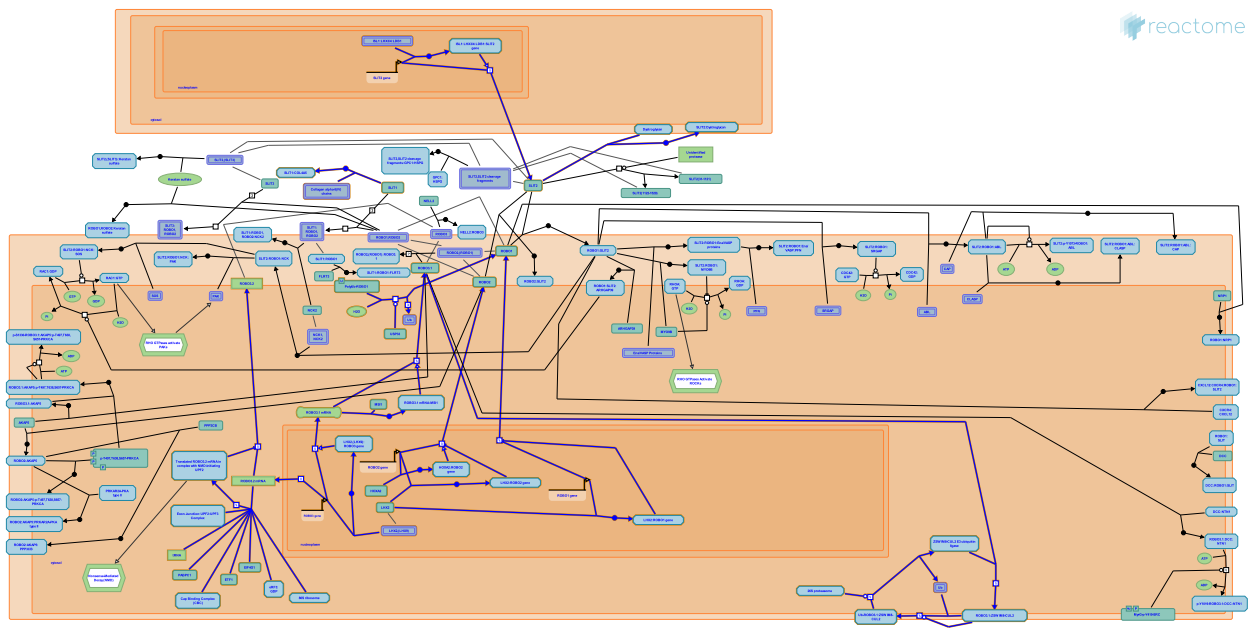


Regulation of expression of SLITs and ROBOs



Jaworski, A., Orlic-Milacic, M.

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](https://creativecommons.org/licenses/by/4.0/). For more information see our [license](https://reactome.org/licenses/).

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/).

05/05/2024

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

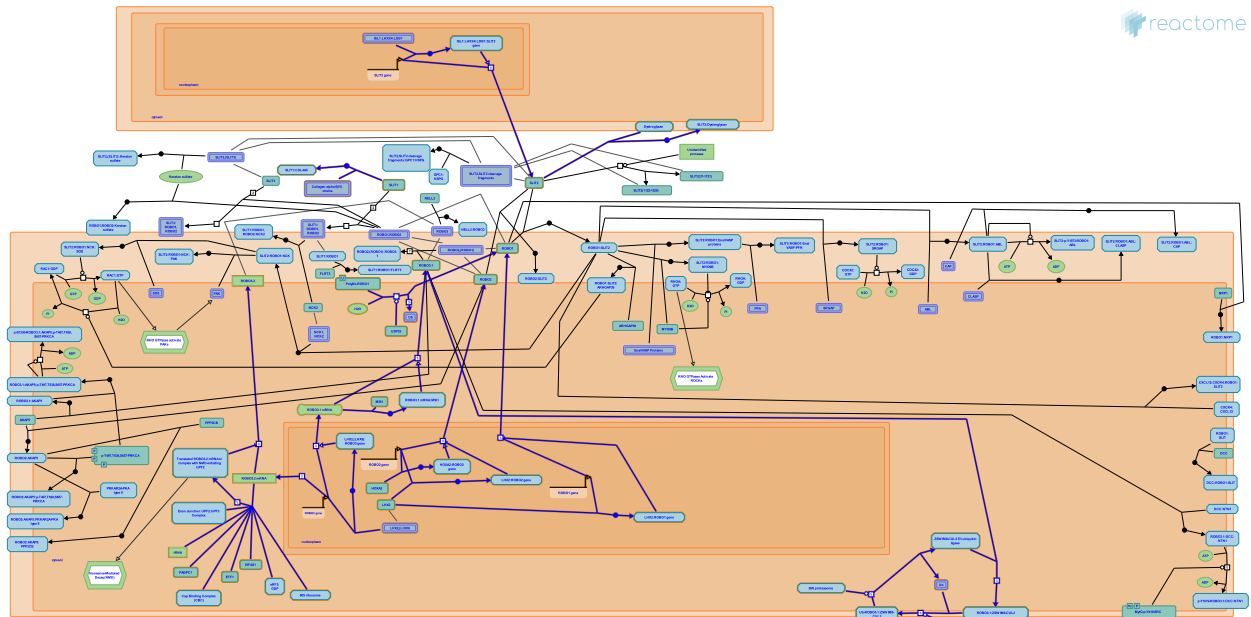
- Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics*, 18, 142. [↗](#)
- Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). 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. [↗](#)

Reactome database release: 88

This document contains 1 pathway and 20 reactions ([see Table of Contents](#))

Regulation of expression of SLITs and ROBOs ↗

Stable identifier: R-HSA-9010553



Expression of SLIT and ROBO proteins is regulated at the level of transcription, translation and protein localization and stability. LIM-homeodomain transcription factors LHX2, LHX3, LHX4, LHX9 and ISL1 have so far been implicated in a cell type-dependent transcriptional regulation of ROBO1, ROBO2, ROBO3 and SLIT2 (Wilson et al. 2008, Marcos-Mondejar et al. 2012, Kim et al. 2016). Homeobox transcription factor HOXA2 is involved in transcriptional regulation of ROBO2 (Geisen et al. 2008). Transcription of SLIT1 during optic tract development in *Xenopus* is stimulated by FGF signaling and may also involve the transcription factor HOXA2, but the mechanism has not been established (Atkinson-Leadbeater et al. 2010). PAX6 and the homeodomain transcription factor NKX2.2 are also implicated in regulation of SLIT1 transcription (Genethliou et al. 2009). An RNA binding protein, MS11, binds ROBO3 mRNA and promotes its translation, thus increasing ROBO3 protein levels (Kuwako et al. 2010). A poorly studied E3 ubiquitin ligase ZSWIM8 promotes degradation of ROBO3 (Wang et al. 2013). ROBO1 is protein half-life is increased via deubiquitination of ROBO1 by a ubiquitin protease USP33 (Yuasa-Kawada et al. 2009, Huang et al. 2015). Interaction of SLIT2 with DAG1 (dystroglycan) is important for proper localization of SLIT2 at the floor plate (Wright et al. 2012). Interaction of SLIT1 with a type IV collagen COL4A5 is important for localization of SLIT1 to the basement membrane of the optical tectum (Xiao et al. 2011).

Literature references

Rao, Y., Kinoshita-Kawada, M., Wu, JY., Yuasa-Kawada, J. (2009). Deubiquitinating enzyme USP33/VDU1 is required for Slit signaling in inhibiting breast cancer cell migration. *Proc. Natl. Acad. Sci. U.S.A.*, 106, 14530-5. ↗

Ma, L., Leung, H., Lyon, KA., Leahy, DJ., Wright, KM., Ginty, DD. (2012). Dystroglycan organizes axon guidance cue localization and axonal pathfinding. *Neuron*, 76, 931-44. ↗

Brunet, JF., Rijli, FM., Pasqualetti, M., Geisen, MJ., Chédotal, A., Di Meglio, T. et al. (2008). Hox paralog group 2 genes control the migration of mouse pontine neurons through slit-robo signaling. *PLoS Biol.*, 6, e142. ↗

Dodd, J., Shafer, B., Lee, KJ., Wilson, SI. (2008). A molecular program for contralateral trajectory: Rig-1 control by LIM homeodomain transcription factors. *Neuron*, 59, 413-24. ↗

Zhu, L., Wen, P., Liu, J., Kong, R., Wu, JY., Chen, X. et al. (2015). USP33 mediates Slit-Robo signaling in inhibiting colorectal cancer cell migration. *Int. J. Cancer*, 136, 1792-802. ↗

Editions

2017-06-27	Authored	Orlic-Milacic, M.
2017-07-31	Reviewed	Jaworski, A.
2017-08-04	Edited	Orlic-Milacic, M.

ISL1 binds the SLIT2 gene enhancer ↗

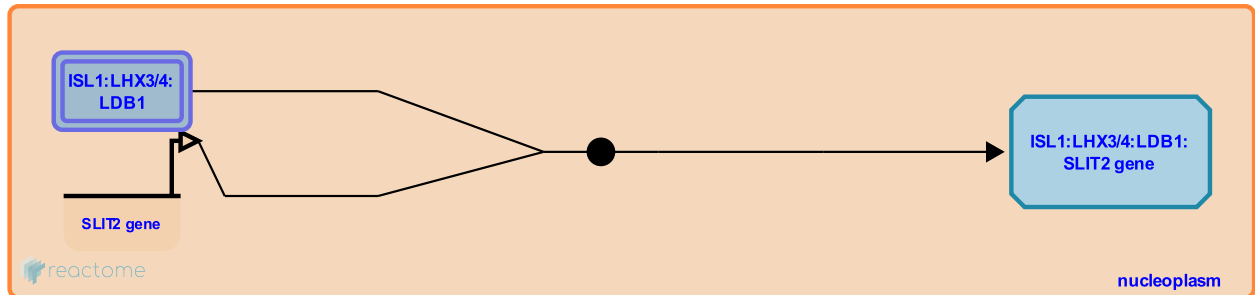
Location: Regulation of expression of SLITs and ROBOs

Stable identifier: R-HSA-9010541

Type: binding

Compartments: nucleoplasm

Inferred from: [Isl1 binds the Slit2 gene enhancer \(Mus musculus\)](#)



Based on studies in mice, the transcription factor ISL1, in complex with either LHX3 or LHX4, binds to an evolutionarily conserved LIM-HD binding site in the enhancer of the SLIT2 gene, located in the sixth intron of the SLIT2 gene. The complex of ISL1 and LHX4 regulates SLIT2 expression in branchiomotor neurons, while the complex of ISL1 and LHX3 regulates SLIT2 expression in somatic motor neurons (Kim et al. 2016). From the previous structural studies of the ISL1 complex with LHX3, conducted using mouse and rat proteins, it is known that LDB1 is also part of this complex (Thaler et al. 2002).

Followed by: [SLIT2 gene expression is stimulated by ISL1](#)

Editions

2017-06-23	Authored	Orlic-Milacic, M.
2017-07-31	Reviewed	Jaworski, A.
2017-08-04	Edited	Orlic-Milacic, M.

SLIT2 gene expression is stimulated by ISL1 ↗

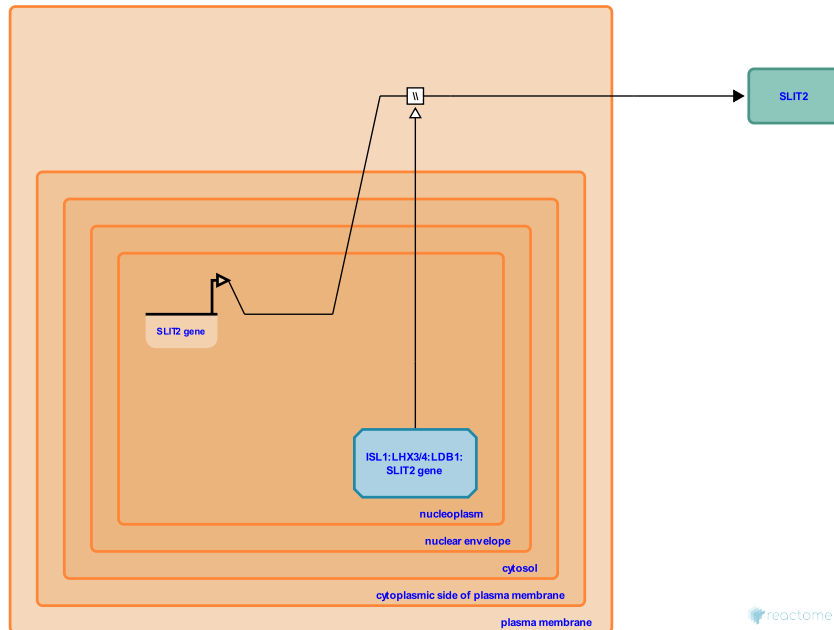
Location: Regulation of expression of SLITs and ROBOs

Stable identifier: R-HSA-9010539

Type: omitted

Compartments: plasma membrane, nucleoplasm

Inferred from: Slit2 gene expression is stimulated by Isl1 (Mus musculus)



Based on studies in mice, the transcription factor ISL1, in complex with either LHX3 or LHX4, directly stimulates transcription of the SLIT2 gene. ISL1-mediated regulation of SLIT2 gene transcription in branchiomotor (BM) neurons and somatic motor (SM) neurons involves LHX4 and LHX3, respectively (Kim et al. 2016). Slit2 expression is diminished in Isl1 mutant mice (Lee et al. 2015).

SLIT2 is one of gene suggested to be repressed by the transcription factor ARX, involved in neuronal proliferation, migration, maturation and differentiation, as well as axon guidance (reviewed by Friocourt and Parnavelas, 2011).

Preceded by: ISL1 binds the SLIT2 gene enhancer

Followed by: SLIT2 binds Dystroglycan

Editions

2017-06-23	Authored	Orlic-Milacic, M.
2017-07-31	Reviewed	Jaworski, A.
2017-08-04	Edited	Orlic-Milacic, M.

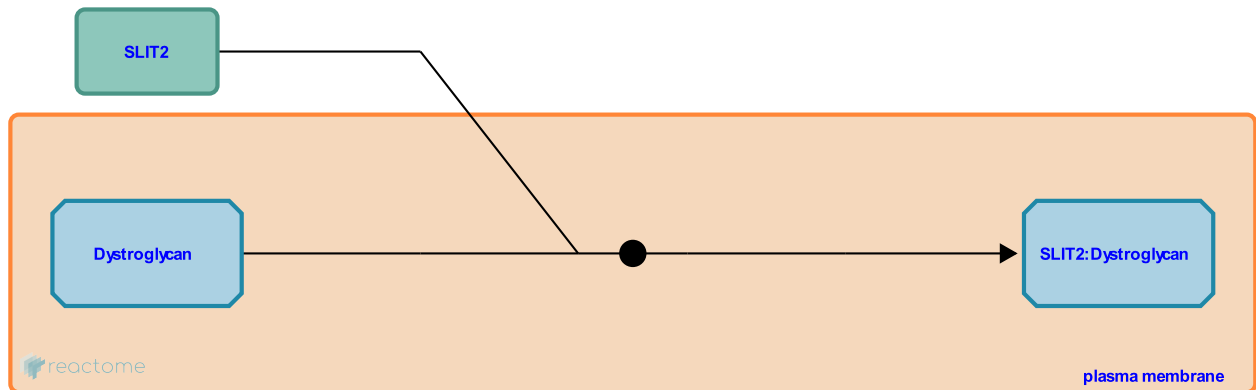
SLIT2 binds Dystroglycan ↗

Location: [Regulation of expression of SLITs and ROBOs](#)

Stable identifier: R-HSA-9010872

Type: binding

Compartments: plasma membrane



SLIT2 binds to dystroglycan (DAG1). The interaction involves the C-terminal region of human SLIT2. The species origin of the DAG1 construct was not specified and is assumed to be human. Dystroglycan is required for proper SLIT2 localization within the basement membrane and the floor plate. Dystroglycan glycosylation, mediated at least in part by B4GAT1 (B3GNT1) and ISPD, is likely required for its interaction with SLIT2, but it has not been annotated. Mice mutant for B4gat1, Ispd or Dag1 have axon guidance defects similar to those observed in Slit or Robo mutant mice (Wright et al. 2012).

Preceded by: [SLIT2 gene expression is stimulated by ISL1](#)

Literature references

Ma, L., Leung, H., Lyon, KA., Leahy, DJ., Wright, KM., Ginty, DD. (2012). Dystroglycan organizes axon guidance cue localization and axonal pathfinding. *Neuron*, 76, 931-44. ↗

Editions

2017-06-23	Authored	Orlic-Milacic, M.
2017-07-31	Reviewed	Jaworski, A.
2017-08-04	Edited	Orlic-Milacic, M.

SLIT1 binds COL4A5 ↗

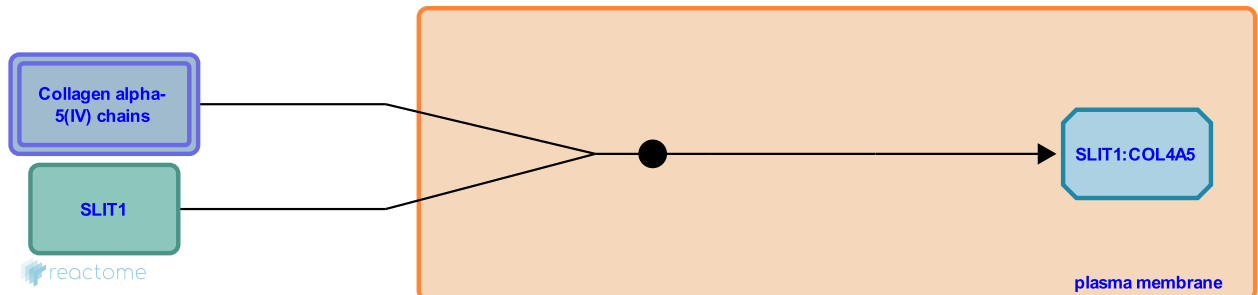
Location: [Regulation of expression of SLITs and ROBOs](#)

Stable identifier: R-HSA-9010396

Type: binding

Compartments: plasma membrane, extracellular region

Inferred from: [Slit1a binds Col4a5 \(Danio rerio\)](#)



Based on studies in zebrafish, SLIT1 binds to a type IV collagen COL4A5, which forms the basement membrane on the surface of the optical tectum. COL4A5 and HSPGs may act synergistically to anchor SLIT1 in the basement membrane. ROBO2 receptor is required for lamina-specific axon pathfinding of retinal ganglion cells in the optical tectum (Xiao et al. 2011).

Editions

2017-06-23	Authored	Orlic-Milacic, M.
2017-07-31	Reviewed	Jaworski, A.
2017-08-04	Edited	Orlic-Milacic, M.

LHX2 binds to ROBO1 gene locus ↗

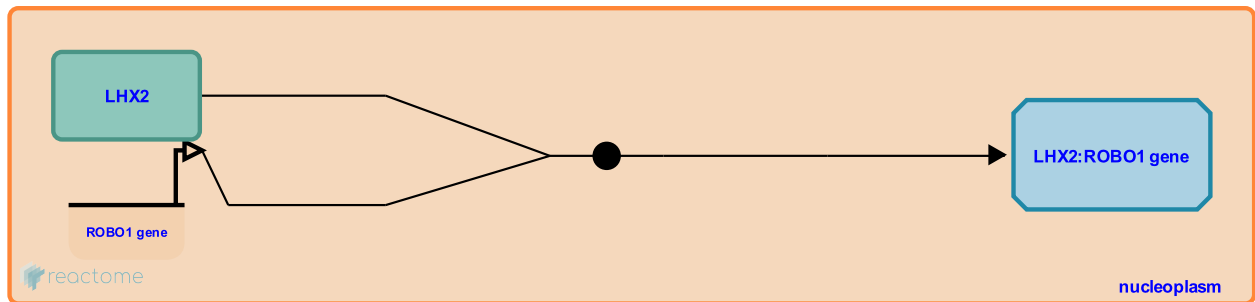
Location: [Regulation of expression of SLITs and ROBOs](#)

Stable identifier: R-HSA-9011074

Type: binding

Compartments: nucleoplasm

Inferred from: [Lhx2 binds to Robo1 gene locus \(Mus musculus\)](#)



Based on studies in mice, a LIM-homeodomain transcription factor LHX2 binds to evolutionarily conserved LHX2 binding elements about 30 kb downstream from the ROBO1 gene transcription start site (Marcos-Mondejar et al. 2012).

Followed by: [ROBO1 gene expression is inhibited by LHX2](#)

Editions

2017-06-23	Authored	Orlic-Milacic, M.
2017-07-31	Reviewed	Jaworski, A.
2017-08-04	Edited	Orlic-Milacic, M.

ROBO1 gene expression is inhibited by LHX2 ↗

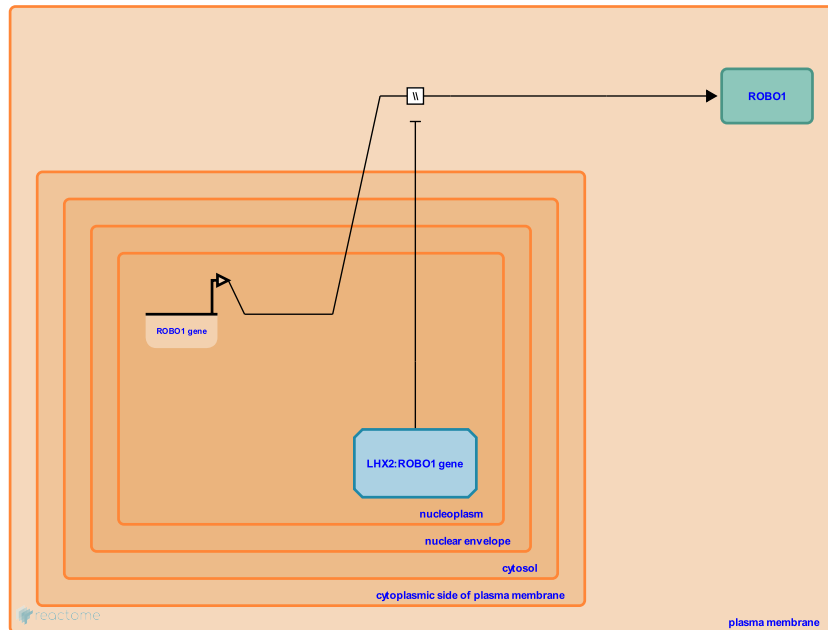
Location: [Regulation of expression of SLITs and ROBOs](#)

Stable identifier: R-HSA-9011083

Type: omitted

Compartments: plasma membrane, nucleoplasm

Inferred from: [Robo1 gene expression is inhibited by Lhx2 \(Mus musculus\)](#)



Based on studies in mice, LHX2, a LIM-homeodomain transcription factor, directly represses transcription of the ROBO1 gene by binding to evolutionarily conserved LHX2 binding sites upstream of the ROBO1 gene promoter region. LHX2 is involved in thalamocortical axon guidance (Marcos-Mondejar et al. 2012). In commissural relay neurons of the dorsal spinal cord, however, ROBO1 expression is not affected by LHX2 (Wilson et al. 2008).

Transcription factors GBX2 and LMO3 may be indirectly involved in ROBO1 gene expression regulation by LHX2 (Chatterjee et al. 2012).

Preceded by: [LHX2 binds to ROBO1 gene locus](#)

Editions

2017-06-23	Authored	Orlic-Milacic, M.
2017-07-31	Reviewed	Jaworski, A.
2017-08-04	Edited	Orlic-Milacic, M.

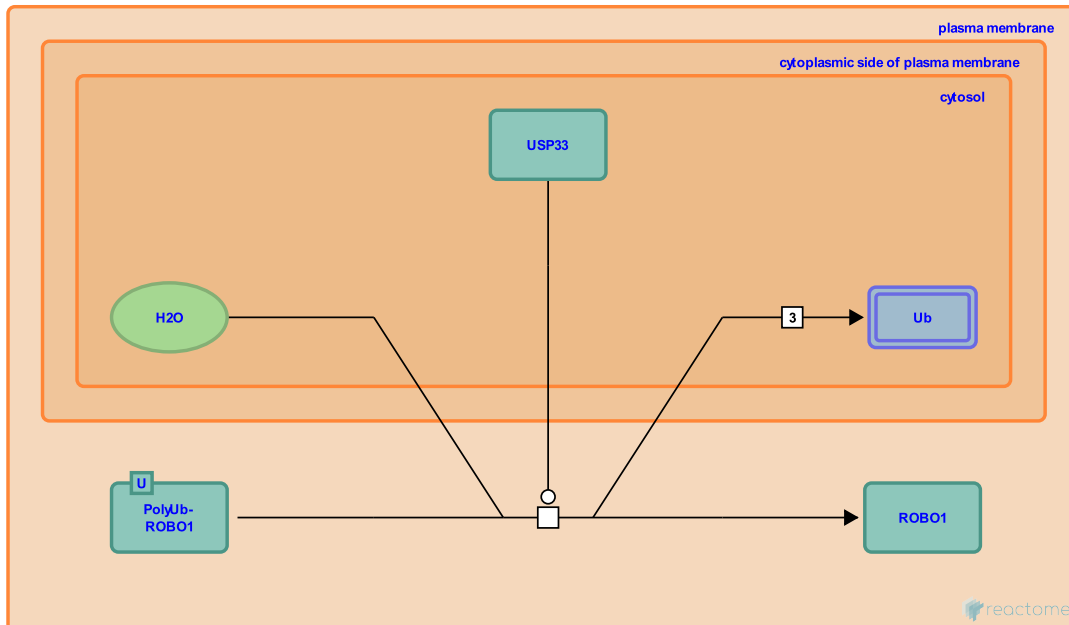
USP33 deubiquitinates ROBO1 ↗

Location: Regulation of expression of SLITs and ROBOs

Stable identifier: R-HSA-8986083

Type: transition

Compartments: plasma membrane, cytosol



The ubiquitin protease USP33 deubiquitinates ROBO1, thus stabilizing it and increasing the concentration of ROBO1 at the plasma membrane (Yuasa-Kawada et al. 2009, Huang et al. 2015). USP33 is frequently downregulated in colorectal cancer, which is associated with lymph node metastasis and poor survival (Huang et al. 2015). USP33 is required for SLIT-ROBO1-mediated inhibition of breast cancer cell migration (Yuasa-Kawada et al. 2009). Ubiquitin ligases that ubiquitinate ROBO1 are not known.

Literature references

Rao, Y., Kinoshita-Kawada, M., Wu, JY., Yuasa-Kawada, J. (2009). Deubiquitinating enzyme USP33/VDU1 is required for Slit signaling in inhibiting breast cancer cell migration. *Proc. Natl. Acad. Sci. U.S.A.*, 106, 14530-5. ↗

Zhu, L., Wen, P., Liu, J., Kong, R., Wu, JY., Chen, X. et al. (2015). USP33 mediates Slit-Robo signaling in inhibiting colorectal cancer cell migration. *Int. J. Cancer*, 136, 1792-802. ↗

Editions

2017-06-23	Authored	Orlic-Milacic, M.
2017-07-31	Reviewed	Jaworski, A.
2017-08-04	Edited	Orlic-Milacic, M.

HOXA2 binds ROBO2 gene promoter ↗

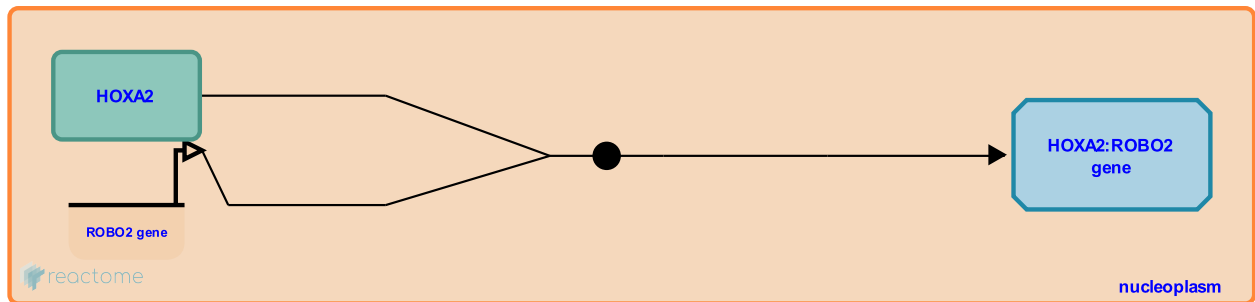
Location: [Regulation of expression of SLITs and ROBOs](#)

Stable identifier: R-HSA-9010503

Type: binding

Compartments: nucleoplasm

Inferred from: [Hoxa2 binds Robo2 gene \(Mus musculus\)](#)



Based on studies in mice, the homeobox transcription factor HOXA2 binds to an evolutionarily conserved (also present in the human gene) HOX-PBX binding site in the second intron of the ROBO2 gene (Geisen et al. 2008). The heterodimerization partner of HOXA2 at the ROBO2 gene binding site is not known.

Followed by: [ROBO2 gene transcription is stimulated by HOXA2 and inhibited by LHX2](#)

Editions

2017-06-23	Authored	Orlic-Milacic, M.
2017-07-31	Reviewed	Jaworski, A.
2017-08-04	Edited	Orlic-Milacic, M.

LHX2 binds to ROBO2 gene locus ↗

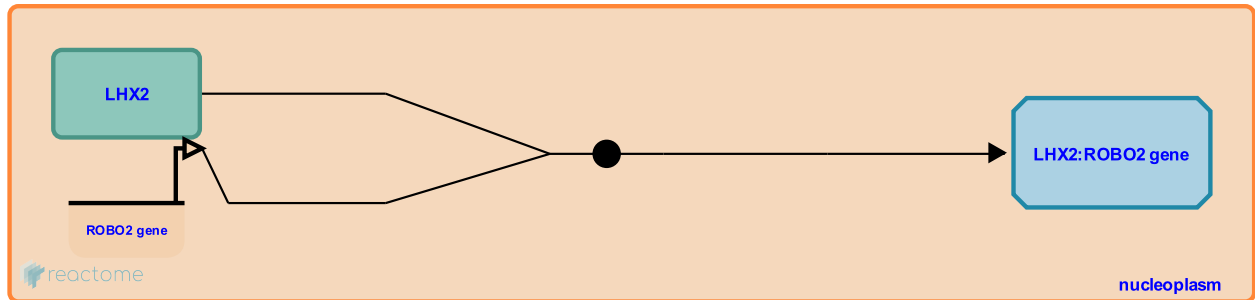
Location: [Regulation of expression of SLITs and ROBOs](#)

Stable identifier: R-HSA-9011077

Type: binding

Compartments: nucleoplasm

Inferred from: [Lhx2 binds to Robo2 gene locus \(Mus musculus\)](#)



Based on studies in mice, a LIM-homeodomain transcription factor LHX2 binds to evolutionarily conserved LHX2 binding elements about 50 kb downstream from the ROBO2 gene transcription start site (Marcos-Mondejar et al. 2012).

Followed by: [ROBO2 gene transcription is stimulated by HOXA2 and inhibited by LHX2](#)

Editions

2017-06-23	Authored	Orlic-Milacic, M.
2017-07-31	Reviewed	Jaworski, A.
2017-08-04	Edited	Orlic-Milacic, M.

ROBO2 gene transcription is stimulated by HOXA2 and inhibited by LHX2 ↗

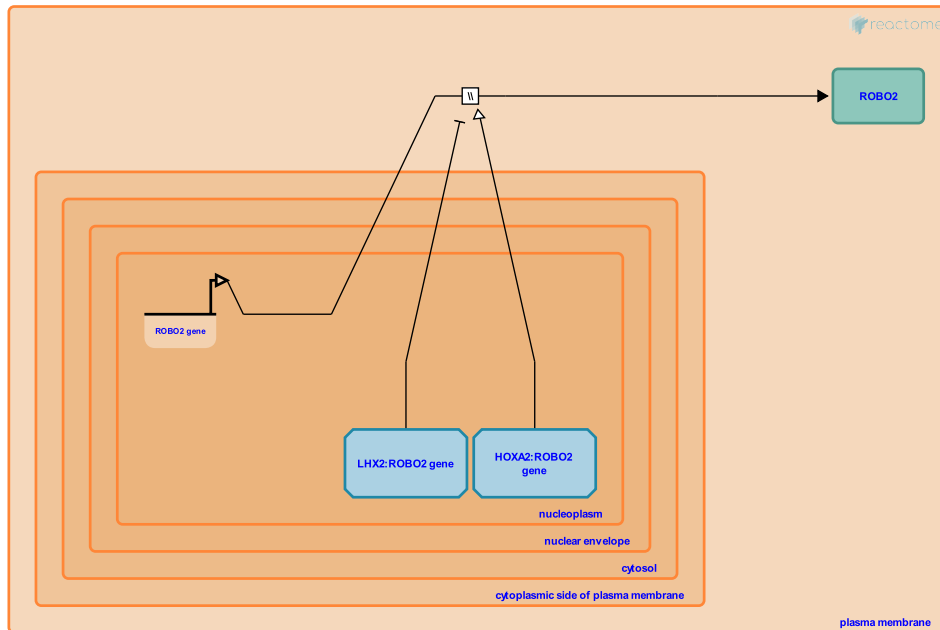
Location: Regulation of expression of SLITs and ROBOs

Stable identifier: R-HSA-9010523

Type: omitted

Compartments: plasma membrane, nucleoplasm

Inferred from: Robo2 gene expression is stimulated by Hoxa2 and inhibited by Lhx2 (Mus musculus)



Based on studies in mice, the homeobox transcription factor HOXA2, which directly binds to an evolutionarily conserved site in the second intron of the ROBO2 gene, is needed for the maintenance of ROBO2 expression during pontine neuron migration (Geisen et al. 2008).

Also based on mouse studies, LHX2, a LIM-homeodomain transcription factor, directly represses transcription of the ROBO2 gene by binding to evolutionarily conserved LHX2 binding sites about 50 kb downstream from the ROBO2 gene transcription start site. LHX2 is involved in thalamocortical axon guidance (Marcos-Mondejar et al. 2012). In commissural relay neurons of the dorsal spinal cord, however, ROBO2 expression is not affected by LHX2 (Wilson et al. 2008).

In zebrafish, transcription of Robo2 is directly stimulated by Mecp2 (Leong et al. 2015).

Preceded by: HOXA2 binds ROBO2 gene promoter, LHX2 binds to ROBO2 gene locus

Editions

2017-06-23	Authored	Orlic-Milacic, M.
2017-07-31	Reviewed	Jaworski, A.
2017-08-04	Edited	Orlic-Milacic, M.

LHX2,(LHX9) binds the ROBO3 gene promoter ↗

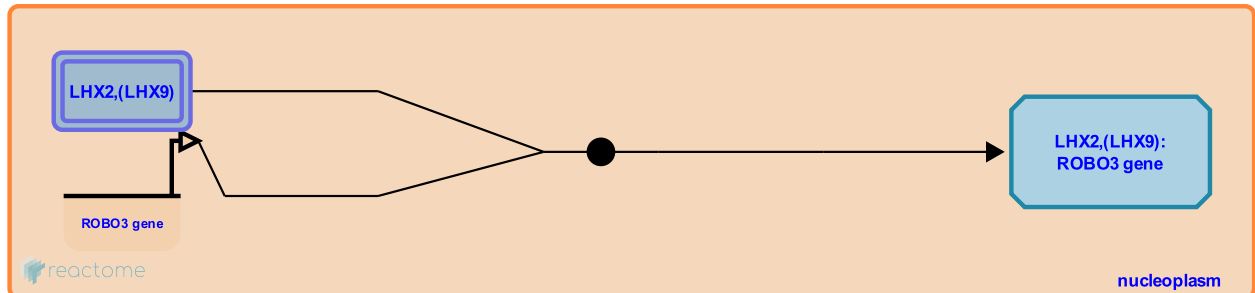
Location: Regulation of expression of SLITs and ROBOs

Stable identifier: R-HSA-9011145

Type: binding

Compartments: nucleoplasm

Inferred from: Lhx2,(Lhx9) binds the Robo3 gene promoter (Mus musculus)



Based on studies in mice, a LIM-homeodomain transcription factor LHX2, and possibly LHX9, binds to conserved LHX2 binding elements in the promoter region of the ROBO3 gene (Wilson et al. 2008).

Followed by: ROBO3.1 expression is stimulated by LHX2,(LHX9)

Editions

2017-06-23	Authored	Orlic-Milacic, M.
2017-07-31	Reviewed	Jaworski, A.
2017-08-04	Edited	Orlic-Milacic, M.

ROBO3.1 expression is stimulated by LHX2,(LHX9) ↗

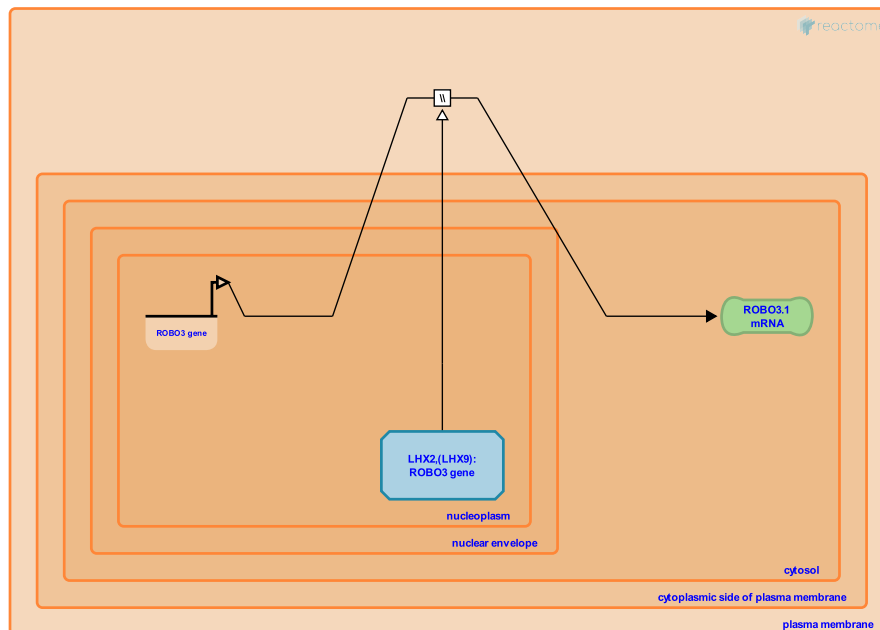
Location: Regulation of expression of SLITs and ROBOs

Stable identifier: R-HSA-9011143

Type: omitted

Compartments: plasma membrane, nucleoplasm

Inferred from: Robo3.1 expression is stimulated by Lhx2,(Lhx9) (Mus musculus)



Based on studies in mice, expression of the ROBO3.1 isoform from the ROBO3 gene is directly stimulated by LHX2 and possibly LHX9. LHX2/9-mediated regulation of ROBO3.1 levels is involved in midline crossing by commissural relay neurons of the dorsal spinal cord (Wilson et al. 2008). ROBO3.1 levels, however, seem to be unaffected by LHX2 in thalamocortical neurons (Marcos-Mondejar et al. 2012).

Preceded by: LHX2,(LHX9) binds the ROBO3 gene promoter

Followed by: MSI1 binds ROBO3.1 mRNA, ROBO3.1 mRNA translation is positively regulated by MSI1

Editions

2017-06-23	Authored	Orlic-Milacic, M.
2017-07-31	Reviewed	Jaworski, A.
2017-08-04	Edited	Orlic-Milacic, M.

MSI1 binds ROBO3.1 mRNA ↗

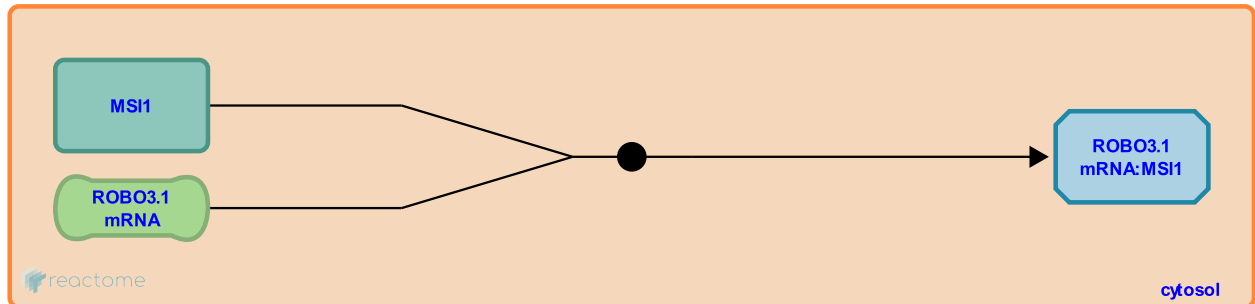
Location: [Regulation of expression of SLITs and ROBOs](#)

Stable identifier: R-HSA-9011346

Type: binding

Compartments: cytosol

Inferred from: [Msi1 binds Robo3 mRNA \(Mus musculus\)](#)



Based on studies in mice, MSI1, and RNA-binding protein, binds to ROBO3.1 mRNA (Kuwako et al. 2010).

Preceded by: [ROBO3.1 expression is stimulated by LHX2,\(LHX9\)](#)

Editions

2017-06-23	Authored	Orlic-Milacic, M.
2017-07-31	Reviewed	Jaworski, A.
2017-08-04	Edited	Orlic-Milacic, M.

ROBO3.1 mRNA translation is positively regulated by MSI1 ↗

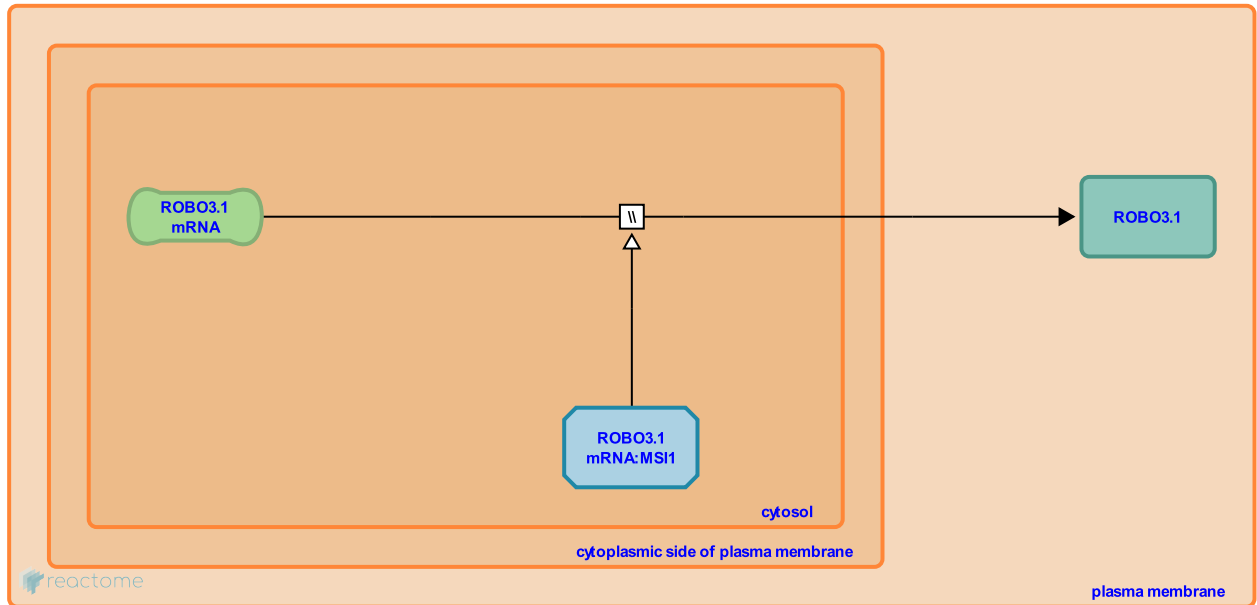
Location: Regulation of expression of SLITs and ROBOs

Stable identifier: R-HSA-9011347

Type: omitted

Compartments: cytosol

Inferred from: Robo3 mRNA translation is positively regulated by Msi1 (Mus musculus)



Based on studies in mice, binding of MSI1 to ROBO3.1 mRNA positively regulates ROBO3.1 mRNA translation, resulting in increased levels of ROBO3.1 protein. Similar to Robo3 knockout mice, Msi1 knockout mice also show severe abnormalities in axonal midline crossing and migration of precerebellar neurons (Kuwako et al. 2010).

Preceded by: ROBO3.1 expression is stimulated by LHX2,(LHX9)

Followed by: ZSWIM8 binds ROBO3.1

Editions

2017-06-23	Authored	Orlic-Milacic, M.
2017-07-31	Reviewed	Jaworski, A.
2017-08-04	Edited	Orlic-Milacic, M.

ZSWIM8 binds ROBO3.1 ↗

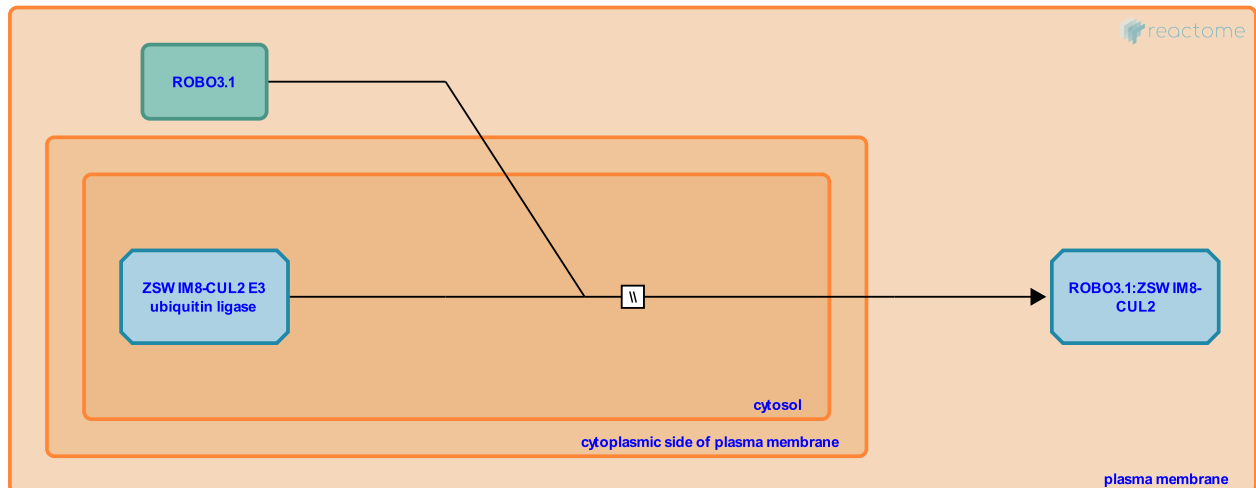
Location: [Regulation of expression of SLITs and ROBOs](#)

Stable identifier: R-HSA-9011289

Type: omitted

Compartments: cytosol

Inferred from: [Zswim8 binds ROBO3.1 \(Homo sapiens\)](#)



Based on studies in *C. elegans* and with recombinant human and mouse proteins, ZSWIM8 and its *C. elegans* orthologue EBAX-1 are predicted to be an E3 ubiquitin ligase component of the CUL2 ubiquitin ligase complex. ZSWIM8 co-immunoprecipitates with the CUL2 ubiquitin ligase complex components Elongin-B (ELOB) and Elongin-C (ELOC). The BC-box and Cul2-box of ZSWIM8 are needed for interaction with ELOB and ELOC, implying the presence of other CUL2 complex components in the complex of ZSWIM8, ELOB and ELOC. ZSWIM8 binds to wild-type ROBO3.1, but preferentially associates with misfolded or mutant ROBO3.1 proteins, suggesting that it is involved in the quality control of ROBO3.1 (Wang et al. 2013).

Preceded by: [ROBO3.1 mRNA translation is positively regulated by MSI1](#)

Followed by: [ZSWIM8 ubiquitinates ROBO3.1](#)

Editions

2017-06-23	Authored	Orlic-Milacic, M.
2017-07-31	Reviewed	Jaworski, A.
2017-08-04	Edited	Orlic-Milacic, M.

ZSWIM8 ubiquitinates ROBO3.1 ↗

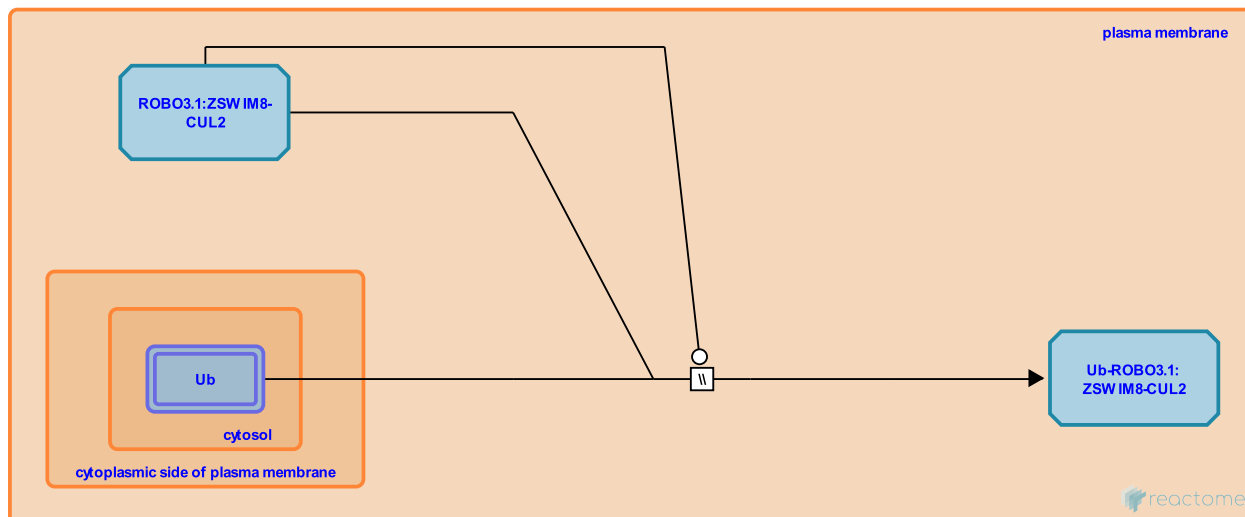
Location: [Regulation of expression of SLITs and ROBOs](#)

Stable identifier: R-HSA-9011300

Type: omitted

Compartments: plasma membrane, cytosol

Inferred from: [EBAX-1 ubiquitinates SAX-3 \(Caenorhabditis elegans\)](#)



Based on studies with *C. elegans* proteins, ZSWIM8 (orthologue of *C. elegans* EBAX-1) promotes ubiquitination of ROBO3.1 (orthologue of *C. elegans* SAX-3) (Wang et al. 2013).

Preceded by: [ZSWIM8 binds ROBO3.1](#)

Followed by: [Proteasome degrades ubiquitinated ROBO3.1](#)

Editions

2017-06-23	Authored	Orlic-Milacic, M.
2017-07-31	Reviewed	Jaworski, A.
2017-08-04	Edited	Orlic-Milacic, M.

Proteasome degrades ubiquitinated ROBO3.1 [↗](#)

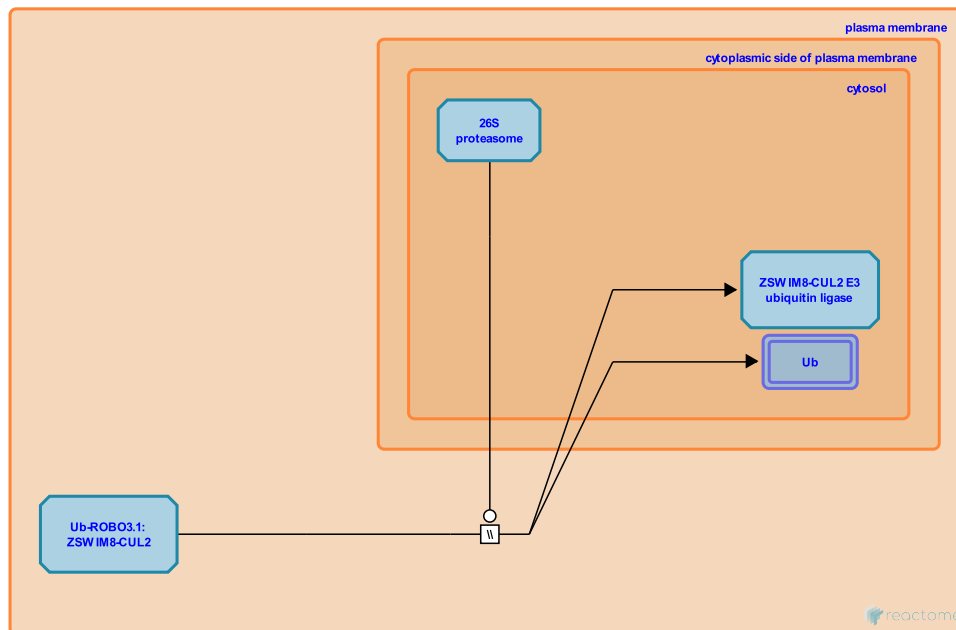
Location: [Regulation of expression of SLITs and ROBOs](#)

Stable identifier: R-HSA-9011313

Type: omitted

Compartments: plasma membrane, cytosol

Inferred from: [Proteasome degrades SAX-3 ubiquitinated by EBAX-1 \(Caenorhabditis elegans\)](#)



Based on studies using recombinant *C. elegans* proteins expressed in human 293T cells, ZSWIM8-mediated ubiquitination of ROBO3.1 targets ROBO3.1 for proteasome-mediated degradation (Wang et al. 2013).

Preceded by: [ZSWIM8 ubiquitinates ROBO3.1](#)

Editions

2017-06-23	Authored	Orlic-Milacic, M.
2017-07-31	Reviewed	Jaworski, A.
2017-08-04	Edited	Orlic-Milacic, M.

Transcription of ROBO3.2 mRNA ↗

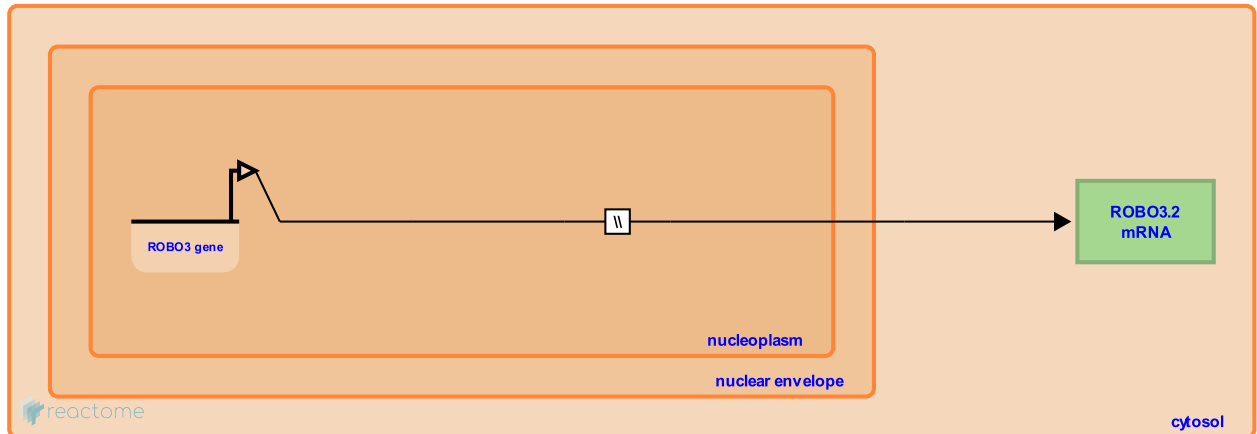
Location: [Regulation of expression of SLITs and ROBOs](#)

Stable identifier: R-HSA-9014587

Type: omitted

Compartments: nucleoplasm, cytosol

Inferred from: [Transcription of Robo3.2 mRNA \(Mus musculus\)](#)



Based on studies in mice, a transcript variant ROBO3.2 is produced from nascent ROBO3 mRNA by alternative splicing. Existence of this splicing isoform is predicted to be conserved in humans and rats. The alternative splicing results in retention of the intronic sequence between exons 26 and 27, which creates a premature stop codon. While Robo3.1 mouse mRNA is expressed in the pre-crossing and crossing commissural axons, Robo3.2 mRNA is expressed after midline crossing and thought to block midline re-crossing (Chen et al. 2008).

Followed by: [Translation of ROBO3.2 mRNA initiates NMD](#), [Translation of ROBO3.2 mRNA is negatively regulated by NMD](#)

Editions

2017-06-23	Authored	Orlic-Milacic, M.
2017-07-31	Reviewed	Jaworski, A.
2017-08-04	Edited	Orlic-Milacic, M.

Translation of ROBO3.2 mRNA initiates NMD ↗

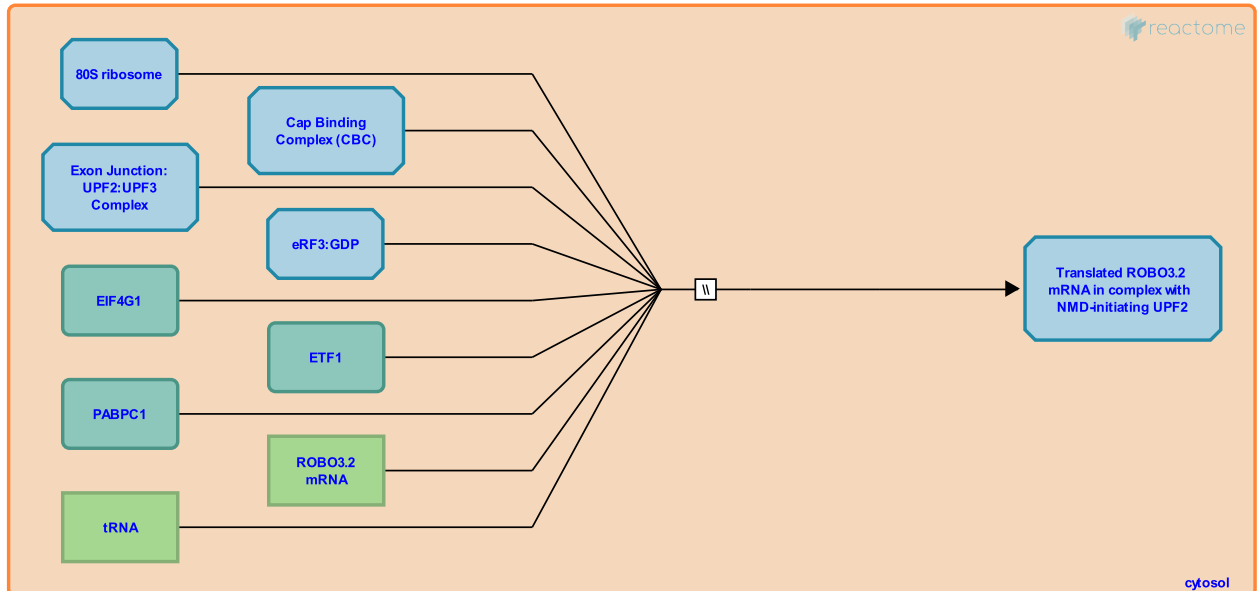
Location: [Regulation of expression of SLITs and ROBOs](#)

Stable identifier: R-HSA-9014610

Type: omitted

Compartments: cytosol

Inferred from: [Translation of Robo3.2 mRNA initiates NMD \(Mus musculus\)](#)



Based on studies in mice, ROBO3.2 mRNA, which contains a premature stop codon, is recognized by components of the nonsense mediated decay (NMD) machinery during translation. Association of ROBO3.2 mRNA with UPF2 and UPF1 was directly demonstrated in mouse cells, and presence of other translation and NMD components is assumed (Colak et al. 2013). In this step, we only show association of ROBO3.2 mRNA with the UPF2-containing exon junction complex. For detailed representation of UPF2 and UPF1 in NMD, please refer to the Reactome pathway 'Nonsense Mediated Decay (NMD)'.

Preceded by: [Transcription of ROBO3.2 mRNA](#)

Editions

2017-06-23	Authored	Orlic-Milacic, M.
2017-07-31	Reviewed	Jaworski, A.
2017-08-04	Edited	Orlic-Milacic, M.

Translation of ROBO3.2 mRNA is negatively regulated by NMD [↗](#)

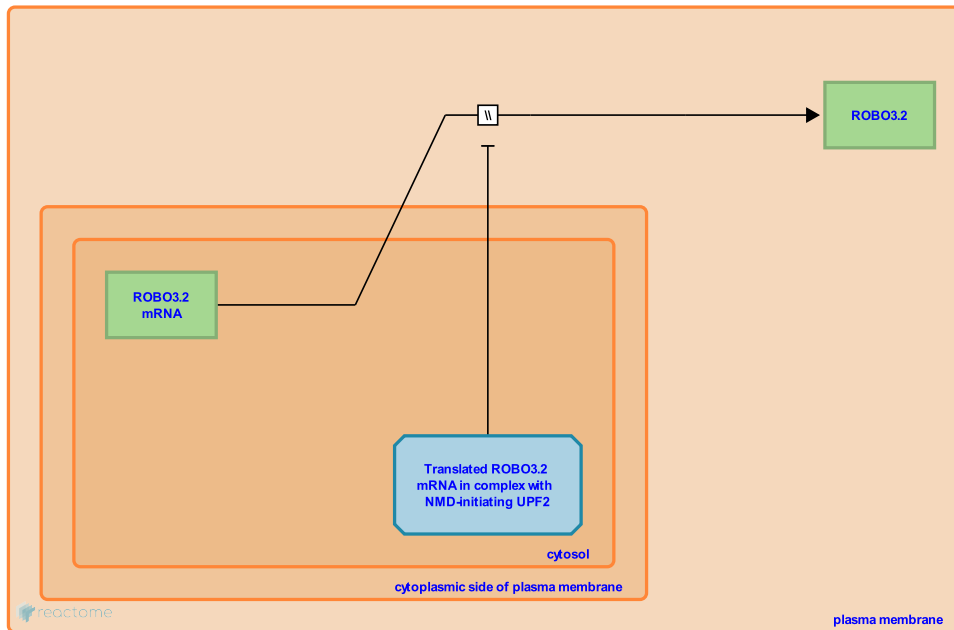
Location: [Regulation of expression of SLITs and ROBOs](#)

Stable identifier: R-HSA-9014652

Type: omitted

Compartments: plasma membrane, cytosol

Inferred from: [Translation of Robo3.2 mRNA is negatively regulated by NMD \(Mus musculus\)](#)



Based on studies in mice, translation of ROBO3.2 mRNA in commissural axons at the floor plate is negatively regulated by nonsense mediated decay (NMD). Deficiency of NMD components results in aberrant axonal trajectories after crossing the midline (Colak et al. 2013).

Preceded by: [Transcription of ROBO3.2 mRNA](#)

Literature references

Jaffrey, SR., Ji, SJ., Porse, BT., Colak, D. (2013). Regulation of axon guidance by compartmentalized nonsense-mediated mRNA decay. *Cell*, 153, 1252-65. [↗](#)

Editions

2017-06-23	Authored	Orlic-Milacic, M.
2017-07-31	Reviewed	Jaworski, A.
2017-08-04	Edited	Orlic-Milacic, M.

Table of Contents

Introduction	1
☒ Regulation of expression of SLITs and ROBOs	2
☞ ISL1 binds the SLIT2 gene enhancer	3
☞ SLIT2 gene expression is stimulated by ISL1	4
☞ SLIT2 binds Dystroglycan	5
☞ SLIT1 binds COL4A5	6
☞ LHX2 binds to ROBO1 gene locus	7
☞ ROBO1 gene expression is inhibited by LHX2	8
☞ USP33 deubiquitinates ROBO1	9
☞ HOXA2 binds ROBO2 gene promoter	10
☞ LHX2 binds to ROBO2 gene locus	11
☞ ROBO2 gene transcription is stimulated by HOXA2 and inhibited by LHX2	12
☞ LHX2,(LHX9) binds the ROBO3 gene promoter	13
☞ ROBO3.1 expression is stimulated by LHX2,(LHX9)	14
☞ MSI1 binds ROBO3.1 mRNA	15
☞ ROBO3.1 mRNA translation is positively regulated by MSI1	16
☞ ZSWIM8 binds ROBO3.1	17
☞ ZSWIM8 ubiquitinates ROBO3.1	18
☞ Proteasome degrades ubiquitinated ROBO3.1	19
☞ Transcription of ROBO3.2 mRNA	20
☞ Translation of ROBO3.2 mRNA initiates NMD	21
☞ Translation of ROBO3.2 mRNA is negatively regulated by NMD	22
Table of Contents	23