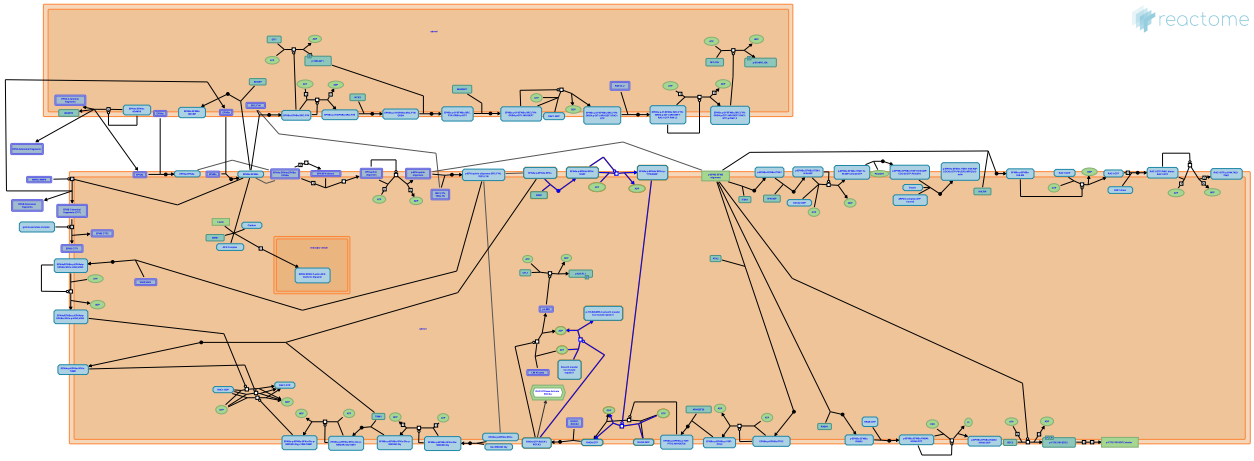
EPHA-mediated growth cone collapse



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Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.
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Literature references

Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics, 18*, 142. ↗

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

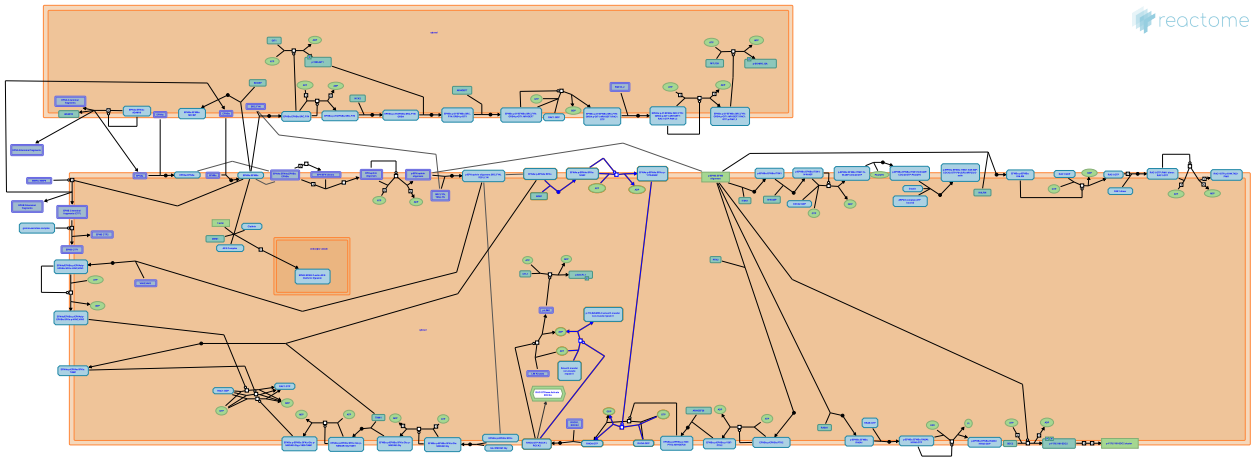
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

EPHA-mediated growth cone collapse ↗

Stable identifier: R-HSA-3928663

Compartments: cytosol, plasma membrane



EPH/Ephrin signaling is coupled to Rho family GTPases such as Rac, Rho and Cdc42 that connect bidirectional receptor-ligand interactions to changes in the actin cytoskeleton (Noren & Pasquale 2004, Groeger & Nobes 2007). RHOA regulates actin dynamics and is involved in EPHA-induced growth cone collapse. This is mediated by ephexins. Ephexin, a guanine nucleotide exchange factor for Rho GTPases, interacts with the EPHA kinase domain and its subsequent activation differentially affects Rho GTPases, such that RHOA is activated, whereas Cdc42 and Rac1 are inhibited. Activation of RHOA, and inhibition of Cdc42 and Rac, shifts actin cytoskeleton to increased contraction and reduced expansion leading to growth-cone collapse (Shamah et al. 2001, Sahin et al. 2005). The activation of EPH receptors in growing neurons typically, but not always, leads to a growth cone collapse response and retraction from an ephrin-expressing substrate (Poliakov et al. 2004, Pasquale 2005). EPHA-mediated repulsive responses prevent axons from growing into regions of excessive ephrin-A concentration, such as the posterior end of the superior colliculus (Pasquale 2005).

Literature references

Hu, L., Sahin, M., Debant, A., Corfas, G., Bazalakova, M., Goldberg, JL. et al. (2001). EphA receptors regulate growth cone dynamics through the novel guanine nucleotide exchange factor ephexin. *Cell, 105*, 233-44. ↗

Poliakov, A., Wilkinson, DG., Cotrina, M. (2004). Diverse roles of eph receptors and ephrins in the regulation of cell migration and tissue assembly. *Dev. Cell, 7*, 465-80. ↗

Debant, A., Greenberg, ME., Corfas, G., Lin, MZ., Wright, TM., Schmidt, S. et al. (2005). Eph-dependent tyrosine phosphorylation of ephexin1 modulates growth cone collapse. *Neuron, 46*, 191-204. ↗

Pasquale, EB., Noren, NK. (2004). Eph receptor-ephrin bidirectional signals that target Ras and Rho proteins. *Cell. Signal., 16*, 655-66. ↗

Pasquale, EB. (2005). Eph receptor signalling casts a wide net on cell behaviour. *Nat. Rev. Mol. Cell Biol., 6*, 462-75. ↗

Editions

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NGEF binds EPHA ↗

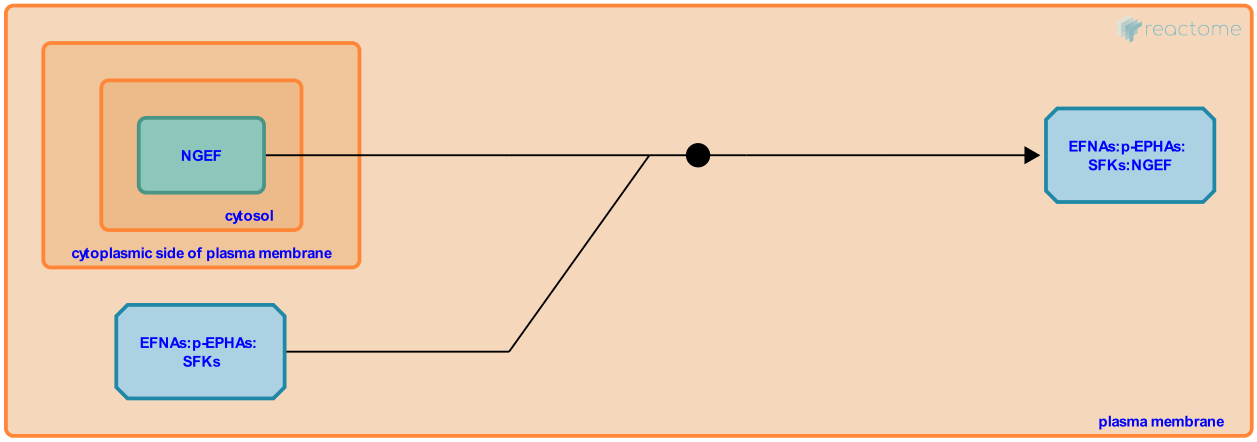
Location: EPHA-mediated growth cone collapse

Stable identifier: R-HSA-3928602

Type: binding

Compartments: plasma membrane, cytosol

Inferred from: Ephexin1 binds to EphA4 (Mus musculus)



Ephexin1/NGEF (Neuronal guanine nucleotide exchange factor) is a member of the Dbl family of guanine nucleotide exchange factors (GEFs) for Rho GTPases, which interacts with cytoplasmic domain of EPHAs. NGEF is highly expressed in the CNS during development and is enriched in neuronal growth cones. NGEF binds to the kinase domain of EPHA through its Dbl homology (DH)-pleckstrin-homology (PH) domains and this binding does not require activation of the receptor. EPHA activation by ephrinA ligands increases the catalytic activity of ephexin1 resulting in enhanced RHOA activation in cortical neurons (Noren & Pasquale 2004, Shamah et al. 2001). Ephrin-A1 also induces the dispersal of acetylcholine receptors clusters at the neuromuscular junction through the activation of NGEF and RhoA (Shi et al., 2010). NGEF is involved in both axonal growth,growth cone collapse, dendritic spine elimination and stabilization of the neuromuscular junction. In the absence of ephrin stimulation, NGEF promotes actin polymerization and axonal growth by stimulating RHOA, RAC1 and CDC42. Whereas in the presence of ephrin stimulation, NGEF induces growth cone collapse by activating RHOA, but not RAC1 and CDC42 (Shamah et al. 2001, Sahin et al. 2005).

Followed by: SFKs phosphorylate NGEF

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SFKs phosphorylate NGEF ↗

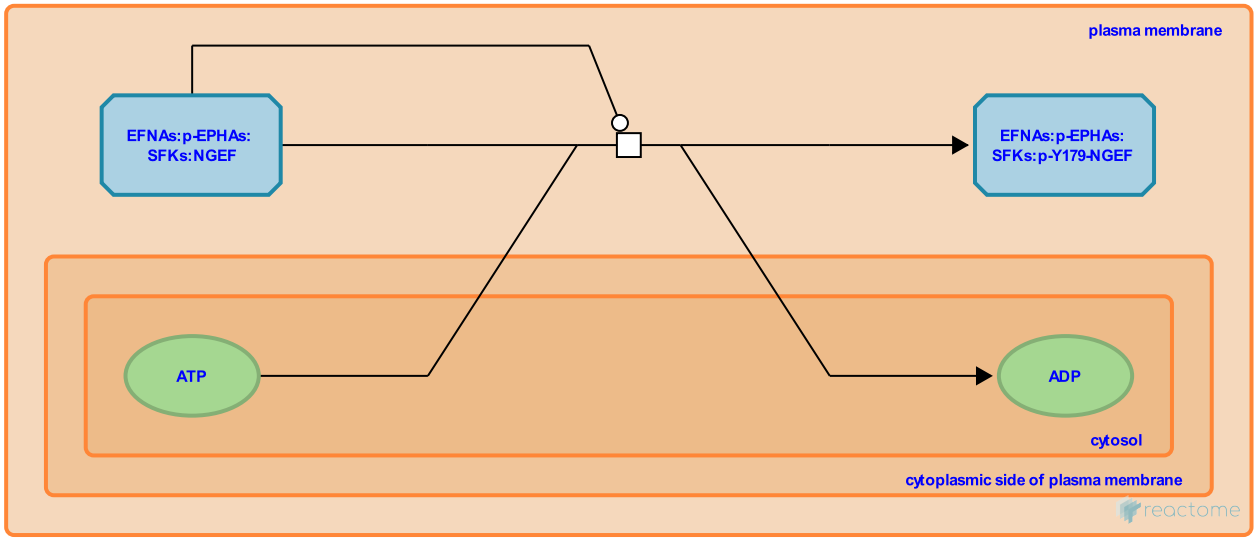
Location: EPHA-mediated growth cone collapse

Stable identifier: R-HSA-3928648

Type: transition

Compartments: plasma membrane, cytosol

Inferred from: Phosphorylation of ephexin1 (Gallus gallus)



Activation of EPHAs leads to phosphorylation of ephexin1 (NGEF) on conserved tyrosine (Y) 179 (Y87 in isoform3) by Src family kinases (SFKs). This phosphorylation preferentially activates NGEF's GDP/GTP exchange activity specifically towards RHOA but not RAC1 and CDC42, thus switching the substrate preference of NGEF and leading to actin cytoskeletal changes that result in growth cone collapse (Sahin et al. 2005, Knoll and Drescher 2004).

Preceded by: NGEF binds EPHA

Followed by: NGEF exchanges GTP for GDP on RHOA

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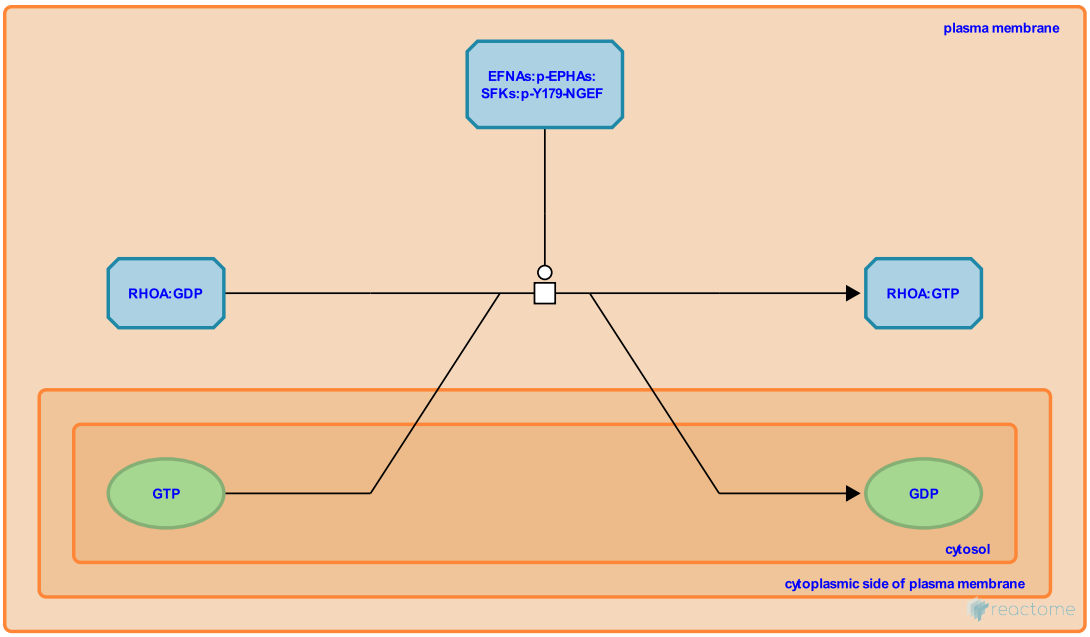
NGEF exchanges GTP for GDP on RHOA ↗

Location: EPHA-mediated growth cone collapse

Stable identifier: R-HSA-3928651

Type: transition

Compartments: plasma membrane, cytosol



The tyrosine phosphorylation of ephexin1 (NGEF)/Ephexin-1 enhances its exchange activity and specifically activates inactive RHOA:GDP to active RHOA:GTP. Activated RHOA regulates myosin II activity in neurons through Rho-associated kinase (ROCK), and leads to rapid growth cone collapse, neurite retraction, or neurite growth inhibition in axons. Through this repulsive mechanism EPH receptors and ephrins (EFNs) guide retinal axons to their targets in the visual centres in the brain (Sahin et al. 2005).

Preceded by: SFKs phosphorylate NGEF

Literature references

Debant, A., Greenberg, ME., Corfas, G., Lin, MZ., Wright, TM., Schmidt, S. et al. (2005). Eph-dependent tyrosine phosphorylation of ephexin1 modulates growth cone collapse. *Neuron, 46*, 191-204. ↗

Aktories, K., Ciossek, T., Wahl, S., Mueller, BK., Barth, H. (2000). Ephrin-A5 induces collapse of growth cones by activating Rho and Rho kinase. *J. Cell Biol., 149*, 263-70. ↗

Dickson, BJ. (2001). Rho GTPases in growth cone guidance. *Curr. Opin. Neurobiol., 11*, 103-10. ↗

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Activated ROCK phosphorylates MRLCs ↗

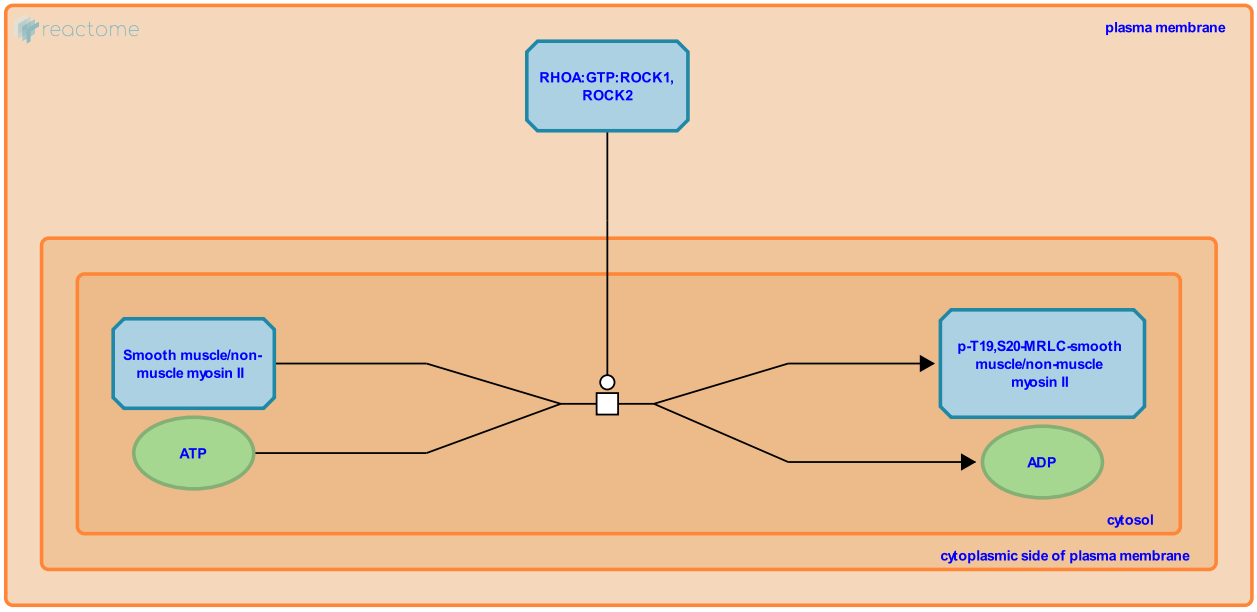
Location: EPHA-mediated growth cone collapse

Stable identifier: R-HSA-3928616

Type: transition

Compartments: cytosol

Inferred from: Myosin regulatory light chain phosphorylation by Rock2 (Gallus gallus)



The RHOA-ROCK-myosin pathway mediates neurite retraction by increasing the phosphorylation of the regulatory chain of myosin (Amano et al. 1998). Non-muscle myosin II (NMM2) is an actin-based motor protein that plays a crucial role in a variety of cellular processes, including cell migration, polarity formation, and cytokinesis. NMM2 consists of two myosin heavy chains encoded by MYH9, MYH10 or MYH14 (NMHC-IIA, B and C), two copies of MYL6 essential light chain protein, and two regulatory light chains (MRLCs), MYL9 and MYLC2B. Myosin II activity is stimulated by phosphorylation of MRLC. Diphosphorylation at Thr-19 and Ser-20 increases both actin-activated Mg2+ ATPase activity and the stability of myosin II filaments; monophosphorylation at Ser-20 is less effective. Kinases responsible for the phosphorylation include myosin light chain kinase (MLCK), ROCK kinase, citron kinase, myotonic dystrophy kinase-related CDC42-binding protein kinase, and Zipper-interacting protein (ZIP) kinase. ROCK activity has been shown to regulate MRLC phosphorylation directly by mono- (Amano et al. 1996) or di- (Ueda et al. 2002) phosphorylation of MRLC.

Editions

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