Neurexins and neuroligins

Garapati, P V., Washbourne, P.

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

The contents of this document may be freely copied and distributed in any media, provided the authors, plus the institutions, are credited, as stated under the terms of Creative Commons Attribution 4.0 International (CC BY 4.0) License. For more information see our license.

17/07/2020
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.

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


Reactome database release: 73

This document contains 1 pathway and 19 reactions (see Table of Contents)
Neurexins (NRXNs) and neuroligins (NLGNs) are best characterized synaptic cell-adhesion molecules. They are part of excitatory glutamatergic and inhibitory GABAergic synapses in mammalian brain, mediate trans-synaptic signaling, and shape neural network properties by specifying synaptic functions. As cell-adhesion molecules, NRXNs and NLGNs probably function by binding to each other and by interacting with intracellular PDZ-domain proteins, but the precise mechanisms involved and their relation to synaptic transmission remain unclear. The binding of NRXNs and NLGNs to their partners, helps to align the pre-synaptic release machinery and post-synaptic receptors. The importance of neurexins and neuroligins for synaptic function is evident from the dramatic deficits in synaptic transmission in mice lacking Nrxns or Nlgns. In humans, alterations in NRXNs or NLGNs genes are implicated in autism and other cognitive diseases, connecting synaptic cell adhesion to cognition and its disorders (Sudhof 2008, Craig et al. 2006, Craig & Kang 2007).

Literature references


Editions

2015-09-04 Authored, Edited Garapati, P V.
2015-11-09 Reviewed Washbourne, P.
NRXNs bind NLGNs

**Location:** Neurexins and neuroligins

**Stable identifier:** R-HSA-6794346

**Type:** binding

**Compartments:** plasma membrane

The mammalian genome contains three NRXN genes (NRXN1, NRXN2 and NRXN3), each of which produce from independent promoters a longer alpha- and a shorter beta neurexin isoform. Furthermore, extensive alternative splicing at five canonical positions generates thousands of NRXN isoforms. In situ hybridizations showed that different alpha and beta-NRXNs are co-expressed in the same class of neurons, but that each type of NRXN is differentially distributed among different classes of neurons (Ullrich et al. 1995, Sudhof 2009, Missler et al. 2012).

Neuroligins (NLGNs) are endogenous NRXN ligands. NLGNs are expressed from four genes in vertebrates (NLGN-1 to -4). All NLGNs are alternatively spliced at a single canonical position (referred to as SS A) (Boucard et al. 2005, Ichtchenko et al. 1996). In contrast to neurexins, neuroligins are specifically localized to particular synapses. NLGN1 is only present at excitatory synapses (Song et al. 1999), NLGN2 and NLGN4 at inhibitory synapses (Varoqueaux et al. 2004, Hoon et al. 2011), whereas NLGN3 is present at both excitatory and inhibitory synapses (Budreck and Scheiffele 2007). alpha- and beta-neurexins both bind to all neuroligins to form cell adhesion complexes (Boucard et al. 2005). alpha-NRXNs with thier sixth LNS (laminin, neurexin and sex hormone-binding globulin-like) domain and beta-NRXNs with their single LNS domain bind to the lateral sides of the NLGNs esterase-homology domain (Fabrichny et al. 2007, Arac et al. 2007, Chen et al. 2008, Boucard et al. 2005, Reissner et al. 2008).

**Followed by:** NRXNs bind CASK:Protein 4.1, NLGNs binds PSD-95 subfamily members

**Literature references**


## Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author/Reviewer</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015-09-04</td>
<td>Authored, Edited</td>
<td>Garapati, P.V.</td>
</tr>
<tr>
<td>2015-11-09</td>
<td>Reviewed</td>
<td>Washbourne, P.</td>
</tr>
</tbody>
</table>
NRXNs bind SYTs

**Location:** Neurexins and neuroligins

**Stable identifier:** R-HSA-6794348

**Type:** binding

**Compartments:** plasma membrane, synaptic vesicle membrane

**Inferred from:** Syt1 binds NRXNs (Bos taurus)

Synaptotagmins (SYTs) are transmembrane proteins involved in membrane trafficking and calcium-dependent exocytosis of synaptic vesicles at the synapse. SYTs may mediate this by binding to presynaptic proteins, the neurexins (NRXNs) (Perin 1994, Hata et al. 1993, Petrenko et al. 1991). The interaction between these two proteins may mediate part of the recognition of presynaptic active sites by synaptic vesicles or may regulate neurotransmitter release (Perin 1996).

**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015-09-04</td>
<td>Authored, Edited</td>
<td>Garapati, P V.</td>
</tr>
<tr>
<td>2015-11-09</td>
<td>Reviewed</td>
<td>Washbourne, P.</td>
</tr>
</tbody>
</table>
NRXNs binds CASK tripartite complex

**Location:** Neurexins and neuroligins

**Stable identifier:** R-HSA-6794352

**Type:** binding

**Compartments:** plasma membrane

**Inferred from:** Nrxs binds Cask tripartite complex (Rattus norvegicus)

CASK (Calcium/calmodulin-dependent serine protein kinase) a multidomain synaptic scaffolding protein binds to the extreme C terminus of neurexins (Hata et al. 1996). In brain, CASK binds to MINT1 with its CaM kinase domain, and all three Velis with the region between the CaM kinase and PDZ domains to form a tight tripartite complex (Butz et al. 1998). This tripartite complex may serve as nucleation site for the assembly of synaptic plasma membrane proteins. Recruitment of this tripartite complex to the plasma membrane by binding to neurexins may be involved in synaptic vesicle traffic.

**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015-09-04</td>
<td>Authored, Edited</td>
<td>Garapati, P V.</td>
</tr>
<tr>
<td>2015-11-09</td>
<td>Reviewed</td>
<td>Washbourne, P.</td>
</tr>
</tbody>
</table>
NRXNs binds MUNC18

Location: Neurexins and neuroligins

Stable identifier: R-HSA-6794353

Type: binding

Compartments: plasma membrane

Inferred from: Nrxns binds Munc18 (Rattus norvegicus)

The cytoplasmic PDZ (PSD-95, Dlg, and ZO-1/2 domain) domain of Neurexin interacts with the intracellular vesicle trafficking protein MUNC18/STXB1 (syntaxin binding protein) via a multiprotein complex that involves MINT1 and MINT2. MUNC18, a sec1-like protein that is essential for neurotransmitter release exists in complex with Syntaxin (STX1A) and MINT1 and MINT2 in the nervous system (Okamoto & Sudhof 1997, Biederer & Sudhof 2000).

Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015-09-04</td>
<td>Authored, Edited</td>
<td>Garapati, P.V.</td>
</tr>
<tr>
<td>2015-11-09</td>
<td>Reviewed</td>
<td>Washbourne, P.</td>
</tr>
</tbody>
</table>
LRRTMs bind NRXNs

**Location:** Neurexins and neuroligins

**Stable identifier:** R-HSA-6797974

**Type:** binding

**Compartments:** plasma membrane

The LRRTM (leucine-rich repeat (LRR) transmembrane neuronal) are a small family of paralogous LRR containing cell surface receptors. This family has four members (LRRTM 1-4) that share similar domain structure with an extracellular domain containing ten extracellular leucine-rich repeats that mediate protein-protein interactions, followed by a single transmembrane domain and a short c-terminal sequence containing a class I PDZ-domain-binding motif. LRRTMs are predominantly expressed in the nervous system. All four LRRTMs family members are post-synaptic localized and bind specifically to presynaptic alpha and beta-Neurexins (NRXNs) lacking an insert at splice site S4 (Siddiqui et al. 2010). Neuroligins bind NRXN containing or lacking an insert in S4, LRRTMs bind only NRXNs lacking an insert in this splicing site (de Wit et al. 2009, Ko et al. 2009).

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015-09-04</td>
<td>Authored, Edited</td>
<td>Garapati, P V.</td>
</tr>
<tr>
<td>2015-11-09</td>
<td>Reviewed</td>
<td>Washbourne, P.</td>
</tr>
</tbody>
</table>
Neuroligins (NLGNs) bind to the third PDZ domain of postsynaptic density (PSD)-95 whereas NMDA receptor and K+ channels interact with the first and the second PDZ domains. The cytoplasmic domains of all three neuroligins interact with the NH2-terminus of PSD-95 and its homologs PSD-93 and SAP102, which contains the three PDZ domains (Irie et al. 1997).

**Preceded by:** NRXNs bind NLGNs

**Followed by:** GKAPs bind PSD-95 members

**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Authorship Details</th>
<th>Author/Editor</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015-09-04</td>
<td>Authored, Edited</td>
<td>Garapati, P V.</td>
</tr>
<tr>
<td>2015-11-09</td>
<td>Reviewed</td>
<td>Washbourne, P.</td>
</tr>
</tbody>
</table>

[Neuroligins and neuroligins](https://reactome.org)
NMDAR binds PSD-95 subfamily members

Location: Neurexins and neuroligins

Stable identifier: R-HSA-6794336

Type: binding

Compartments: plasma membrane, cytosol

Inferred from: Nmdar binds Psd-95 (Rattus norvegicus)

NMDA receptors are multimeric glutamate-gated cation channels, which are major constituents of the postsynaptic density (PSD). PSD-95/SAP90 protein is a member of the membrane-associated guanylate kinase (MAGUK) family and a prominent component of the PSD and associates with NMDA receptors. The interaction is mediated by binding of the C-terminus of the NMDA receptor subunits to the first two PDZ (also known as GLGF or DHR) domains of PSD-95 (Kornau et al. 1995, Niethammer et al. 1996). PSD-95 acts as a scaffolding protein in NMDA receptor signalling by bringing together NMDA receptor and various proteins like enzyme neuronal nitric oxide synthase (nNOS) (Brenman et al. 1996), SynGAP (Kim et al. 1998), GKAP (Kim et al. 1997), SHANK (Naisbitt et al. 1999) and multiple non-receptor tyrosine kinases (Sala & Sheng 1999). In this way, the multidomain PSD-95 molecule connects NMDA receptors to a variety of intracellular signaling proteins and anchors the whole complex to the postsynaptic density. PSD-95 subfamily includes other three more members: PSD-93/chapsyn-110, SAP97/hDlg, and SAP102. All except SAP97 appear to be components of the PSD and associated with NMDA receptors.

Followed by: BEGAIN binds DLG2,DLG3,DLG4, NMDA receptor complex:DLG2,DLG3,DLG4 binds SPAR

Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author/Editor</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015-09-04</td>
<td>Authored, Edited</td>
<td>Garapati, P V.</td>
</tr>
<tr>
<td>2015-11-09</td>
<td>Reviewed</td>
<td>Washbourne, P.</td>
</tr>
</tbody>
</table>
GKAPs bind PSD-95 members

**Location:** Neurexins and neuroligins

**Stable identifier:** R-HSA-6794338

**Type:** binding

**Compartments:** plasma membrane, cytosol

**Inferred from:** GKAP bind Psd-95 (Rattus norvegicus)

Guanylate kinase-associated protein (GKAP; also known as synapse-associated 42 protein 90-postsynaptic density-95-associated protein (SAPAP) and Discs-large-associated 43 protein (DAP) family proteins) a synaptic protein is one of the major constituent of the postsynaptic density (PSD). GKAP binds directly to the GK (guanylate kinase-like) domain of the four known members of the PSD-95 (postsynaptic density protein 95) family (Kim et al. 1997, Naisbitt et al. 1997, Takeuchi et al. 1997). GKAP is therefore one of the major scaffold proteins organizing glutamate receptors in the PSD.

**Preceded by:** NLGNs binds PSD-95 subfamily members

**Followed by:** SHANK proteins bind GKAPs

**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Author/Editor</th>
<th>Person</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015-09-04</td>
<td>Authored, Edited</td>
<td>Garapati, P V.</td>
</tr>
<tr>
<td>2015-11-09</td>
<td>Reviewed</td>
<td>Washbourne, P.</td>
</tr>
</tbody>
</table>
SHANK proteins bind GKAPs

**Location:** Neurexins and neuroligins

**Stable identifier:** R-HSA-6794357

**Type:** binding

**Compartments:** plasma membrane, cytosol

**Inferred from:** Shank binds Gkap1 (Rattus norvegicus)

PSD-95 interacts with GKAP through its GK domain (Kim et al. 1997). In turn, the C-terminus of GKAP binds to the Shank family of PDZ-containing scaffold proteins. The Shank family of proteins is highly enriched in the postsynaptic density (PSD) of excitatory synapses in brain. There are three known SHANK proteins: SHANK1, SHANK2, and SHANK3. SHANK contains multiple domains for protein-protein interactions, including ankyrin repeats, SH3 domain, PDZ domain, SAM domain, and an extensive proline-rich region (Sheng & Kim 2000). Shank may function as a scaffold protein in the PSD, potentially crosslinking NMDA receptor or Neuroligin:PSD-95 complexes and coupling them to regulators of the actin cytoskeleton (Naisbitt et al.1999).

**Preceded by:** GKAPs bind PSD-95 members

**Followed by:** ABP1 binds SHANK proteins, HOMER binds SHANK proteins

**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Details</th>
<th>Author(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015-09-04</td>
<td>Authored, Edited</td>
<td>Garapati, P V.</td>
</tr>
<tr>
<td>2015-11-09</td>
<td>Reviewed</td>
<td>Washbourne, P.</td>
</tr>
</tbody>
</table>
**SHARPIN binds SHANK proteins**

**Location:** Neurexins and neuroligins

**Stable identifier:** R-HSA-6794351

**Type:** binding

**Compartments:** cytosol

**Inferred from:** Shank1 binds Sharpin (Rattus norvegicus)

SHANK with its ankyrin repeats has been found to bind SHARPIN a molecule that can form homomers. SHARPIN is another PSD protein enriched at synaptic sites in mature neurons and may be involved in the formation and maintenance of excitatory synaptic structures (Lim et al. 2001).

**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Role</th>
<th>Author(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015-09-04</td>
<td>Authored, Edited</td>
<td>Garapati, P V.</td>
</tr>
<tr>
<td>2015-11-09</td>
<td>Reviewed</td>
<td>Washbourne, P.</td>
</tr>
</tbody>
</table>
Homer\textsubscript{1,2,3} binds mGluR\textsubscript{1a,5}

**Location:** Neurexins and neuroligins

**Stable identifier:** R-HSA-6794355

**Type:** binding

**Compartments:** plasma membrane, cytosol

Homer proteins are closely related neuronal scaffolding molecules that selectively binds the C-terminus of group 1 metabotropic or heterotrimeric GTP-binding protein-linked glutamate receptors (mGluR\textsubscript{1a} and mGluR\textsubscript{5}) and are enriched at excitatory synapses (Brakeman et al. 1997, Xiao et al. 1998). Homer proteins contain an amino-terminal EVH1 domain followed by a rod-shaped coiled-coil domain. The EVH1 domain of Homer can bind the proline rich motifs in mGluRs and the inositol 1,4,5-trisphosphate (IP\textsubscript{3}) receptors, thereby linking these receptors in a signalling complex (Tu et al. 1998, 1999).

**Followed by:** Homer\textsubscript{1,2,3} dimerizes

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015-09-04</td>
<td>Authored, Edited</td>
<td>Garapati, P V.</td>
</tr>
<tr>
<td>2015-11-09</td>
<td>Reviewed</td>
<td>Washbourne, P.</td>
</tr>
</tbody>
</table>
**Homer1,2,3 dimerizes**

**Location:** Neurexins and neuroligins

**Stable identifier:** R-HSA-6794347

**Type:** binding

**Compartments:** plasma membrane, cytosol

Homer dimerizes via the coiled-coil domains to form a rod with EVH1 domains on either end. It could interact with mGluRs on one end and with the other EVH1 domain can bind to Shank proteins linking the two receptors together (Hayashi et al. 2009).

**Preceded by:** Homer1,2,3 binds mGluR1a,5

**Followed by:** HOMER binds SHANK proteins

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author/Reviewer</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015-09-04</td>
<td>Authored, Edited</td>
<td>Garapati, P.V.</td>
</tr>
<tr>
<td>2015-11-09</td>
<td>Reviewed</td>
<td>Washbourne, P.</td>
</tr>
</tbody>
</table>
**HOMER binds SHANK proteins**

**Location:** Neurexins and neuroligins

**Stable identifier:** R-HSA-6794344

**Type:** binding

**Compartments:** plasma membrane

**Inferred from:** Shank1,3 binds Homer1a (Rattus norvegicus)

Homer with its EVH1 domain binds to proline-rich motif of Shank family members. Shank and Homer coimmunoprecipitate from brain and colocalize at postsynaptic densities. Shank uses distinct domains to bind to GKAP and Homer, thus it can bridge between these two proteins. Thus, Shank may cross-link Homer and PSD-95 complexes in the PSD and play a role in the signaling mechanisms of both mGluRs and NMDA receptors (Tu et al. 1999).

**Preceded by:** SHANK proteins bind GKAPs, Homer1,2,3 dimerizes

**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Author/Editor</th>
<th>Reviewer</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015-09-04</td>
<td>Authored, Edited</td>
<td>Garapati, P.V.</td>
</tr>
<tr>
<td>2015-11-09</td>
<td>Reviewed</td>
<td>Washbourne, P.</td>
</tr>
</tbody>
</table>
ABP1 binds SHANK proteins

**Location:** Neurexins and neuroligins

**Stable identifier:** R-HSA-6797554

**Type:** binding

**Compartments:** plasma membrane, cytosol

At the PSD (postsynaptic density), activity-dependent reorganizations of the cortical actin cytoskeleton are hypothesized to play a role in synaptic plasticity. Drebrin-like protein (DBNL) (also referred as Filamentous actin (F-actin)-binding protein 1 (ABP1)), which controls Arp2/3 complex-mediated actin nucleation binds to postsynaptic scaffold proteins of the ProSAP (proline-rich synapse-associated protein 1)/Shank family. This DBNL–ProSAP/Shank complexes serve to connect synaptic signal reception to postsynaptic structural plasticity via rearrangements of the actin cytoskeleton in spines (Haeckel et al. 2008).

**Preceded by:** SHANK proteins bind GKAPs

**Literature references**

Haeckel, A., Ahuja, R., Gundelfinger, ED., Qualmann, B., Kessels, MM. (2008). The actin-binding protein Abp1 controls dendritic spine morphology and is important for spine head and synapse formation. *J. Neurosci.*, 28, 10031-44.

**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015-09-04</td>
<td>Authored, Edited</td>
<td>Garapati, P V.</td>
</tr>
<tr>
<td>2015-11-09</td>
<td>Reviewed</td>
<td>Washbourne, P.</td>
</tr>
</tbody>
</table>
**BEGAIN binds DLG2, DLG3, DLG4**

**Location:** Neurexins and neuroligins

**Stable identifier:** R-HSA-6794356

**Type:** binding

**Compartments:** plasma membrane, cytosol

**Inferred from:** Begain binds Psd-95 (Rattus norvegicus)

Disks large homolog proteins (DLGs, Post synaptic density proteins) 2, 3 and 4 interact with BEGAIN (Brain-enriched Guanylate Kinase-associated Protein) via their guanylate kinase-like (GK) domain. BEGAIN is specifically expressed in brain and enriched in the PSD fraction and may be involved in the organization of the components of synaptic junctions (Deguchi et al. 2001).

**Preceded by:** NMDAR binds PSD-95 subfamily members

**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author/Editor</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015-09-04</td>
<td>Authored, Edited</td>
<td>Garapati, P.V.</td>
</tr>
<tr>
<td>2015-11-09</td>
<td>Reviewed</td>
<td>Washbourne, P.</td>
</tr>
</tbody>
</table>
Spine-Associated RapGAP (SPAR) is a postsynaptic Rap-specific GTPase-activating protein (RapGAP) that reorganizes actin cytoskeleton and drives dendritic spine head growth. SPAR interacts with the guanylate kinase-like (GK) domain of Disks large homolog proteins (DSGs) forming a complex with NMDA receptors in brain (Pak et al. 2001).

**Preceded by:** NMDAR binds PSD-95 subfamily members

**Followed by:** NMDA receptor complex:DLG2,DLG3,DLG4:SPAR binds PDLIM5

**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author/Editor</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015-09-04</td>
<td>Authored, Edited</td>
<td>Garapati, P. V.</td>
</tr>
<tr>
<td>2015-11-09</td>
<td>Reviewed</td>
<td>Washbourne, P.</td>
</tr>
</tbody>
</table>
Spine-Associated RapGAP (SPAR) interacts with a PDZ-LIM domain family protein called PDZ and LIM domain 5 (PDLIM5), formerly known as Enigma Homolog (ENH). PDLIM5 is expressed postsynaptically in excitatory pyramidal neurons of the hippocampus and associates with SPAR protein in the brain. In hippocampal neurons, PDLIM5 promotes decreased dendritic spine size, opposite to the effect of SPAR overexpression that causes spine head enlargement.

Single nucleotide polymorphisms in PDLIM5 have been associated with schizophrenia, depression, and bipolar disorder (Kato et al. 2005, Li et al. 2008, Liu et al. 2008), although the physiological functions of PDLIM5 are not well understood.

**Preceded by:** NMDA receptor complex:DLG2,DLG3,DLG4 binds SPAR

**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author/Editor</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015-09-04</td>
<td>Authored, Edited</td>
<td>Garapati, P V.</td>
</tr>
<tr>
<td>2015-11-09</td>
<td>Reviewed</td>
<td>Washbourne, P.</td>
</tr>
</tbody>
</table>
Protein 4.1 binds CASK

Location: Neurexins and neuroligins

Stable identifier: R-HSA-6797553

Type: binding

Compartments: cytosol

The protein 4.1 family includes four well-defined members: erythroid protein 4.1 (4.1R), the best known and characterized member, 4.1G (general), 4.1N (neuronal), and 4.1 B (brain). Protein 4.1N is a neuronal homologue of erythrocyte membrane cytoskeletal protein 4.1 (4.1R). Protein 4.1N can stabilize the plasticity of the neuronal membrane via interactions with the spectrin-actin-based skeleton, integral membrane channels and receptors, and membrane-associated guanylate kinases (Diakowski et al. 2006). This brain-specific protein 4.1N isoform interacts with CASK and recruits actin and spectrin (Biederer & Südhof 2001).

Followed by: NRXNs bind CASK:Protein 4.1

Literature references


Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015-09-04</td>
<td>Authored, Edited</td>
<td>Garapati, P V.</td>
</tr>
<tr>
<td>2015-11-09</td>
<td>Reviewed</td>
<td>Washbourne, P.</td>
</tr>
</tbody>
</table>
**NRXNs bind CASK:Protein 4.1**

**Location:** Neurexins and neuroligins

**Stable identifier:** R-HSA-6797568

**Type:** binding

**Compartments:** plasma membrane, cytosol

In neurons, CASK forms a stable tripartite complex with brain-enriched Veli proteins and brain-specific Mint1 and anchors this complex to neurexins (Butz et al. 1998). CASK also binds to a brain-enriched isoform of protein 4.1, and nucleates local assembly of actin/spectrin filaments. Neurexins are recruited together with CASK and protein 4.1 into these actin filaments and thus intercellular junctions initiated by neurexins with neuroligins are at least partially coupled to the actin cytoskeleton (Biederer & Südhof 2001).

**Preceded by:** NRXNs bind NLGNs, Protein 4.1 binds CASK

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015-09-04</td>
<td>Authored, Edited</td>
<td>Garapati, P V.</td>
</tr>
<tr>
<td>2015-11-09</td>
<td>Reviewed</td>
<td>Washbourne, P.</td>
</tr>
</tbody>
</table>
# Table of Contents

- Introduction
  - Neurexins and neuroligins
    - NRXNs bind NLGNs
    - NRXNs bind SYTs
    - NRXNs bind CASK tripartite complex
    - NRXNs binds MUNC18
    - LRRTMs bind NRXNs
  - NLGNs binds PSD-95 subfamily members
  - NMDAR binds PSD-95 subfamily members
  - GKAPs bind PSD-95 members
  - SHANK proteins bind GKAPs
  - SHARPIN binds SHANK proteins
  - Homer1,2,3 binds mGluR1a,5
  - Homer1,2,3 dimerizes
  - HOMER binds SHANK proteins
  - ABP1 binds SHANK proteins
  - BEGAIN binds DLG2,DLG3,DLG4
  - NMDA receptor complex:DLG2,DLG3,DLG4 binds SPAR
  - NMDA receptor complex:DLG2,DLG3,DLG4:SPAR binds PDLIM5
  - Protein 4.1 binds CASK
  - NRXNs bind CASK:Protein 4.1