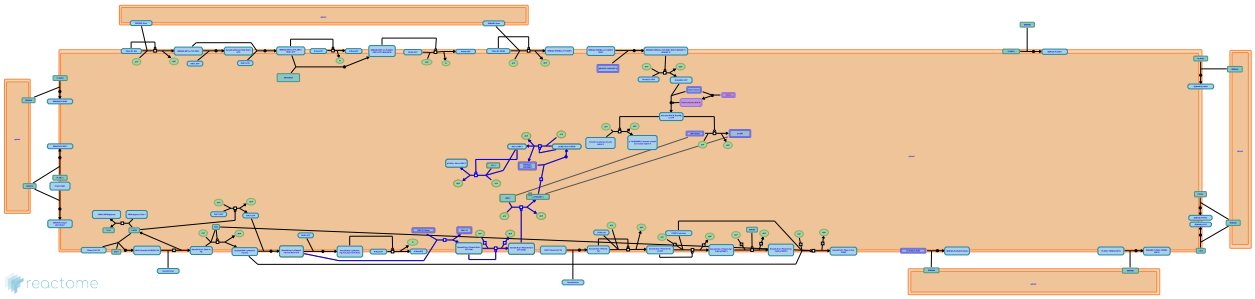
Sema3A PAK dependent Axon repulsion



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29/01/2023

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. ↗

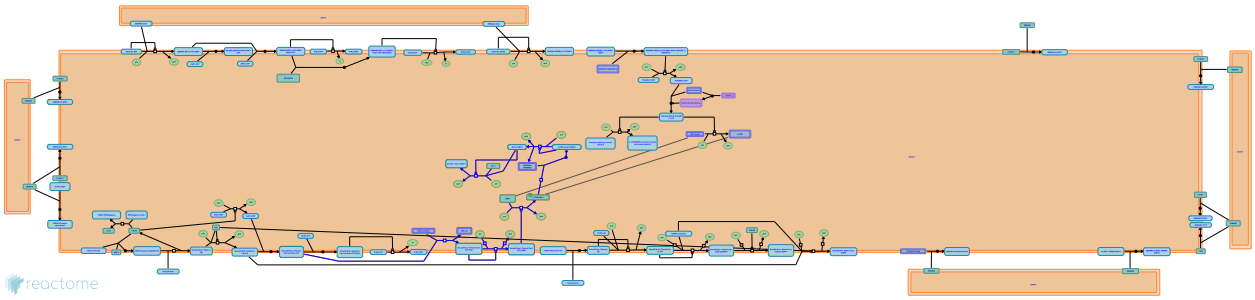
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

Sema3A PAK dependent Axon repulsion ↗

Stable identifier: R-HSA-399954



Activated Rac1 bound to plexin-A might modulate actin dynamics through the sequential phosphorylation and activation of PAK, LIMK1 and cofilin.

Literature references

Sekine-Aizawa, Y., Wakatsuki, S., Sehara-Fujisawa, A., Ohashi, K., Goshima, Y., Aizawa, H. et al. (2001). Phosphorylation of cofilin by LIM-kinase is necessary for semaphorin 3A-induced growth cone collapse. *Nat Neurosci, 4*, 367-73. ↗

Whitford, KL., Ghosh, A. (2001). Plexin signaling via off-track and rho family GTPases. *Neuron, 32*, 1-3. ↗

Zhou, Y., Pasterkamp, RJ., Gunput, RA. (2008). Semaphorin signaling: progress made and promises ahead. *Trends Biochem Sci, 33*, 161-70. ↗

Pasterkamp, RJ., Kolodkin, AL. (2003). Semaphorin junction: making tracks toward neural connectivity. *Curr Opin Neurobiol, 13*, 79-89. ↗

Editions

2009-03-23	Authored, Edited	Garapati, P V.
2009-09-02	Reviewed	Kikutani, H., Kumanogoh, A.

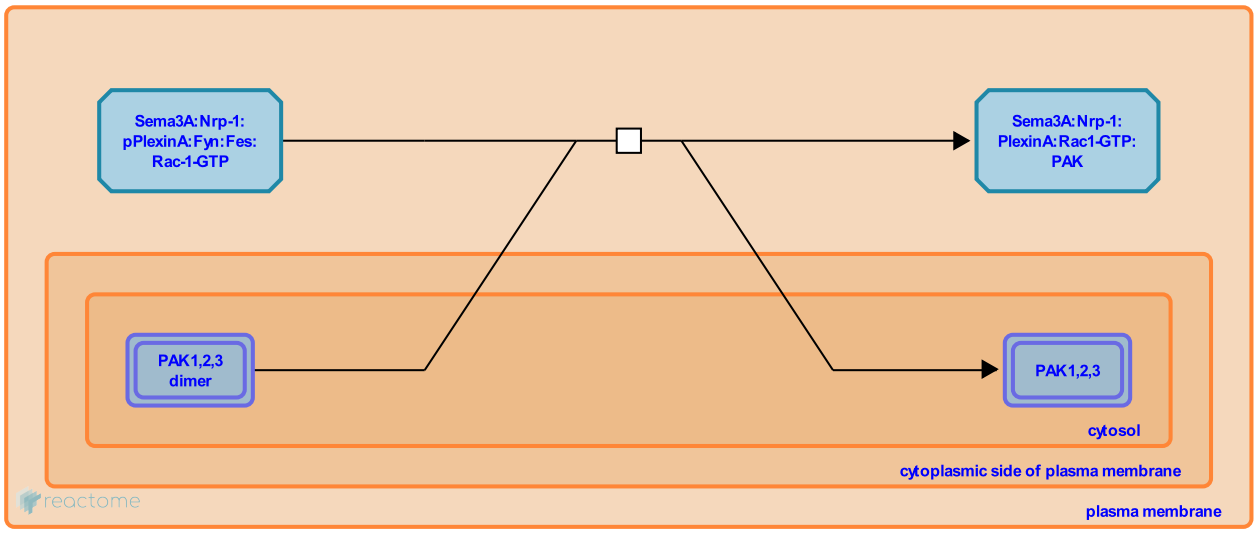
Activation of PAK by Rac1 ↗

Location: Sema3A PAK dependent Axon repulsion

Stable identifier: R-HSA-399930

Type: transition

Compartments: plasma membrane, cytosol



Plexin-bound Rac1 binds to and stimulates the kinase activity of PAK. PAK dimers are arranged in head-to-tail fashion, in which the catalytic domain binds the kinase inhibitory (KI) domain and is supported by associated PAK-interacting exchange factor (PIX) dimers. Upon Rac1 binding the kinase undergoes conformational change that allows autophosphorylation. Phosphorylation of serine residues disables the KI-domain-kinase interaction and thereby reduces the affinity of PIX.

Followed by: Autophosphorylation of PAK

Literature references

Whitford, KL., Ghosh, A. (2001). Plexin signaling via off-track and rho family GTPases. *Neuron, 32*, 1-3. ↗

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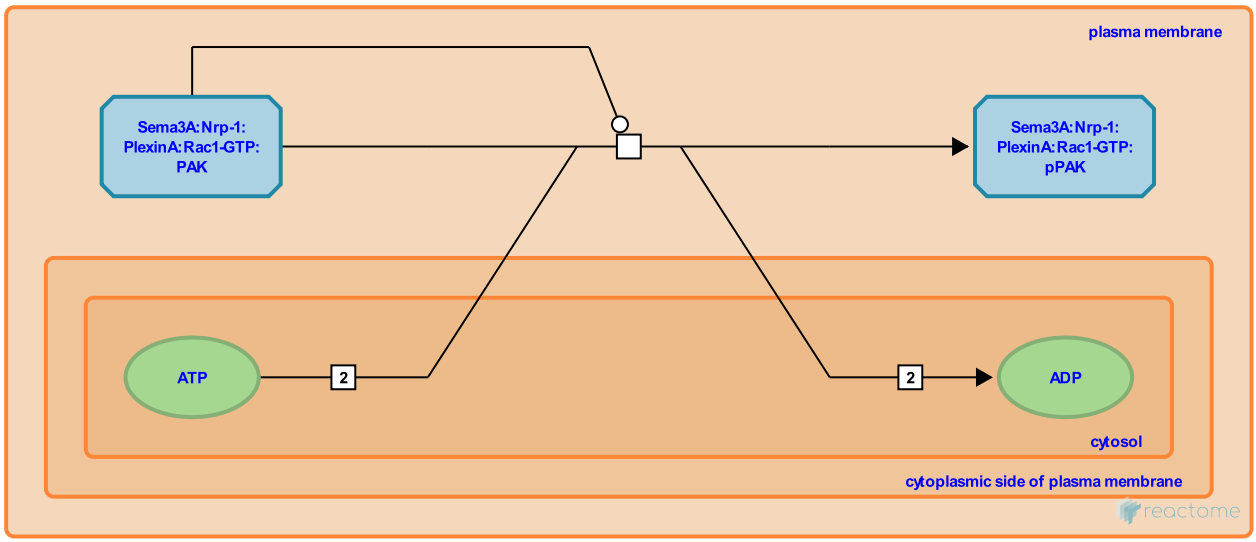
Autophosphorylation of PAK ↗

Location: Sema3A PAK dependent Axon repulsion

Stable identifier: R-HSA-399939

Type: transition

Compartments: plasma membrane, cytosol



PAK is autophosphorylated at several sites but S-144 flanking the kinase inhibitor region and T-423 (S-141/T-402 in PAK-gamma) within the catalytic domain are the two conserved sites that regulate the catalytic activity.

Preceded by: Activation of PAK by Rac1

Followed by: Phosphorylation of LIMK-1 by PAK

Literature references

Manser, E., Lim, L., Chong, C., Tan, L. (2001). The mechanism of PAK activation. Autophosphorylation events in both regulatory and kinase domains control activity. *J Biol Chem, 276*, 17347-53. ↗

Huang, Z., Traugh, JA., Tuazon, PT., Gatti, A. (1999). Multisite autophosphorylation of p21-activated protein kinase gamma-PAK as a function of activation. *J Biol Chem, 274*, 8022-8. ↗

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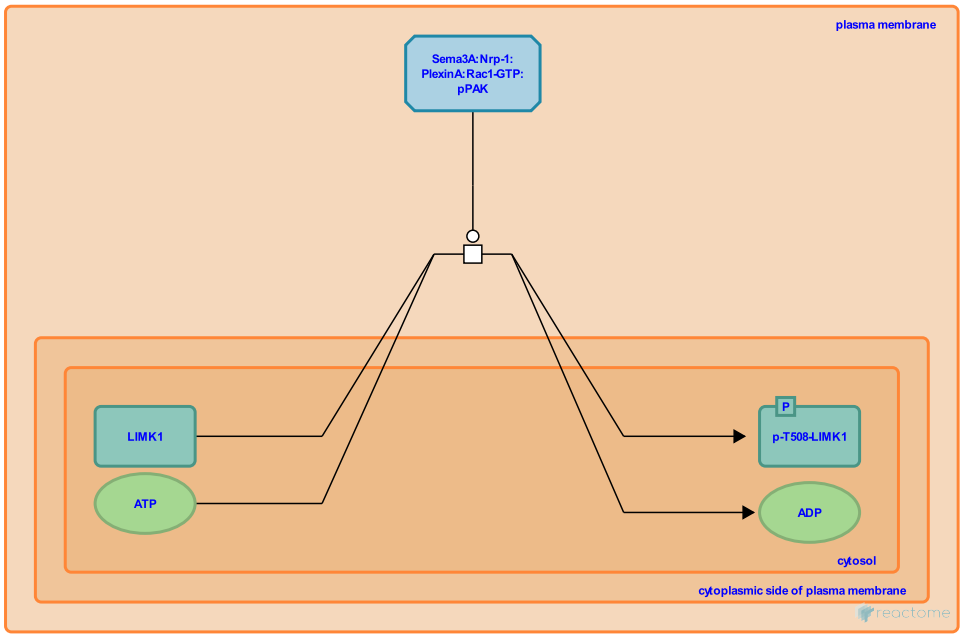
Phosphorylation of LIMK-1 by PAK ↗

Location: Sema3A PAK dependent Axon repulsion

Stable identifier: R-HSA-399952

Type: transition

Compartments: plasma membrane, cytosol



LIM kinases are serine protein kinases with a unique combination of two N-terminal LIM motifs, a central PDZ domain, and a C-terminal protein kinase domain. LIMK1 is one of the downstream targets of PAK1 and is activated through phosphorylation by PAK1 on T508 within its activation loop (Edwards et al. 1999, Aizawa et al. 2001). LIM-kinase is responsible for the tight regulation of the activity of cofilin (a protein that depolymerizes actin filaments) and thus maintains the balance between actin assembly and disassembly. Phosphorylated cofilin is inactive, resulting in stabilization of the actin cytoskeleton.

Preceded by: Autophosphorylation of PAK

Followed by: Dimerization of LIMK1 by Hsp90

Literature references

Sekine-Aizawa, Y., Wakatsuki, S., Sehara-Fujisawa, A., Ohashi, K., Goshima, Y., Aizawa, H. et al. (2001). Phosphorylation of cofilin by LIM-kinase is necessary for semaphorin 3A-induced growth cone collapse. *Nat Neurosci, 4*, 367-73. ↗

Sanders, LC., Edwards, DC., Bokoch, GM., Gill, GN. (1999). Activation of LIM-kinase by Pak1 couples Rac/Cdc42 GTPase signalling to actin cytoskeletal dynamics. *Nat Cell Biol, 1*, 253-9. ↗

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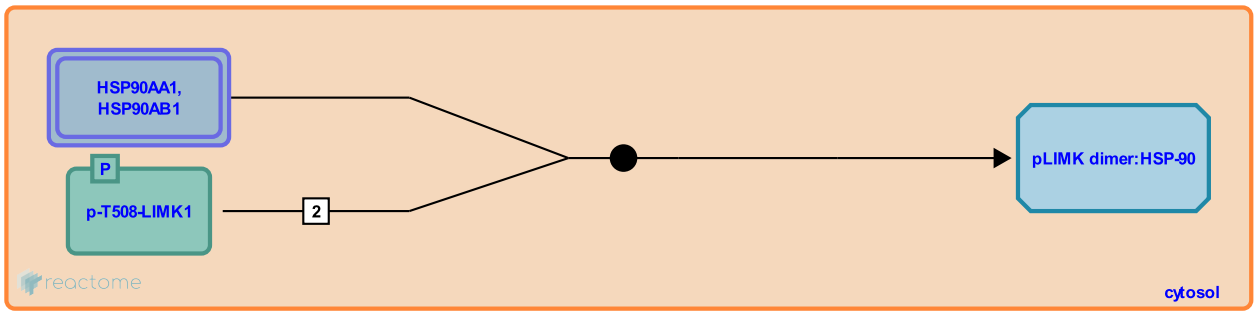
Dimerization of LIMK1 by Hsp90 ↗

Location: Sema3A PAK dependent Axon repulsion

Stable identifier: R-HSA-419645

Type: binding

Compartments: cytosol



After phosphorylation on Thr 508, LIMK undergoes homodimerization. Homodimer formation is promoted by the binding of heat shock protein 90 (Hsp90) to a short sequence in the kinase domain of LIMKs. LIMKs are further phosphorylated after homodimer formation and transphosphorylation of the kinase domain.

Preceded by: Phosphorylation of LIMK-1 by PAK

Literature references

Yarden, Y., Soosairajah, J., Morton, CJ., Harari, D., Li, R., Bernard, O. et al. (2006). Hsp90 increases LIM kinase activity by promoting its homo-dimerization. *FASEB J, 20*, 1218-20. ↗

Bernard, O. (2007). Lim kinases, regulators of actin dynamics. *Int J Biochem Cell Biol, 39*, 1071-6. ↗

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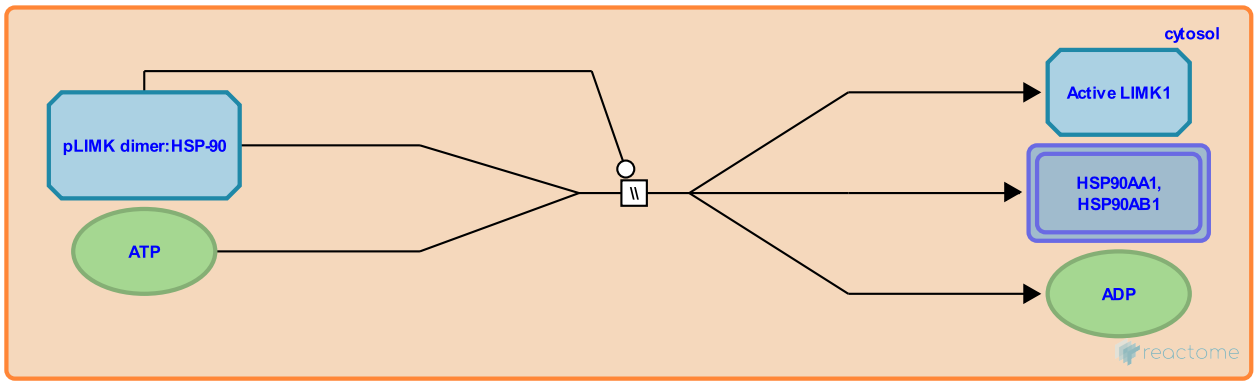
Transphosphorylation of pLIMK1 ↗

Location: Sema3A PAK dependent Axon repulsion

Stable identifier: R-HSA-419644

Type: omitted

Compartments: cytosol



Binding of Hsp90 to the LIMK proteins protects them from degradation and promotes their dimer formation and transphosphorylation. It is estimated that LIMK1 contains at least 5 phospho-amino acids primarily phospho-serines, in its kinase domain. The positions of these serine residues are not known. Transphosphorylation of these serine residues in LIMK1 increases its stability.

Literature references

Yarden, Y., Soosairajah, J., Morton, CJ., Harari, D., Li, R., Bernard, O. et al. (2006). Hsp90 increases LIM kinase activity by promoting its homo-dimerization. *FASEB J, 20*, 1218-20. ↗

Kannourakis, G., Ganiatsas, S., Dringen, R., Bernard, O. (1994). Kiz-1, a protein with LIM zinc finger and kinase domains, is expressed mainly in neurons. *Cell Growth Differ, 5*, 1159-71. ↗

Bernard, O. (2007). Lim kinases, regulators of actin dynamics. *Int J Biochem Cell Biol, 39*, 1071-6. ↗

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Phosphorylation of cofilin by LIMK-1 ↗

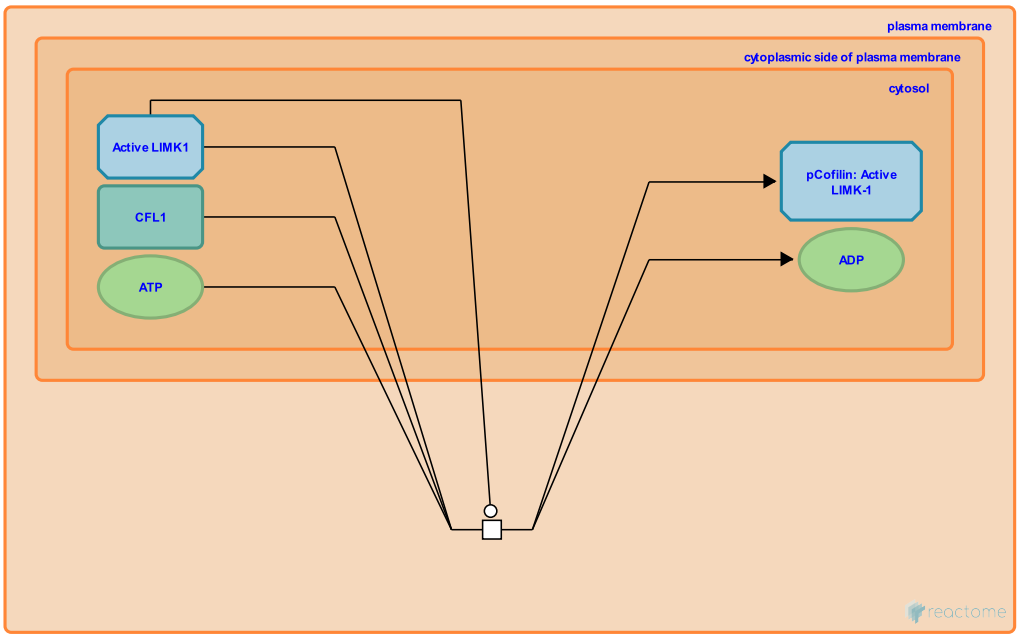
Location: Sema3A PAK dependent Axon repulsion

Stable identifier: R-HSA-399950

Type: transition

Compartments: plasma membrane, 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).

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Table of Contents