Netrin-1 signaling

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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.

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https://reactome.org
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: 82

This document contains 5 pathways and 11 reactions (see Table of Contents)
Netrin-1 signaling

Stable identifier: R-HSA-373752

Netrins are secreted proteins that play a crucial role in neuronal migration and in axon guidance during the development of the nervous system. To date, several Netrins have been described in mouse and humans: Netrin-1, -3/NTL2, -4/h and G-Netrins. Netrin-1 is the most studied member of the family and has been shown to play a crucial role in neuronal navigation during nervous system development mainly through its interaction with its receptors DCC and UNC5. Members of the Deleted in colorectal cancer (DCC) family- which includes DCC and Neogenin in vertebrates- mediate netrin-induced axon attraction, whereas the C. elegans UNC5 receptor and its four vertebrate homologs Unc5a-Unc5d mediate repulsion.

Literature references


Editions

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The DCC family includes DCC and neogenin in vertebrates. DCC is required for netrin-induced axon attraction. DCC is a transmembrane protein lacking any identifiable catalytic activity. Protein tyrosine kinase 2/FAK and src family kinases bind constitutively to the cytoplasmic domain of DCC and their activation couples to downstream intracellular signaling complex that directs the organization of actin.

**Literature references**


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Unc5 netrin receptors mediate repellent responses to netrin. Four Unc5 members have been found in humans: Unc5A, B, C and D. Different studies have suggested that long-range repulsion to netrin requires the cooperation of Unc5 and DCC, but that Unc5 without DCC is sufficient for short-range repulsion. The binding of netrin to Unc5 triggers the phosphorylation of Unc5 in its ZU-5 domain. Several proteins have been proposed to interact with Unc5 family members in mediating a repellent response, including tyrosine phosphatase Shp2, the F-actin anti-capping protein Mena, and ankyrin.

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DCC interaction with ROBO1

**Location:** Netrin-1 signaling

**Stable identifier:** R-HSA-373715

**Type:** binding

**Compartments:** plasma membrane

**Inferred from:** DCC interaction with Robo-1 (Drosophila melanogaster)

DCC and ROBO1 heterodimerize via conserved sequence elements in their cytoplasmic domains, namely CC1 (conserved cytoplasmic region1) in ROBO1 and P3 in DCC. The formation of this complex is dependent on the previous interaction between ROBO and its ligand (SLIT). This physical interaction between ROBO:SLIT and DCC silences the attractive effect of Netrin:DCC and regulates the midline crossing of axons.

From the analysis of multiple double mutant combinations of the ROBO:SLIT and Netrin:DCC receptor-ligand pairs, it was deduced that ROBO repulsion on its own is sufficient to prevent commissural axons from re-crossing the midline, and that Netrin:DCC is not the only source of attraction at the midline (Stein and Tessier-Lavigne 2001, Garbe and Bashaw 2007).
DCC interaction with SIAH1

Location: Netrin-1 signaling

Stable identifier: R-HSA-374665

Type: binding

Compartments: plasma membrane, cytosol

Siah-1 binds DCC and promotes its proteolysis via the ubiquitin-proteasome pathway. Siah-1 contains an N-terminal RING domain that is involved in proteolysis function and a C-terminal sequence that is involved in its oligomerization and binding to target proteins, such as DCC.

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Siah-2 binds to the DCC protein and promotes its proteolysis via the ubiquitin-proteasome pathway.

**Literature references**

**Translocation of Ezrin to plasma membrane**

**Location:** Netrin-1 signaling

**Stable identifier:** R-HSA-374662

**Type:** binding

**Compartments:** plasma membrane, cytosol

Ezrin is a member of the ezrin/radixin/moesin (ERM) family that acts as a linker between the plasma membrane and the actin cytoskeleton. Ezrin exists in a dormant, monomeric form in which its FERM/NERMAD and C-ERMAD domains are associated, masking membrane and F-actin binding regions. On production of PIP2, ezrin binds it, is recruited to the plasma membrane, and undergoes conformational changes unmasking the two binding sites.

**Followed by:** Phosphorylation and activation of Ezrin

**Literature references**

Phosphorylation and activation of Ezrin

Location: Netrin-1 signaling

Stable identifier: R-HSA-374664

Type: transition

Compartments: plasma membrane, cytosol

PIP2 places Ezrin at the membrane in a location to be phosphorylated, and thereby activated, by protein kinase-C theta.

**Preceded by:** Translocation of Ezrin to plasma membrane

**Followed by:** DCC interaction with Ezrin

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Phosphorylated Ezrin can link in microfilaments to the plasma membrane by direct association with transmembrane proteins such as the cytoplasmic domain of DCC.

**Preceded by:** Phosphorylation and activation of Ezrin

**Literature references**

Netrin-4 binds DCC/UNC5A

Location: Netrin-1 signaling

Stable identifier: R-HSA-593685

Type: binding

Compartments: plasma membrane

DCC and UNC5A, are also receptors for Netrin-4. The LNT domain of Netrin-4 is the key domain for this specific binding. Netrin-4 might also mediate attractive action through DCC and repulsive action through UNC5A.

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Neogenin binds Netrin-1

Location: Netrin-1 signaling

Stable identifier: R-HSA-374689

Type: binding

Compartments: plasma membrane, extracellular region

Inferred from: Neogenin binds Netrin-1 (Mus musculus)

Netrin-1 is not only involved as an axon guidance cue during the development of nervous system but is also involved in the morphogenesis of the mammary glands. Netrin-1 acts as a short-range attractant and has an adhesive, rather than a guidance, function during mammary gland morphogenesis. In the developing mammary gland, netrin-1 acts locally through neogenin to maintain close apposition of cap cells and prelumenal cells at the leading edge of the TEB (Terminal end bud).

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Neogenin binds repulsive guidance molecules (RGDs)

**Location:** Netrin-1 signaling

**Stable identifier:** R-HSA-374692

**Type:** binding

**Compartments:** plasma membrane

**Inferred from:** Neogenin binds repulsive guidance molecules (Gallus gallus)

Among netrin1 receptors neogenin is the only protein to interact with the repulsive guidance molecules (RGM). RGMs are membrane bound proteins involved in axon guidance in the visual system. Neogenin is the dependence receptor and cleaved by activated caspase-3 to trigger apoptotic cell death. RGM binding blocks the cleavage of neogenin so RGM functions as a cell survival factor.

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Myosin-X binds DCC/Neogenin

**Location:** Netrin-1 signaling

**Stable identifier:** R-HSA-593672

**Type:** binding

**Compartments:** plasma membrane, cytosol

**Inferred from:** Myosin-X binds DCC/Neogenin (Mus musculus)

Myosin-X, an unconventional myosin implicated in cell adhesion and filopodia elongation interacts with DCC and Neogenin and helps in their distribution in neurites. Myosin-X functions to transfer cargo proteins into filopodia and its hypothesized that Myosin-X may deliver DCC to filopodia on Netrin-1 stimulation.

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PIKE-L interaction with UNC5B

**Location:** Netrin-1 signaling

**Stable identifier:** R-HSA-622357

**Type:** binding

**Compartments:** plasma membrane, cytosol

**Inferred from:** PIKE-L interaction with UNC5B (Rattus norvegicus)

PIKE-L a brain-specific GTPase selectively associates with UNC5B but not with other family members of UNC5. Netrin-1 enhances this interaction and this interaction triggers the activation of PI3K kinase signalling, prevents UNC5B's pro-apoptotic activity and enhances neuronal survival.

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The levels of second messengers such as Ca+2, cAMP and cGMP may regulate the response of the growth cone to a particular cue. Netrin-1 as a guidance molecule depends on intracellular Ca+2 concentration, coactivation of PI3K and PLCgamma, and the type of response depends on the levels of cAMP.

Netrin first stimulates its receptor DCC, resulting in the activation of the enzyme phospholipase C. This then produces the messenger molecules, inositol-1,4,5-trisphosphate (IP3) and DAG, which in turn causes the release of Ca+2 from intracellular stores. Ca+2 release from the stores then activates TRPC channels on the cell surface. DAG activates TRPC3 and TRPC6 in a direct, membrane delimited manner, and IP3 may activate TRPC channels by depleting the ER Ca+2 levels.

**Literature references**


DSCAM (Down syndrome cell adhesion molecule) is one of the members of the Ig superfamily CAMs with a domain architecture comprising 10 Ig domains, 6 fibronectin type III (FN) repeats, a single transmembrane and a C terminal cytoplasmic domain. DSCAM is implicated in Down syndrome (DS) due to the chromosomal location of the DSCAM gene, but no evidence supports a direct involvement of DSCAM with DS. It likely functions as a cell surface receptor mediating axon pathfinding. Besides these important implications, little is known about the physiological function or the molecular mechanism of DSCAM signal transduction in mammalian systems. A closely related DSCAM paralogue Down syndrome cell adhesion moleculerlike protein 1 (DSCAML1) is present in humans. Both these proteins are involved in homophilic intercellular interactions.

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