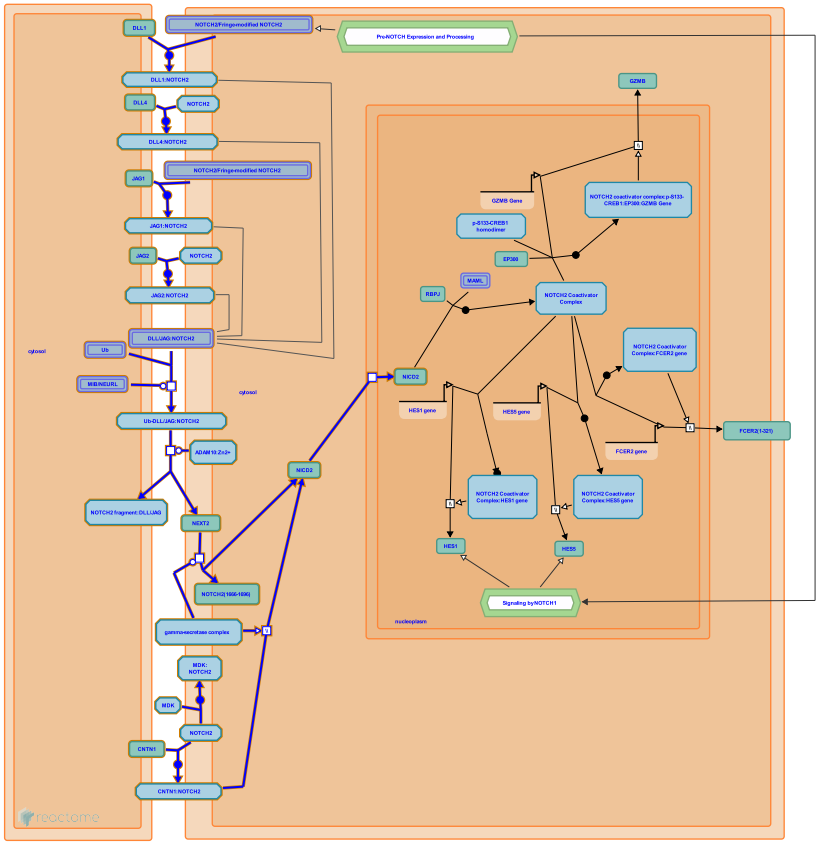
NOTCH2 Activation and Transmission of Signal to the Nucleus



Boyle, S., D'Eustachio, P., Haw, R., Ilagan, MXG., Jassal, B., Orlic-Milacic, M.

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

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.

16/05/2024

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. ↗

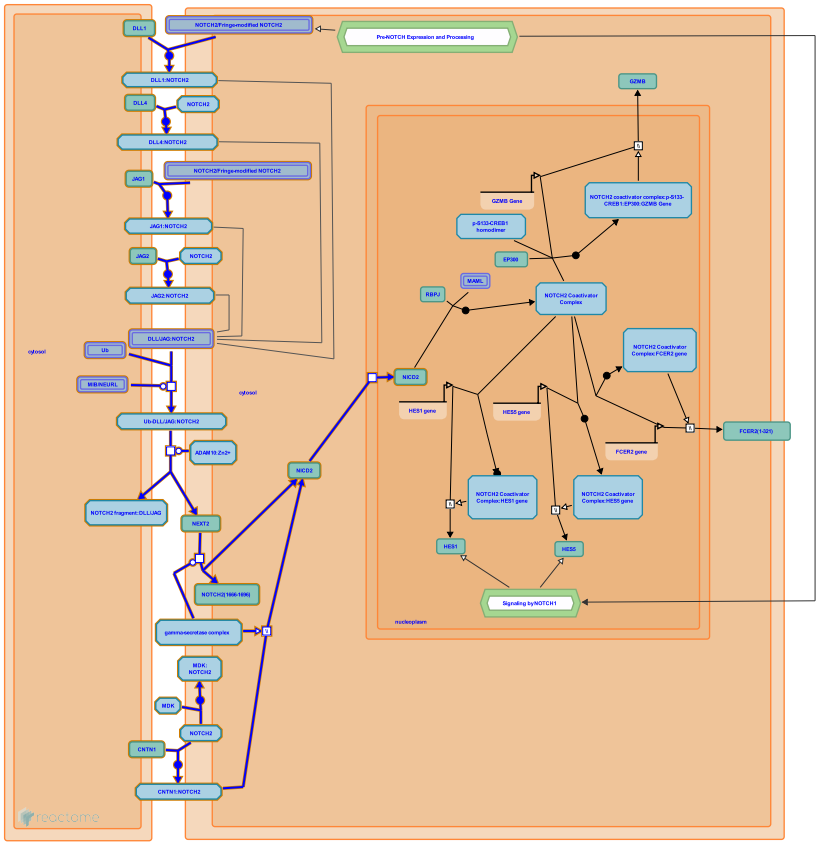
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

NOTCH2 Activation and Transmission of Signal to the Nucleus ↗

Stable identifier: R-HSA-2979096



Similar to NOTCH1, NOTCH2 is activated by Delta-like and Jagged ligands (DLL/JAG) expressed in trans on a neighboring cell (Shimizu et al. 1999, Shimizu et al. 2000, Hicks et al. 2000, Ji et al. 2004). The activation triggers cleavage of NOTCH2, first by ADAM10 at the S2 cleavage site (Gibb et al. 2010, Shimizu et al. 2000), then by gamma-secretase at the S3 cleavage site (Saxena et al. 2001, De Strooper et al. 1999), resulting in the release of the intracellular domain of NOTCH2, NICD2, into the cytosol. NICD2 subsequently traffics to the nucleus where it acts as a transcription regulator.

While DLL and JAG ligands are well established, canonical NOTCH2 ligands, there is limited evidence that NOTCH2, similar to NOTCH1, can be activated by CNTN1 (contactin 1), a protein involved in oligodendrocyte maturation (Hu et al. 2003). MDK (midkine), which plays an important role in epithelial to mesenchymal transition, can also activate NOTCH2 signaling and is able to bind to the extracellular domain of NOTCH2, but the exact mechanism of MDK-induced NOTCH2 activation has not been elucidated (Huang et al. 2008, Gungor et al. 2011).

Literature references

Kanda, Y., Kurokawa, M., Shimizu, K., Hirai, H., Kumano, K., Hamada, Y. et al. (2000). Binding of Delta1, Jagged1, and Jagged2 to Notch2 rapidly induces cleavage, nuclear translocation, and hyperphosphorylation of Notch2. *Mol Cell Biol, 20*, 6913-22. ↗

Collazo, A., Johnston, SH., Hicks, C., Weinmaster, G., diSibio, G., Vogt, TF. (2000). Fringe differentially modulates Jagged1 and Delta1 signalling through Notch1 and Notch2. *Nat Cell Biol, 2*, 515-20. ↗

Saxena, MT., Kopan, R., Schroeter, EH., Mumm, JS. (2001). Murine notch homologs (N1-4) undergo presenilin-dependent proteolysis. *J Biol Chem, 276*, 40268-73. ↗

Huang, Y., Wu, F., Sidransky, D., Ratovitski, EA., Trink, B., Hoque, MO. (2008). Midkine induces epithelial-mesenchymal transition through Notch2/Jak2-Stat3 signaling in human keratinocytes. *Cell Cycle, 7*, 1613-22. ↗

Izbicki, JR., Güngör, C., Kalinina, T., Vashist, YK., Bockhorn, M., Yekebas, E. et al. (2011). Notch signaling activated by replication stress-induced expression of midkine drives epithelial-mesenchymal transition and chemoresistance in pancreatic cancer. *Cancer Res., 71*, 5009-19. ↗

Editions

2013-01-11	Authored	Orlic-Milacic, M.
2013-01-14	Edited	Haw, R.
2013-04-25	Reviewed	Ilagan, MXG., Boyle, S.

DLL1 binds NOTCH2 ↗

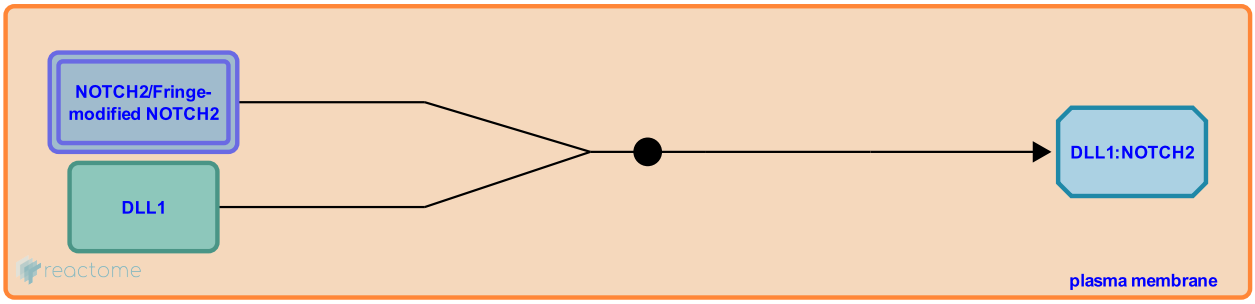
Location: NOTCH2 Activation and Transmission of Signal to the Nucleus

Stable identifier: R-HSA-1980048

Type: binding

Compartments: plasma membrane

Inferred from: Dll1 binds Notch2 (Mus musculus)



DLL1, expressed on the surface of a neighboring cell, binds NOTCH2 and activates NOTCH2-mediated intracellular signaling (Shimizu et al. 2000). Modification of NOTCH2 extracellular domain by fringe enzymes enhances NOTCH2 activation by DLL1 (Hicks et al. 2000). Activation of NOTCH2 signaling by DLL1 may regulate regeneration and proliferation of renal tubules during acute kidney injury (Kobayashi et al. 2008).

Followed by: Ubiquitination of DLL/JAG ligands upon binding to NOTCH2

Literature references

Kanda, Y., Kurokawa, M., Shimizu, K., Hirai, H., Kumano, K., Hamada, Y. et al. (2000). Binding of Delta1, Jagged1, and Jagged2 to Notch2 rapidly induces cleavage, nuclear translocation, and hyperphosphorylation of Notch2. *Mol Cell Biol, 20*, 6913-22. ↗

Collazo, A., Johnston, SH., Hicks, C., Weinmaster, G., diSibio, G., Vogt, TF. (2000). Fringe differentially modulates Jagged1 and Delta1 signalling through Notch1 and Notch2. *Nat Cell Biol, 2*, 515-20. ↗

Kuwana, H., Tanaka, H., Kuwahara, M., Tohda, S., Kobayashi, T., Sasaki, S. et al. (2008). Expression and function of the Delta-1/Notch-2/Hes-1 pathway during experimental acute kidney injury. *Kidney Int, 73*, 1240-50. ↗

Editions

2013-01-11	Authored	Orlic-Milacic, M.
2013-01-14	Edited, Reviewed	Haw, R.
2013-04-25	Reviewed	Ilagan, MXG., Boyle, S.

JAG1 binds NOTCH2 ↗

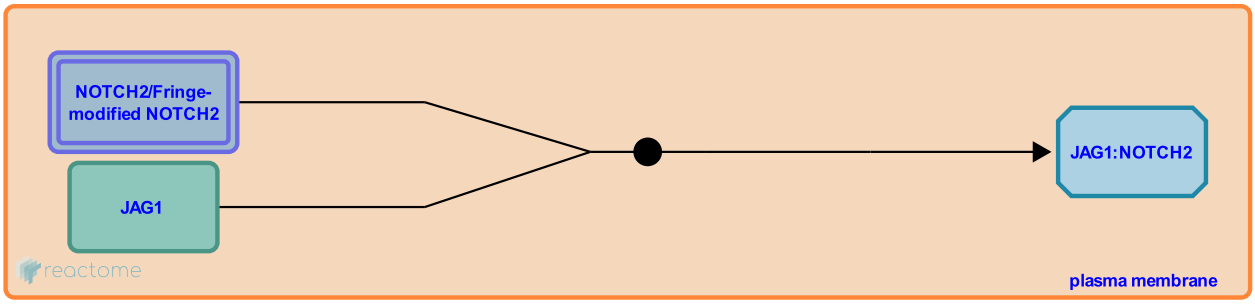
Location: NOTCH2 Activation and Transmission of Signal to the Nucleus

Stable identifier: R-HSA-1980056

Type: binding

Compartments: plasma membrane

Inferred from: Jag1 binds Notch2 (Mus musculus)



JAG1, expressed on a neighboring cell, binds NOTCH2 and activates intracellular NOTCH2 signaling (Shimizu et al. 1999, Shimizu et al. 2000). In contrast to NOTCH1, where fringe-mediated modification reduces the affinity of JAG1 for NOTCH1, it seems that fringe-mediated modification of NOTCH2 extracellular domain enhances activation of NOTCH2 signaling by JAG1 (Hicks et al. 2000).

JAG1-NOTCH2 signaling axis is affected in Alagille syndrome (AGS), a dominant congenital disorder characterized by hepatic bile duct abnormalities, as well as craniofacial, heart and kidney defects (Alagille et al. 1975, Habib et al. 1987). AGS is predominantly caused by mutations in JAG1 (Oda et al. 1997, Li et al. 1997) and less frequently by mutations in NOTCH2 (McDaniell et al. 2006).

JAG1 and NOTCH2 are expressed in kidney glomeruli and JAG1-NOTH2 signaling plays an important role in kidney development, as shown in mice mutant for JAG1 or NOTCH2 or both (McCright et al. 2001, McCright et al. 2002).

Followed by: Ubiquitination of DLL/JAG ligands upon binding to NOTCH2

Literature references

Kanda, Y., Kurokawa, M., Shimizu, K., Hirai, H., Kumano, K., Hamada, Y. et al. (2000). Binding of Delta1, Jagged1, and Jagged2 to Notch2 rapidly induces cleavage, nuclear translocation, and hyperphosphorylation of Notch2. *Mol Cell Biol, 20*, 6913-22. ↗

Collazo, A., Johnston, SH., Hicks, C., Weinmaster, G., diSibio, G., Vogt, TF. (2000). Fringe differentially modulates Jagged1 and Delta1 signalling through Notch1 and Notch2. *Nat Cell Biol, 2*, 515-20. ↗

Gridley, T., McCright, B., Lozier, J. (2002). A mouse model of Alagille syndrome: Notch2 as a genetic modifier of Jag1 haploinsufficiency. *Development, 129*, 1075-82. ↗

Spinner, NB., Okajima, K., Meltzer, PS., Collins, FS., Genin, A., Oda, T. et al. (1997). Mutations in the human Jagged1 gene are responsible for Alagille syndrome. *Nat. Genet., 16*, 235-42. ↗

Odièvre, M., Gautier, M., Alagille, D., Dommergues, JP. (1975). Hepatic ductular hypoplasia associated with characteristic facies, vertebral malformations, retarded physical, mental, and sexual development, and cardiac murmur. *J. Pediatr., 86*, 63-71. ↗

Editions

2013-01-11	Authored	Orlic-Milacic, M.
2013-01-14	Edited, Reviewed	Haw, R.
2013-04-25	Reviewed	Ilagan, MXG., Boyle, S.

JAG2 binds NOTCH2 ↗

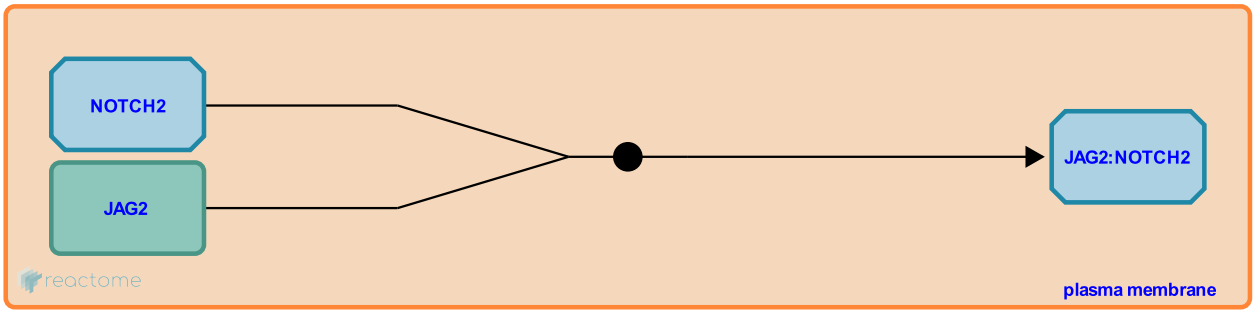
Location: NOTCH2 Activation and Transmission of Signal to the Nucleus

Stable identifier: R-HSA-1980061

Type: binding

Compartments: plasma membrane

Inferred from: Jag2 binds Notch2 (Mus musculus)



JAG2, expressed on a neighboring cell, binds NOTCH2 and activates intracellular NOTCH2 signaling (Shimizu et al. 2000).

Followed by: Ubiquitination of DLL/JAG ligands upon binding to NOTCH2

Literature references

Kanda, Y., Kurokawa, M., Shimizu, K., Hirai, H., Kumano, K., Hamada, Y. et al. (2000). Binding of Delta1, Jagged1, and Jagged2 to Notch2 rapidly induces cleavage, nuclear translocation, and hyperphosphorylation of Notch2. *Mol Cell Biol, 20*, 6913-22. ↗

Editions

2013-01-11	Authored	Orlic-Milacic, M.
2013-01-14	Edited, Reviewed	Haw, R.
2013-04-25	Reviewed	Ilagan, MXG., Boyle, S.

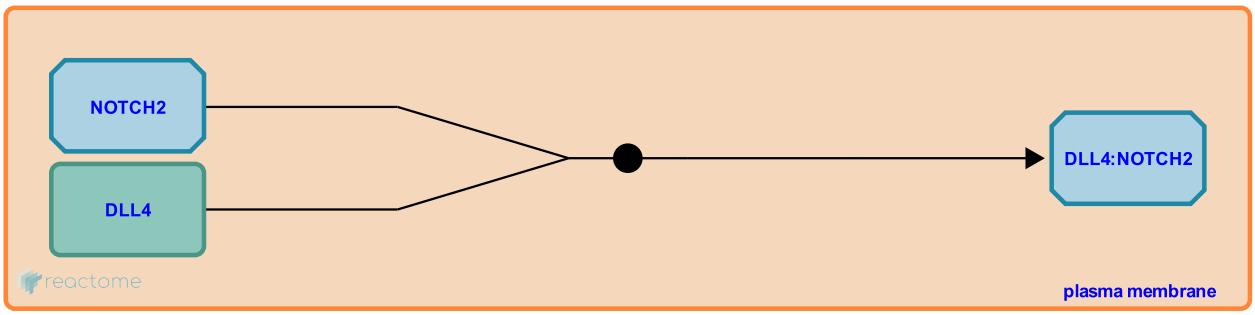
DLL4 binds NOTCH2 ↗

Location: NOTCH2 Activation and Transmission of Signal to the Nucleus

Stable identifier: R-HSA-1980051

Type: binding

Compartments: plasma membrane



DLL4, expressed on a neighboring cell, binds NOTCH2 receptor and activates NOTCH2 intracellular signaling. The study used recombinant NOTCH2 and DLL4, exogenously expressed in Chinese hamster ovary cells. The species origin of NOTCH2 and DLL4 is not specified in the manuscript by Ji et al. 2004. The impact of fringe-mediated modification of NOTCH2 on activation by DLL4 has not been examined.

Followed by: Ubiquitination of DLL/JAG ligands upon binding to NOTCH2

Literature references

Zhang, MH., Ji, CY., Zhao, JQ., Ma, DX., Cui, CS., Guo, NJ. (2004). Function of Delta4 gene and its effects on 32D cell differentiation. *Chin Med J (Engl), 117*, 1687-92. ↗

Editions

2013-01-11	Authored	Orlic-Milacic, M.
2013-01-14	Edited, Reviewed	Haw, R.
2013-04-25	Reviewed	Ilagan, MXG., Boyle, S.

Ubiquitination of DLL/JAG ligands upon binding to NOTCH2 ↗

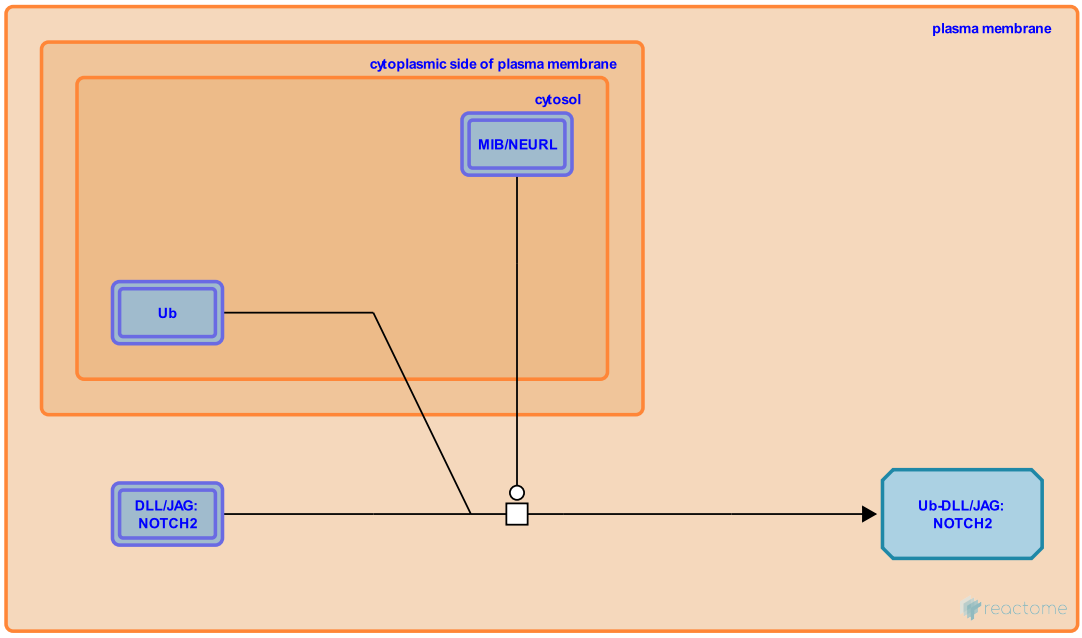
Location: NOTCH2 Activation and Transmission of Signal to the Nucleus

Stable identifier: R-HSA-2172172

Type: transition

Compartments: plasma membrane, cytosol

Inferred from: DL/SER is ubiquitinated by E3 ubiquitination ligases (NEUR/MIB1) (Drosophila melanogaster)



NOTCH ligands DLL1, DLL4, JAG1 and JAG2 undergo ubiquitination and endocytosis after binding NOTCH2 in trans. Integrity of the intracellular domain of DLL1 was shown to be essential for the successful release of NOTCH2 intracellular domain, NICD2, in response to DLL1 binding (Shimizu et al. 2002). In Drosophila, ubiquitination of Delta and Serrate ligands is performed by either Mindbomb or Neuralized ubiquitin ligase. In mammals, there are two Mindbomb homologues, MIB1 and MIB2 and two Neuralized homologues, NEURL (also known as NEUR1) and NEURL1B (also known as NEUR2). Although both Mib1 and Mib2 ubiquitinate Delta (Koo et al. 2005), only Mib1 was shown to be essential for normal development in mice, with Mib1 deficient mice exhibiting typical Notch deficiency phenotypes (Koo et al. 2007). This could be due to different expression patterns of Mib1 and Mib2. While Mib1 is abundantly expressed in embryos and adult tissues, Mib2 expression is limited to adult tissues only (Koo et al. 2005). Mouse Neurl was directly shown to ubiquitinate Jag1 but not other Notch ligands in vitro. N-terminal myristoylation targets Neurl to the plasma membrane and this is a prerequisite for Jag1 internalization (Koutelou et al. 2008). Mouse Neurl1b was shown to directly bind and ubiquitinate recombinant Xenopus Delta and to cooperate with Mib1 in Delta endocytosis (Song et al. 2006). Ubiquitination of NOTCH ligands by MIB and NEURL ubiquitin ligases triggers ligand endocytosis. Drosophila Neuralized needs to interact with membrane phosphoinositides through its phosphoinositide-binding motif to trigger endocytosis of ubiquitinated Delta (Skwarek et al. 2007). The pulling force model states that the endocytosis of ubiquitinated Notch ligands mechanically pulls the ligand-bound Notch receptor, exposing the S2 cleavage site and resulting in Notch receptor cleavage by ADAM10 and/or ADAM17 metalloproteases (Itoh et al. 2003). Using a cell-bead optical tweezers system to measure rupture force specific for cells expressing Dll1 bound to laser trapped Notch1 beads, it was shown that the mechanical force required for the activation of Notch signaling depends on ligand ubiquitination and subsequent clathrin-mediated endocytosis that involves dynamin, epsins and actin (Meloty-Kapella et al. 2012). Ligand endocytosis and recycling does not directly influence Dll1 and Notch1 interaction, except that it regulates the amount of ligand on the cell surface that is available to activate Notch (Shergill et al. 2012).

Preceded by: DLL1 binds NOTCH2, DLL4 binds NOTCH2, JAG1 binds NOTCH2, JAG2 binds NOTCH2

Followed by: NOTCH2-ligand complex is cleaved to produce NEXT2

Literature references

Delidakis, C., Pitsouli, C. (2005). The interplay between DSL proteins and ubiquitin ligases in Notch signaling. *Development, 132*, 4041-50.

Botvinick, E., Meloty-Kapella, L., Weinmaster, G., Shergill, B., Kuon, J. (2012). Notch ligand endocytosis generates mechanical pulling force dependent on dynamin, epsins, and actin. *Dev. Cell, 22*, 1299-312.

Shimizu, K., Takahashi, T., Hirai, H., Kumano, K., Hamada, Y., Saito, T. et al. (2002). Integrity of intracellular domain of Notch ligand is indispensable for cleavage required for release of the Notch2 intracellular domain. *EMBO J, 21*, 294-302.

Remaud, S., Hamel, S., Schweisguth, F., Le Borgne, R. (2005). Two distinct E3 ubiquitin ligases have complementary functions in the regulation of delta and serrate signaling in Drosophila. *PLoS Biol, 3*, e96.

Kim, CH., Kim, YY., Yoon, MJ., Koo, BK., Suh, PG., Im, SK. et al. (2007). An obligatory role of mind bomb-1 in notch signaling of mammalian development. *PLoS One, 2*, e1221.

Editions

2012-02-07	Edited	D'Eustachio, P.
2012-02-11	Edited	Orlic-Milacic, M.
2013-01-11	Authored	Orlic-Milacic, M.
2013-01-14	Edited, Reviewed	Haw, R.
2013-04-25	Reviewed	Ilagan, MXG., Boyle, S.

NOTCH2-ligand complex is cleaved to produce NEXT2 ↗

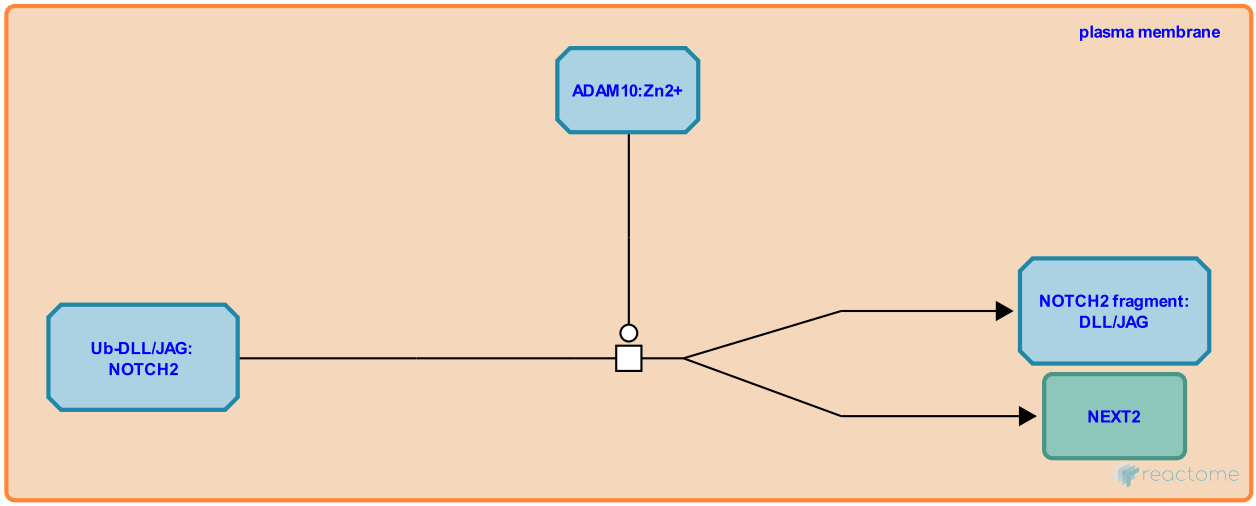
Location: NOTCH2 Activation and Transmission of Signal to the Nucleus

Stable identifier: R-HSA-157629

Type: transition

Compartments: plasma membrane

Inferred from: Adam10 cleaves Notch2 (Mus musculus)



Ligand binding induces a conformational change in NOTCH2, through mechanical pulling of NOTCH triggered by endocytosis of the receptor-attached ligand (Meloty-Kapella et al. 2012). This conformational change exposes the S2 site in the extracellular region of NOTCH2 and results in cleavage of NOTCH2 by ADAM10 metalloprotease (Gibb et al. 2010, Groot et al. 2014), generating the membrane-anchored NOTCH2 fragment NEXT2 (Shimizu et al. 2000). The extracellular NOTCH2 portion remains attached to the ligand presented on the plasma membrane of a neighboring cell.

Preceded by: Ubiquitination of DLL/JAG ligands upon binding to NOTCH2

Followed by: NEXT2 is cleaved to produce NICD2

Literature references

Kanda, Y., Kurokawa, M., Shimizu, K., Hirai, H., Kumano, K., Hamada, Y. et al. (2000). Binding of Delta1, Jagged1, and Jagged2 to Notch2 rapidly induces cleavage, nuclear translocation, and hyperphosphorylation of Notch2. *Mol Cell Biol, 20*, 6913-22. ↗

Botvinick, E., Meloty-Kapella, L., Weinmaster, G., Shergill, B., Kuon, J. (2012). Notch ligand endocytosis generates mechanical pulling force dependent on dynamin, epsins, and actin. *Dev. Cell, 22*, 1299-312. ↗

Groot, AJ., Habets, R., Vooijs, M., Saftig, P., Hodin, CM., Theys, J. et al. (2014). Regulated proteolysis of NOTCH2 and NOTCH3 receptors by ADAM10 and presenilins. *Mol. Cell. Biol., 34*, 2822-32. ↗

Tew, JG., Gibb, DR., Rowe, WJ., Dempsey, PJ., Kang, DJ., Cichy, J. et al. (2010). ADAM10 is essential for Notch2-dependent marginal zone B cell development and CD23 cleavage in vivo. *J Exp Med, 207*, 623-35. ↗

Editions

2013-01-11	Authored	Orlic-Milacic, M.
2013-01-14	Edited	Haw, R.
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NEXT2 is cleaved to produce NICD2 ↗

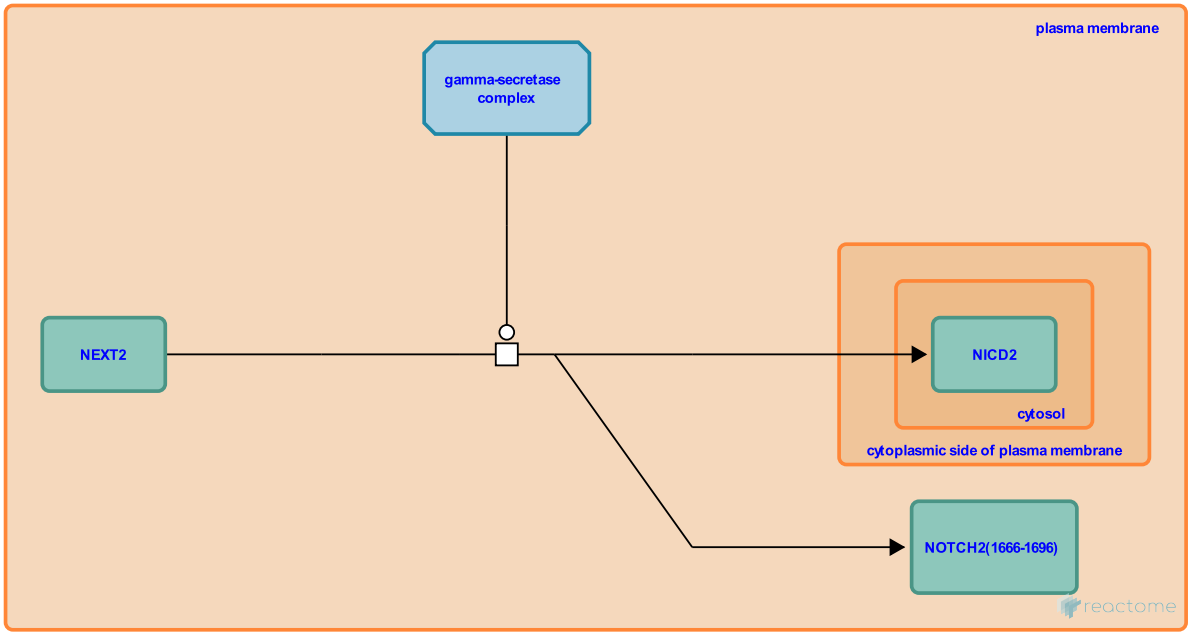
Location: NOTCH2 Activation and Transmission of Signal to the Nucleus

Stable identifier: R-HSA-157640

Type: transition

Compartments: plasma membrane, cytosol

Inferred from: Gamma-secretase complex cleaves mNEXT2 (Homo sapiens)



NEXT2 fragment of NOTCH2 is further cleaved at the S3 site by the gamma-secretase complex, which releases the intracellular domain NICD2 into the cytosol (Saxena et al. 2001, De Strooper et al. 1999, Schroeter et al. 1998, Fortini 2002).

Preceded by: NOTCH2-ligand complex is cleaved to produce NEXT2

Followed by: NICD2 traffics to the nucleus

Literature references

Groot, AJ., Habets, R., Vooijs, M., Saftig, P., Hodin, CM., Theys, J. et al. (2014). Regulated proteolysis of NOTCH2 and NOTCH3 receptors by ADAM10 and presenilins. *Mol. Cell. Biol., 34*, 2822-32. ↗

Saxena, MT., Kopan, R., Schroeter, EH., Mumm, JS. (2001). Murine notch homologs (N1-4) undergo presenilin-dependent proteolysis. *J Biol Chem, 276*, 40268-73. ↗

Fortini, ME. (2002). Gamma-secretase-mediated proteolysis in cell-surface-receptor signalling. *Nat Rev Mol Cell Biol, 3*, 673-84. ↗

Kopan, R., Kisslinger, JA., Schroeter, EH. (1998). Notch-1 signalling requires ligand-induced proteolytic release of intracellular domain. *Nature, 393*, 382-6. ↗

Wolfe, MS., Kopan, R., De Strooper, B., Schrijvers, V., Schroeter, EH., Cupers, P. et al. (1999). A presenilin-1-dependent gamma-secretase-like protease mediates release of Notch intracellular domain. *Nature, 398*, 518-22. ↗

Editions

2004-12-15	Authored	Jassal, B.
2013-01-11	Revised	Orlic-Milacic, M.
2013-01-14	Edited	Haw, R.
2013-04-25	Reviewed	Ilagan, MXG., Boyle, S.

NICD2 traffics to the nucleus ↗

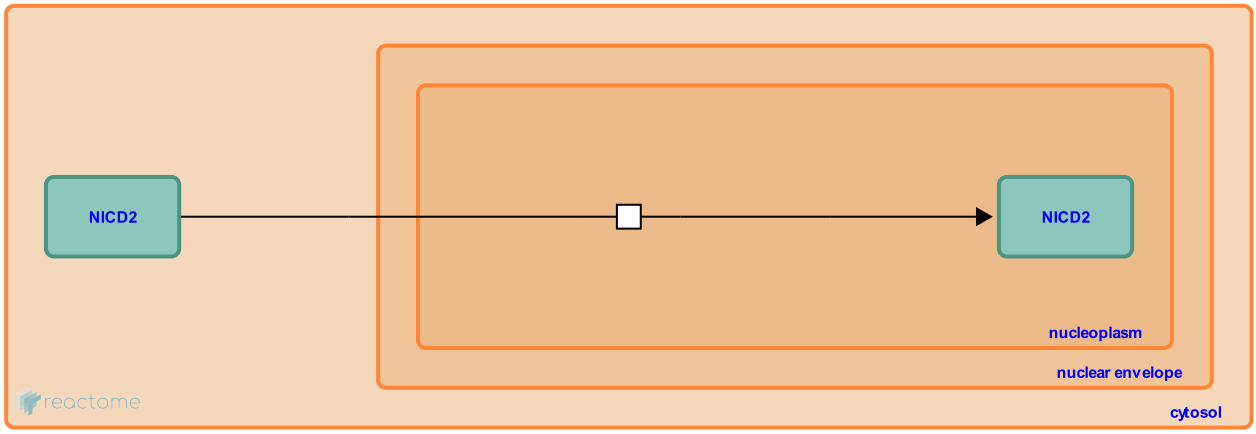
Location: NOTCH2 Activation and Transmission of Signal to the Nucleus

Stable identifier: R-HSA-157933

Type: transition

Compartments: nucleoplasm, cytosol

Inferred from: Drosophila NICD traffics to nucleus (Drosophila melanogaster)



The cytosolic NICD2 translocates to the nucleus.

Preceded by: NEXT2 is cleaved to produce NICD2

Literature references

Struhl, G., Adachi, A. (1998). Nuclear access and action of notch in vivo. *Cell, 93*, 649-60. ↗

Schweisguth, F., Lecourtois, M. (1998). Indirect evidence for Delta-dependent intracellular processing of notch in Drosophila embryos. *Curr Biol, 8*, 771-4. ↗

Editions

2004-12-15	Authored	Jassal, B.
2013-01-11	Revised	Orlic-Milacic, M.
2013-01-14	Edited	Haw, R.
2013-04-25	Reviewed	Ilagan, MXG., Boyle, S.

NOTCH2 binds CNTN1 ↗

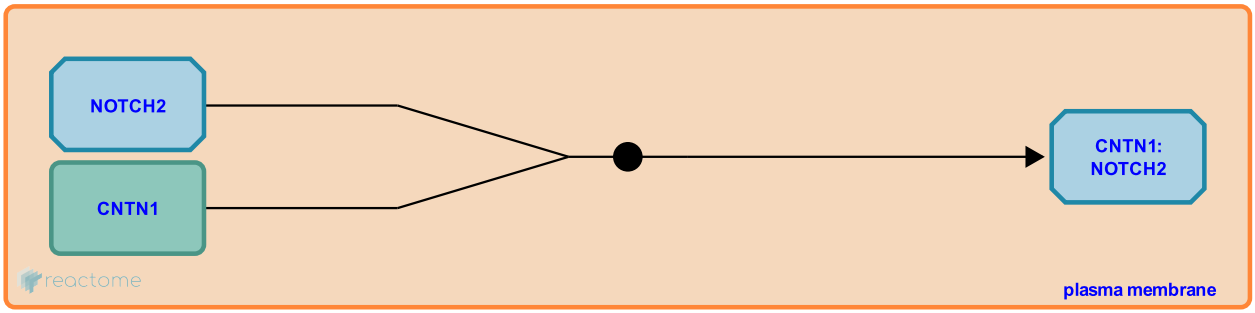
Location: NOTCH2 Activation and Transmission of Signal to the Nucleus

Stable identifier: R-HSA-2220816

Type: binding

Compartments: plasma membrane

Inferred from: Notch2 binds Cntn1 (Rattus norvegicus)



CNTN1 (F3, contactin-1) is a neuronal cell adhesion protein that can bind and activate NOTCH2, as well as NOTCH1, and these interactions are thought to play a role in oligodendrocyte maturation. While NOTCH1 activation by CNTN1 was shown to be deltex-dependent, the involvement of deltex in CNTN1-mediated activation of NOTCH2, although likely, has not been examined (Hu et al. 2003).

Followed by: Gamma-secretase cleaves CNTN1:NOTCH2 to release NICD2

Literature references

Small, D., Cui, XY., Ling, EA., Hirai, H., Pallen, CJ., Okano, H. et al. (2003). F3/contactin acts as a functional ligand for Notch during oligodendrocyte maturation. *Cell, 115*, 163-75. ↗

Editions

2013-01-11	Authored	Orlic-Milacic, M.
2013-01-14	Edited	Haw, R.
2013-04-25	Reviewed	Ilagan, MXG., Boyle, S.

Gamma-secretase cleaves CNTN1:NOTCH2 to release NICD2 ↗

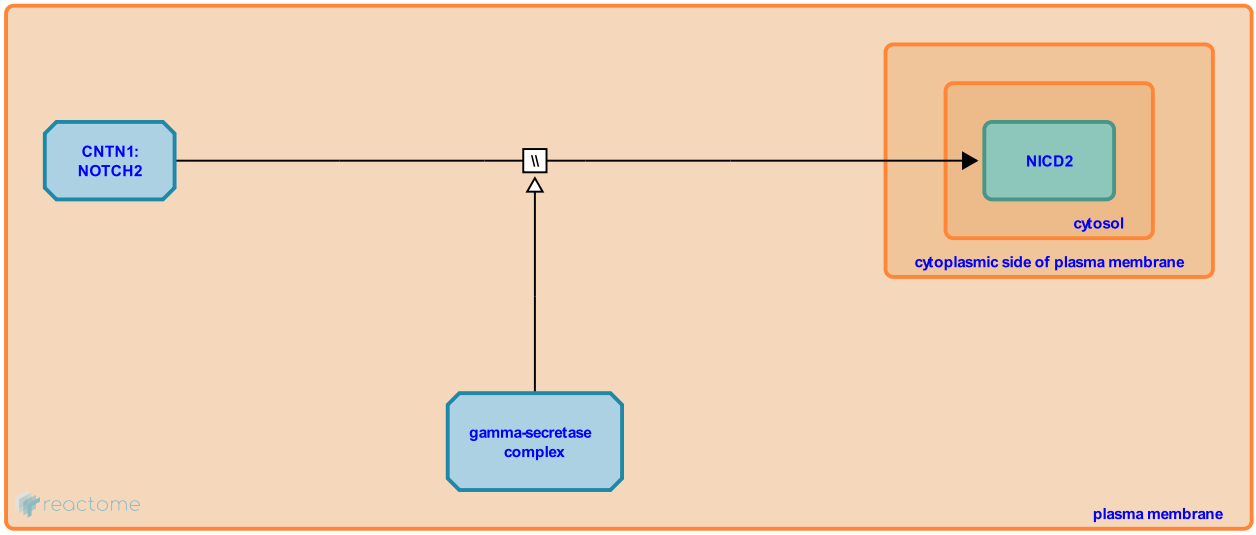
Location: NOTCH2 Activation and Transmission of Signal to the Nucleus

Stable identifier: R-HSA-2974731

Type: omitted

Compartments: plasma membrane, cytosol

Inferred from: Gamma-secretase cleaves Cntn1:Notch2 to release NICD2 (Mus musculus)



Binding of CNTN1 to NOTCH2 results in release of the intracellular domain of NOTCH2, NICD2 in a gamma-secretase-dependent way. The role of ADAM10 metalloprotease in this process has not been directly examined (Hu et al. 2003).

Preceded by: NOTCH2 binds CNTN1

Literature references

Small, D., Cui, XY., Ling, EA., Hirai, H., Pallen, CJ., Okano, H. et al. (2003). F3/contactin acts as a functional ligand for Notch during oligodendrocyte maturation. *Cell, 115*, 163-75. ↗

Editions

2013-01-11	Authored	Orlic-Milacic, M.
2013-01-14	Edited	Haw, R.
2013-04-25	Reviewed	Ilagan, MXG., Boyle, S.

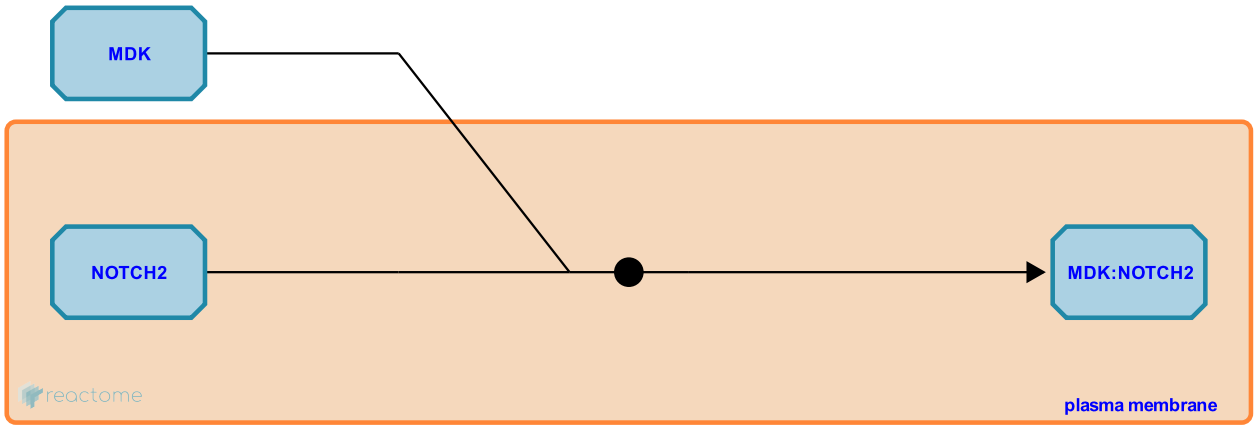
NOTCH2 binds MDK ↗

Location: NOTCH2 Activation and Transmission of Signal to the Nucleus

Stable identifier: R-HSA-2974737

Type: binding

Compartments: plasma membrane, extracellular region



MDK (Midkine, MK) is a secreted, heparin-binding growth factor that acts as a homodimer (Iwasaki et al. 1997). Both the full-length and the C-terminal region of MDK can bind the N-terminus of NOTCH2. In the presence of MDK, NICD2 accumulates in the nucleus in a dose-dependent fashion and epithelial-to-mesenchymal-transition (EMT) morphological changes are induced through a mechanism that has not been fully elucidated (Huang et al. 2008, Gungor et al. 2011).

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Editions

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