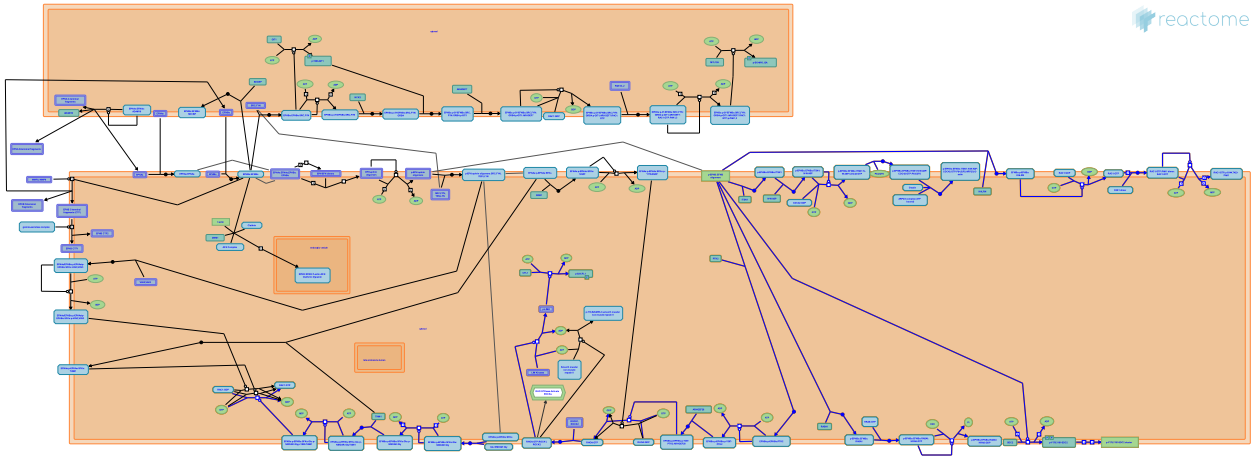
EPHB-mediated forward signaling



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29/04/2024

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. ↗

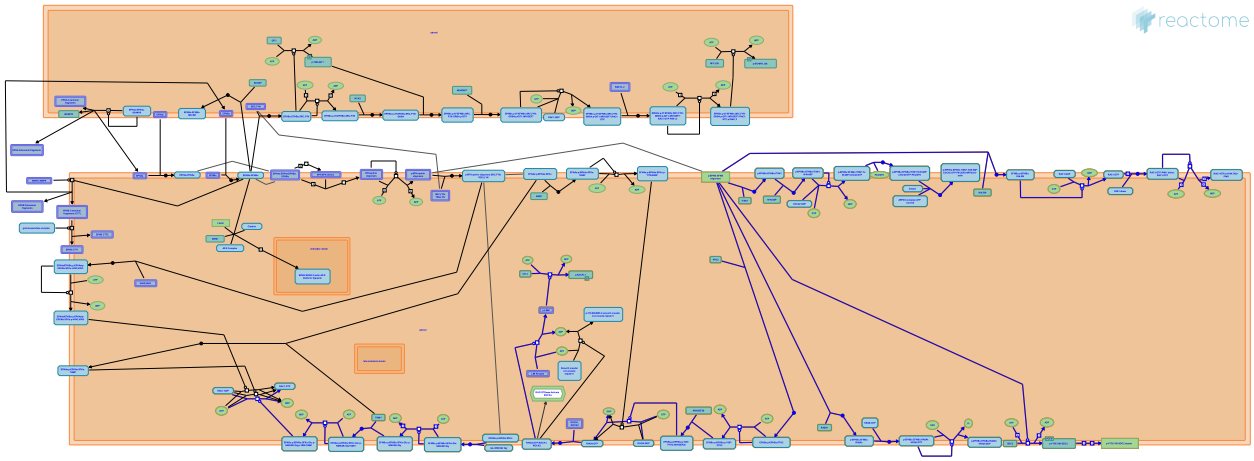
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

EPHB-mediated forward signaling ↗

Stable identifier: R-HSA-3928662

Compartments: cytosol, plasma membrane



Multiple EPHB receptors contribute directly to dendritic spine development and morphogenesis. These are more broadly involved in post-synaptic development through activation of focal adhesion kinase (FAK) and Rho family GTPases and their GEFs. Dendritic spine morphogenesis is a vital part of the process of synapse formation and maturation during CNS development. Dendritic spine morphogenesis is characterized by filopodia shortening followed by the formation of mature mushroom-shaped spines (Moeller et al. 2006). EPHBs control neuronal morphology and motility by modulation of the actin cytoskeleton. EPHBs control dendritic filopodia motility, enabling synapse formation. EPHBs exert these effects through interacting with the guanine exchange factors (GEFs) such as intersectin and kalirin. The intersectin-CDC42-WASP-actin and kalirin-RAC-PAK-actin pathways have been proposed to regulate the EPHB receptor mediated morphogenesis and maturation of dendritic spines in cultured hippocampal and cortical neurons (Irie & Yamaguchi 2002, Penzes et al. 2003). EPHBs are also involved in the regulation of dendritic spine morphology through FAK which activates the RHOA-ROCK-LIMK-1 pathway to suppress cofilin activity and inhibit cofilin-mediated dendritic spine remodeling (Shi et al. 2009).

Literature references

Murai, KK., Pasquale, EB. (2003). 'Eph'ective signaling: forward, reverse and crosstalk. *J. Cell. Sci., 116*, 2823-32. ↗

Editions

2013-07-23	Authored, Edited	Garapati, P V.
2014-05-19	Reviewed	Ip, NY.

EPHB binds ITSN1 ↗

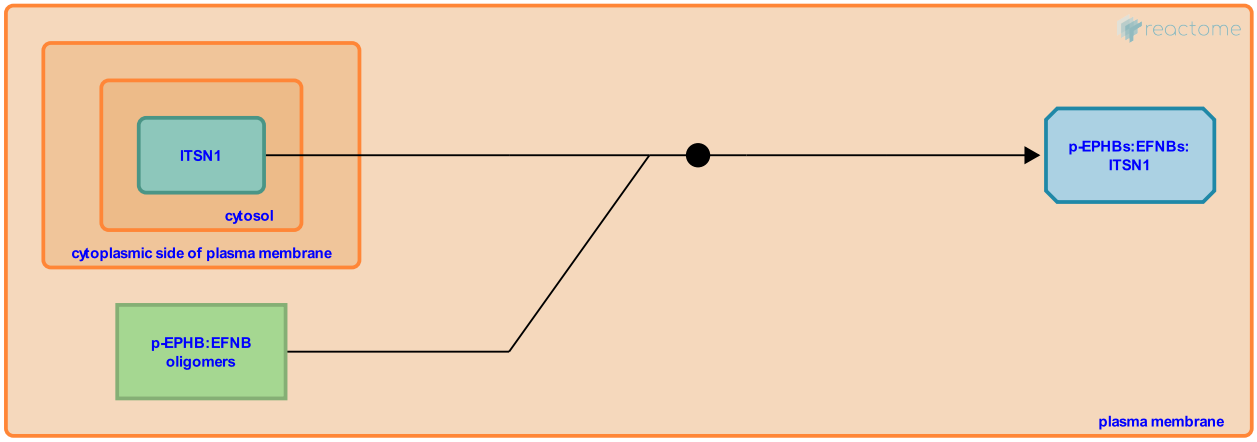
Location: EPHB-mediated forward signaling

Stable identifier: R-HSA-3928644

Type: binding

Compartments: plasma membrane, cytosol

Inferred from: EphB2 recruits inetersectin-1 (Mus musculus)



Intersectin-1 (ITSN1), a guanine nucleotide exchange factor (GEF) for CDC42 is one of the binding partners of EPH receptors class B (EPHBs) in synapses. ITSN1 is expressed specifically in the brain and acts as the functional link between CDC42 and EPHB. EPHB2 receptor FORMS a complex with ITSN1 and N-WASP, triggers the activation of CDC42 to promote actin polymerization via N-WASP and the ARP2/3 complex, leading to spherical expansion of dendritic spine heads. EPHB co-immunoprecipitates with ITSN1, mediated by the kinase domain-containing fragment of EPHB and the amino (N)-terminal region of ITSN1 (Irie & Yamaguchi 2002).

Followed by: N-WASP binds ITSN1

Editions

2013-07-23	Authored, Edited	Garapati, P V.
2014-05-19	Reviewed	Ip, NY.

N-WASP binds ITSN1 ↗

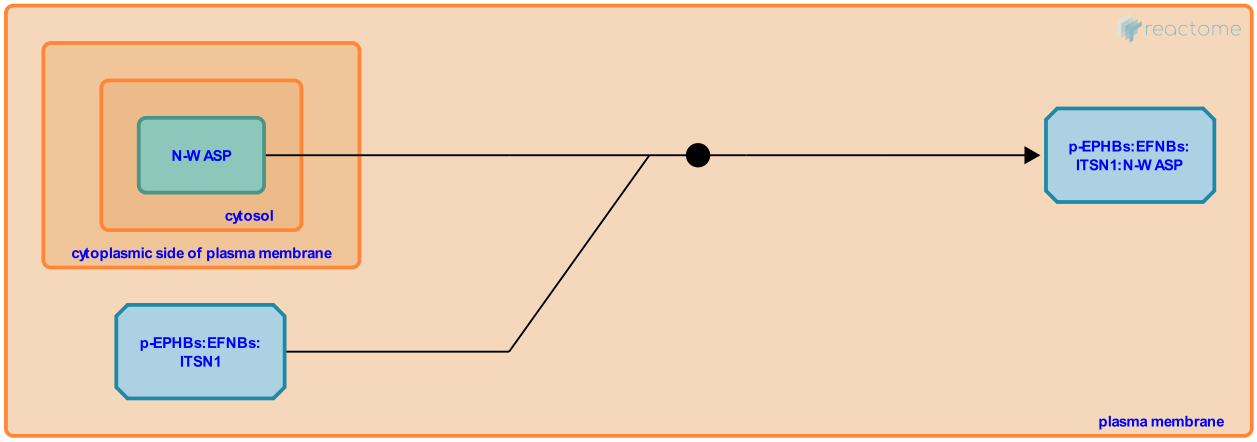
Location: EPHB-mediated forward signaling

Stable identifier: R-HSA-3928600

Type: binding

Compartments: plasma membrane, cytosol

Inferred from: N-Wasp binds intersectin-1 (Mus musculus)



Neural Wiskott-Aldrich syndrome protein (N-WASP, WASL) with its extended proline-rich region binds simultaneously to several of the five SH3 domains of intersectin-1 (ITSN1). Double-label immunofluorescence confirmed the colocalization of ITSN1, N-WASP and EPHB2 in spines. N-WASP in cooperation with EPHB2 activates the GEF activity of intersectin-1 (Irie & Yamaguchi 2002).

Preceded by: EPHB binds ITSN1

Followed by: ITSN1 exchanges GTP for GDP on CDC42, activating it

Editions

2013-07-23	Authored, Edited	Garapati, P V.
2014-05-19	Reviewed	Ip, NY.

ITSN1 exchanges GTP for GDP on CDC42, activating it ↗

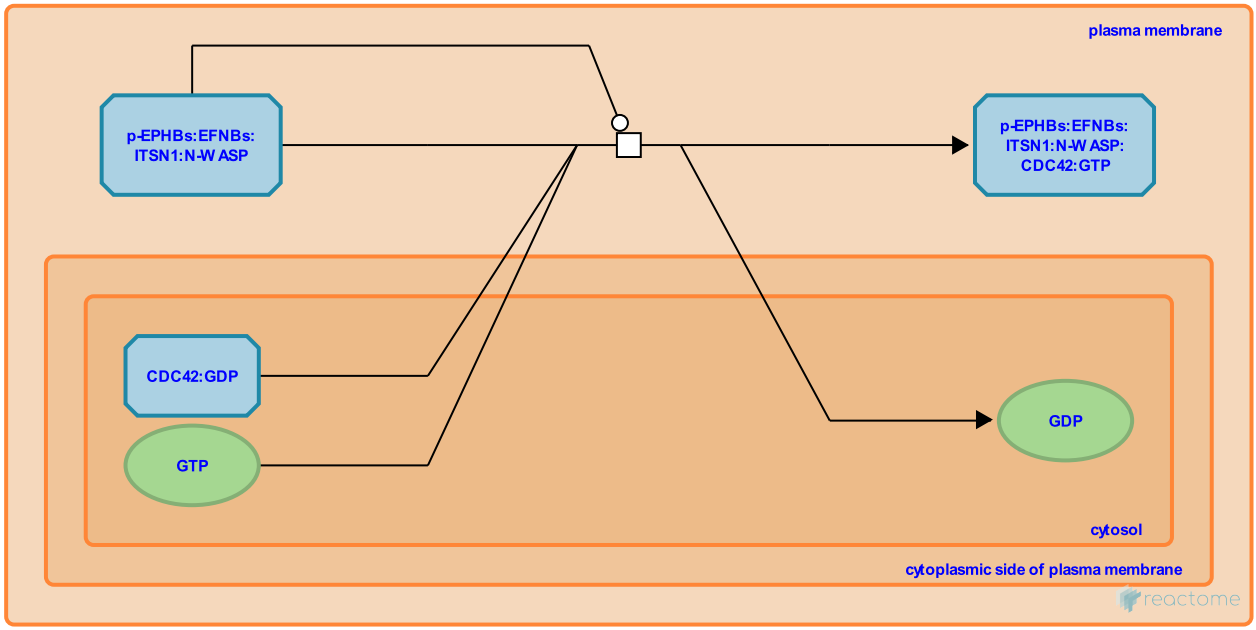
Location: EPHB-mediated forward signaling

Stable identifier: R-HSA-3928632

Type: transition

Compartments: plasma membrane, cytosol

Inferred from: Activation of CDC42 by intersectin-1 (Mus musculus)



Activated intersectin 1 (ITSN1) activates CDC42 by exchanging GDP with GTP, resulting in high levels of CDC42:GTP in spines.

Preceded by: N-WASP binds ITSN1

Followed by: CDC42 and PIP2 bind WASL, activating it

Editions

2013-07-23	Authored, Edited	Garapati, P V.
2014-05-19	Reviewed	Ip, NY.

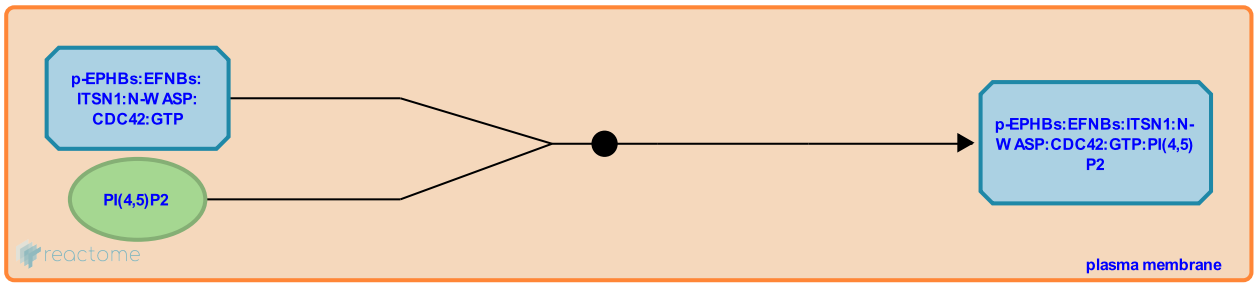
CDC42 and PIP2 bind WASL, activating it ↗

Location: EPHB-mediated forward signaling

Stable identifier: R-HSA-3928601

Type: binding

Compartments: plasma membrane



Neural Wiskott-Aldrich syndrome protein (WASL, N-WASP) is a scaffold protein that transduces signals from cell surface receptors to the activation of the ARP2/3 complex and actin polymerization. N-WASP possesses a central GTPase binding domain (GBD) and an NH2-terminal WASP homology domain 1 (WH1). Adjacent to this is a basic region (B) and a C-terminal containing VCA region that contains a V domain (verprolin homology/WASP homology 2), a C domain (connecting), and an A motif (acidic). The VCA region is responsible for binding to and activating the ARP2/3 complex (Bompard & Caron 2004, Callebaut et al. 1998). Under resting conditions, N-WASP is maintained in an auto-inhibition state via interaction of the N-terminal GBD and the C-terminal VCA domains. This prevents access of the ARP2/3 complex to the VCA region. Activated CDC42 binds to the GBD region in N-WASP and this interaction releases the VCA region from auto-inhibition enabling binding of the ARP2/3 complex stimulating actin polymerization (Kim et al. 2000, Park & Cox 2009). Phosphoinositides (PtdIns(4,5)P2) interact with the basic (B) region in WASP and this interaction is important for activation of the WASP and ARP2/3 complex (Higgs & Pollard 2000).

Preceded by: ITSN1 exchanges GTP for GDP on CDC42, activating it

Followed by: N-WASP binds ARP2/3 and G-actin

Literature references

Miki, H., Takenawa, T., Ma, L., Kirschner, MW., Lopez, M., Kirchhausen, Tomas. et al. (1999). The interaction between N-WASP and the Arp2/3 complex links Cdc42-dependent signals to actin assembly. *Cell, 97*, 221-31. ↗

Kirschner, MW., Ho, HY., Rohatgi, R. (2000). Mechanism of N-WASP activation by CDC42 and phosphatidylinositol 4, 5-bisphosphate. *J Cell Biol, 150*, 1299-310. ↗

Editions

2013-07-23	Authored, Edited	Garapati, P V.
2014-05-19	Reviewed	Ip, NY.

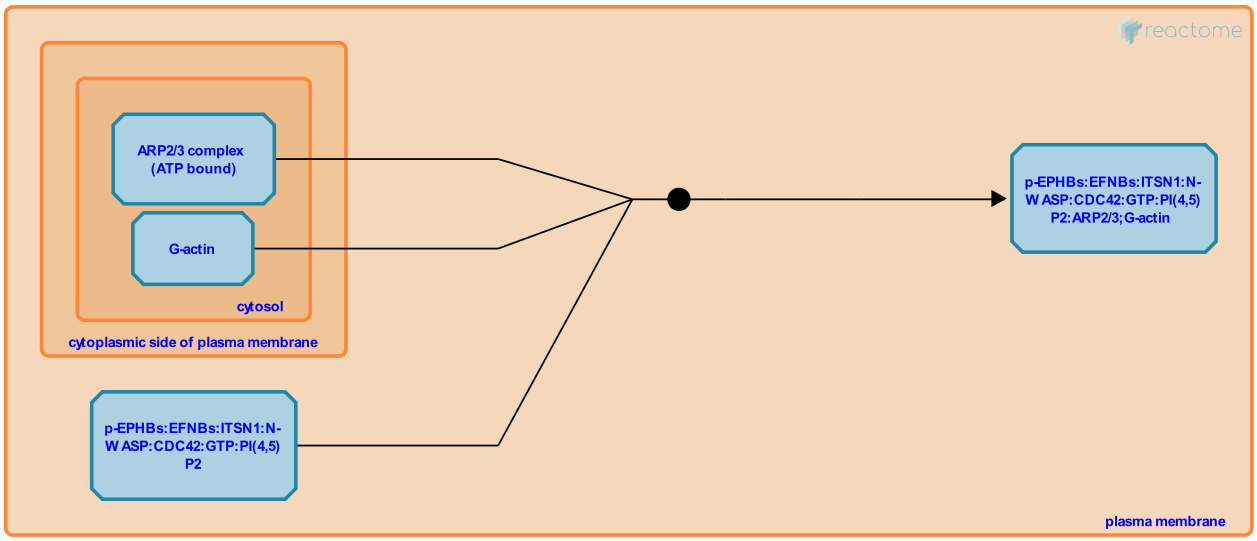
N-WASP binds ARP2/3 and G-actin ↗

Location: EPHB-mediated forward signaling

Stable identifier: R-HSA-3928595

Type: binding

Compartments: plasma membrane, cytosol



Once neural Wiskott-Aldrich syndrome protein (WASL, N-WASP) is activated its VCA region becomes available for binding to actin-related protein (ARP2/3) complex and actin monomer. The actin monomer binds to the V-domain and ARP2/3 complex binds to the CA-domain. The simultaneous binding of G-actin and the ARP2/3 complex to the VCA region contributes to the activation of ARP2/3-complex-mediated actin polymerization (Takenawa & Suetsugu 2007). Actin polymerization via N-WASP and the ARP2/3 complex leads to spherical expansion of dendritic spine heads.

Preceded by: CDC42 and PIP2 bind WASL, activating it

Literature references

Miki, H., Takenawa, T., Ma, L., Kirschner, MW., Lopez, M., Kirchhausen, Tomas. et al. (1999). The interaction between N-WASP and the Arp2/3 complex links Cdc42-dependent signals to actin assembly. *Cell, 97*, 221-31. ↗

Kranitz, H., Lempert, L., Zalevsky, J., Mullins, RD. (2001). Different WASP family proteins stimulate different Arp2/3 complex-dependent actin-nucleating activities. *Curr Biol, 11*, 1903-13. ↗

Editions

2013-07-23	Authored, Edited	Garapati, P V.
2014-05-19	Reviewed	Ip, NY.

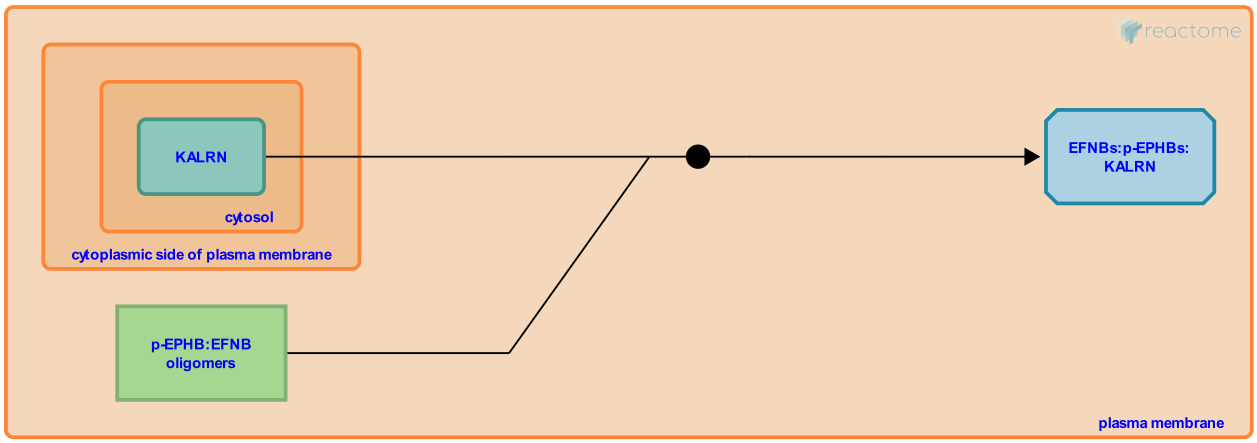
EPHB2 binds KALRN ↗

Location: EPHB-mediated forward signaling

Stable identifier: R-HSA-3928617

Type: binding

Compartments: plasma membrane, cytosol



Penzes et al. showed that the Kalirin-Rac1-PAK pathway is another signaling cascade downstream of EPHB2 that leads to dendritic spine maturation (Penzes et al. 2003). Kalirin (KALRN) is a Rac-GEF expressed postnatally in neurons and localised to the postsynaptic densities at excitatory synapses, where it participates in the formation and maintenance of dendritic spines. In young hippocampal pyramidal neurons, KALRN links trans-synaptic signaling through ephrinB (EFNB) and EPHB receptors to spine formation and maturation. Upon EFNB activation, KALRN binds EPHB2 and translocates to the postsynaptic membrane.

Followed by: KALRN exchanges GTP for GDP on RAC1, activating it

Literature references

Penzes, P., Eipper, BA., Schiller, MR., Huganir, RL., Chernoff, J., Beeser, A. et al. (2003). Rapid induction of dendritic spine morphogenesis by trans-synaptic ephrinB-EphB receptor activation of the Rho-GEF kalirin. *Neuron, 37*, 263-74. ↗

Editions

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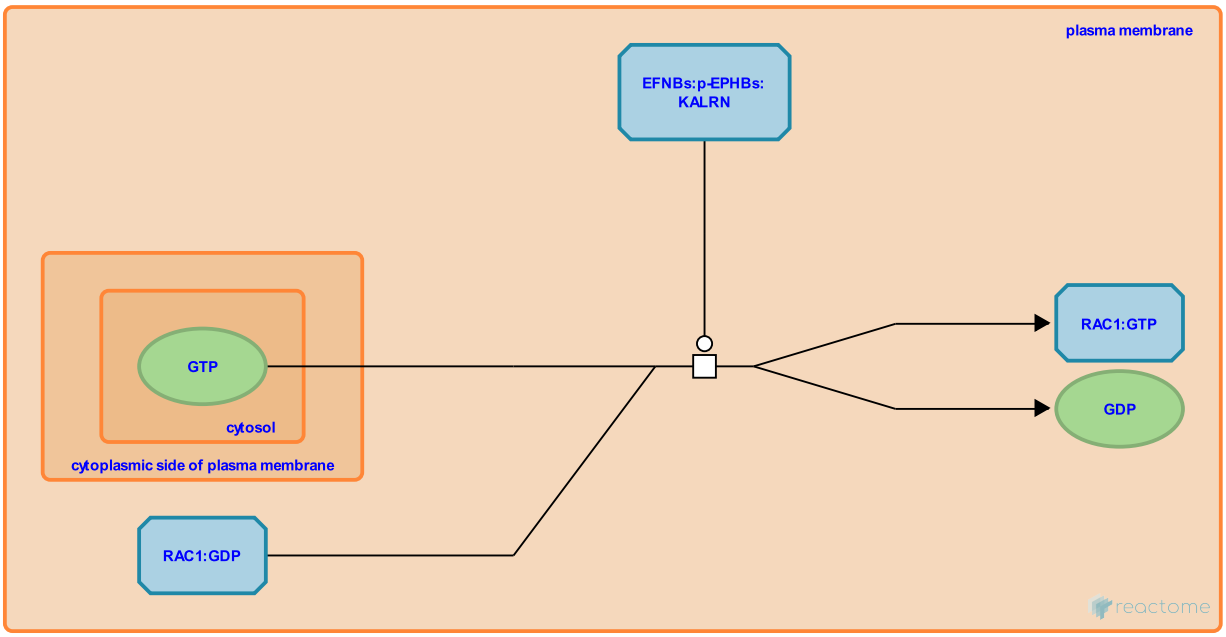
KALRN exchanges GTP for GDP on RAC1, activating it ↗

Location: EPHB-mediated forward signaling

Stable identifier: R-HSA-3928612

Type: transition

Compartments: plasma membrane



The Dbl homology (DH) and pleckstrin homology (PH) domains of kalirin (KALRN) provides the GEF activity and is activated upon binding to EPHB. Activated KALRN with its GEF domains activates RAC1, and controls spine remodelling by modulating actin cytoskeletal rearrangements (Penzes & Jones 2008, Penzes et al. 2003).

Preceded by: EPHB2 binds KALRN

Followed by: PAK1 binds RAC1:GTP

Literature references

Penzes, P., Eipper, BA., Schiller, MR., Huganir, RL., Chernoff, J., Beeser, A. et al. (2003). Rapid induction of dendritic spine morphogenesis by trans-synaptic ephrinB-EphB receptor activation of the Rho-GEF kalirin. *Neuron, 37*, 263-74. ↗

Editions

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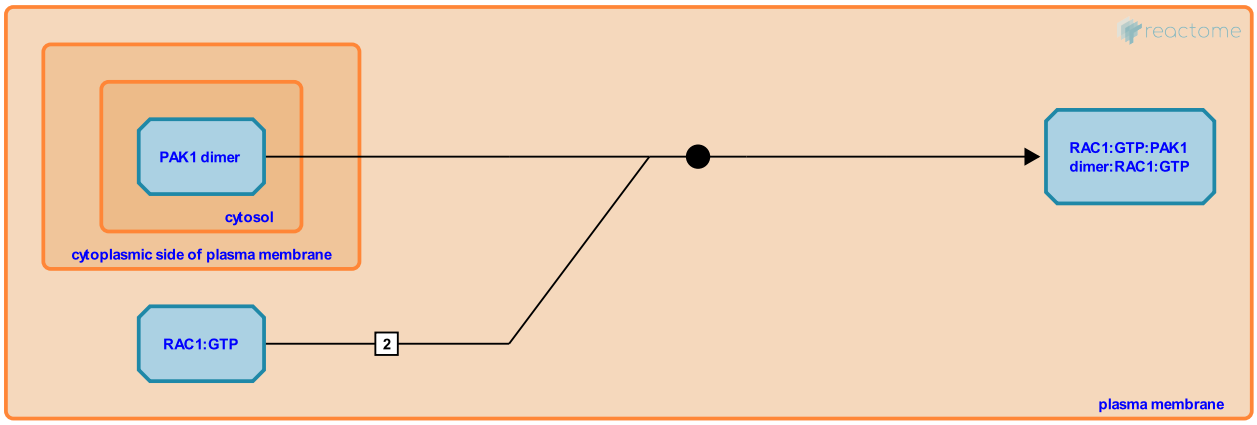
PAK1 binds RAC1:GTP ↗

Location: EPHB-mediated forward signaling

Stable identifier: R-HSA-3928619

Type: binding

Compartments: plasma membrane, cytosol



Serine/threonine-protein kinase PAK1 (PAK1) exists as homodimer in a trans-inhibited conformation. PAK1 translocates from cytosol to plasma membrane and comes in close proximity to RAC1. The kinase inhibitory (KI) domain of one PAK1 molecule binds to the C-terminal catalytic domain of the other and inhibits catalytic activity. RAC1:GTP bind to the GBD domain of PAK1 thereby altering the conformation of the KI domain, relieving inhibition of its catalytic domain, and allowing PAK1 autophosphorylation that is required for full kinase activity (Parrini et al. 2002, Zhao & Manser 2005, Sells et al. 2000).

Preceded by: KALRN exchanges GTP for GDP on RAC1, activating it

Followed by: PAK1 autophosphorylates

Literature references

Parrini, MC., Lei, M., Mayer, BJ., Harrison, SC. (2002). Pak1 kinase homodimers are autoinhibited in trans and dissociated upon activation by Cdc42 and Rac1. *Mol Cell, 9*, 73-83. ↗

Manser, E., Zhao, ZS. (2005). PAK and other Rho-associated kinases--effectors with surprisingly diverse mechanisms of regulation. *Biochem J, 386*, 201-14. ↗

Pfaff, A., Chernoff, J., Sells, MA. (2000). Temporal and spatial distribution of activated Pak1 in fibroblasts. *J. Cell Biol. , 151*, 1449-58. ↗

Editions

2013-07-23	Authored, Edited	Garapati, P V.
2014-05-19	Reviewed	Ip, NY.

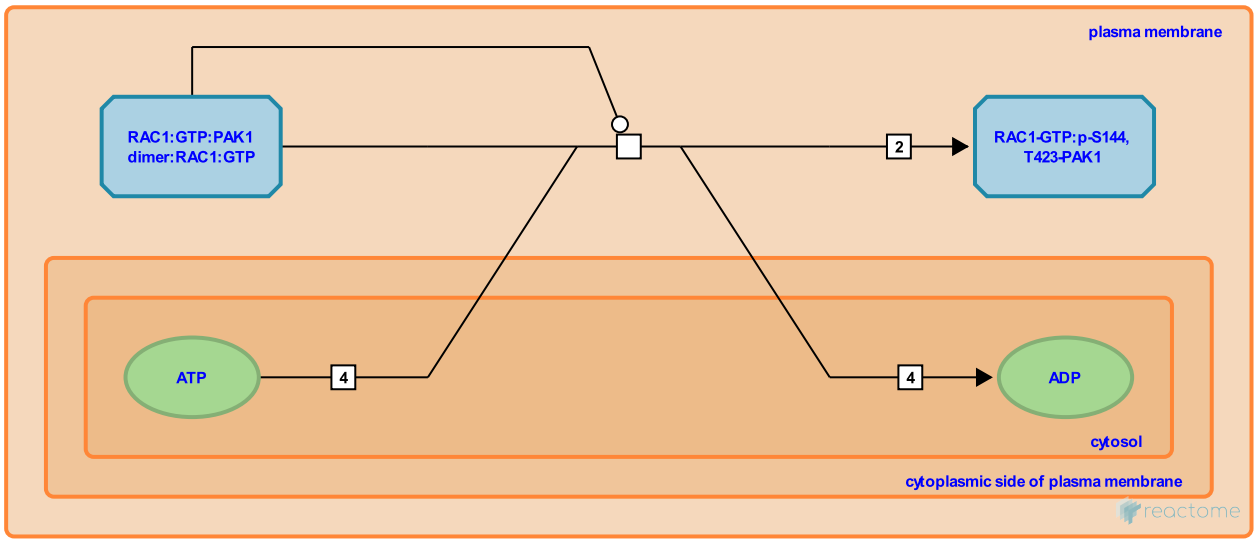
PAK1 autophosphorylates ↗

Location: EPHB-mediated forward signaling

Stable identifier: R-HSA-3928620

Type: transition

Compartments: plasma membrane, cytosol



Autophosphorylation of serine/threonine-protein kinase PAK1 (PAK1) is required for complete activation. PAK1 is autophosphorylated at several sites, but serine 144 (S144) in the GTPase binding domain and threonine 423 (T423) in the activation loop are the two conserved sites that regulate catalytic activity. As a result, active PAK1 phosphorylates substrates like LIMK (LIM domain kinase) that are involved in remodelling of the actin cytoskeleton.

Preceded by: PAK1 binds RAC1:GTP

Literature references

Parrini, MC., Lei, M., Mayer, BJ., Harrison, SC. (2002). Pak1 kinase homodimers are autoinhibited in trans and dissociated upon activation by Cdc42 and Rac1. *Mol Cell, 9*, 73-83. ↗

Pfaff, A., Chernoff, J., Sells, MA. (2000). Temporal and spatial distribution of activated Pak1 in fibroblasts. *J. Cell Biol. , 151*, 1449-58. ↗

Editions

2013-07-23	Authored, Edited	Garapati, P V.
2014-05-19	Reviewed	Ip, NY.

EPHBs binds PTK2 ↗

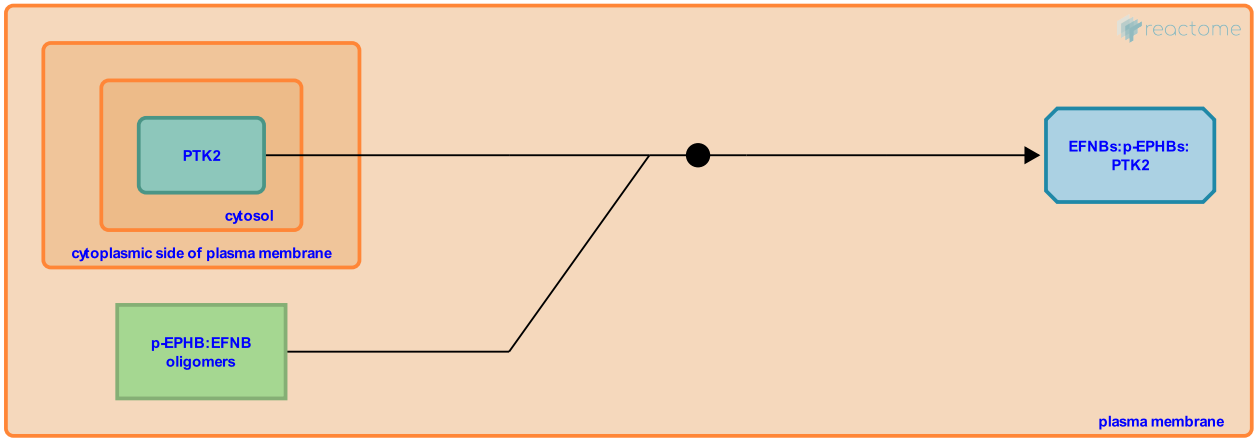
Location: EPHB-mediated forward signaling

Stable identifier: R-HSA-3928588

Type: binding

Compartments: plasma membrane, cytosol

Inferred from: EphBs binds Ptk2 (Mus musculus)



Focal adhesion kinase 1 (PTK2, FAK, FAK1) acts downstream of EPHB receptors in hippocampal neurons and the EPHB2-FAK signaling contributes to the dendritic spine morphogenesis and synapse maturation by suppressing the activity of actin severing cofilin through phosphorylation. Activation of EPHBs by ephrin-B (EFNB) stimulates the binding of FAK to EPHB. Knock out of FAK in mature neurons induces a shift of mushroom shaped mature dendritic spines to long filopodia like structures, suggesting that synapse formation or maturation is affected in FAK-/- neurons (Shi et al. 2009, Moeller et al. 2006).

Followed by: PTK2 autophosphorylates at Y397

Editions

2013-07-23	Authored, Edited	Garapati, P V.
2014-05-19	Reviewed	Ip, NY.

PTK2 autophosphorylates at Y397 ↗

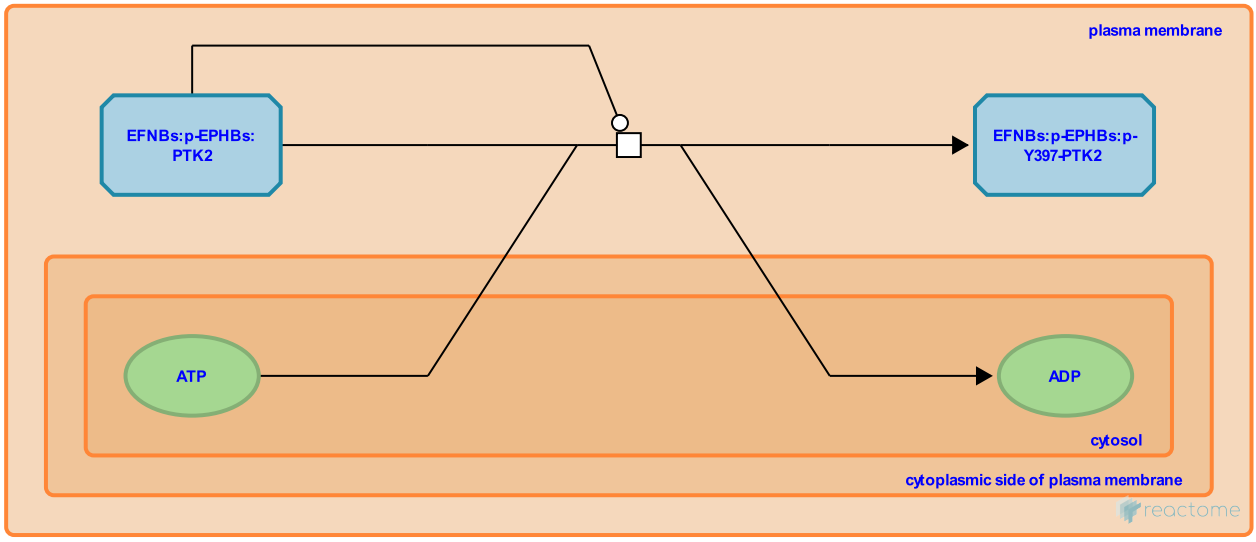
Location: EPHB-mediated forward signaling

Stable identifier: R-HSA-3928610

Type: transition

Compartments: plasma membrane, cytosol

Inferred from: Ptk2 autophosphorylates at Y397 (Mus musculus)



Focal adhesion kinase 1 (PTK2, FAK, FAK1) activation plays a critical role in EPHB receptor signaling in dendritic spines. PTK2 has six tyrosine phosphorylation sites, with tyrosine 397 being the main auto-phosphorylation site present upstream of the kinase domain (Schaller et al. 1994). Activation of EPHB receptors induces long-lasting phosphorylation of PTK2 on tyrosine 397 (Shi et al. 2009). This phosphorylated tyrosine then creates a binding site for other signaling proteins that link PTK2 to downstream signaling pathways and actin cytoskeleton.

Preceded by: EPHBs binds PTK2

Followed by: Recruitment of p190RhoGEF to p-FAK

Editions

2013-07-23	Authored, Edited	Garapati, P V.
2014-05-19	Reviewed	Ip, NY.

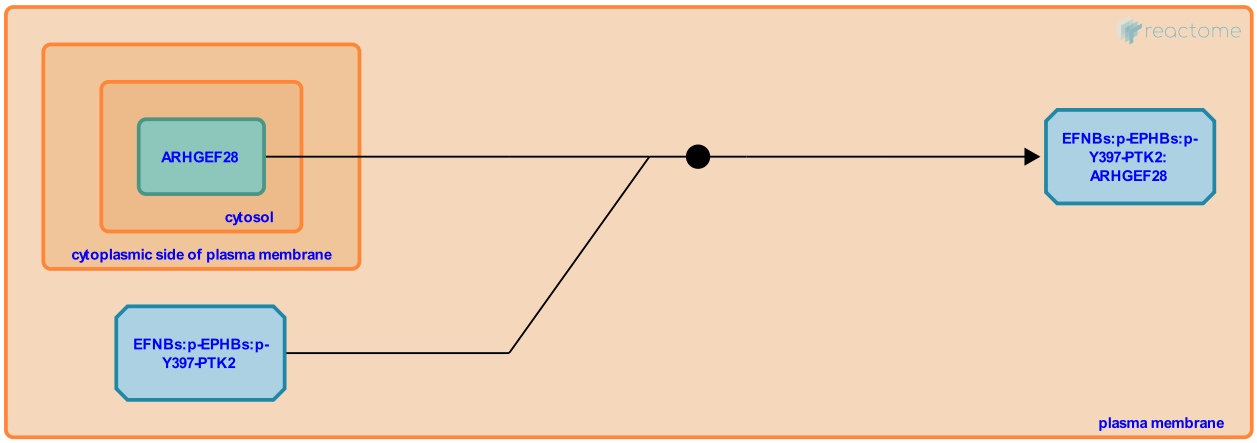
Recruitment of p190RhoGEF to p-FAK ↗

Location: EPHB-mediated forward signaling

Stable identifier: R-HSA-3928598

Type: binding

Compartments: plasma membrane, cytosol



FAK-mediated spine morphogenesis was shown to occur, in part through Rho guanine nucleotide exchange factor 28 (ARHGEF28, p190RhoGEF), suggesting that FAK-mediated spine maturation might proceed through a FAK-RhoGEF-RHOA mechanism. p190RhoGEF binds directly to phosphorylated PTK2 through a motif in the RhoGEF C-terminal domain, a feature not shared with other GEFs (Moeller et al. 2006, Rico et al. 2004, Zhai et al. 2003).

Preceded by: PTK2 autophosphorylates at Y397

Followed by: p190RhoGEF exchanges GTP for GDP on RHOA, activating it

Literature references

Schlaepfer, WW., Cañete-Soler, R., Nie, Z., Wu, J., Zhai, J., Lin, H. et al. (2003). Direct interaction of focal adhesion kinase with p190RhoGEF. *J. Biol. Chem., 278*, 24865-73. ↗

Moeller, ML., Reichardt, LF., Shi, Y., Ethell, IM. (2006). EphB receptors regulate dendritic spine morphogenesis through the recruitment/phosphorylation of focal adhesion kinase and RhoA activation. *J. Biol. Chem., 281*, 1587-98. ↗

Schmidt, A., Beggs, HE., Reichardt, LF., Schahin-Reed, D., Kimes, N., Rico, B. (2004). Control of axonal branching and synapse formation by focal adhesion kinase. *Nat. Neurosci., 7*, 1059-69. ↗

Editions

2013-07-23	Authored, Edited	Garapati, P V.
2014-05-19	Reviewed	Ip, NY.

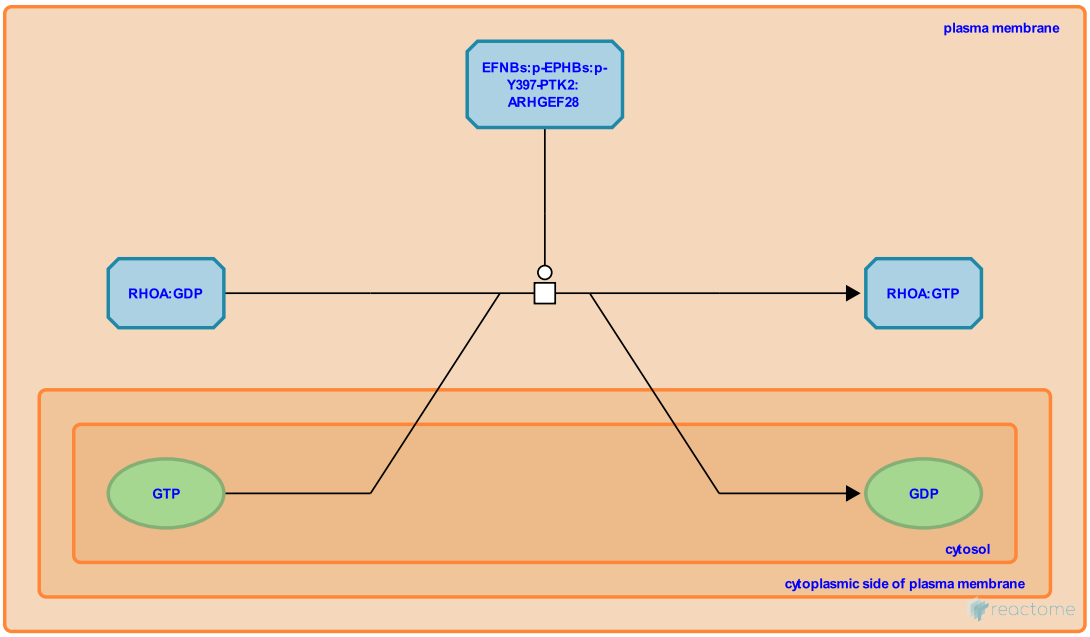
p190RhoGEF exchanges GTP for GDP on RHOA, activating it ↗

Location: EPHB-mediated forward signaling

Stable identifier: R-HSA-3928592

Type: transition

Compartments: plasma membrane, cytosol



Receptor stimulation induces translocation of RHOA from the cytosol to the plasma membrane and subsequent activation of RHOA. Rho guanine nucleotide exchange factor 28 (p190RhoGEF, ARHGEF28) is a specific activator of RHOA that stimulates the exchange of GDP for GTP. In neuronal cells p190RhoGEF binds to and activates RHOA with its Dbl homology/pleckstrin homology domain (van Horck et al. 2001).

Preceded by: Recruitment of p190RhoGEF to p-FAK

Followed by: RHOA:GTP binds ROCK, activating it

Literature references

van Horck, FP., Ahmadian, MR., Moolenaar, WH., Haeusler, LC., Kranenburg, O. (2001). Characterization of p190RhoGEF, a RhoA-specific guanine nucleotide exchange factor that interacts with microtubules. *J. Biol. Chem. , 276*, 4948-56. ↗

Editions

2013-07-23	Authored, Edited	Garapati, P V.
2014-05-19	Reviewed	Ip, NY.

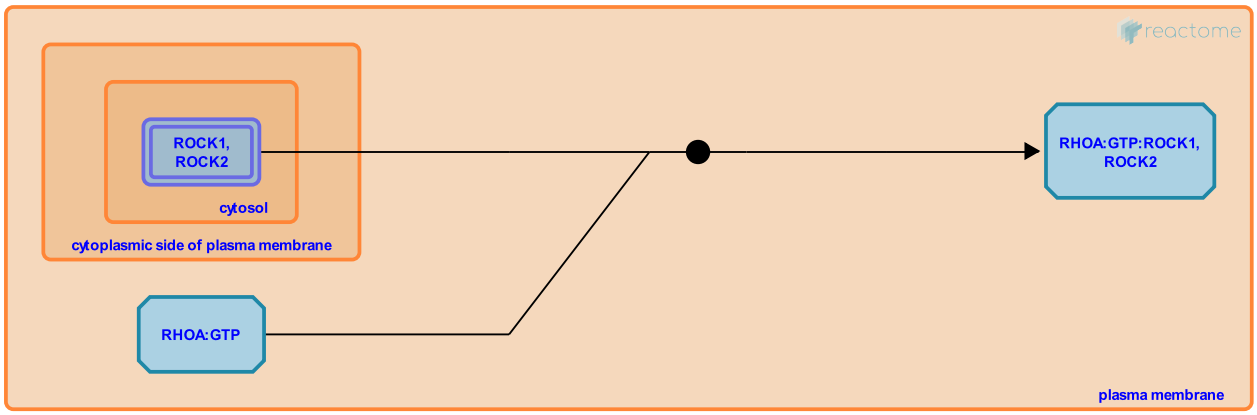
RHOA:GTP binds ROCK, activating it ↗

Location: EPHB-mediated forward signaling

Stable identifier: R-HSA-3928576

Type: binding

Compartments: plasma membrane, cytosol



EPHB receptor-induced phosphorylation of coffin is at least partially controlled by Rho-associated kinase (ROCK) and LIM domain kinase (LIMK) activities (Shi et al. 2009). ROCK structure comprises a kinase domain located at the amino terminus of the protein, a coiled-coil region containing the Rho-binding domain (RBD), and a pleckstrin-homology (PH) domain with a cysteine-rich domain (CRD). In resting cells ROCKs exist in an autoinhibition state where the kinase domain interacts with the C-terminal inhibitory region. Binding of active RHOA:GTP to RBD stimulates the phosphotransferase activity of ROCK by disrupting the interaction between the catalytic and the inhibitory C-terminal region of the enzyme (Khalil 2010).

Preceded by: p190RhoGEF exchanges GTP for GDP on RHOA, activating it

Followed by: ROCK phosphorylates LIMK1,2

Literature references

Reichardt, LF., Shi, Y., Pontrello, CG., DeFea, KA., Ethell, IM. (2009). Focal adhesion kinase acts downstream of EphB receptors to maintain mature dendritic spines by regulating cofilin activity. *J. Neurosci., 29*, 8129-42. ↗

Editions

2013-07-23	Authored, Edited	Garapati, P V.
2014-05-19	Reviewed	Ip, NY.

ROCK phosphorylates LIMK1,2 ↗

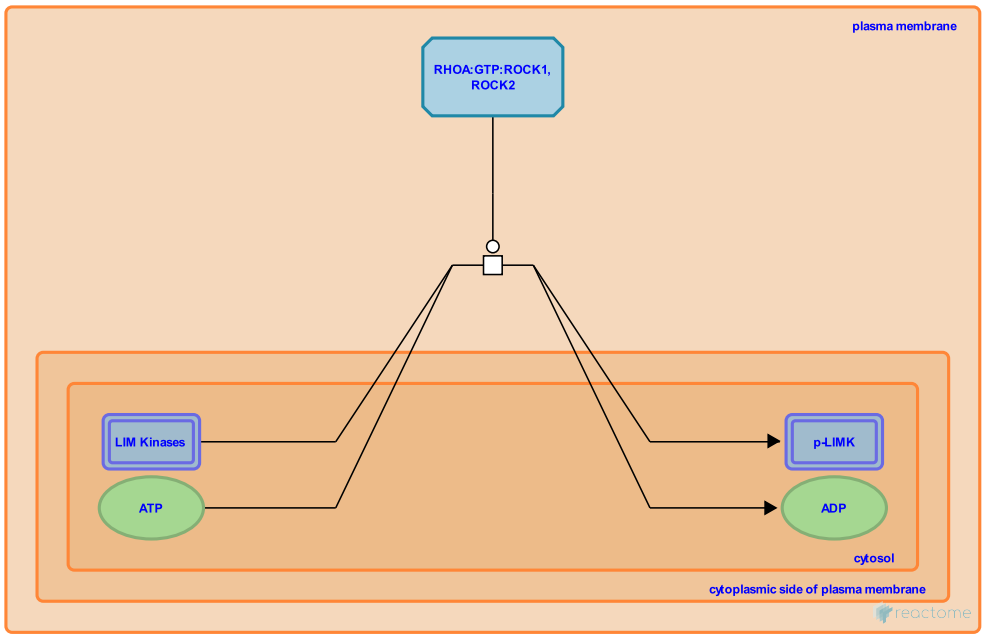
Location: EPHB-mediated forward signaling

Stable identifier: R-HSA-3928577

Type: transition

Compartments: plasma membrane, cytosol

Inferred from: ROCK1 phosphorylates LIMK2 (rat) (Homo sapiens)



Rho-associated kinases (ROCKs) contribute to the formation of actin filaments by inactivating cofilin via phosphorylation of LIM domain kinases (LIMKs). ROCKs phosphorylate LIMK1 at Thr508 and LIMK2 at Thr505, enhancing the ability of LIMKs to phosphorylate cofilin. LIMK1 has been shown to be involved in dendritic spine development, as LIMK1 KO mice fail to form morphologically mature dendritic spines (Meng et al. 2002).

Preceded by: RHOA:GTP binds ROCK, activating it

Followed by: LIMK phosphorylates CFL1, inactivating it

Editions

2013-07-23	Authored, Edited	Garapati, P V.
2014-05-19	Reviewed	Ip, NY.

LIMK phosphorylates CFL1, inactivating it ↗

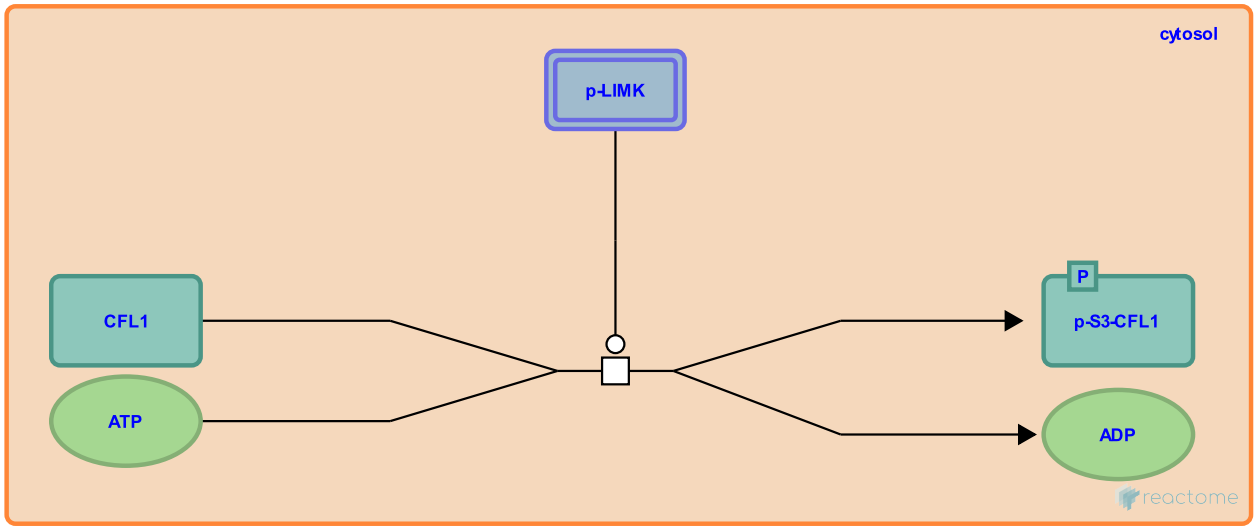
Location: EPHB-mediated forward signaling

Stable identifier: R-HSA-3928608

Type: transition

Compartments: cytosol

Inferred from: Limk1 phosphorylates Cfl1, inactivating it (Homo sapiens)



The EPHB2-FAK pathway partially promotes dendritic spine stability through LIMK-mediated cofilin (CFL1) phosphorylation (Shi et al. 2009). CFL1 is a member of the ADF (actin-depolymerizing factor) protein family that is involved in regulating actin dynamics in the growth cone. It binds to actin in a one-to-one molar ratio, and stimulates both the severing of actin filaments and depolymerization of actin subunits from the actin filament end. Activated LIMK phosphorylates CFL1 on the conserved serine 3 residue located near the actin-binding site. After phosphorylation, CFL1 is inactive, loses its affinity for actin and dissociates from G-actin monomers. Once freed, ADP-actin monomers can exchange ADP with cytoplasmic ATP, ready for reincorporation at the barbed end of a growing filament (Gungabissoon & Bamburg 2003).

Preceded by: ROCK phosphorylates LIMK1,2

Editions

2013-07-23	Authored, Edited	Garapati, P V.
2014-05-19	Reviewed	Ip, NY.

EPHBs bind NMDARs ↗

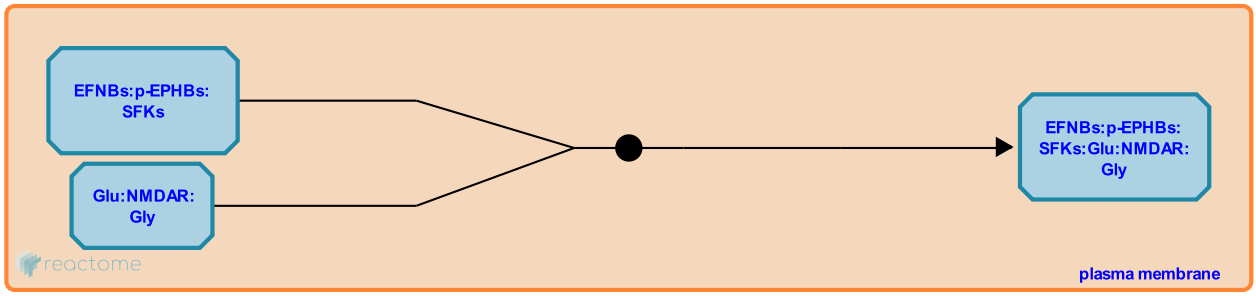
Location: EPHB-mediated forward signaling

Stable identifier: R-HSA-3928623

Type: binding

Compartments: plasma membrane

Inferred from: Ephb2 bind Nmdar (Mus musculus)



EPHBs are involved in spine synapse formation and also for the recruitment and clustering of glutamate receptors to synapses. At the time of synaptogenesis, EPHBs are localized to the postsynaptic region of excitatory synapses. These postsynaptic EPHBs, upon activation by presynaptic ephrinBs (EFNBs), directly interact with ionotropic glutamate receptor, NR1 and NR2B (NMDAR1and 2B aka GRIN1and 2B). The interaction between EPHB and NMDARs is mediated by the extracellular domains of these two proteins. This interaction promotes clustering of NMDARs at synaptic locations and leads to the formation of functional presynaptic release sites. Activated EPHBs function as tyrosine kinases and may also indirectly potentiate NMDAR-mediated calcium influx (Dalva et al. 2000, Takasu et al. 2002).

Followed by: FYN phosphorylates NMDAR2B

Editions

2013-07-23	Authored, Edited	Garapati, P V.
2014-05-19	Reviewed	Ip, NY.

FYN phosphorylates NMDAR2B ↗

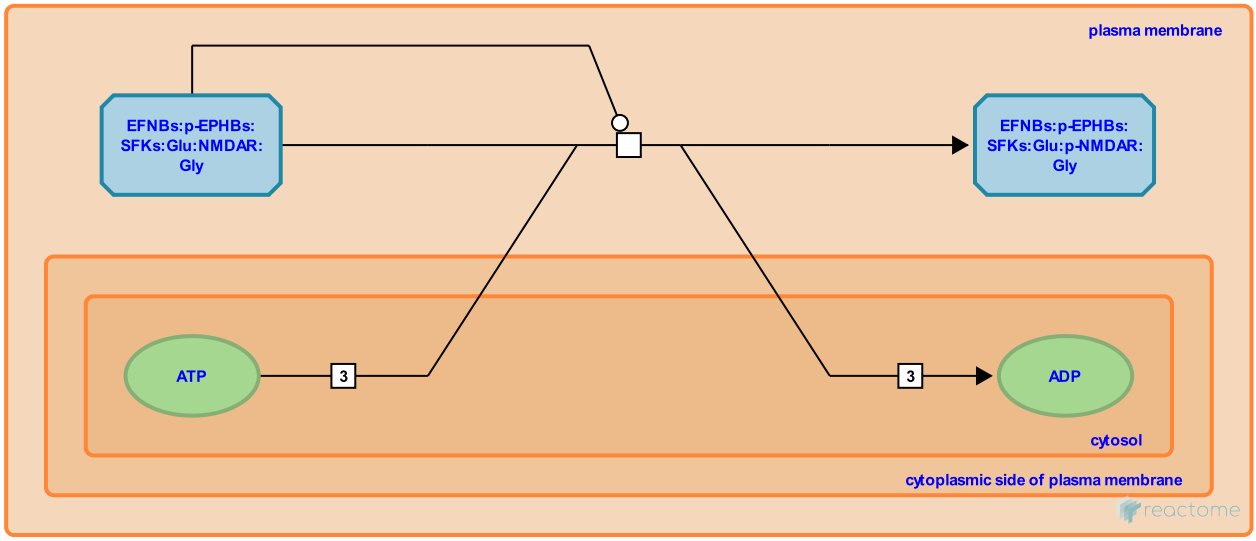
Location: EPHB-mediated forward signaling

Stable identifier: R-HSA-3928583

Type: transition

Compartments: plasma membrane, cytosol

Inferred from: Fyn phosphorylates Nmdar2b (Mus musculus)



Protein phosphorylation is an important mechanism modulating the function of NMDA receptors (NMDARs). SRC-family kinases that associate with EPHB are important for the phosphorylation of ionotropic glutamate receptor, NR2B (NMDAR2B, GRIN2B) Tyrosines 1252, 1336, and 1474 (1252, 1336, and 1472 in mouse) on NR2B are phosphorylated by FYN/SRC bound to EPHB2, thereby enhancing NMDA-dependent calcium influx upon glutamate stimulation (Takasu et al. 2002, Dalva et al. 2000). Tyrosine phosphorylation of NMDAR2B also regulates the surface expression of NMDARs. EPHB mediated phosphorylation of NMDARs can also increase the surface retention of NMDAR2B-containing NMDARs by preventing clathrin-dependent endocytosis. Phosphorylation at tyrosine 1474 (mouse Y1472) of NMDAR2B blocks binding of the mu2 subunit of clathrin adaptor protein 2 (AP2) complex thus preventing clathrin-dependent endocytosis (Chen & Roche 2007).

Preceded by: EPHBs bind NMDARs

Followed by: EPHB:NMDAR binds TIAM1

Editions

2013-07-23	Authored, Edited	Garapati, P V.
2014-05-19	Reviewed	Ip, NY.

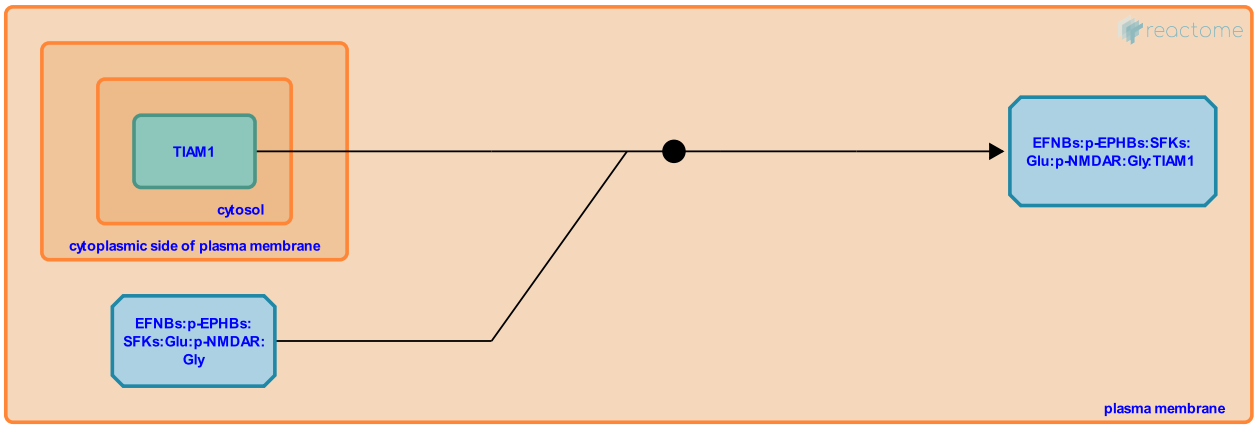
EPHB:NMDAR binds TIAM1 ↗

Location: EPHB-mediated forward signaling

Stable identifier: R-HSA-3928645

Type: binding

Compartments: plasma membrane, cytosol



T-lymphoma invasion and metastasis-inducing protein 1 (TIAM1) is a Rac1-specific GEF, highly expressed in the nervous system, which is necessary for proper spinal and synapse development. It is one of the critical mediators of NMDA receptor (NMDAR)-dependent spine development (Tolias et al. 2005). TIAM1 might also play a role in regulating EPHB-dependent spine morphogenesis. TIAM1 appears to be required for ephrinB (EFNB)-induced increase in spine density. TIAM1 is recruited to EPHB complexes containing NMDAR after EPHB receptor activation in neurons. The PH-CC-Ex (consisting of a pleckstrin homology (PH) domain followed by a coiled-coiled (CC) domain and an adjacent region (Ex) domain) of TIAM1 is required for binding to EPHB2 (Tolias et al. 2007).

Preceded by: FYN phosphorylates NMDAR2B

Followed by: EPHB phosphorylates TIAM1

Literature references

Kane, CG., Greenberg, ME., Hu, L., Bikoff, JB., Tolias, KF., Tolias, CS. (2007). The Rac1 guanine nucleotide exchange factor Tiam1 mediates EphB receptor-dependent dendritic spine development. *Proc. Natl. Acad. Sci. U.S.A., 104*, 7265-70. ↗

Shinmura, K., Sakai, R., Ohashi, R., Tanaka, M., Kamo, T., Nakamura, R. et al. (2004). Tiam1 mediates neurite outgrowth induced by ephrin-B1 and EphA2. *EMBO J., 23*, 1075-88. ↗

Editions

2013-07-23	Authored, Edited	Garapati, P V.
2014-05-19	Reviewed	Ip, NY.

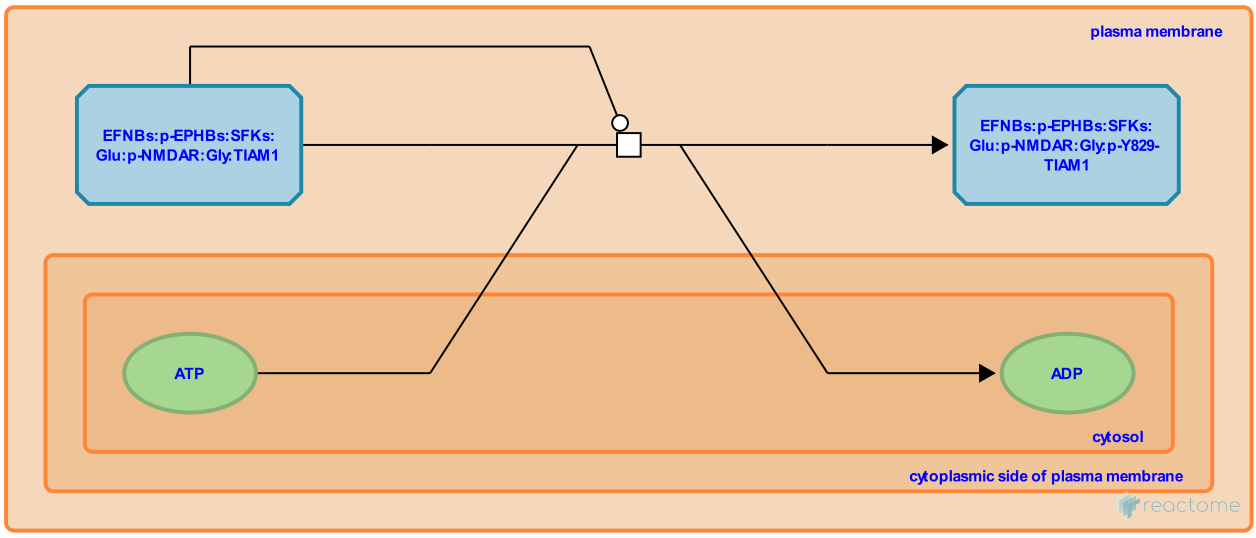
EPHB phosphorylates TIAM1 ↗

Location: EPHB-mediated forward signaling

Stable identifier: R-HSA-3928627

Type: transition

Compartments: plasma membrane, cytosol



Once recruited to the EPHB:NMDAR complex, T-lymphoma invasion and metastasis-inducing protein 1 (TIAM1) is phosphorylated on tyrosine 829 by either EPHB or a kinase that associates with activated EPHB. TIAM1 may then activate Rac1, leading to actin cytoskeletal remodelling required for spine development and morphogenesis (Tolias et al. 2007).

Preceded by: EPHB:NMDAR binds TIAM1

Followed by: p-TIAM1 exchanges GTP for GDP on RAC1, activating it

Literature references

Kane, CG., Greenberg, ME., Hu, L., Bikoff, JB., Tolias, KF., Tolias, CS. (2007). The Rac1 guanine nucleotide exchange factor Tiam1 mediates EphB receptor-dependent dendritic spine development. *Proc. Natl. Acad. Sci. U.S.A., 104,* 7265-70. ↗

Editions

2013-07-23	Authored, Edited	Garapati, P V.
2014-05-19	Reviewed	Ip, NY.

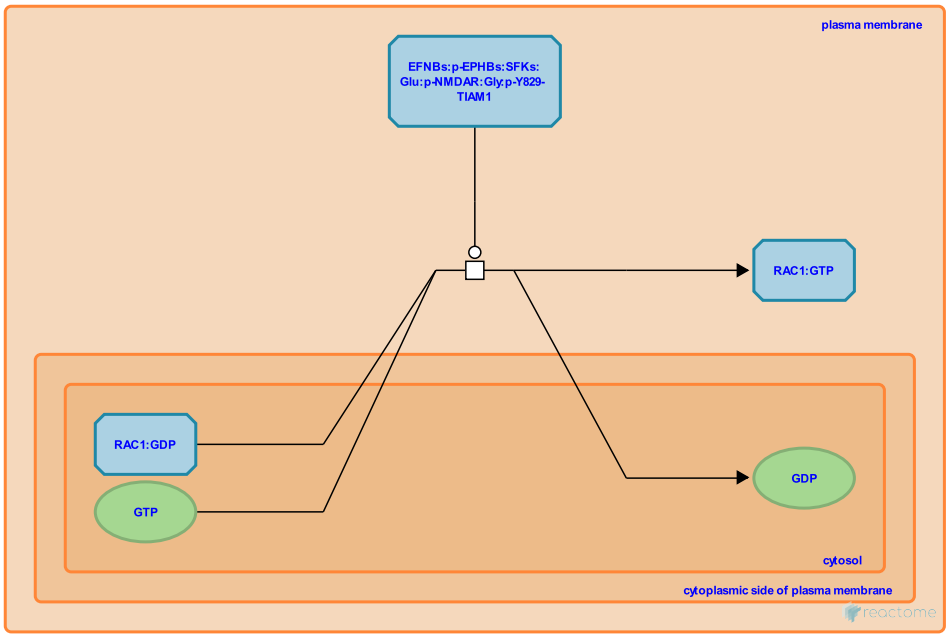
p-TIAM1 exchanges GTP for GDP on RAC1, activating it ↗

Location: EPHB-mediated forward signaling

Stable identifier: R-HSA-4093336

Type: transition

Compartments: plasma membrane, cytosol



Phosphorylated T-lymphoma invasion and metastasis-inducing protein 1 (p-TIAM1) bound to EPHB complexes containing NMDARs, promotes spine morphogenesis by activating RAC1, which triggers actin cytoskeletal remodelling that is essential for spine development (Tolias et al. 2007, Tolias et al. 2005).

Preceded by: EPHB phosphorylates TIAM1

Literature references

Greenberg, ME., Tavazoie, S., Harrar, D., Paradis, S., Burette, A., Weinberg, RJ. et al. (2005). The Rac1-GEF Tiam1 couples the NMDA receptor to the activity-dependent development of dendritic arbors and spines. *Neuron, 45*, 525-38. ↗

Editions

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2014-05-19	Reviewed	Ip, NY.

EPHB binds p120-RasGAP ↗

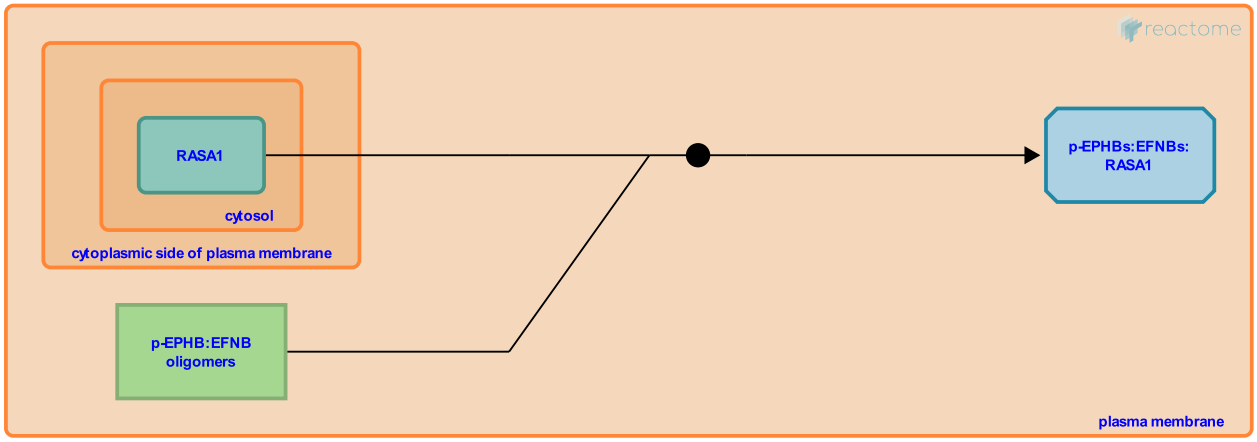
Location: EPHB-mediated forward signaling

Stable identifier: R-HSA-4093330

Type: binding

Compartments: plasma membrane, cytosol

Inferred from: Ephb2 binds p120-RasGAP (Mus musculus)



In addition to regulating Rho family proteins, the EPH receptors and ephrins (EFNs) also regulate the activity of Ras family proteins. Ras-MAPK pathway is a key regulator of cell proliferation, adhesion and transformation, but can also influence axon guidance (Forcet et al. 2002). EPHB receptors downregulate H-Ras and consequently its downstream effector extracellular signal-regulated kinase (ERK) mitogen-activated protein kinase (MAPK) pathway in neuronal cells (Elowe et al. 2001, Miao et al. 2000). EPHB2 signals through the SH2 domain protein p120-RasGAP (RASA1) to inhibit the Ras-MAPK pathway. p120-RasGAP binds directly through its SH2 domains to the autophosphorylated EPHB2 juxtamembrane region (Holland et al. 1997, Elowe et al. 2001).

Followed by: Ras:GTP binds p120-RasGAP

Editions

2013-07-23	Authored, Edited	Garapati, P V.
2014-05-19	Reviewed	Ip, NY.

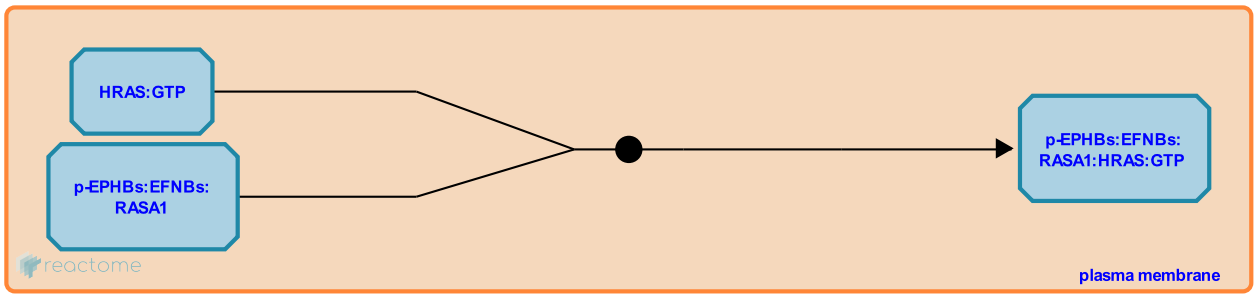
Ras:GTP binds p120-RasGAP ↗

Location: EPHB-mediated forward signaling

Stable identifier: R-HSA-4093331

Type: binding

Compartments: plasma membrane, cytosol



p120-RasGAP (RASA1) binds to activated Ras (Ras:GTP) through its GAP-related catalytic domain, which is sufficient for stimulating the Ras GTPase activity. p120-RasGAP accelerates the intrinsic GTPase activity of Ras to promote Ras inactivation (Yao et al. 1995).

Preceded by: EPHB binds p120-RasGAP

Followed by: p120-RasGAP activates GTP hydrolysis on RAS, inactivating it

Literature references

Cooper, GM., Yao, R. (1995). Regulation of the Ras signaling pathway by GTPase-activating protein in PC12 cells. *Oncogene, 11*, 1607-14. ↗

DeClue, JE., McCormick, F., Zhang, K., Lowy, DR., Papageorge, AG., Vass, WC. (1990). Suppression of c-ras transformation by GTPase-activating protein. *Nature, 346*, 754-6. ↗

Editions

2013-07-23	Authored, Edited	Garapati, P V.
2014-05-19	Reviewed	Ip, NY.

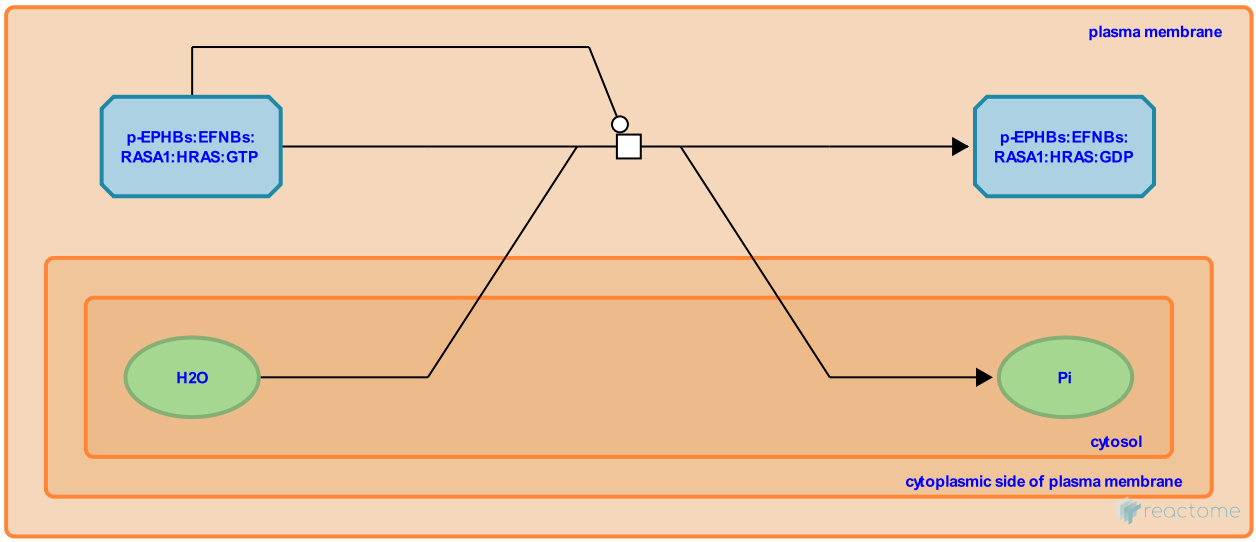
p120-RasGAP activates GTP hydrolysis on RAS, inactivating it ↗

Location: EPHB-mediated forward signaling

Stable identifier: R-HSA-4093339

Type: transition

Compartments: plasma membrane, cytosol



The p120-RasGAP C-terminus contains a GAP domain that catalyses the activation of H-Ras by hydrolyzing GTP-bound active Ras into an inactive GDP-bound form of Ras. Inactivation of H-Ras by EPHB2 down regulates MAP kinase phosphorylation and induces neurite retraction in neuronal cells (Elowe et al. 2001, Tong et al. 2003).

Preceded by: Ras:GTP binds p120-RasGAP

Literature references

Cooper, GM., Yao, R. (1995). Regulation of the Ras signaling pathway by GTPase-activating protein in PC12 cells. *Oncogene, 11*, 1607-14. ↗

DeClue, JE., McCormick, F., Zhang, K., Lowy, DR., Papageorge, AG., Vass, WC. (1990). Suppression of c-ras transformation by GTPase-activating protein. *Nature, 346*, 754-6. ↗

Editions

2013-07-23	Authored, Edited	Garapati, P V.
2014-05-19	Reviewed	Ip, NY.

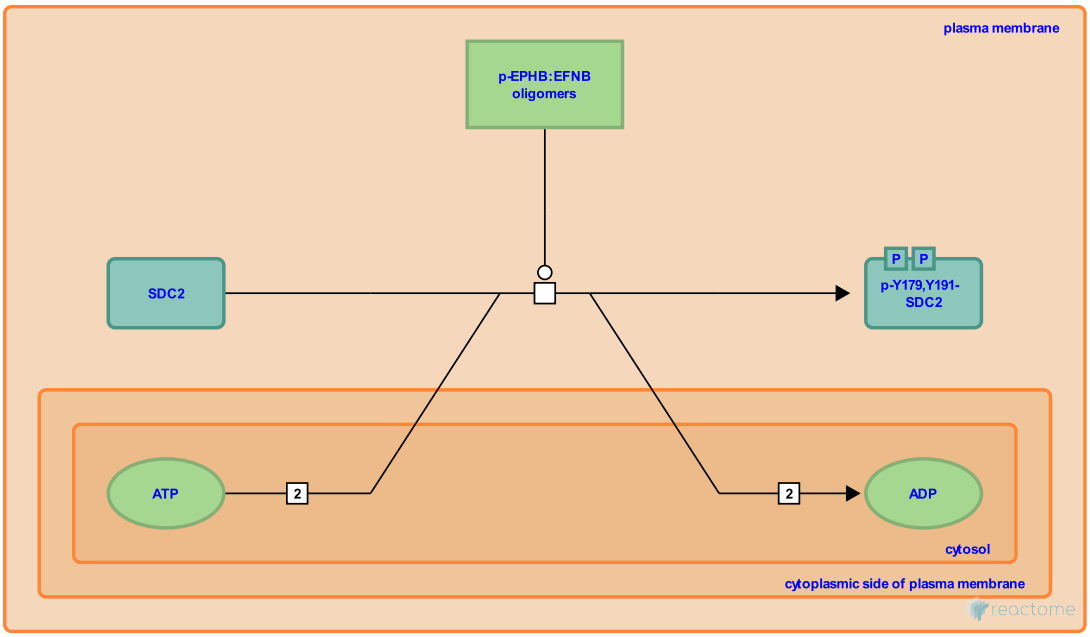
p-EPHB phosphorylates SDC2 ↗

Location: EPHB-mediated forward signaling

Stable identifier: R-HSA-4093332

Type: transition

Compartments: plasma membrane, cytosol



Syndecans (SDCs) are a major class of cell surface heparan sulphate proteoglycans (HSPGs) and the member syndecan-2 (SDC2) plays a critical role in EPHB-mediated spine formation in hippocampal neurons. Ethell et al. suggest that one of the mechanisms by which EPHB receptors regulate spine morphology is through phosphorylation of SDC2 (Ethell et al. 2001, Ethell & Yamaguchi 1999). Activated EPHB2 phosphorylates SDC2 at tyrosine residues Y189 and Y201 (Y179 and Y191 according to uniprot reference sequence) in the C1 and V regions respectively (Ethell et al. 2001).

Followed by: SDC2 multimerises

Literature references

Irie, F., Pasquale, EB., Couchman, JR., Yamaguchi, Y., Ethell, IM., Kalo, MS. (2001). EphB/syndecan-2 signaling in dendritic spine morphogenesis. *Neuron, 31*, 1001-13. ↗

Editions

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2014-05-19	Reviewed	Ip, NY.

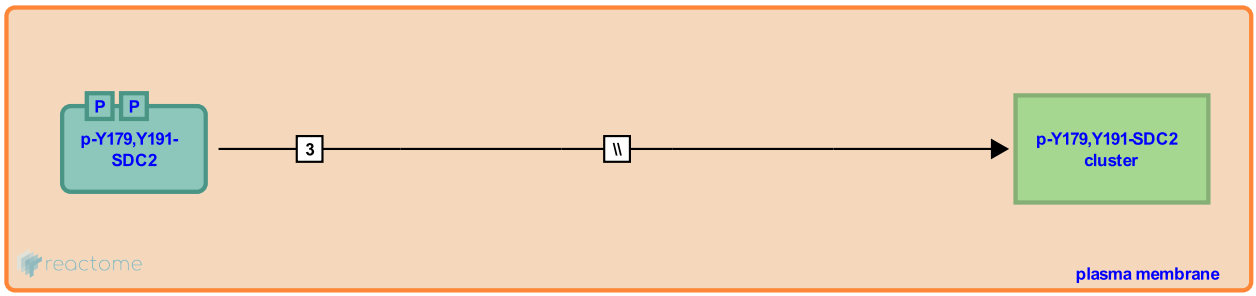
SDC2 multimerises ↗

Location: EPHB-mediated forward signaling

Stable identifier: R-HSA-4093342

Type: omitted

Compartments: plasma membrane



Syndecan-2 (SDC2), upon phosphorylation by EPHB2, undergoes multimerization and clustering on dendrites leading to spinogenesis. Pathways downstream of SDC2 that ultimately leads to cytoskeletal rearrangement of the spine have yet to be elucidated. Ethell et al. hypothesised that EPHB2 may associate with SDC2 after clustering and localise SDC2 to sites of nascent spines. Subsequent recruitment of syntenin and CASK by SDC2 via PDZ interactions may promote spinogenesis (Ethell et al. 2001, Lin et al. 2007).

Preceded by: p-EPHB phosphorylates SDC2

Literature references

Irie, F., Pasquale, EB., Couchman, JR., Yamaguchi, Y., Ethell, IM., Kalo, MS. (2001). EphB/syndecan-2 signaling in dendritic spine morphogenesis. *Neuron, 31*, 1001-13. ↗

Lin, YL., Hong, CJ., Hsueh, YP., Lei, YT. (2007). Syndecan-2 induces filopodia and dendritic spine formation via the neurofibromin-PKA-Ena/VASP pathway. *J. Cell Biol., 177*, 829-41. ↗

Editions

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2014-05-19	Reviewed	Ip, NY.

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