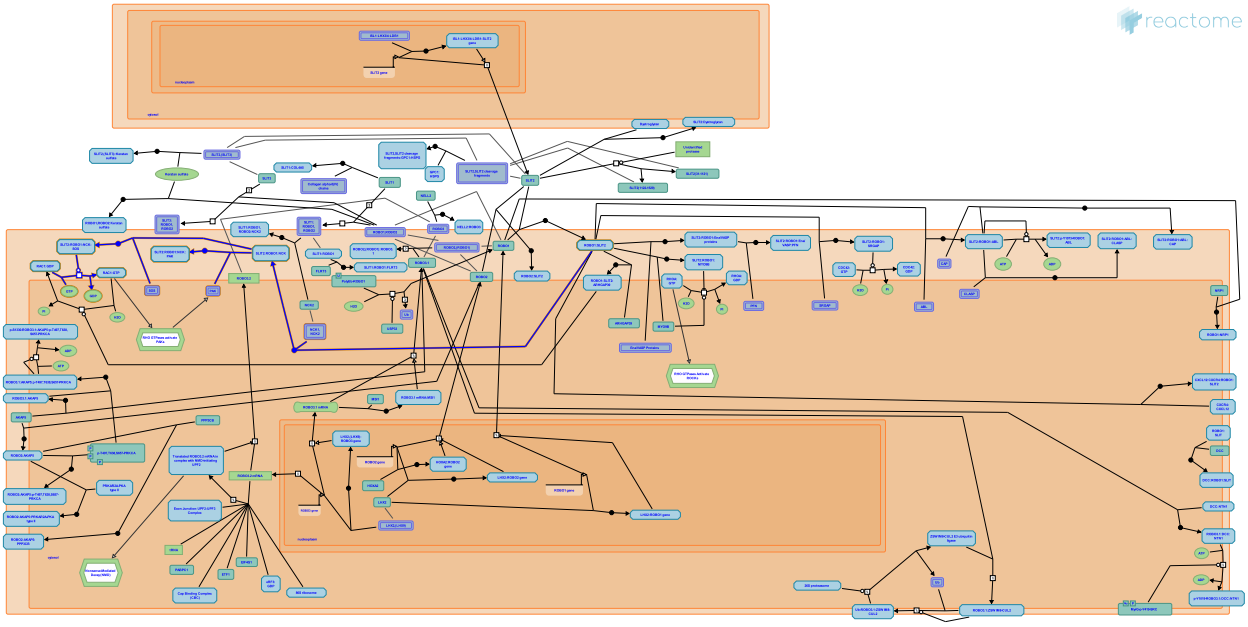
Activation of RAC1



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06/05/2024

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. ↗

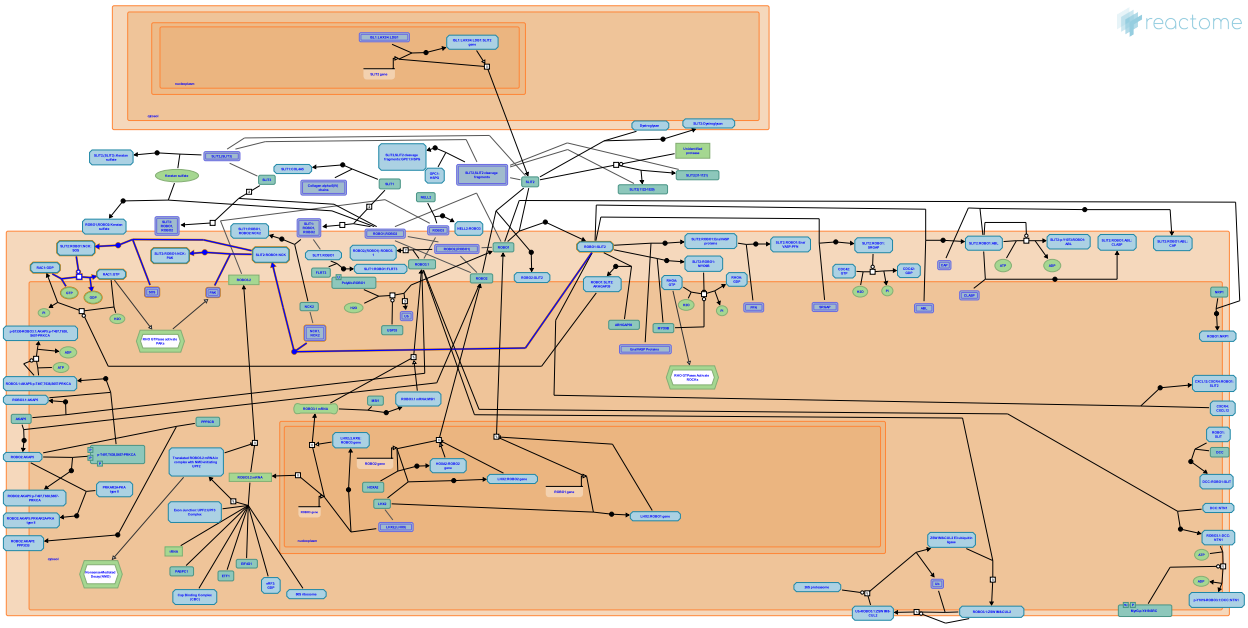
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

Activation of RAC1 ↗

Stable identifier: R-HSA-428540



A low level of RAC1 activity is essential to maintain axon outgrowth. ROBO activation recruits SOS, a dual specificity GEF, to the plasma membrane via Dock homolog NCK (NCK1 or NCK2) to activate RAC1 during midline repulsion.

Editions

2008-09-05	Authored, Edited	Garapati, P V.
2009-08-18	Reviewed	Kidd, T.
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NCK binds ROBO1:SLIT2 ↗

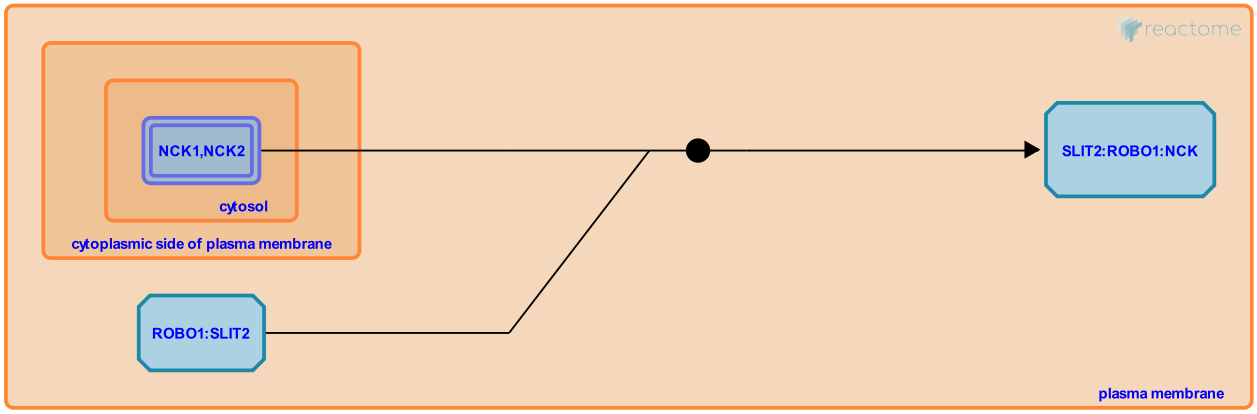
Location: Activation of RAC1

Stable identifier: R-HSA-428511

Type: binding

Compartments: plasma membrane, cytosol

Inferred from: Dock binds Robo:Slit (Drosophila melanogaster)



SLIT stimulation recruits SH3-SH2 adaptor protein Dreadlocks (Dock) (NCK in vertebrates) to the ROBO1 receptor. This interaction involves the CC2 and CC3 motifs of ROBO1 (Fan et al. 2003, Ang et al. 2003).

Followed by: Recruitment of PAK to NCK

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Recruitment of PAK to NCK ↗

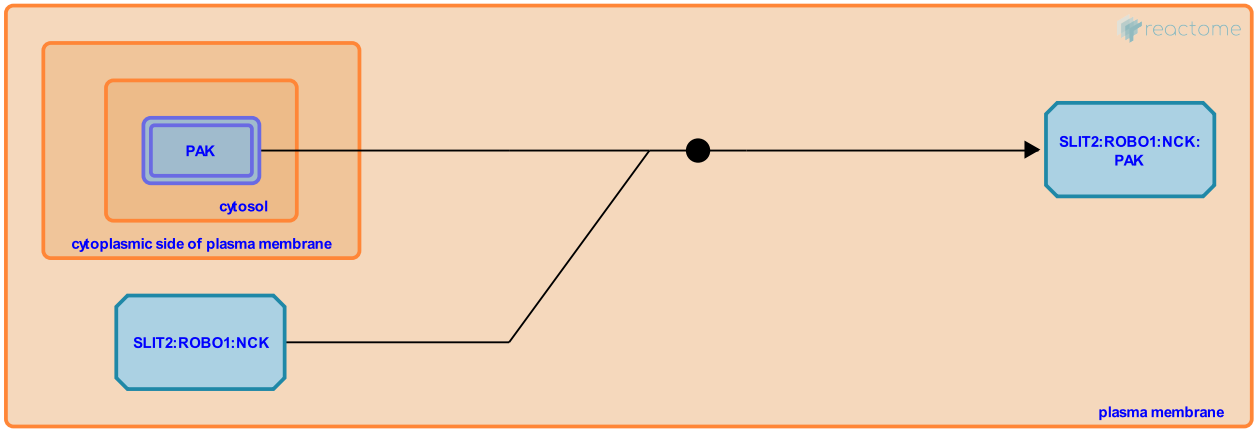
Location: Activation of RAC1

Stable identifier: R-HSA-428531

Type: binding

Compartments: plasma membrane, cytosol

Inferred from: Recruitment of Pak to Dock (Drosophila melanogaster)



NCK1 or NCK2, orthologues of Drosophila Dock, bound to ROBO1 receptor, recruits PAK to specific sites at the growth cone membrane, where PAK, activated by RAC1, regulates the recycling and retrograde flow of actin filaments. In mammals, there are six PAK isoforms (PAK1-6) and PAK binds to the 2nd SH3 domain of NCK with its proline rich PxxP motif (Galisteo et al. 1996, Fan et al. 2003). PAK autophosphorylation triggered by RAC1/CDC42 activation disrupts PAK interaction with NCK proteins (Zhao et al. 2000).

Preceded by: NCK binds ROBO1:SLIT2

Followed by: Recruitment of SOS to plasma membrane

Literature references

Lim, L., Manser, E., Zhao, ZS. (2000). Interaction between PAK and nck: a template for Nck targets and role of PAK autophosphorylation. *Mol. Cell. Biol., 20*, 3906-17. ↗

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Recruitment of SOS to plasma membrane ↗

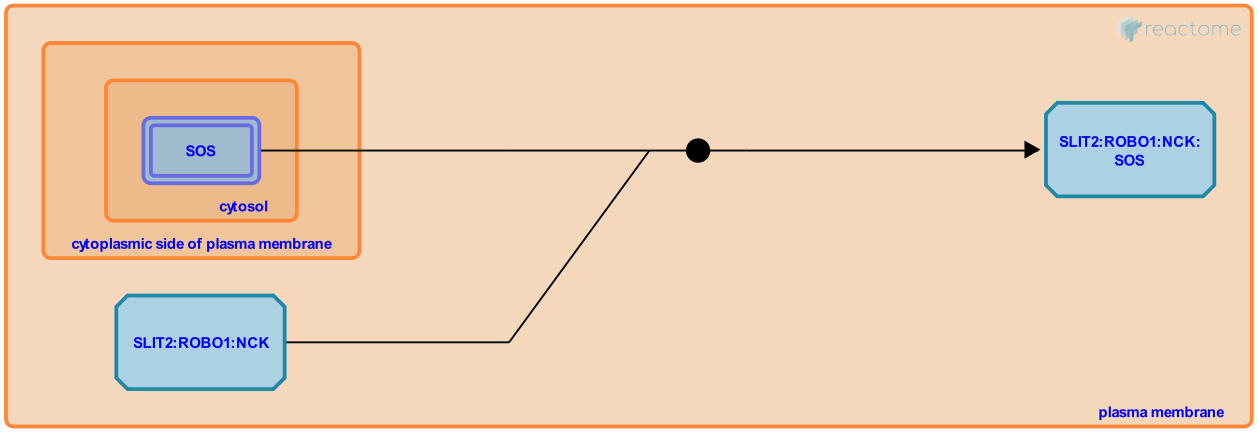
Location: Activation of RAC1

Stable identifier: R-HSA-428515

Type: binding

Compartments: plasma membrane, cytosol

Inferred from: Recruitment of Sos to plasma membrane (Drosophila melanogaster)



Upon SLIT-mediated ROBO stimulation, SOS1 or SOS2 is recruited into the multiprotein complex consisting of SLIT2, ROBO1 and the SH3-SH2 protein NCK1 or NCK2 (orthologues of Drosophila Dock). NCK bridges the physical association between ROBO and SOS. This interaction was demonstrated in both Drosophila and human cells (Hu et al. 1995, Fritz et al. 2000, Yang and Bashaw 2006).

Preceded by: Recruitment of PAK to NCK

Followed by: Activation of RAC1 by SOS

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Activation of RAC1 by SOS ↗

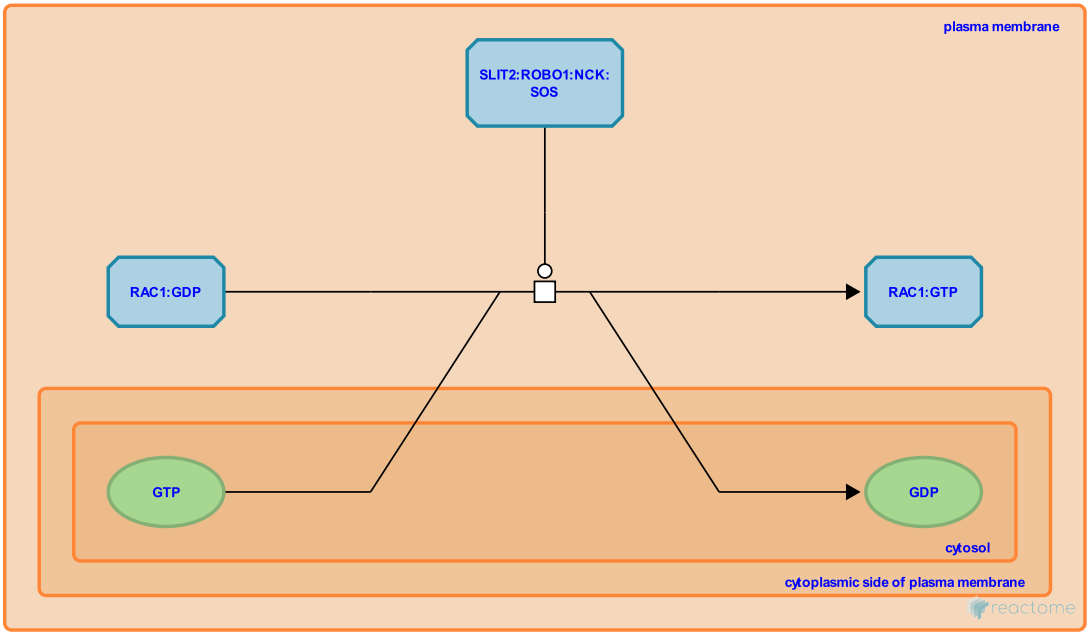
Location: Activation of RAC1

Stable identifier: R-HSA-428535

Type: transition

Compartments: plasma membrane, cytosol

Inferred from: Activation of Rac by Sos (Drosophila melanogaster)



SOS (SOS1 or SOS2), bound to Dock orholog NCK (NCK1 or NCK2), has a Rac GEF activity and activates RAC1. Son of sevenless (SOS) is a dual specificity guanine nucleotide exchange factor (GEF) that regulates both Ras and Rho family GTPases. The Ras and Rac-GEF activities of Sos can be uncoupled during ROBO-mediated axon repulsion; SOS axon guidance function depends on its Rac-GEF activity, but not its Ras-GEF activity (Yang and Bashaw 2006).

Preceded by: Recruitment of SOS to plasma membrane

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