKC contains a N-terminal C2 like domain, a pseudosubstrate (PS), DAG binding (C1) domain and a C-terminal kinase domain. The PS sequence resembles an ideal substrate with the exception that it contains an alanine residue instead of a substrate serine residue. It is bound to the kinase domain in the resting state. As a result, PKC is maintained in a closed inactive state, inaccessible to cellular substrates. On stimulation of receptors there is an increase in intracellular calcium and diacylglycerol (DAG) levels which leads to the activation of PKC and its translocation from the cytosol to the plasma membrane. PKCs tether to the plasma membrane through DAG binding to the C1 domain. This confers a high-affinity interaction between PKC and the membrane, leading to a massive conformational change that releases the PS domain from the catalytic site, the system becomes both competent and accessible (Colon-Gonzalez & Kazanietz 2006).

Preceded by: PKC autophosphorylates, Active PLCG1 hydrolyses PIP2, IP3R:I(1,4,5)P3 tetramer transports Ca2+ from ER lumen to cytosol

Followed by: PKC phosphorylates sphingosine kinase 1

Literature references

Colón-González, F., Kazanietz, MG. (2006). C1 domains exposed: from diacylglycerol binding to protein-protein interactions. *Biochim. Biophys. Acta, 1761*, 827-37. ↗

Editions

2013-08-30	Authored, Edited	Garapati, P V.
2014-05-12	Reviewed	Welsh, M., Ballmer-Hofer, K., Berger, P.

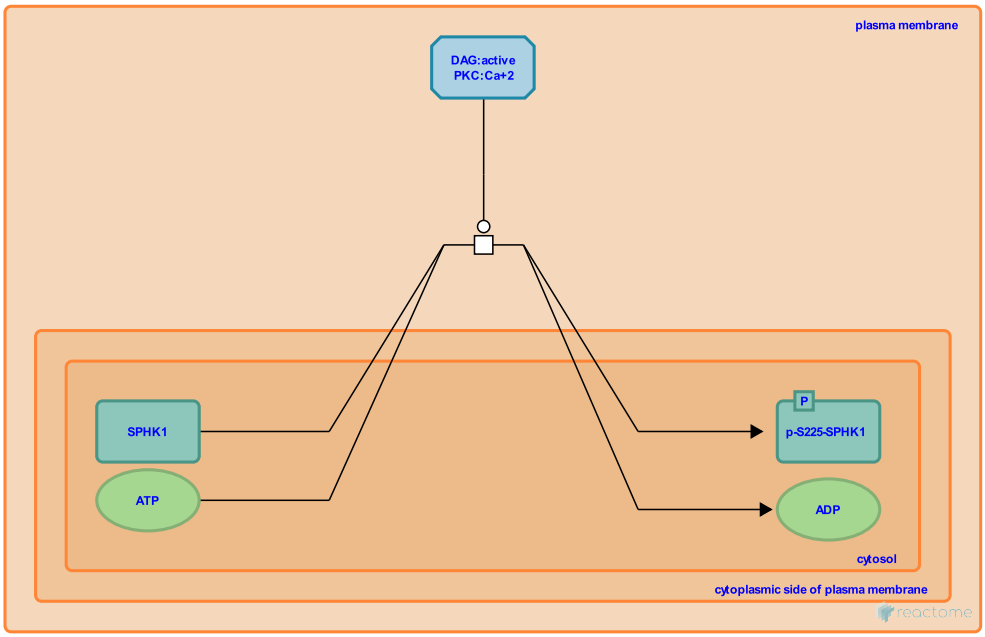
PKC phosphorylates sphingosine kinase 1 ↗

Location: VEGFR2 mediated cell proliferation

Stable identifier: R-HSA-5218823

Type: transition

Compartments: plasma membrane, cytosol



VEGF mediated activation of ERK1/2 depends on the activity of PKC. Sphingosine kinase 1 (SPHK1) has been identified as the connecting link between PKC and Ras activation. Activated SPHK1 does not activate Ras-GEF directly but rather modulates Ras-GAP activity to favour Ras activation. VEGF-mediated stimulation of SPHK1 results from the direct phosphorylation of SPHK1 by PKC (Shu et al. 2002). S225 in SPHK1 may be the target site of phosphorylation (Piston et al. 2003).

Preceded by: DAG and Ca+2 bind to PKC and tether it to membrane

Followed by: p-SPHK1 phosphorylates sphingosine to sphingosine 1-phosphate

Literature references

Wu, W., Mosteller, RD., Shu, X., Broek, D. (2002). Sphingosine kinase mediates vascular endothelial growth factor-induced activation of ras and mitogen-activated protein kinases. *Mol. Cell. Biol., 22*, 7758-68. ↗

Pitson, SM., Lynn, HE., Vadas, MA., Wattenberg, BW., Moretti, PA., Zebol, JR. et al. (2003). Activation of sphingosine kinase 1 by ERK1/2-mediated phosphorylation. *EMBO J., 22*, 5491-500. ↗

Editions

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2014-05-12	Reviewed	Welsh, M., Ballmer-Hofer, K., Berger, P.

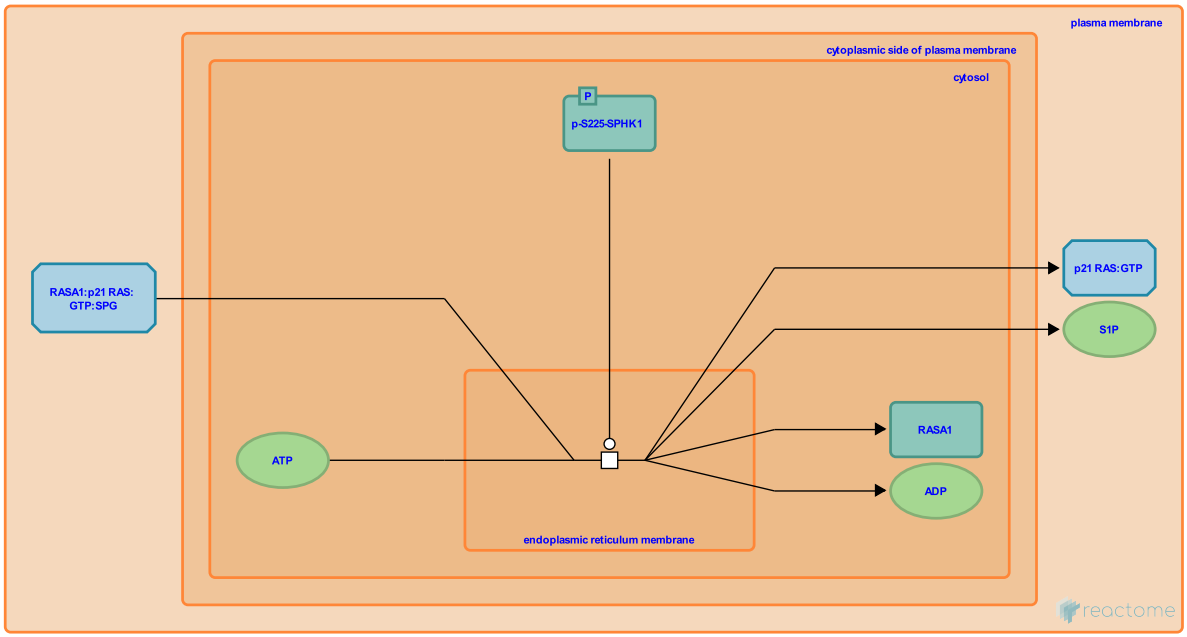
p-SPHK1 phosphorylates sphingosine to sphingosine 1-phosphate ↗

Location: VEGFR2 mediated cell proliferation

Stable identifier: R-HSA-5218845

Type: transition

Compartments: endoplasmic reticulum membrane, cytosol



Membrane-bound sphingosine (SPG) in cells attenuates basal Ras activity by stimulating the activity of Ras GTPase-activating proteins (RasGAPs). Upon its phosphorylation by SPHK1, SPG is converted to sphingosine 1-phosphate (S1P) which then displaces from GAP downregulating RASA1 (p120GAP) activity and thereby induces Ras-GTP accumulation. This overall increases the level of activated Ras-GTP leading to activation of the ERK/mitogen-activated protein kinase (MAPK) pathway and cell division (Shu et al. 2002, Wu et al. 2003, Spiegel & Milstien 2006).

Preceded by: PKC phosphorylates sphingosine kinase 1

Literature references

Sugiura, M., Poulton, S., Liu, H., Nava, VE., Spiegel, S., Kohama, T. et al. (2000). Functional characterization of human sphingosine kinase-1. *FEBS Lett, 473*, 81-4. ↗

Wu, W., Mosteller, RD., Shu, X., Broek, D. (2002). Sphingosine kinase mediates vascular endothelial growth factor-induced activation of ras and mitogen-activated protein kinases. *Mol. Cell. Biol., 22*, 7758-68. ↗

Wu, W., Mosteller, RD., Shu, X., Hovsepyan, H., Broek, D. (2003). VEGF receptor expression and signaling in human bladder tumors. *Oncogene, 22*, 3361-70. ↗

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2014-05-12	Reviewed	Welsh, M., Ballmer-Hofer, K., Berger, P.

Table of Contents