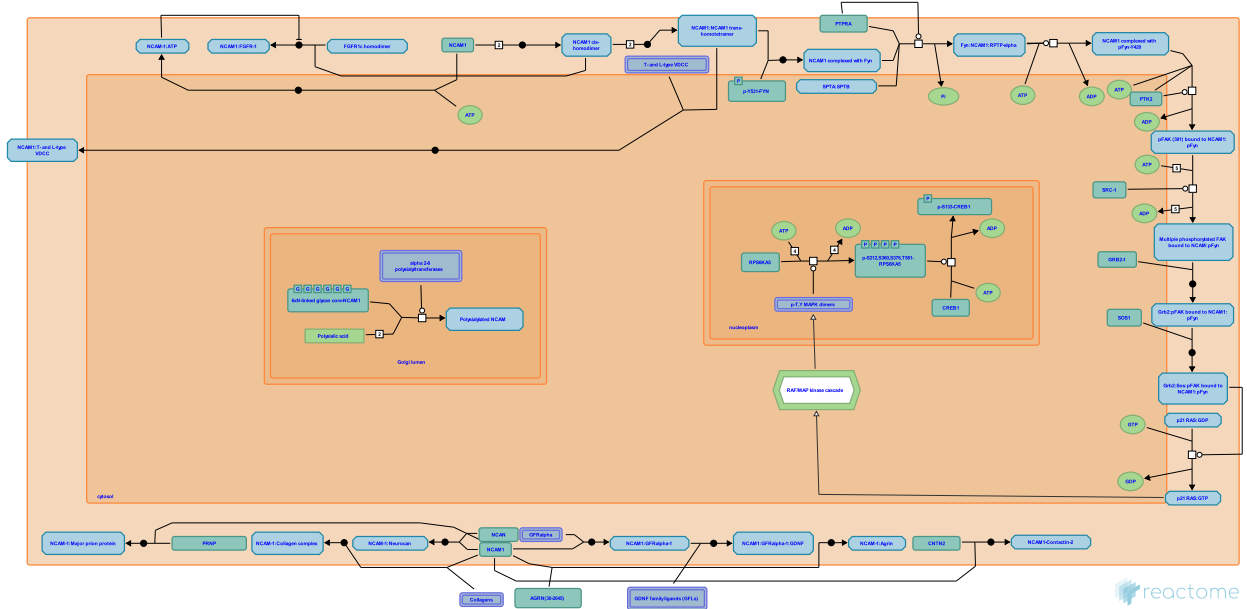


NCAM signaling for neurite out-growth



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This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the [Reactome Textbook](https://reactome.org/textbook).

01/05/2024

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.

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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. [↗](#)

Reactome database release: 88

This document contains 2 pathways and 13 reactions ([see Table of Contents](#))

Editions

2009-02-24	Authored, Edited	Garapati, P V.
2009-05-26	Reviewed	Maness, PF., Walmod, PS.

NCAM1 cis-homophilic interaction ↗

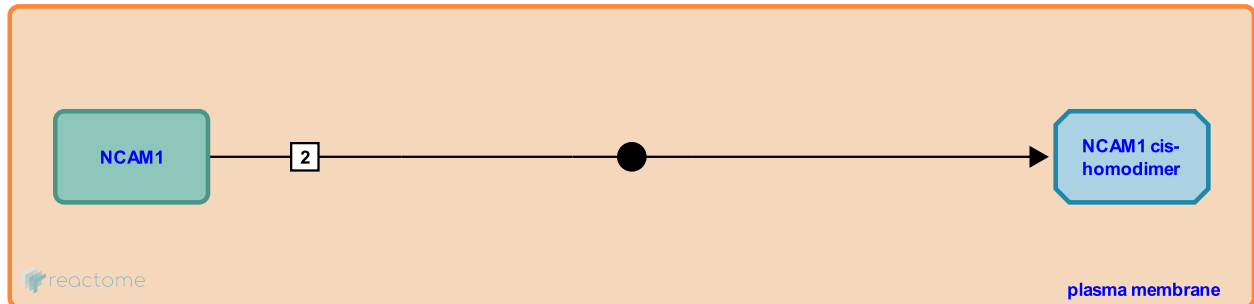
Location: [NCAM signaling for neurite out-growth](#)

Stable identifier: R-HSA-391872

Type: binding

Compartments: plasma membrane

Inferred from: [NCAM1 cis-homophilic interaction \(Rattus norvegicus\)](#)



NCAM1 located on the cell membrane can participate in parallel cis and antiparallel trans-homophilic interactions. The cis-interaction is mediated by reciprocal IgI-IgII interactions: the IgI domain of one NCAM1 molecule interacts with the IgII domain of a second.

Followed by: [NCAM1 binds FGFR-1](#)

Editions

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NCAM1 trans-homophilic interaction ↗

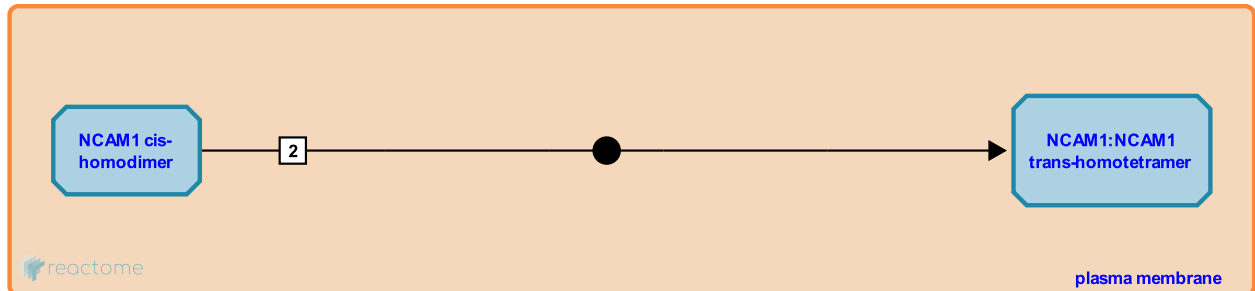
Location: [NCAM signaling for neurite out-growth](#)

Stable identifier: R-HSA-375161

Type: binding

Compartments: plasma membrane

Inferred from: [NCAM1 trans-homophilic interaction \(Rattus norvegicus\)](#)



Antiparallel NCAM interactions involve trans-interactions of NCAM molecules on opposed cell membranes. Based on structural and functional studies a 'double zipper' model has been proposed to describe these interactions. The first model - the 'flat zipper'- formed between NCAM1 cis-dimers from one cell surface interacting in trans through IgII-IgIII contacts with NCAM1 cis-dimers from another cell surface. The second model - the 'compact zipper'- is formed between NCAM1 cis-dimers from one cell surface interacting in trans through IgI-IgIII and IgII-IgII contacts with cis-dimers from another cell surface.

Abrogation of cis-dimerization inhibits NCAM mediated neurite outgrowth, and cis-dimerization of NCAM1 may be a necessary prerequisite for subsequent trans-interactions.

Followed by: [Fyn binds NCAM1](#)

Editions

2009-02-24	Authored, Edited	Garapati, P V.
2009-05-26	Reviewed	Maness, PF., Walmod, PS.

NCAM1 binds FGFR-1 ↗

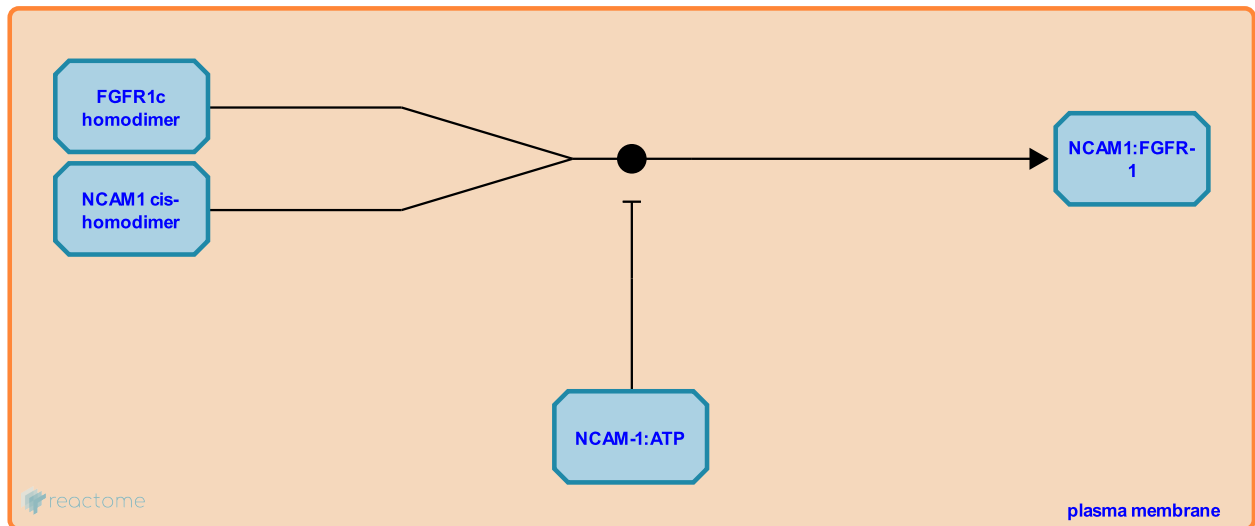
Location: [NCAM signaling for neurite out-growth](#)

Stable identifier: R-HSA-419033

Type: binding

Compartments: plasma membrane

Inferred from: [NCAM1 binds FGFR-1 \(Mus musculus\)](#)



FGFR is one of the heterophilic interactors of NCAM. The FG loop region of the second Fn3 module of NCAM binds to Ig domains 2 and 3 of FGFR. The FGFR binding site to NCAM overlaps with the site of NCAM-ATP interaction, and ATP is capable of disrupting NCAM-FGFR binding and signaling.

The interaction of NCAM activates FGFR and NCAM might merely mimic FGF's in FGFR stimulation, but there is a difference in the activation pattern induced by NCAM and FGF-2. NCAM activated FGFR stimulates neurite outgrowth by stimulating PLCgamma and DAG lipase leading to generation of arachidonic acid.

Preceded by: [NCAM1 cis-homophilic interaction](#)

Editions

2009-02-24	Authored, Edited	Garapati, P V.
2009-05-26	Reviewed	Maness, PF., Walmod, PS.

Fyn binds NCAM1 ↗

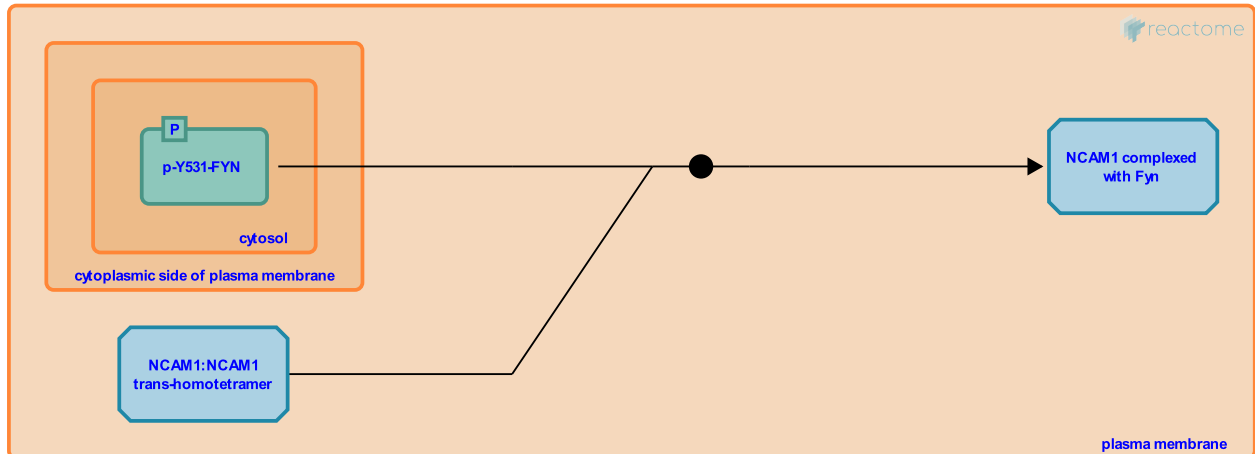
Location: [NCAM signaling for neurite out-growth](#)

Stable identifier: R-HSA-391867

Type: binding

Compartments: plasma membrane, cytosol

Inferred from: [Fyn binds NCAM1 \(Mus musculus\)](#)



Fyn constitutively associates with the 140 kD isoform of NCAM1 in the plasma membrane, probably indirectly. Fyn is attached to the lipid raft membrane compartment via palmitoylation and is inactivated by tyrosine phosphorylation (Y531) within its C-terminal regulatory region. Fyn kinase has two well-known phosphorylation sites which affect its activity in opposite ways. The phosphorylation of Tyr531 located in the C-terminus of the protein inhibits the Fyn kinase activity, due to the binding of this tyrosine residue to the SH2 domain of the protein, which stabilizes its catalytically inactive conformation.

Preceded by: [NCAM1 trans-homophilic interaction](#)

Followed by: [Dephosphorylation of NCAM1 bound pFyn](#)

Editions

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2009-05-26	Reviewed	Maness, PF., Walmod, PS.

Dephosphorylation of NCAM1 bound pFyn ↗

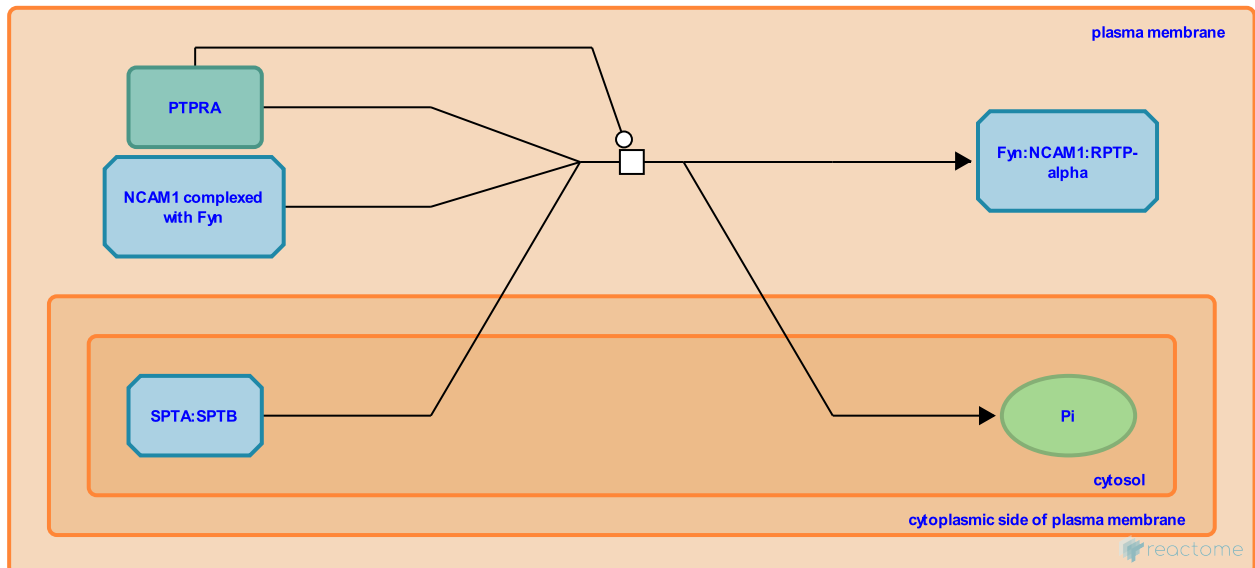
Location: [NCAM signaling for neurite out-growth](#)

Stable identifier: R-HSA-391868

Type: transition

Compartments: plasma membrane, cytosol

Inferred from: [Dephosphorylation of NCAM1 bound pFyn \(Homo sapiens\)](#)



The homophilic NCAM1:NCAM1 interaction redistributes these molecules and leads to the formation of clusters within lipid rafts. Spectrin, an NCAM1 binding cytoskeletal protein, colocalizes with NCAM1 and codistributes to lipid rafts. Spectrin associates with RPTP-alpha, linking it to the cytoplasmic NCAM1 domain and causing its core distribution to lipid rafts on NCAM1 clustering. The receptor tyrosine phosphatase RPTP-alpha is an activator of all kinases of the Src family, including Fyn kinase.

The interaction of RPTP-alpha and the SH2 domain of Fyn induces an interaction of Fyn Tyr531 with the D1 domain of RPTP-alpha. This induces dephosphorylation of Tyr531 and activates Fyn.

Preceded by: [Fyn binds NCAM1](#)

Followed by: [Autophosphorylation of NCAM1 bound Fyn](#)

Editions

2009-02-24	Authored, Edited	Garapati, P V.
2009-05-26	Reviewed	Maness, PF., Walmod, PS.

Autophosphorylation of NCAM1 bound Fyn ↗

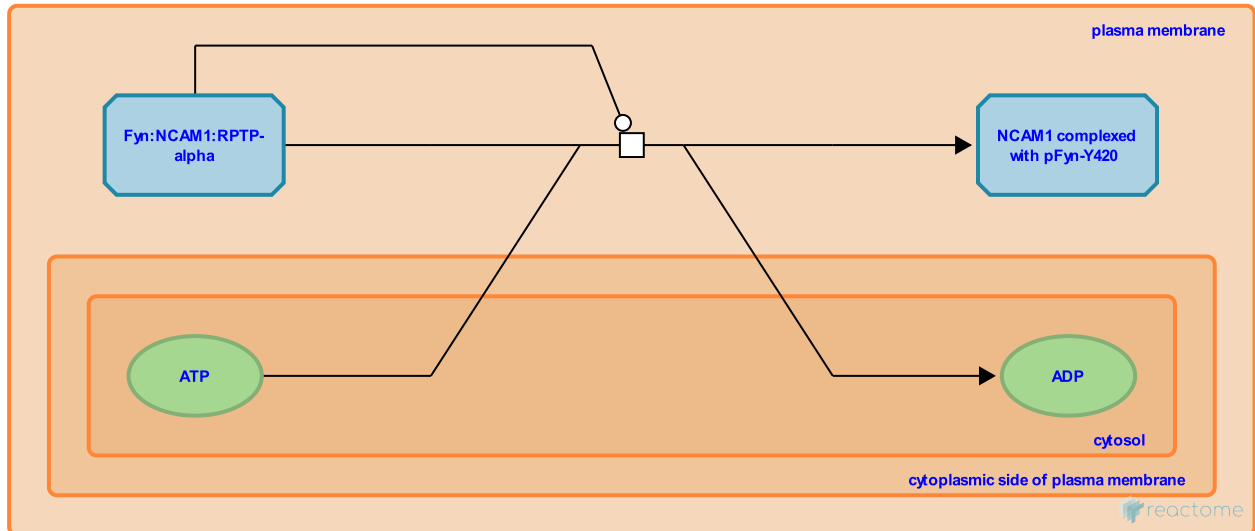
Location: [NCAM signaling for neurite out-growth](#)

Stable identifier: R-HSA-391871

Type: transition

Compartments: plasma membrane, cytosol

Inferred from: [Autophosphorylation of NCAM1 bound Fyn \(Mus musculus\)](#)



The Tyr420 residue located in the activation loop of Fyn is responsible for its enzymatic activity. Once the Tyr531 in its negative regulatory site is dephosphorylated by RPTPalpha, Fyn undergoes autophosphorylation on Tyr420 for its maximum activity.

Preceded by: [Dephosphorylation of NCAM1 bound pFyn](#)

Followed by: [Recruitment of FAK to NCAM1:Fyn in lipid rafts](#)

Editions

2009-02-24	Authored, Edited	Garapati, P V.
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Recruitment of FAK to NCAM1:Fyn in lipid rafts ↗

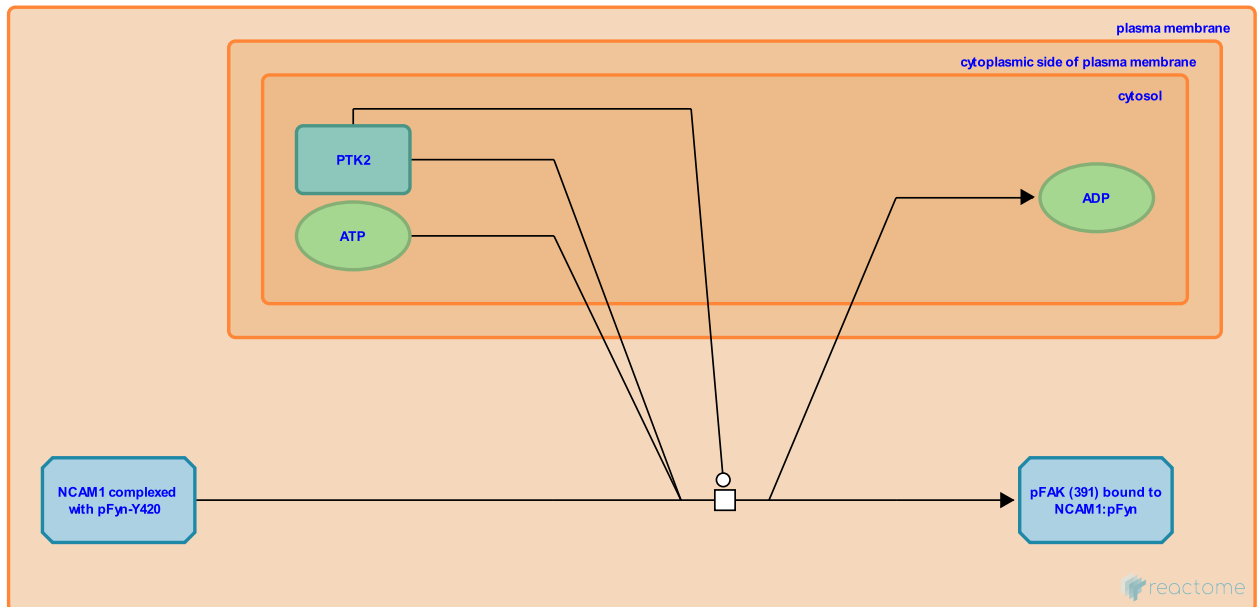
Location: [NCAM signaling for neurite out-growth](#)

Stable identifier: R-HSA-391865

Type: transition

Compartments: plasma membrane, cytosol

Inferred from: [Recruitment of FAK to NCAM1:Fyn in lipid rafts \(Mus musculus\)](#)



Fyn activation leads to the recruitment and activation of the non-receptor tyrosine kinase FAK. Once recruited to Fyn, FAK undergoes autophosphorylation on tyrosine 397. This tyrosine allows the binding of SH2 domain containing proteins.

Preceded by: [Autophosphorylation of NCAM1 bound Fyn](#)

Followed by: [Phosphorylation of FAK by Src kinase](#)

Editions

2009-02-24	Authored, Edited	Garapati, P V.
2009-05-26	Reviewed	Maness, PF., Walmod, PS.

Phosphorylation of FAK by Src kinase ↗

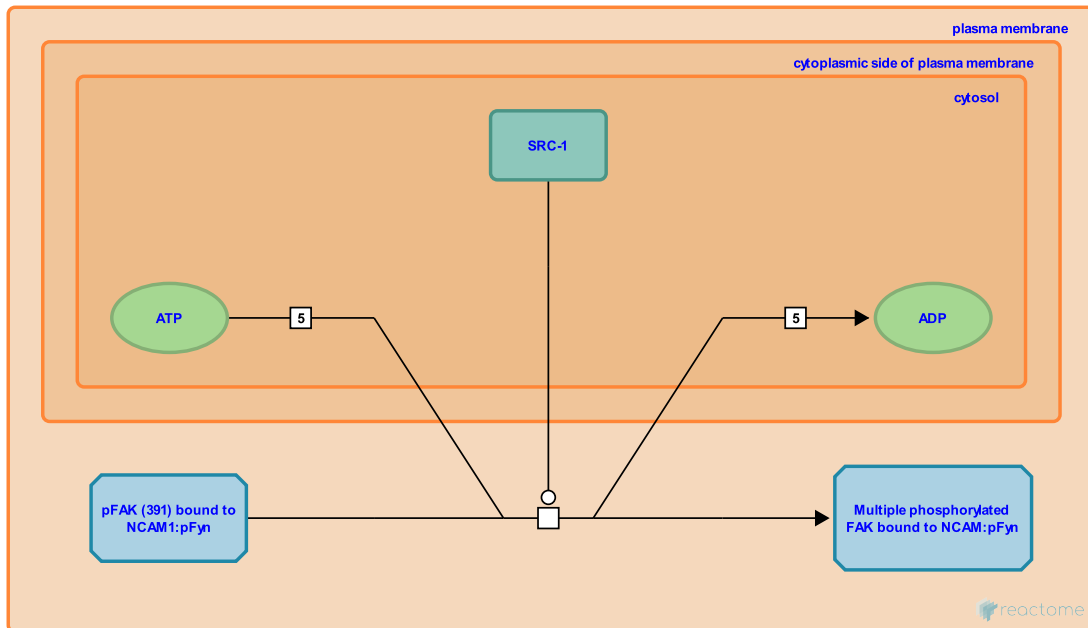
Location: [NCAM signaling for neurite out-growth](#)

Stable identifier: R-HSA-391866

Type: transition

Compartments: plasma membrane, cytosol

Inferred from: [Phosphorylation of FAK by Src kinases \(Mus musculus\)](#)



Phosphorylation of Tyr397 in FAK triggers the phosphorylation of other tyrosine residues (Tyr407, Tyr576, Tyr577, Tyr861 and Tyr925) in a Src-dependent manner. The initial phosphorylation of FAK at Tyr397 is thought to create a high-affinity binding site for SH2 domains, enabling formation of a signalling complex between FAK and members of the Src-family kinases. Tyr-576 and Tyr-577 are located in the central catalytic domain and their phosphorylation is required for the maximum kinase activity of FAK. The tyrosine phosphorylation of these residues is likely to be mediated by Src (or other members of the src family).

Preceded by: [Recruitment of FAK to NCAM1:Fyn in lipid rafts](#)

Followed by: [Recruitment of Grb2 to pFAK:NCAM1](#)

Editions

2009-02-24	Authored, Edited	Garapati, P V.
2009-05-26	Reviewed	Maness, PF., Walmod, PS.

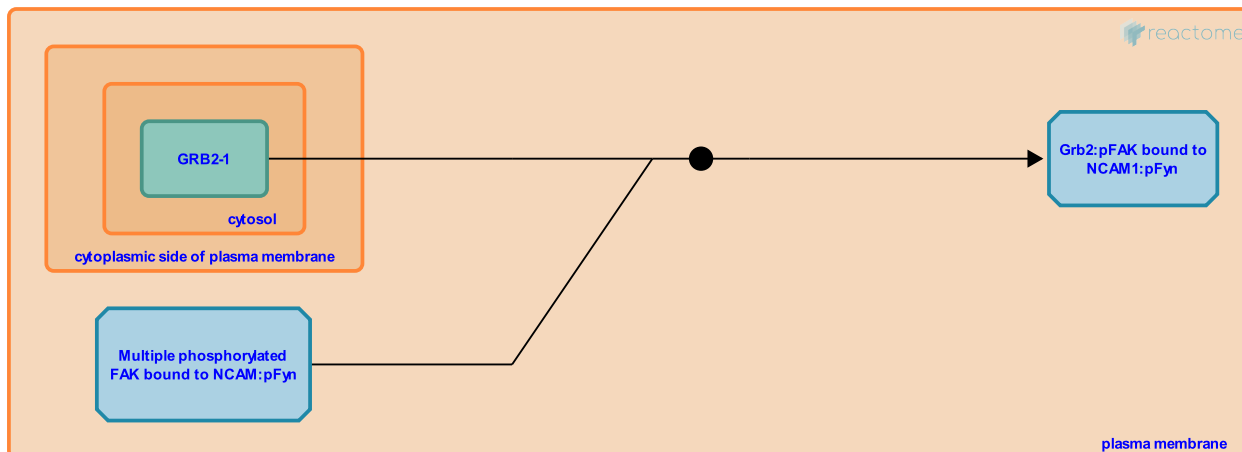
Recruitment of Grb2 to pFAK:NCAM1 ↗

Location: [NCAM signaling for neurite out-growth](#)

Stable identifier: R-HSA-392051

Type: binding

Compartments: plasma membrane, cytosol



Phosphorylated tyrosine 925 in the FAT domain of PTK2/FAK creates a docking site for the SH2 domain of GRB2 and recruits the GRB2/SOS complex. PTK2 may use this mechanism to activate Ras and the MAP kinase pathway.

Preceded by: [Phosphorylation of FAK by Src kinase](#)

Followed by: [SOS binds Grb2 bound to pFAK:NCAM1](#)

Literature references

Schlaepfer, DD., van der Geer, P., Hanks, SK., Hunter, T. (1994). Integrin-mediated signal transduction linked to Ras pathway by GRB2 binding to focal adhesion kinase. *Nature*, 372, 786-91. ↗

Panicker, AK., Thelen, K., Buhusi, M., Maness, PF. (2003). Cellular signalling mechanisms of neural cell adhesion molecules. *Front Biosci*, 8, d900-11. ↗

Kuhn, K., Probstmeier, R., Schachner, M. (1989). Binding properties of the neural cell adhesion molecule to different components of the extracellular matrix. *J Neurochem*, 53, 1794-801. ↗

Editions

2009-02-24	Authored, Edited	Garapati, P V.
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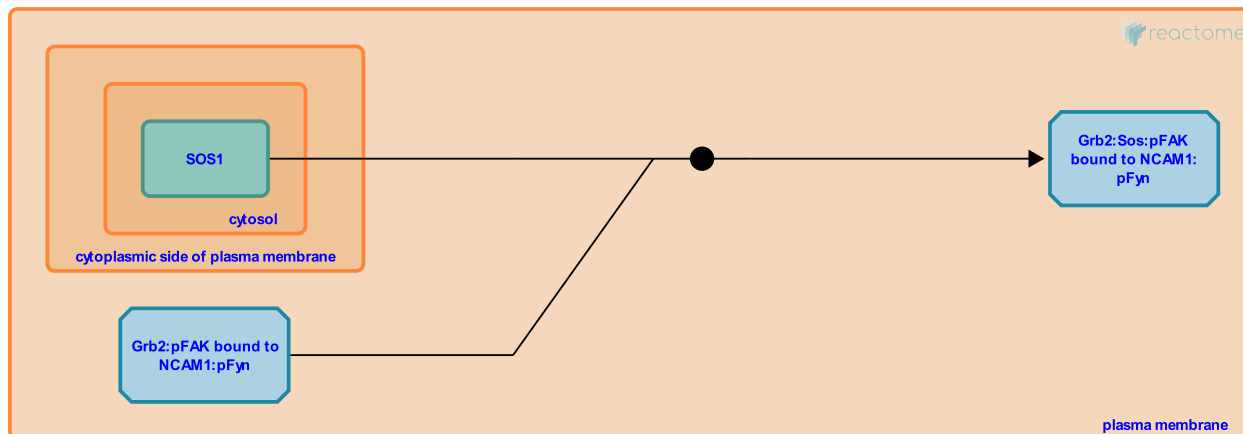
SOS binds Grb2 bound to pFAK:NCAM1 ↗

Location: [NCAM signaling for neurite out-growth](#)

Stable identifier: R-HSA-392053

Type: binding

Compartments: plasma membrane, cytosol



Guanine nucleotide releasing factor Sos associates with FAK bound Grb2 to activate Ras and initiate Ras-MAPK signaling. This interaction occurs between the carboxy terminal domain of SOS and the Src homology 3 (SH3) domains of GRB2.

Preceded by: [Recruitment of Grb2 to pFAK:NCAM1](#)

Followed by: [NCAM1:pFAK:Grb2:Sos-mediated nucleotide exchange of Ras](#)

Literature references

Panicker, AK., Thelen, K., Buhusi, M., Maness, PF. (2003). Cellular signalling mechanisms of neural cell adhesion molecules. *Front Biosci*, 8, d900-11. ↗

Kuhn, K., Probstmeier, R., Schachner, M. (1989). Binding properties of the neural cell adhesion molecule to different components of the extracellular matrix. *J Neurochem*, 53, 1794-801. ↗

Editions

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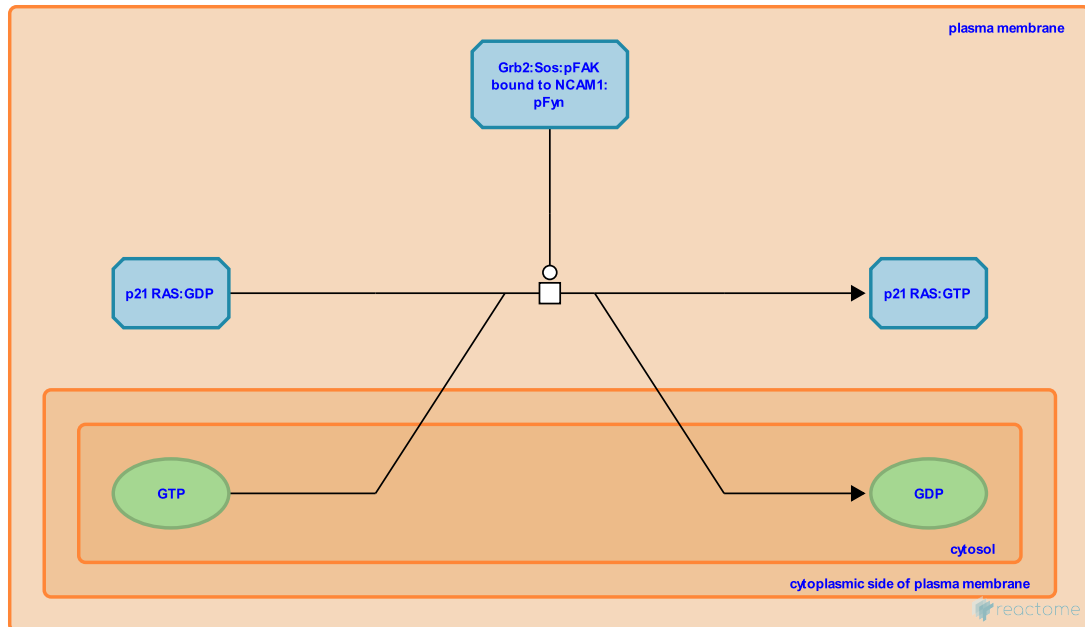
NCAM1:pFAK:Grb2:Sos-mediated nucleotide exchange of Ras ↗

Location: [NCAM signaling for neurite out-growth](#)

Stable identifier: R-HSA-392054

Type: transition

Compartments: plasma membrane, cytosol



The guanine nucleotide exchange factor SOS interacts with GRB2 bound to phosphorylated FAK bound to NCAM. Upon formation of this complex, SOS activates Ras by promoting GDP release and GTP binding.

Preceded by: [SOS binds Grb2 bound to pFAK:NCAM1](#)

Literature references

Gale, NW., Camonis, JH., Chardin, P., Schlessinger, J., Wigler, MH., Bar-Sagi, D. et al. (1993). Human Sos1: a guanine nucleotide exchange factor for Ras that binds to GRB2. *Science*, 260, 1338-43. ↗

Editions

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2009-05-26	Reviewed	Maness, PF., Walmod, PS.

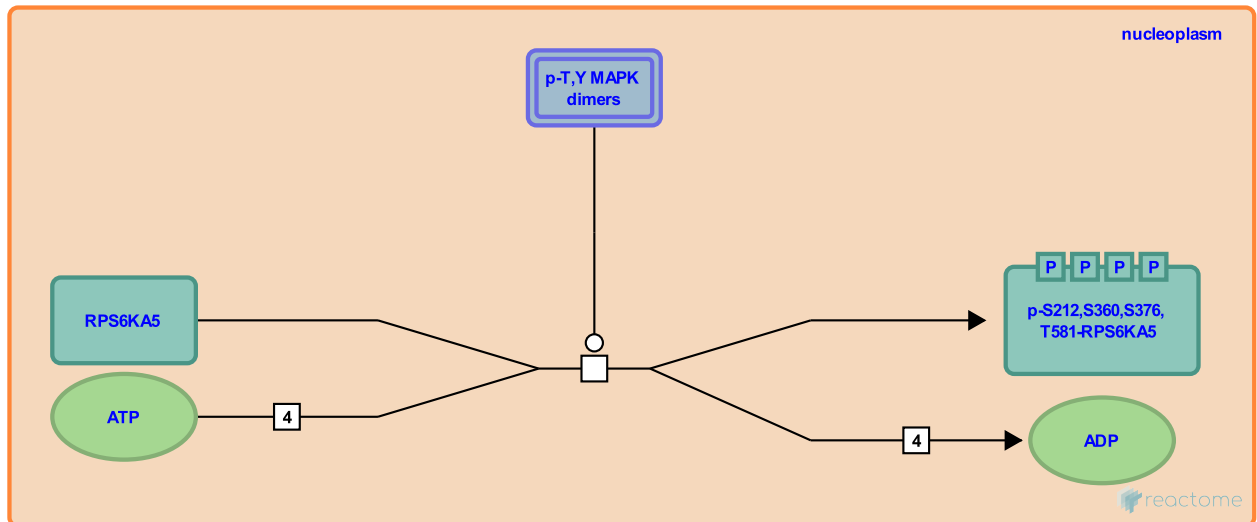
ERK1/2 phosphorylates MSK1 ↗

Location: [NCAM signaling for neurite out-growth](#)

Stable identifier: R-HSA-198756

Type: transition

Compartments: nucleoplasm



MSK1 (Ribosomal protein S6 kinase alpha-5) is a serine/threonine kinase that is localised in the nucleus. It contains two protein kinase domains in a single polypeptide. It can be activated 5-fold by ERK1/2 through phosphorylation at four key residues.

Followed by: [MSK1 activates CREB](#)

Literature references

Lucocq, LM., Alessi, DR., Clifton, AD., Deak, M. (1998). Mitogen- and stress-activated protein kinase-1 (MSK1) is directly activated by MAPK and SAPK2/p38, and may mediate activation of CREB. *EMBO J*, 17, 4426-41. ↗

Editions

2006-10-10	Authored	Annibali, D., Nasi, S.
2007-11-08	Reviewed	Greene, LA.

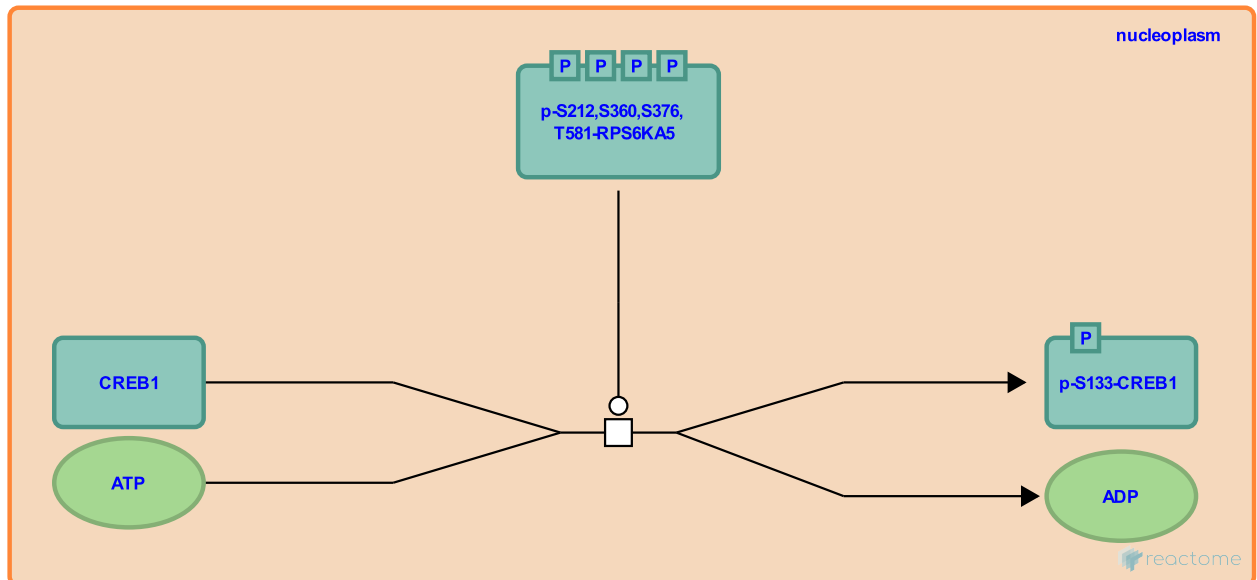
MSK1 activates CREB ↗

Location: [NCAM signaling for neurite out-growth](#)

Stable identifier: R-HSA-199935

Type: transition

Compartments: nucleoplasm



MSK1 is required for the mitogen-induced phosphorylation of the transcription factor, cAMP response element-binding protein (CREB).

Preceded by: [ERK1/2 phosphorylates MSK1](#)

Literature references

Lucocq, LM., Alessi, DR., Clifton, AD., Deak, M. (1998). Mitogen- and stress-activated protein kinase-1 (MSK1) is directly activated by MAPK and SAPK2/p38, and may mediate activation of CREB. *EMBO J*, 17, 4426-41. ↗

Editions

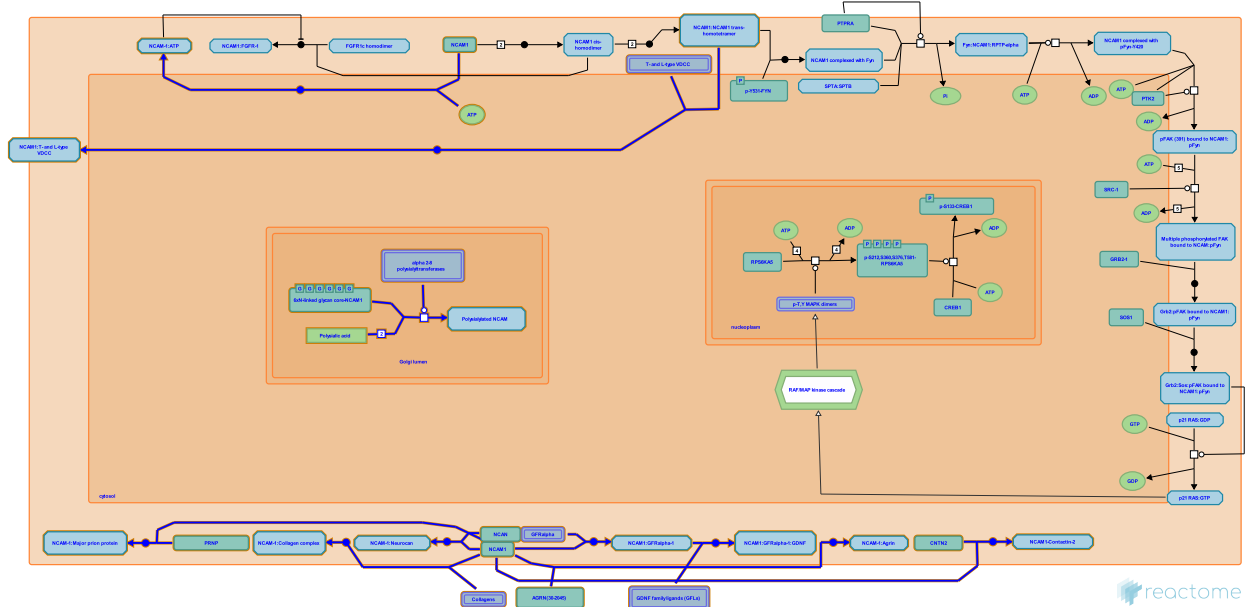
2006-10-10	Authored	Annibali, D., Nasi, S.
2007-11-08	Reviewed	Greene, LA.

NCAM1 interactions [↗](#)

Location: NCAM signaling for neurite out-growth

Stable identifier: R-HSA-419037

Compartments: plasma membrane



The neural cell adhesion molecule, NCAM1 is generally considered as a cell adhesion mediator, but it is also considered to be a signal transducing receptor molecule. NCAM1 is involved in multiple cis- and trans-homophilic interactions. It is also involved in several heterophilic interactions with a broad range of other molecules, thereby modulating diverse biological phenomena including cellular adhesion, migration, proliferation, differentiation, survival and synaptic plasticity.

Literature references

- Nielsen, J., Kulahin, N., Walmod, PS. (2008). Extracellular Protein Interactions Mediated by the Neural Cell Adhesion Molecule, NCAM: Heterophilic Interactions Between NCAM and Cell Adhesion Molecules, Extracellular Matrix Proteins, and Viruses. *Neurochem Res.* [↗](#)
- Walmod, PS., Kolkova, K., Berezin, V., Bock, E. (2004). Zippers make signals: NCAM-mediated molecular interactions and signal transduction. *Neurochem Res*, 29, 2015-35. [↗](#)

Editions

2009-02-24	Authored, Edited	Garapati, P V.
2009-05-26	Reviewed	Maness, PF., Walmod, PS.

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