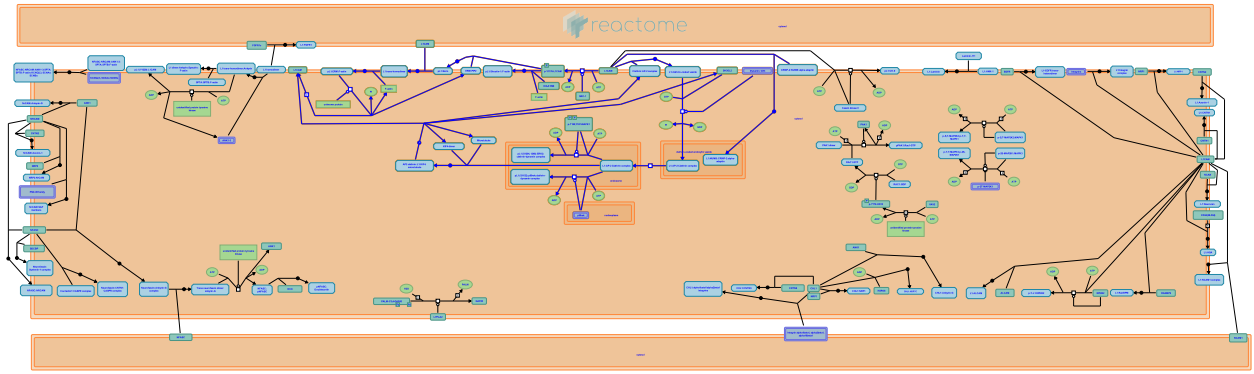
Recycling pathway of L1



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03/12/2020

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. ↗

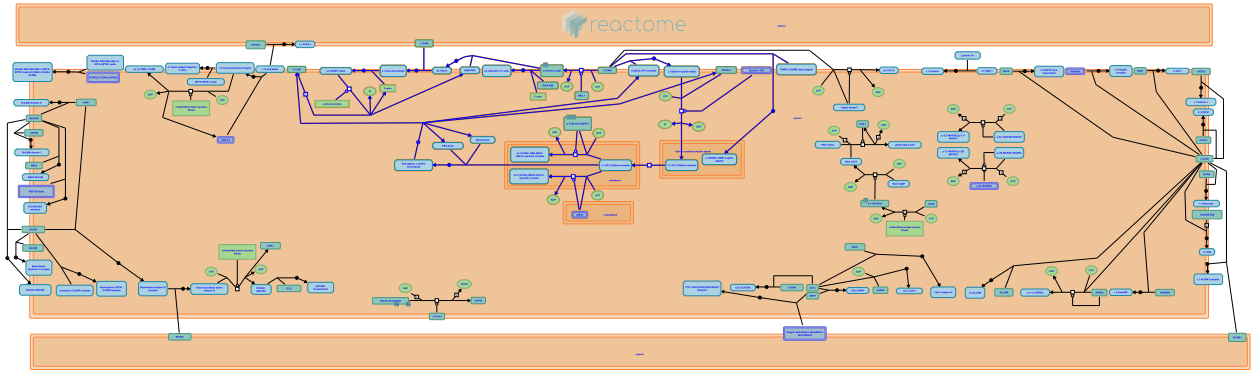
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

Recycling pathway of L1 ↗

Stable identifier: R-HSA-437239



L1 functions in many aspects of neuronal development including axon outgrowth and neuronal migration. These functions require coordination between L1 and the actin cytoskeleton. F-actin continuously moves in a retrograde direction from the P-(peripheral) domain of the growth cone towards the growth cone's C-(central) domain. L1, attached to the actin cytoskeleton via membrane cytoskeletal linkers (MCKs) such as ankyrins (Ankyrin-G, -B and -R) and members of the ERMs (ezrin, radixin, and moesin) family, link this retrograde F-actin flow with extracellular immobile ligands.

Forward translocation of growth cone requires not only the CAM-actin linkage but also a gradient of cell substrate adhesion (strong adhesion at the front and weak adhesion at the rear) so that the cytoskeletal machinery is able to pull the cell forward as attachments at the rear are released. This asymmetry is achieved in part by internalizing L1 molecules as they are moved to the rear of the growth cone coupled to retrograde F-actin flow and recycling them to the leading edge plasma membrane.

L1 internalization is mediated by phosphorylation and dephosphorylation. The L1 cytoplasmic domain (L1CD) carries an endocytic or sorting motif, YRSLE, that is recognized by the clathrin associated adaptor protein-2 (AP-2). AP-2 binds the YRSLE motif only when its tyrosine is not phosphorylated and triggers L1 endocytosis. SRC kinase associated with lipid rafts in the P-domain membrane phosphorylates L1 molecules on tyrosine-1176, stabilizing them in the plasma membrane. L1 endocytosis is triggered by the dephosphorylation of Y1176 within the C domain. Some of these internalized L1 molecules are transported in an anterograde direction along microtubules for reuse in the leading edge.

Literature references

Kamiguchi, H. (2003). The mechanism of axon growth: what we have learned from the cell adhesion molecule L1. *Mol Neurobiol, 28*, 219-28. ↗

Kamiguchi, H., Yoshihara, F. (2001). The role of endocytic l1 trafficking in polarized adhesion and migration of nerve growth cones. *J Neurosci, 21*, 9194-203. ↗

Kamiguchi, H., Lemmon, V. (2000). Recycling of the cell adhesion molecule L1 in axonal growth cones. *J Neurosci, 20* , 3676-86. ↗

Editions

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

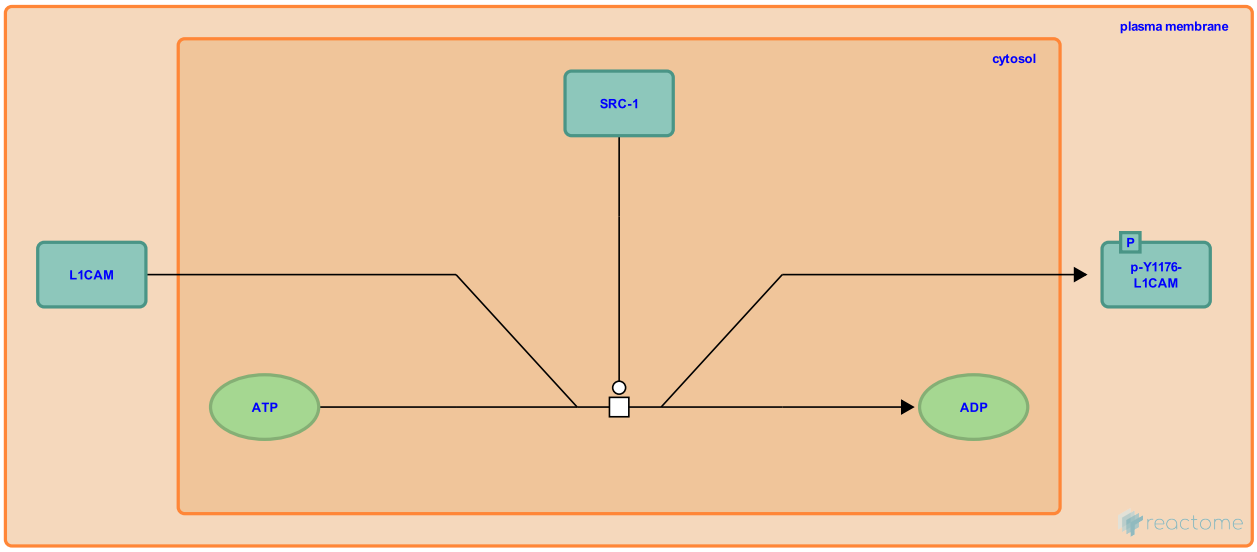
Phosphorylation of L1 by SRC ↗

Location: Recycling pathway of L1

Stable identifier: R-HSA-445084

Type: transition

Compartments: cytosol, plasma membrane



The tyrosine based sorting motif (YRSLE) in L1CD is required for clathrin mediated endocytosis. Y1176 of the YRSLE motif is phosphorylated by SRC tyrosine kinase associated with lipid rafts in the P-domain of the growth cone. Phosphorylation of Y1176 prevents L1 binding to AP-2, an adaptor required for clathrin mediated internalization of L1.

Preceded by: Reinsertion of L1 into the plasma membrane

Followed by: L1 binds ERM family members

Literature references

Schaefer, AW., Kamei, Y., Kamiguchi, H., Wong, EV., Rapoport, I., Kirchhausen, Tomas. et al. (2002). L1 endocytosis is controlled by a phosphorylation-dephosphorylation cycle stimulated by outside-in signaling by L1. *J Cell Biol, 157*, 1223-32. ↗

Editions

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

L1 binds ERM family members ↗

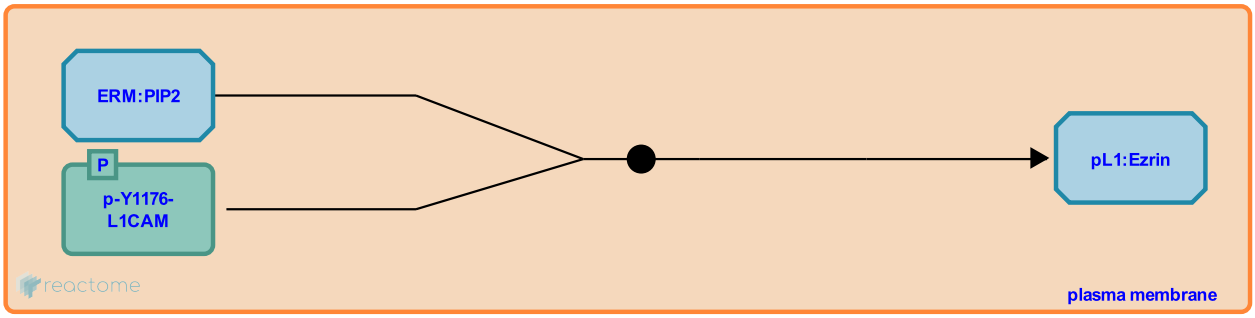
Location: Recycling pathway of L1

Stable identifier: R-HSA-374677

Type: binding

Compartments: plasma membrane

Inferred from: L1 binds ERM family members (Rattus norvegicus)



Ezrin Radixin Moesin (ERM) are the members of the FERM domain (F for Band 4.1 protein, E for ezrin, R for radixin and M for moesin) containing proteins involved in localizing proteins to the plasma membrane. L1 is coupled to the tread milling actin cytoskeleton through interaction with ERM proteins. The motif KxxKYxV in the juxtamembrane region and the YRSLE sequence in L1CD are important for the ERM binding. This interaction provides a link between L1 and the actin cytoskeleton and plays a critical role in the traction force generation and regulation of neurite branching.

Preceded by: Phosphorylation of L1 by SRC

Followed by: L1 trans-homophilic interaction

Editions

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

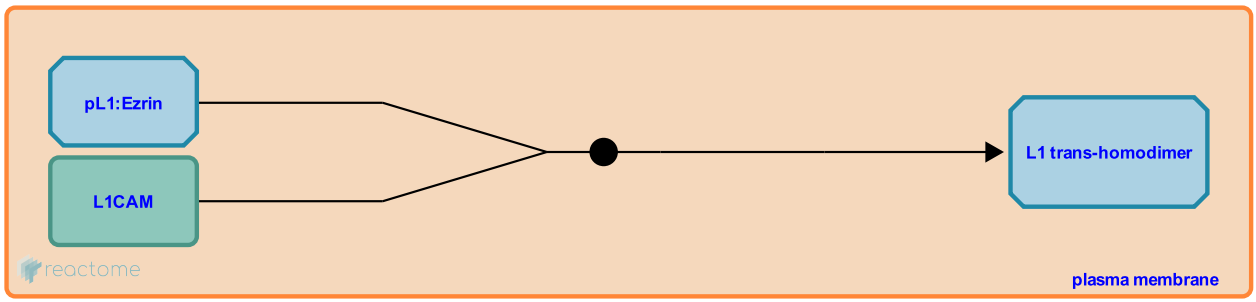
L1 trans-homophilic interaction ↗

Location: Recycling pathway of L1

Stable identifier: R-HSA-374680

Type: binding

Compartments: plasma membrane



Interaction with ERM may lead to lateral oligomerization of phosphorylated L1 and this enhances the homophilic trans adhesion of L1.

L1 mediates cell-cell adhesion by a trans-homophilic binding mechanism. In the nonengaged resting state the L1 N-terminal Ig domains adopt a horseshoe like structure due to an intramolecular binding between domains 1 and 4 or 2 and 3, respectively. When engaged in homophilic binding between adjacent cells, L1 could undergo a conformational change leading to a pairwise antiparallel alignment of Ig domains 1-4 and 2-3.

Preceded by: L1 binds ERM family members

Followed by: Linkage of L1 with treadmilling F-actin

Literature references

Grumet, M., Edelman, GM. (1988). Neuron-glia cell adhesion molecule interacts with neurons and astroglia via different binding mechanisms. *J Cell Biol, 106*, 487-503. ↗

Zhao, X., Yip, PM., Siu, CH. (1998). Identification of a homophilic binding site in immunoglobulin-like domain 2 of the cell adhesion molecule L1. *J Neurochem, 71*, 960-71. ↗

Zhao, X., Siu, CH. (1995). Colocalization of the homophilic binding site and the neuritogenic activity of the cell adhesion molecule L1 to its second Ig-like domain. *J Biol Chem, 270*, 29413-21. ↗

He, Y., Jensen, GJ., Bjorkman, PJ. (2009). Cryo-electron tomography of homophilic adhesion mediated by the neural cell adhesion molecule L1. *Structure, 17*, 460-71. ↗

Editions

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

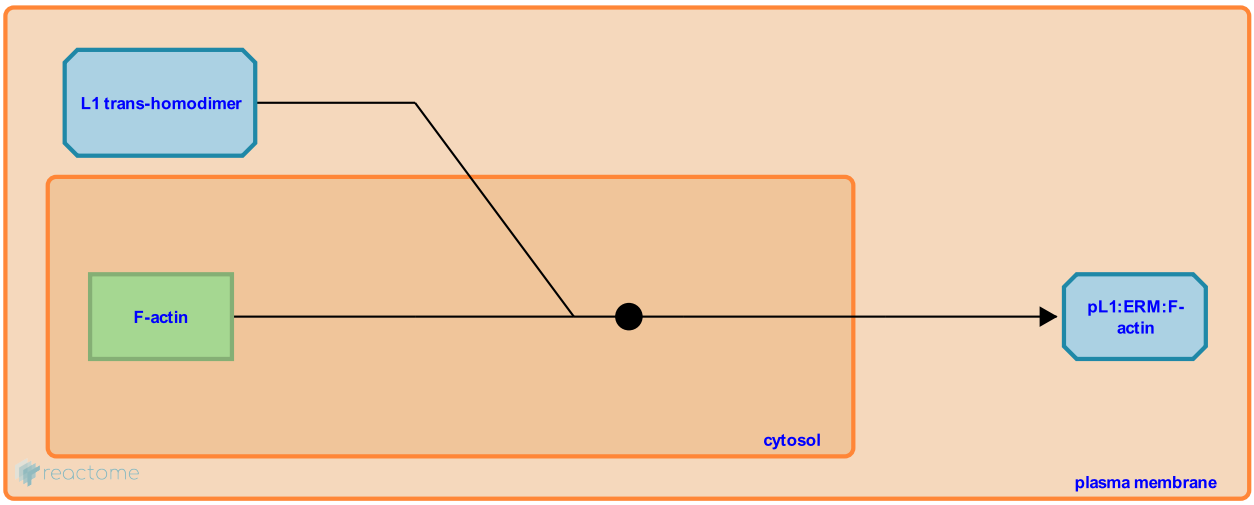
Linkage of L1 with treadmilling F-actin ↗

Location: Recycling pathway of L1

Stable identifier: R-HSA-443779

Type: binding

Compartments: cytosol, plasma membrane



The COOH termini of all ERM proteins have sequence motifs that bind directly to F-actin. The L1 molecules on the cell surface are translocated to the C-domain by coupling with the retrograde F-actin. The force generated by linking L1 clusters with retrograde F-actin flow leads to the migration of the growth cone.

Preceded by: L1 trans-homophilic interaction

Followed by: Dephosphorylation of pL1 (Y1176)

Literature references

Sakurai, T., Gil, OD., Whittard, JD., Gazdoiu, M., Joseph, T., Wu, J. et al. (2008). Interactions between the L1 cell adhesion molecule and ezrin support traction-force generation and can be regulated by tyrosine phosphorylation. *J Neurosci Res, 86*, 2602-14. ↗

Editions

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

Shootin-1 links L1 and retrograde actin flow ↗

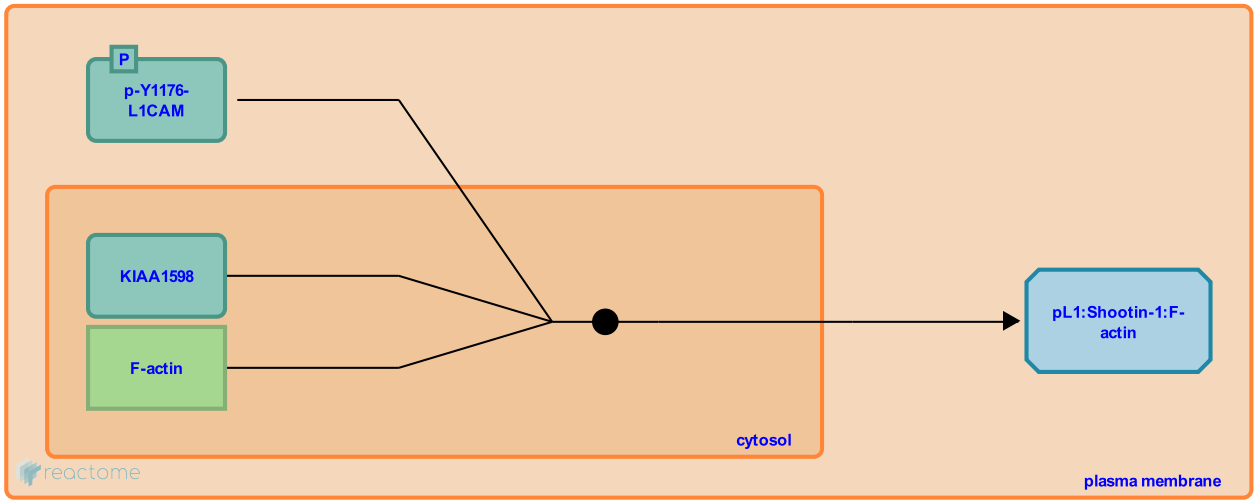
Location: Recycling pathway of L1

Stable identifier: R-HSA-373736

Type: binding

Compartments: cytosol, plasma membrane

Inferred from: Shootin-1 links L1 and retrograde actin flow (Rattus norvegicus)



Shootin-1 acts as a linker protein, binding L1 to moving actin filaments in axonal growth cones. This interaction mediates the migration of L1 on the plasma membrane from P-domain to the C-domain of the growth cone and enhances neurite elongation.

Editions

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

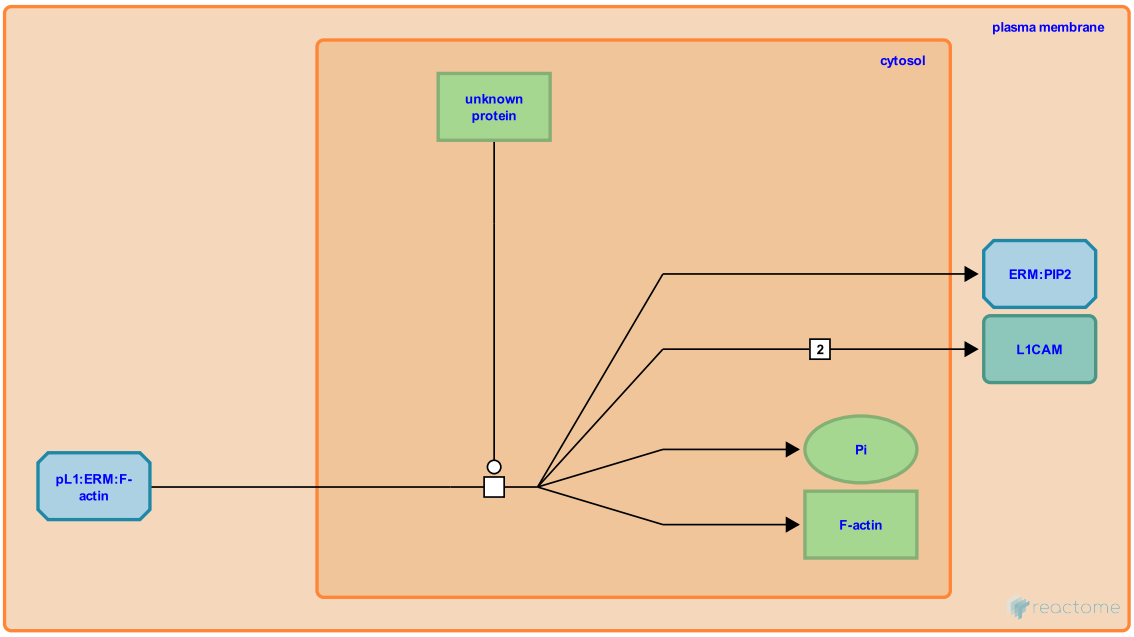
Dephosphorylation of pL1 (Y1176) ↗

Location: Recycling pathway of L1

Stable identifier: R-HSA-445089

Type: transition

Compartments: cytosol, plasma membrane



L1 translocated to the non raft membranes of the C-domain is dephosphorylated. A number of potential candidate phosphatases exist including phosphotyrosine phosphatases. Dephosphorylation of Y1176 allows L1 binding to AP-2, an adaptor required for clathrin mediated internalization of L1.

Preceded by: Linkage of L1 with treadmilling F-actin

Followed by: L1 binds to AP-2 Clathrin complex

Literature references

Schaefer, AW., Kamei, Y., Kamiguchi, H., Wong, EV., Rapoport, I., Kirchhausen, Tomas. et al. (2002). L1 endocytosis is controlled by a phosphorylation-dephosphorylation cycle stimulated by outside-in signaling by L1. *J Cell Biol, 157*, 1223-32. ↗

Editions

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

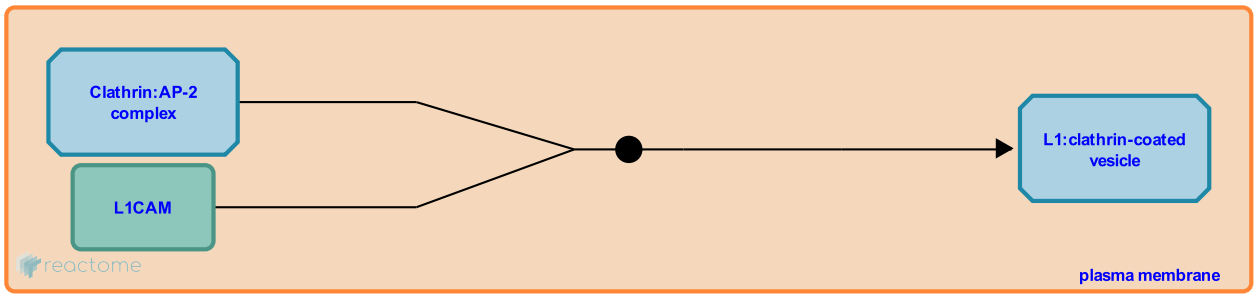
L1 binds to AP-2 Clathrin complex ↗

Location: Recycling pathway of L1

Stable identifier: R-HSA-392748

Type: binding

Compartments: plasma membrane



L1 in the C-domain membrane is internalized via clathrin mediated endocytosis. The assembly of clathrin coats at the plasma membrane depends on the adaptor complex AP-2 which is composed of two large chains (alpha and beta1 or beta2 adaptin), one medium (mu2) chain, and one small chain (sigma2). When dephosphorylated, the sorting signal/endocytic motif YRSLE sequence enables L1 to directly bind the mu2 subunit of AP-2, and concentrates L1 molecules in clathrin coated areas of the plasma membrane.

Preceded by: Dephosphorylation of pL1 (Y1176)

Followed by: Formation of clathrin coated vesicle, Transport of L1 into endosomes

Literature references

Kamiguchi, H., Long, KE., Pendergast, M., Schaefer, AW., Rapoport, I., Kirchhausen, T. et al. (1998). The neural cell adhesion molecule L1 interacts with the AP-2 adaptor and is endocytosed via the clathrin-mediated pathway. *J Neurosci, 18*, 5311-21. ↗

Editions

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

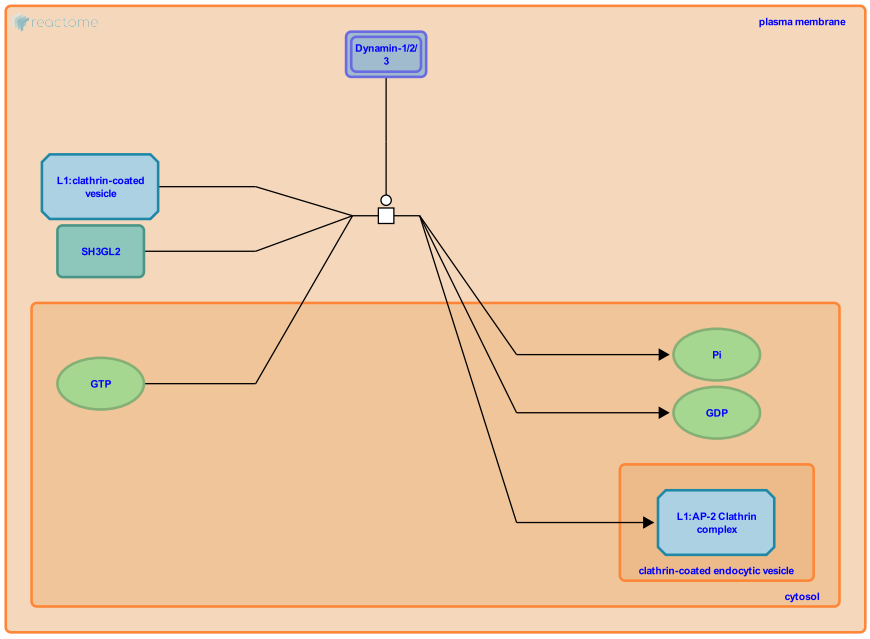
Formation of clathrin coated vesicle ↗

Location: Recycling pathway of L1

Stable identifier: R-HSA-555065

Type: transition

Compartments: plasma membrane



Dynamin is a neuronal phosphoprotein and a GTPase enzyme which mediates late stages of endocytosis in both neural and non-neural cells. Dynamin is involved in the membrane fusion event that results in the formation of clathrin-coated vesicles.

Preceded by: L1 binds to AP-2 Clathrin complex

Literature references

Kamiguchi, H., Long, KE., Pendergast, M., Schaefer, AW., Rapoport, I., Kirchhausen, T. et al. (1998). The neural cell adhesion molecule L1 interacts with the AP-2 adaptor and is endocytosed via the clathrin-mediated pathway. *J Neurosci, 18*, 5311-21. ↗

Editions

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

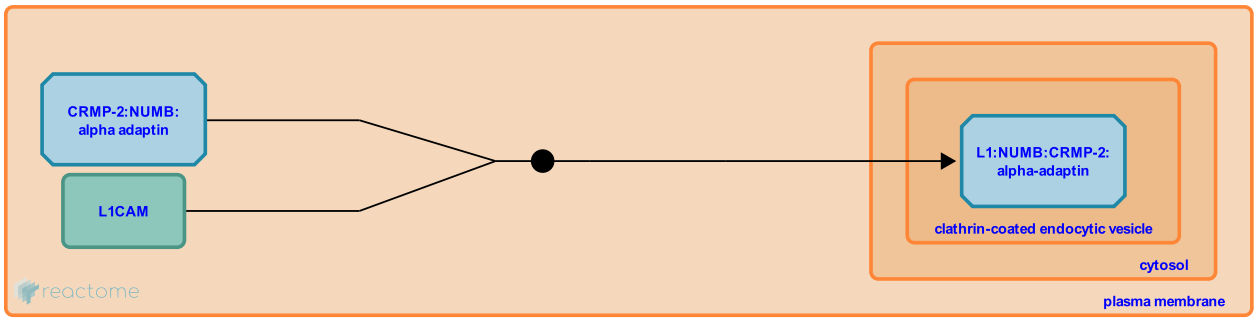
Interaction of NUMB with L1 ↗

Location: Recycling pathway of L1

Stable identifier: R-HSA-443783

Type: binding

Compartments: plasma membrane



Numb is thought to be a phosphotyrosine binding (PTB) domain containing cargo specific adaptor protein, which links specific cargo to the endocytic machinery. It associates with collapsin response mediator protein-2 (CRMP 2) with its PTB domain and alpha adaptin (a subunit of the AP 2 adaptor complex) through its tripeptide Asp-Pro-Phe (DPF) motif, and is involved in clathrin dependent endocytosis at the plasma membrane. Numb is associated with L1 under physiological conditions and functions in endocytosis of L1 in the C domain membrane of axonal growth cones.

Literature references

Nishimura, T., Fukata, Y., Kato, K., Yamaguchi, T., Matsuura, Y., Kamiguchi, H. et al. (2003). CRMP-2 regulates polarized Numb-mediated endocytosis for axon growth. *Nat Cell Biol, 5*, 819-26. ↗

Editions

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

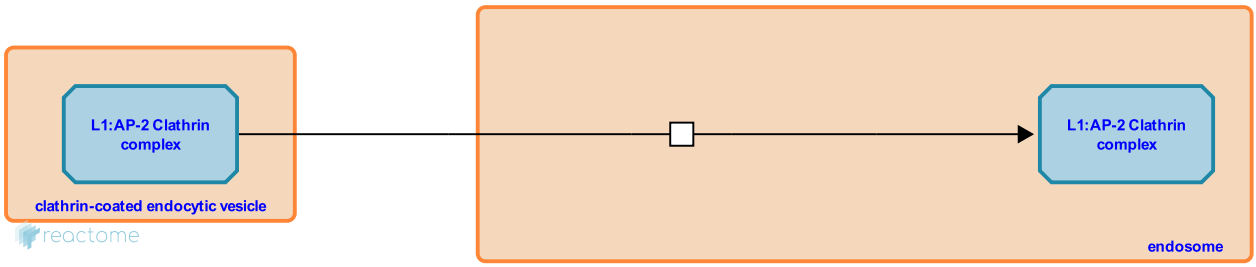
Transport of L1 into endosomes ↗

Location: Recycling pathway of L1

Stable identifier: R-HSA-392749

Type: transition

Compartments: endosome



Membrane bound L1 is internalized through clathrin coated vesicles and is endocytosed into recycling endosomes. Moreover, L1 promotes co-endocytosis of beta1 integrins with which it is associated into early endosomes.

Preceded by: L1 binds to AP-2 Clathrin complex

Followed by: Phosphorylation of L1 by ERK, Phosphorylation of L1 by p90rsk, Transport of L1 from C-domain to P-domain

Literature references

Kamiguchi, H., Long, KE., Pendergast, M., Schaefer, AW., Rapoport, I., Kirchhausen, T. et al. (1998). The neural cell adhesion molecule L1 interacts with the AP-2 adaptor and is endocytosed via the clathrin-mediated pathway. *J Neurosci, 18*, 5311-21. ↗

Kamiguchi, H., Lemmon, V. (2000). Recycling of the cell adhesion molecule L1 in axonal growth cones. *J Neurosci, 20* , 3676-86. ↗

Panicker, AK., Buhusi, M., Erickson, A., Maness, PF. (2006). Endocytosis of beta1 integrins is an early event in migration promoted by the cell adhesion molecule L1. *Exp Cell Res, 312*, 299-307. ↗

Editions

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

Phosphorylation of L1 by p90rsk ↗

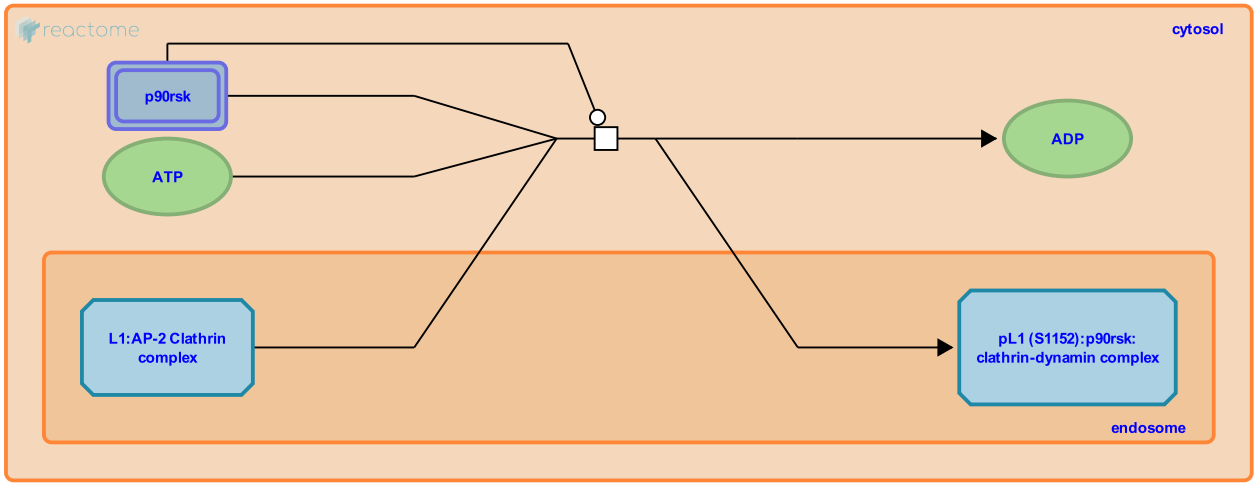
Location: Recycling pathway of L1

Stable identifier: R-HSA-374696

Type: transition

Compartments: cytosol

Inferred from: Phosphorylation of L1 by p90rsk (Homo sapiens)



p90rsk associates with the internalized L1 in the endosomes and phosphorylates it at Ser1152. This phosphorylation may regulate the interactions of L1 and intracellular signaling cascades or cytoskeletal elements involved in neurite outgrowth on specific substrates.

Preceded by: Transport of L1 into endosomes

Editions

2008-07-30	Authored, Edited	Garapati, P V.
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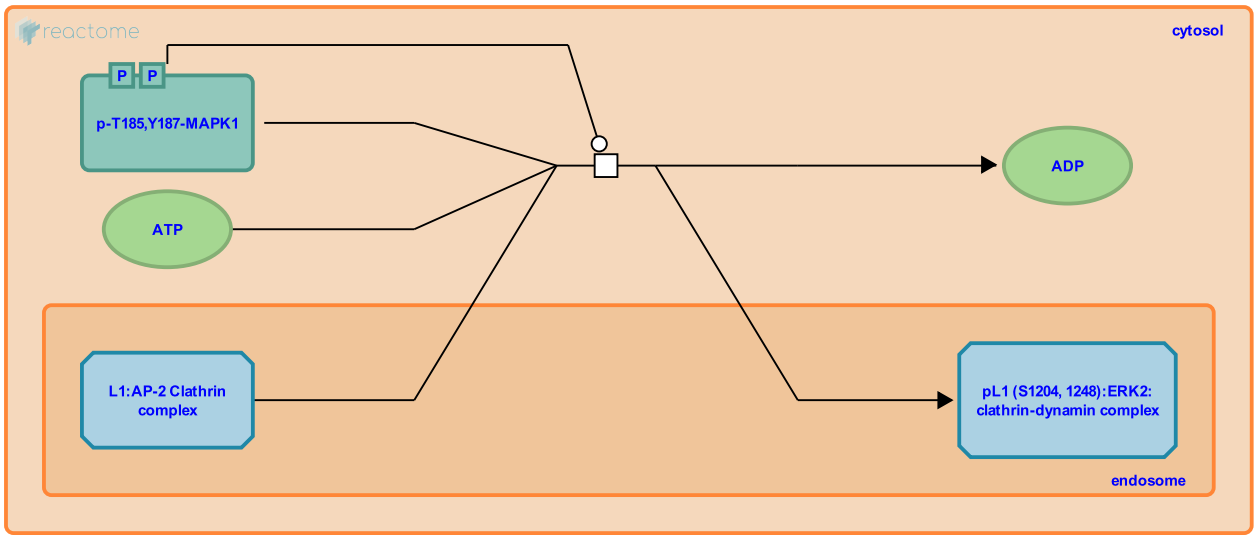
Phosphorylation of L1 by ERK ↗

Location: Recycling pathway of L1

Stable identifier: R-HSA-445079

Type: transition

Compartments: cytosol



L1 cross linking can activate MAPK cascade components MEK1/2, ERK1/2, as well as Src, Raf-1,and p90rsk. MAP kinase signaling requires endocytosis mediated by Src. ERK2 can phos-phorylate internal-ized L1 at serine residues 1204 and 1248. This phosphorylation may increase the neurite growth.

Preceded by: Transport of L1 into endosomes

Literature references

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

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. ↗

Editions

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

Transport of L1 from C-domain to P-domain ↗

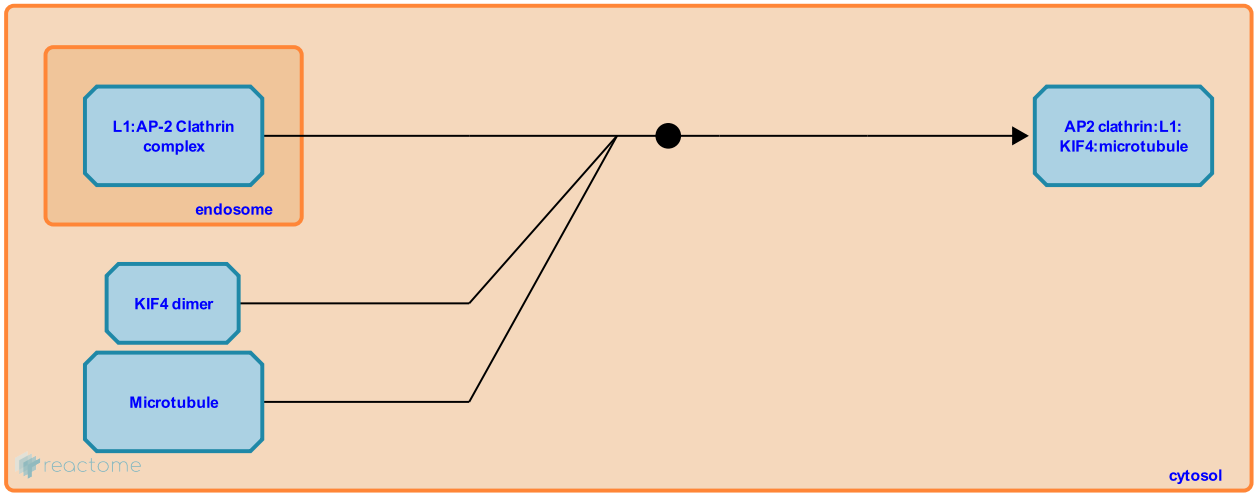
Location: Recycling pathway of L1

Stable identifier: R-HSA-445077

Type: binding

Compartments: cytosol

Inferred from: Transport of L1 from C-domain to P-domain (Mus musculus)



Endocytosis is followed by the vesicular transport and recycling of L1 from central (C)-domain into the peripheral (P)-domain of growth cones.

Microtubules serve as a rail on which motor proteins convey L1 containing organelles. KIF4 is a plus end motor protein involved in the anterograde transport of L1 containing vesicles along microtubules.

Preceded by: Transport of L1 into endosomes

Followed by: Reinsertion of L1 into the plasma membrane

Editions

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

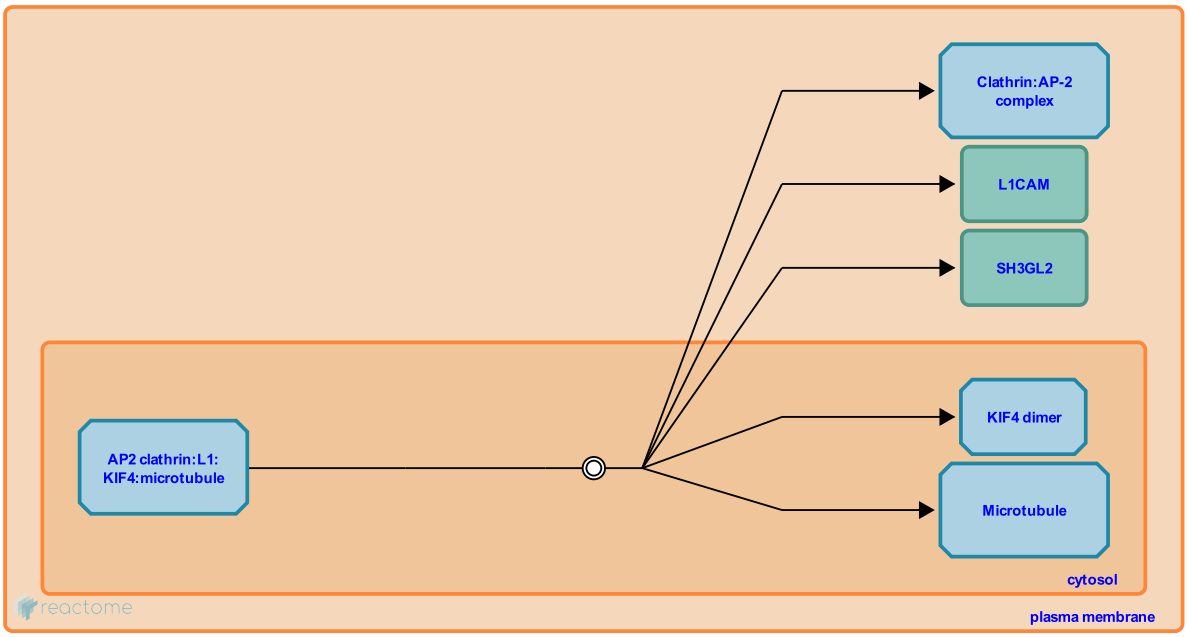
Reinsertion of L1 into the plasma membrane ↗

Location: Recycling pathway of L1

Stable identifier: R-HSA-445071

Type: dissociation

Compartments: cytosol, plasma membrane



L1 transported to the P-domain of growth cones is reinserted into the plasma membrane at the leading edge.

Preceded by: Transport of L1 from C-domain to P-domain

Followed by: Phosphorylation of L1 by SRC

Literature references

Peretti, D., Peris, L., Rosso, S., Quiroga, S., Caceres, A. (2000). Evidence for the involvement of KIF4 in the anterograde transport of L1-containing vesicles. *J Cell Biol, 149*, 141-52. ↗

Kamiguchi, H., Lemmon, V. (2000). Recycling of the cell adhesion molecule L1 in axonal growth cones. *J Neurosci, 20* , 3676-86. ↗

Editions

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

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