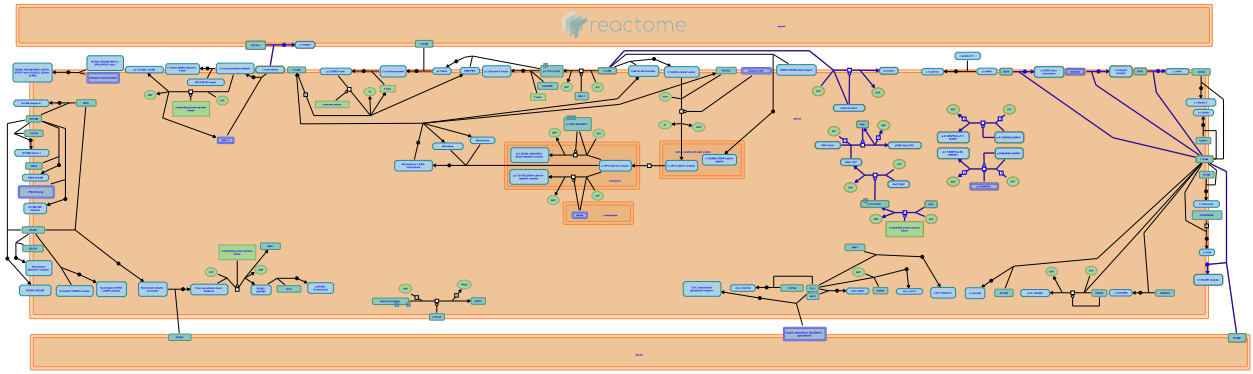
Signal transduction by L1



Charalambous, M., Garapati, P V., Greene, LA., Maness, PF., Schmidt, EE.

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

16/05/2024

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. ↗

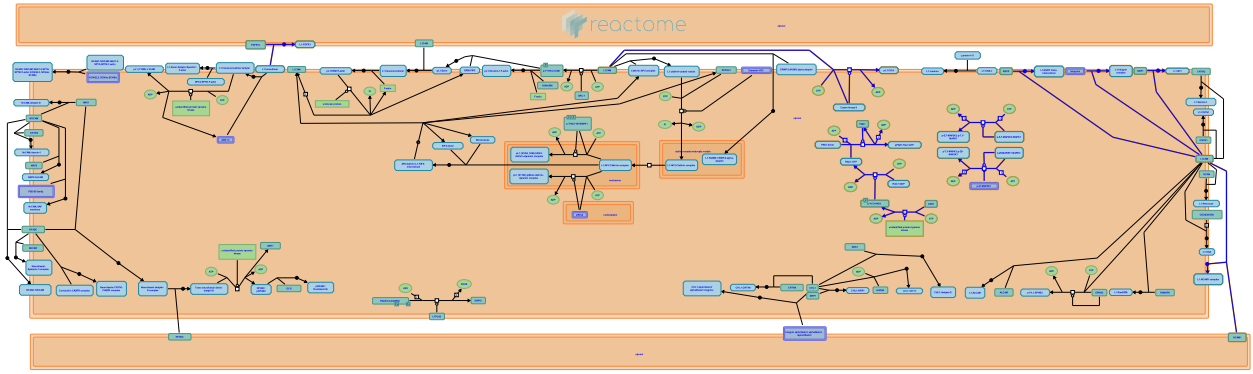
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

Signal transduction by L1 ↗

Stable identifier: R-HSA-445144



Besides adhesive roles in cell cell interaction, L1 functions as a signal transducing receptor providing neurons with cues from their environment for axonal growth and guidance. L1 associates with beta1 integrins on the cell surface to induce a signaling pathway involving sequential activation of pp60csrc, Vav2 -GEF, Rac1, PAK1, MEK and ERK1/2. L1 stimulates cell migration and neurite outgrowth through the MAP kinases ERK1/2. CHL1 also associates with integrins and activates a MAPK signaling pathway via pp60c-src, MEK and ERK1/2.
L1 also binds the Sema3A receptor neuropilin1 and acts as an obligate coreceptor to mediate Sema3A induced growth cone collapse and axon repulsion. This repulsion can be converted to attraction by homophilic binding of L1 on an apposing cell in trans with L1 complexed with Neuropilin1 (NP1) in the responding neuron.
L1 also interacts with FGF receptor and activates PLC gamma and DAG, resulting in the production of arachidonic acid and subsequent opening of voltage-gated channels.

Literature references

Schmid, RS., Pruitt, WM., Maness, PF. (2000). A MAP kinase-signaling pathway mediates neurite outgrowth on L1 and requires Src-dependent endocytosis. *J Neurosci, 20*, 4177-88. ↗

Landreth, G., Schaefer, AW., Beach, CM., Kamiguchi, H., Lemmon, V., Wong, EV. (1999). Activation of the MAPK signal cascade by the neural cell adhesion molecule L1 requires L1 internalization. *J Biol Chem, 274*, 37965-73. ↗

Gazdoiu, M., Sakurai, T., Felsenfeld, DP., Cassella, MR., Whittard, JD. (2006). MAP kinase pathway-dependent phosphorylation of the L1-CAM ankyrin binding site regulates neuronal growth. *Mol Biol Cell, 17*, 2696-706. ↗

Schmid, RS., Midkiff, BR., Maness, PF., Kedar, VP. (2004). Adhesion molecule L1 stimulates neuronal migration through Vav2-Pak1 signaling. *Neuroreport, 15*, 2791-4. ↗

Schachner, M., Maness, PF. (2007). Neural recognition molecules of the immunoglobulin superfamily: signaling transducers of axon guidance and neuronal migration. *Nat Neurosci, 10*, 19-26. ↗

Editions

2008-07-30	Authored, Edited	Garapati, P V.
2010-02-16	Reviewed	Maness, PF.

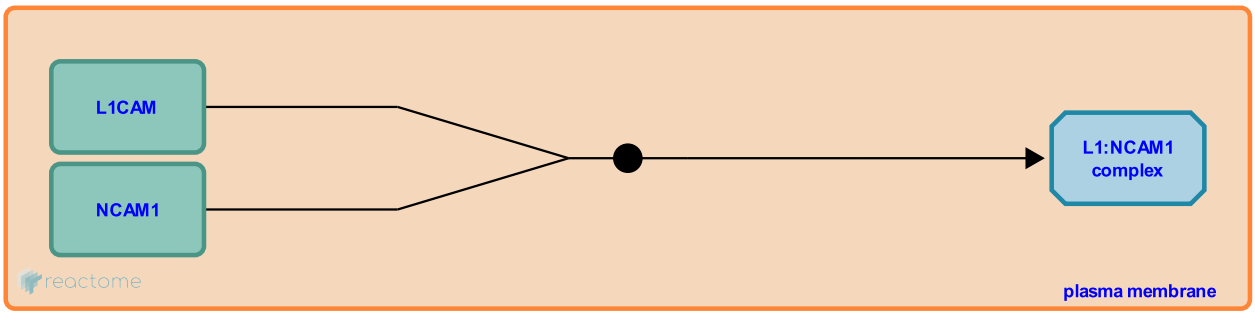
L1 and NCAM1 engaged in cis-interaction ↗

Location: Signal transduction by L1

Stable identifier: R-HSA-374681

Type: binding

Compartments: plasma membrane



L1 and NCAM1 co-expressed on a single cell interact with each other via the fourth Ig domain of NCAM1 and the oligomannose type oligosaccharides carried by L1. This interaction has synergetic effects on L1-mediated cell aggregation and adhesion, a phenomenon referred to as 'assisted homophilic L1-L1 trans-binding'.

Literature references

Soroka, V., Ronn, LC., Kristiansen, LV., Pedersen, N., Berezin, V., Kiselyov, V. et al. (1999). Homophilic NCAM interactions interfere with L1 stimulated neurite outgrowth. *FEBS Lett, 464*, 30-4. ↗

Magyar, JP., Horstkorte, R., Vorherr, T., Schmitz, B., Schachner, M. (1993). The fourth immunoglobulin-like domain of NCAM contains a carbohydrate recognition domain for oligomannosidic glycans implicated in association with L1 and neurite outgrowth. *J Cell Biol, 121*, 1409-21. ↗

Kadmon, G., Kowitz, A., Altevogt, P., Schachner, M. (1990). The neural cell adhesion molecule N-CAM enhances L1-dependent cell-cell interactions. *J Cell Biol, 110*, 193-208. ↗

Editions

2008-07-30	Authored, Edited	Garapati, P V.
2010-02-16	Reviewed	Maness, PF.

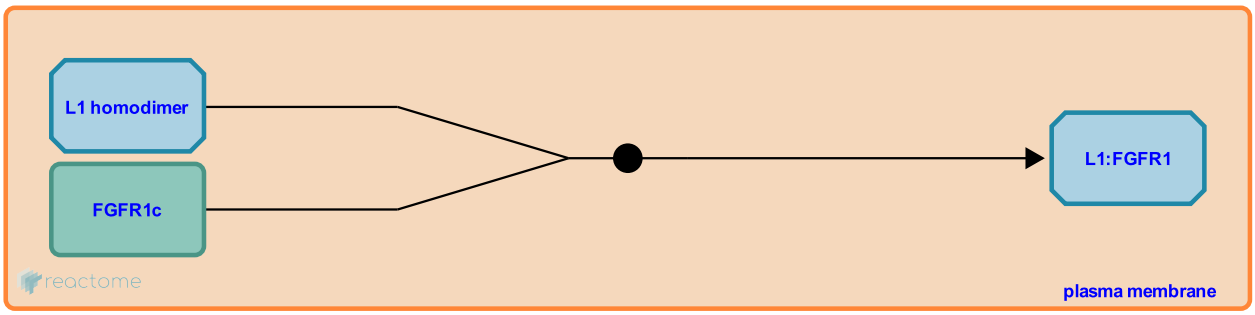
L1-FGFR cis-heterodimerization ↗

Location: Signal transduction by L1

Stable identifier: R-HSA-437230

Type: binding

Compartments: plasma membrane



L1-L1 trans-homodimers interact with the fibroblast growth factor receptor (FGFR). The CAM homology domain (CHD) in the FGFR, which resides between Ig like domains 1 and 2, interacts with the putative FGFR-CHD binding motif in the Fn3 module 4 of L1. This interaction leads to activation of the tyrosine kinase domain of the FGFR and subsequent activation of PLCgamma. PLCgamma then hydrolyses PIP2 to generate IP3 and DAG which finally leads to an increase in localized Ca+2 influx and activation of Ca+2/Calmodulin kinase II.

Literature references

Kulahin, N., Li, S., Hinsby, A., Berezin, V., Kiselyov, V., Bock, E. (2008). Fibronectin type III (FN3) modules of the neuronal cell adhesion molecule L1 interact directly with the fibroblast growth factor (FGF) receptor. *Mol Cell Neurosci, 37*, 528-36. ↗

Editions

2008-07-30	Authored, Edited	Garapati, P V.
2010-02-16	Reviewed	Maness, PF.

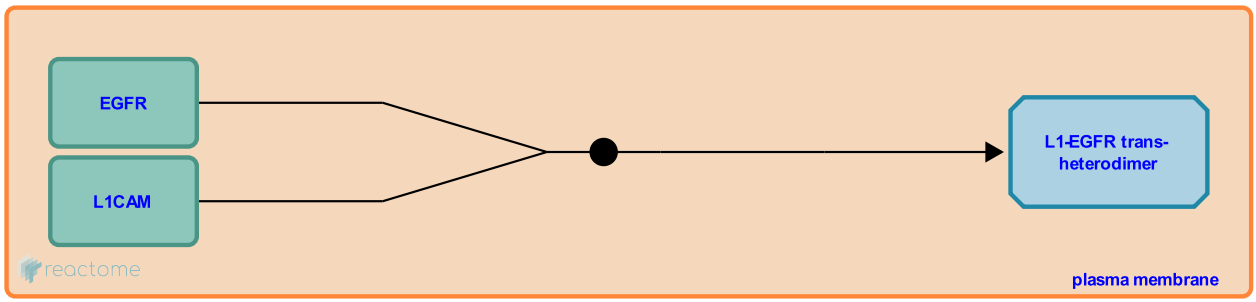
L1-EGFR trans-heterodimerization ↗

Location: Signal transduction by L1

Stable identifier: R-HSA-445069

Type: binding

Compartments: plasma membrane



L1CAM and EGFR engage in a weak heterophilic trans interaction and this induces EGFR tyrosine kinase activity and its activation. However, this trans interaction alone is not sufficient to induce EGFR autophosphorylation, which requires additional cis type interactions between the two proteins.

Literature references

Islam, R., Kristiansen, LV., Garcia-Alonso, L., Romani, S., Hortsch, M. (2004). Activation of EGF receptor kinase by L1-mediated homophilic cell interactions. *Mol Biol Cell, 15*, 2003-12. ↗

Editions

2008-07-30	Authored, Edited	Garapati, P V.
2010-02-16	Reviewed	Maness, PF.

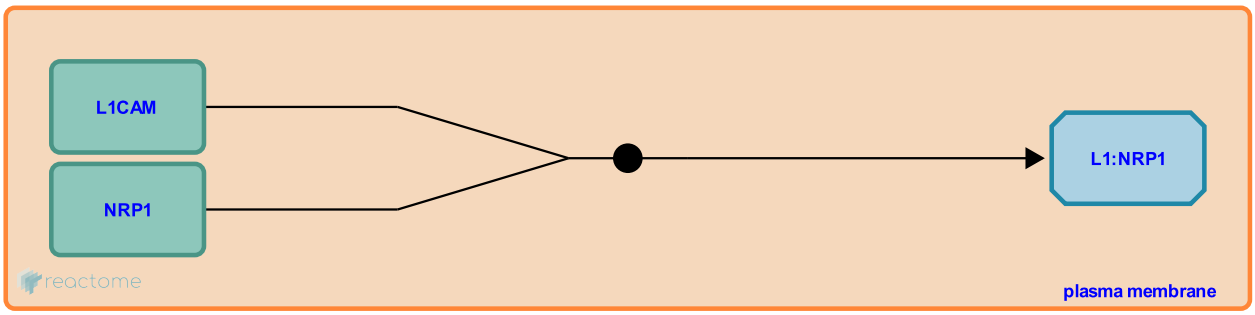
L1 binds NRP1 ↗

Location: Signal transduction by L1

Stable identifier: R-HSA-374669

Type: binding

Compartments: plasma membrane



L1 interacts with neuropilin 1 (NP-1) through a conserved sequence (FASNKL) present with in the Ig1 domain of L1 and this association is required as a part of semaphorin 3A (Sema3A) receptor complex for axon guidance responses.

L1 interacts with NP-1 in cis to form a receptor complex that induces repulsive turning of the growth cone in response to Sema3A binding, whereas trans interaction of L1 with NP-1 switches Sema3A triggered repulsion to attraction.

Literature references

Castellani, V., De Angelis, E., Rougon, G., Kenwrick, S. (2002). Cis and trans interactions of L1 with neuropilin-1 control axonal responses to semaphorin 3A. *EMBO J, 21*, 6348-57. ↗

Editions

2008-07-30	Authored, Edited	Garapati, P V.
2010-02-16	Reviewed	Maness, PF.

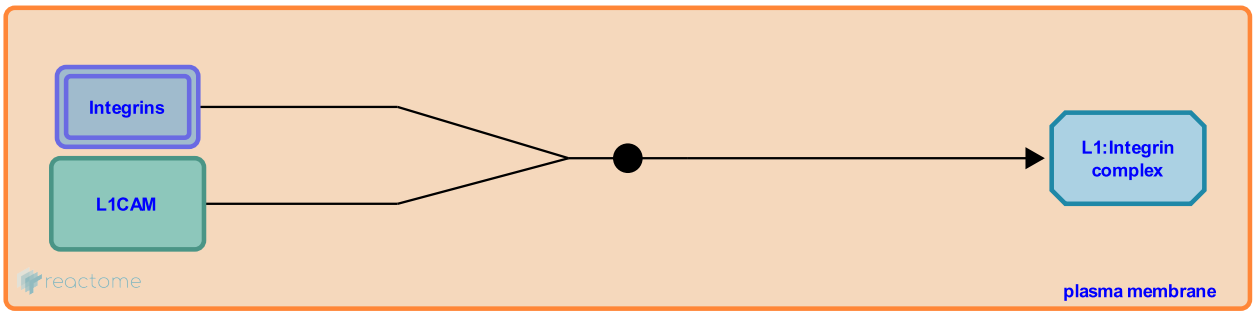
L1 interaction with Integrins ↗

Location: Signal transduction by L1

Stable identifier: R-HSA-374686

Type: binding

Compartments: plasma membrane



L1 can function as a trans-heterophilic ligand for multiple members of the integrin superfamily. It binds multiple integrins including alphavbeta3, alphavbeta1, alpha5beta1, alphaIIbbeta3 and alpha9beta 1. The RGD motif in the sixth Ig domain and the third FnIII repeat of L1 are important for these interactions, which serves to strengthen the adhesion of the neuron to the extracellular matrix.
L1 and beta1 integrins association activates a common intracellular signaling pathway. This pathway involves the sequential activation of the tyrosine kinase c-Src, PI3 kinase, Vav2 guanine nucleotide exchange factor, Rac1 GTPase, PAK1, MEK, and the MAP kinases ERK1/2, which is essential for L1 induced neurite outgrowth and cell motility.

Literature references

Montgomery, AM., Siu, CH., Silletti, S., Ginsberg, MH., Cheresh, DA., Brooks, PC. et al. (1997). A single immunoglobulin-like domain of the human neural cell adhesion molecule L1 supports adhesion by multiple vascular and platelet integrins. *J Cell Biol, 139*, 1567-81. ↗

Müerköster, SS., Kiefel, H., Riedle, S., Altevogt, P., Gast, D., Schäfer, H. et al. (2008). The RGD integrin binding site in human L1-CAM is important for nuclear signaling. *Exp Cell Res, 314*, 2411-8. ↗

Editions

2008-07-30	Authored, Edited	Garapati, P V.
2010-02-16	Reviewed	Maness, PF.

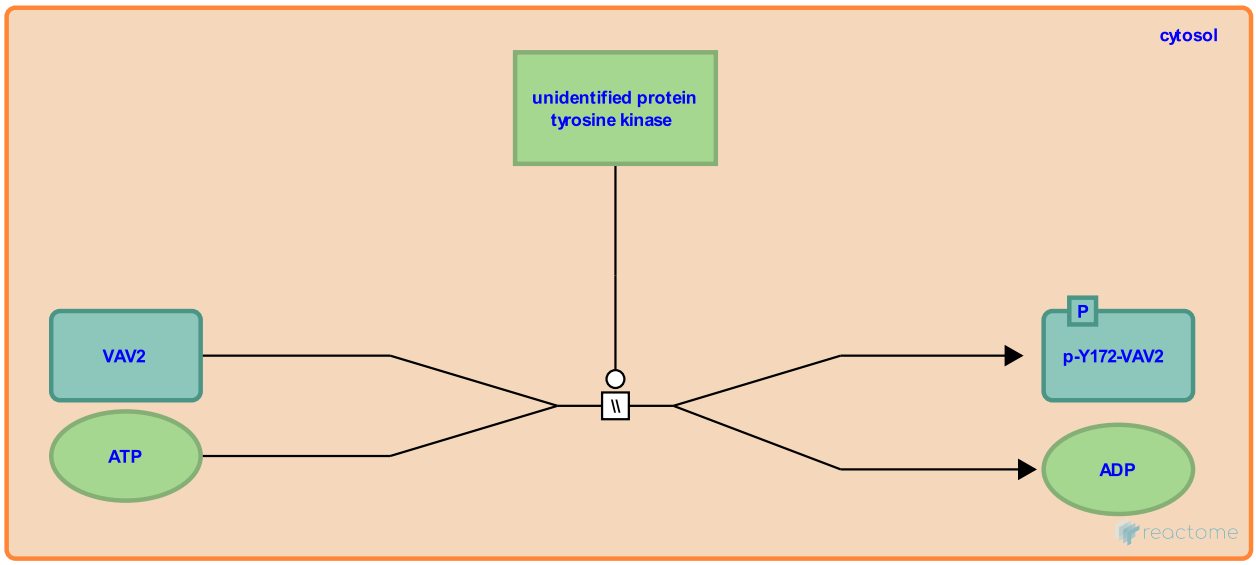
Phosphorylation of VAV2 ↗

Location: Signal transduction by L1

Stable identifier: R-HSA-445085

Type: omitted

Compartments: cytosol



L1 crosslinking leads to the tyrosine phosphorylation and activation of VAV2. Tyr-172 in VAV2 binds to the DBL homology region autoinhibiting its GEF-activity. Tyrosine kinase src may phosphorylate this residue and relieve the autoinhibition.

Followed by: Activation of Rac1 by VAV2

Literature references

Schmid, RS., Midkiff, BR., Maness, PF., Kedar, VP. (2004). Adhesion molecule L1 stimulates neuronal migration through Vav2-Pak1 signaling. *Neuroreport, 15*, 2791-4. ↗

Editions

2008-07-30	Authored, Edited	Garapati, P V.
2010-02-16	Reviewed	Maness, PF.

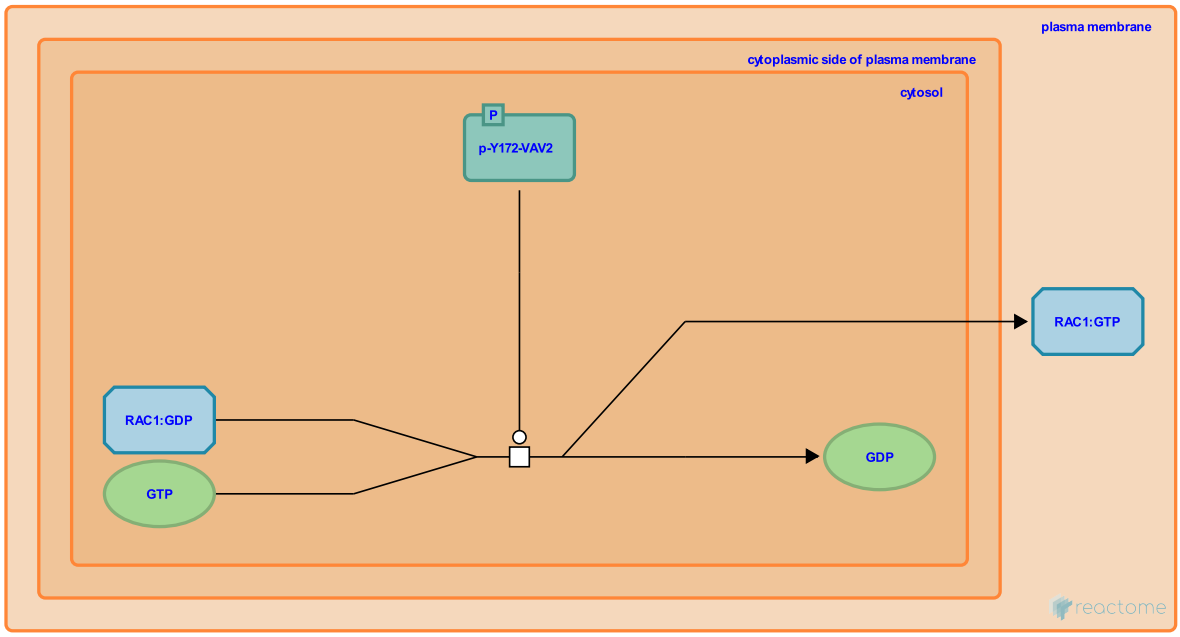
Activation of Rac1 by VAV2 ↗

Location: Signal transduction by L1

Stable identifier: R-HSA-445064

Type: transition

Compartments: cytosol



The small GTPase p21Rac1 is one of the important targets of VAV2 GEF activity. On L1 stimulation tyrosine phosphorylated VAV2, catalyses GDP/GTP exchange on Rac1.

Preceded by: Phosphorylation of VAV2

Followed by: Interaction of PAK1 with Rac1-GTP

Literature references

Schmid, RS., Pruitt, WM., Maness, PF. (2000). A MAP kinase-signaling pathway mediates neurite outgrowth on L1 and requires Src-dependent endocytosis. *J Neurosci, 20*, 4177-88. ↗

Schmid, RS., Midkiff, BR., Maness, PF., Kedar, VP. (2004). Adhesion molecule L1 stimulates neuronal migration through Vav2-Pak1 signaling. *Neuroreport, 15*, 2791-4. ↗

Editions

2008-07-30	Authored, Edited	Garapati, P V.
2010-02-16	Reviewed	Maness, PF.

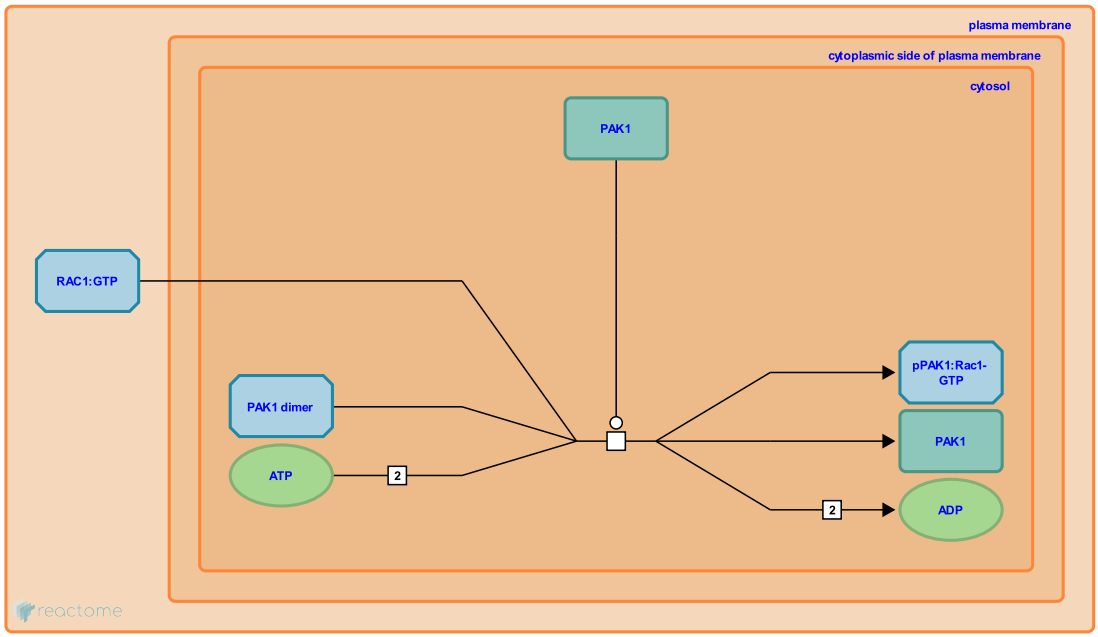
Interaction of PAK1 with Rac1-GTP ↗

Location: Signal transduction by L1

Stable identifier: R-HSA-445072

Type: transition

Compartments: cytosol



In its bound state PAK dimers are arranged in head-to-tail fashion and are maintained in inactive conformation in which the catalytic domain binds the kinase inhibitory (KI) domain.
All PAK family members are direct effectors of Rac1. Rac1 binds to a conserved Cdc42/Rac interactive binding (CRIB) domain in PAK1. This binding stimulates serine/threonine kinase activity of PAK1 by a mechanism involving autophosphorylation. Phosphorylation of S-144 and T-423 are required for the activation of PAK1. This phosphorylation disables the KI-domain-kinase interaction and thereby reduces the affinity of the PAK dimers.
Its been demonstarted that L1 stimulation propagates through VAV2-Rac1-Pak1 to MEK-ERK. It has been shown that Pak1 is able to phosphoarylate T292 and S298 on MEK, which is essential for the functional association of MEK with Raf.

Preceded by: Activation of Rac1 by VAV2

Literature references

Schmid, RS., Midkiff, BR., Maness, PF., Kedar, VP. (2004). Adhesion molecule L1 stimulates neuronal migration through Vav2-Pak1 signaling. *Neuroreport, 15*, 2791-4. ↗

Editions

2008-07-30	Authored, Edited	Garapati, P V.
2010-02-16	Reviewed	Maness, PF.

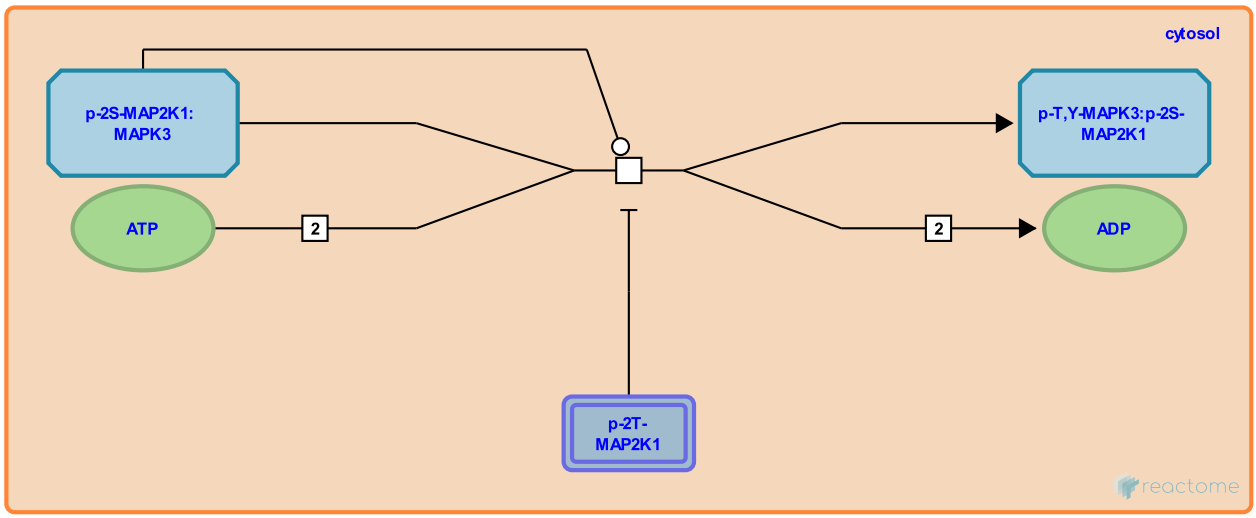
MAP2K1 phosphorylates MAPK3 ↗

Location: Signal transduction by L1

Stable identifier: R-HSA-109860

Type: transition

Compartments: cytosol



MAP2K1 (also known as MEK1) phosphorylates the critical Thr202 and Tyr204 on MAPK3 (ERK1), converting two ATP to ADP. Phosphorylation of MAPK3 activates its kinase activity.

MAP2K1 activation requires the phosphorylation of two serine residues (S218 and S222) in the activation loop.

Literature references

Roskoski, R Jr. (2012). MEK1/2 dual-specificity protein kinases: structure and regulation. *Biochem. Biophys. Res. Commun., 417*, 5-10. ↗

Ley, SC., Arthur, JS. (2013). Mitogen-activated protein kinases in innate immunity. *Nat. Rev. Immunol., 13*, 679-92. ↗

Zheng, CF., Guan, KL. (1993). Cloning and characterization of two distinct human extracellular signal-regulated kinase activator kinases, MEK1 and MEK2. *J Biol Chem, 268*, 11435-9. ↗

Editions

2005-02-04	Authored	Charalambous, M.
2007-11-08	Reviewed	Greene, LA.
2024-03-06	Edited	Schmidt, EE.

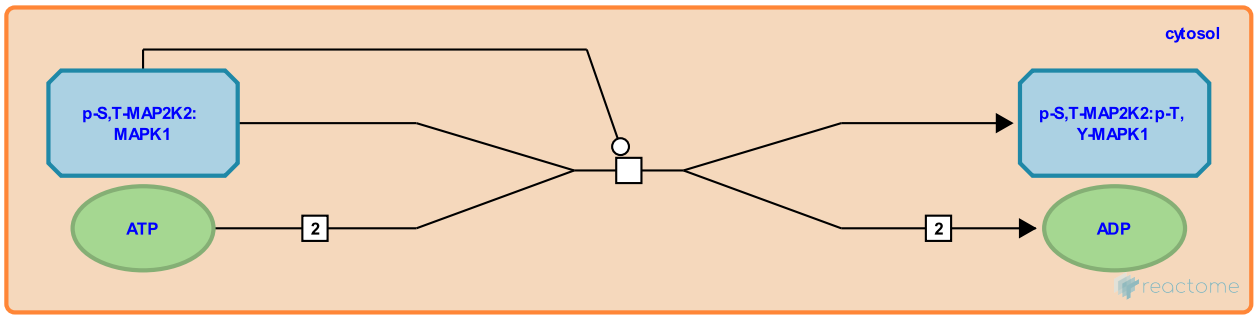
MAP2K2 phosphorylates MAPK1 ↗

Location: Signal transduction by L1

Stable identifier: R-HSA-109862

Type: transition

Compartments: cytosol



MAP2K2 (MEK2) phosphorylates MAPK1 (ERK2). Phosphorylation of MAPK1 activates its kinase activity.

Literature references

Roskoski, R Jr. (2012). MEK1/2 dual-specificity protein kinases: structure and regulation. *Biochem. Biophys. Res. Commun., 417*, 5-10. ↗

Zheng, CF., Guan, KL. (1993). Cloning and characterization of two distinct human extracellular signal-regulated kinase activator kinases, MEK1 and MEK2. *J Biol Chem, 268*, 11435-9. ↗

Editions

2005-02-04	Authored	Charalambous, M.
2007-11-08	Reviewed	Greene, LA.
2024-03-06	Edited	Schmidt, EE.

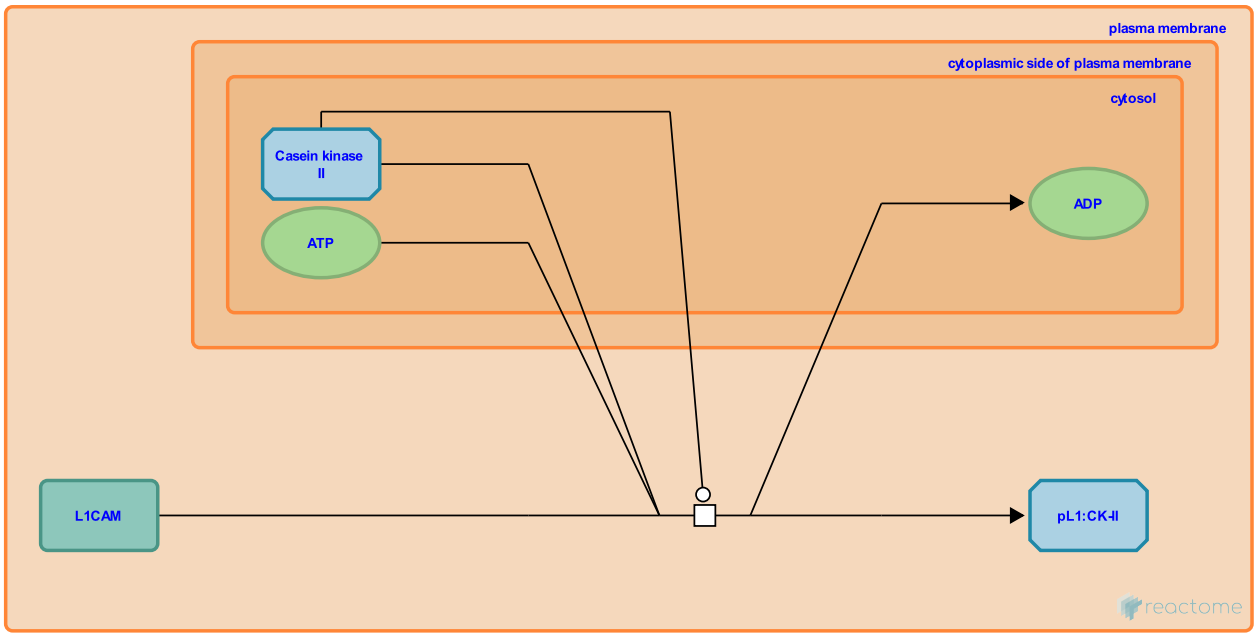
Phosphorylation of L1 by CK-II ↗

Location: Signal transduction by L1

Stable identifier: R-HSA-392752

Type: transition

Compartments: plasma membrane, cytosol



CKII phosphorylates L1CAM at serine 1181, just after the AP-2 recognition site (Y1176RSLE motif). CKII-dependent phosphorylation of S1181 has been shown to regulate trafficking of the internalized L1 and subsequent axon growth.

Literature references

Nakata, A., Kamiguchi, H. (2007). Serine phosphorylation by casein kinase II controls endocytic L1 trafficking and axon growth. *J Neurosci Res, 85*, 723-34. ↗

Landreth, G., Schaefer, AW., Lemmon, V., Wong, EV. (1996). Casein kinase II phosphorylates the neural cell adhesion molecule L1. *J Neurochem, 66*, 779-86. ↗

Editions

2008-07-30	Authored, Edited	Garapati, P V.
2010-02-16	Reviewed	Maness, PF.

Table of Contents