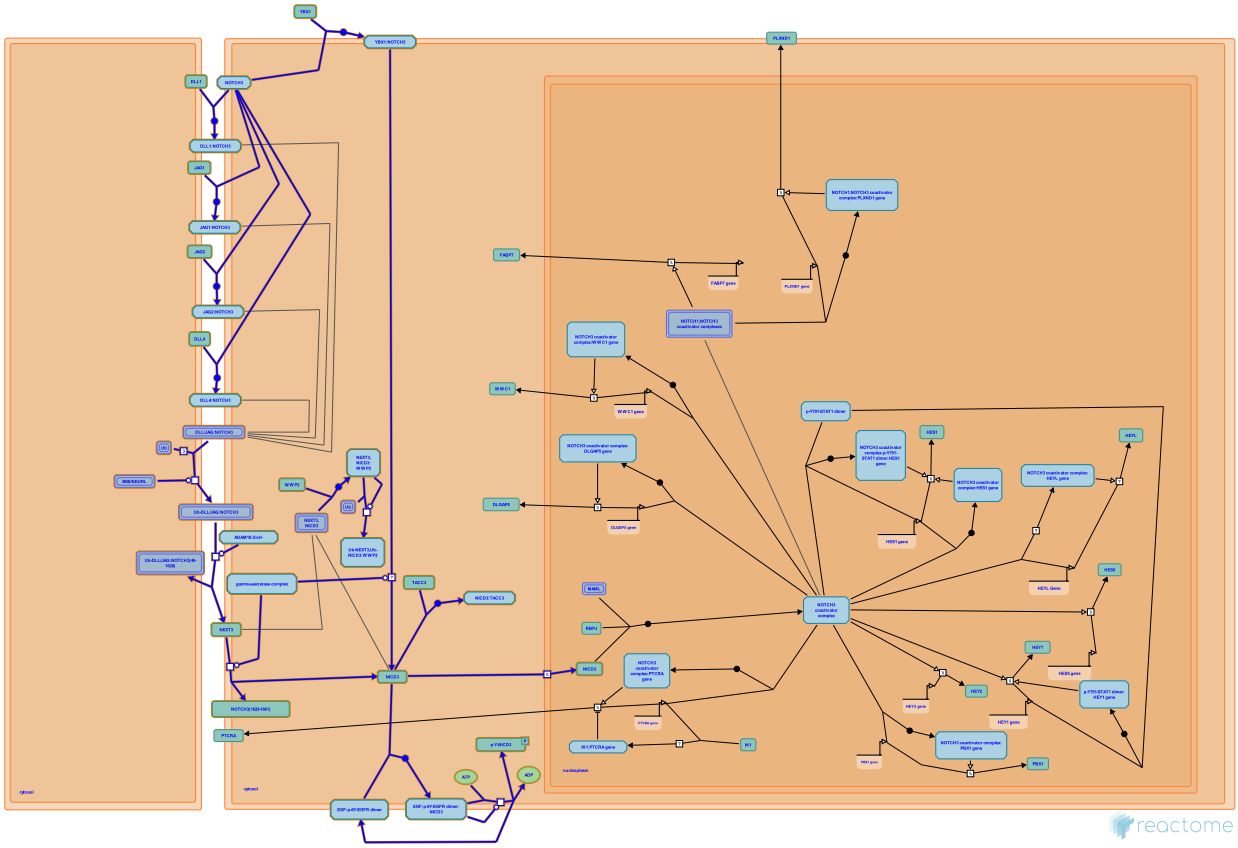
NOTCH3 Activation and Transmission of Signal to the Nucleus



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03/10/2022

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. ↗

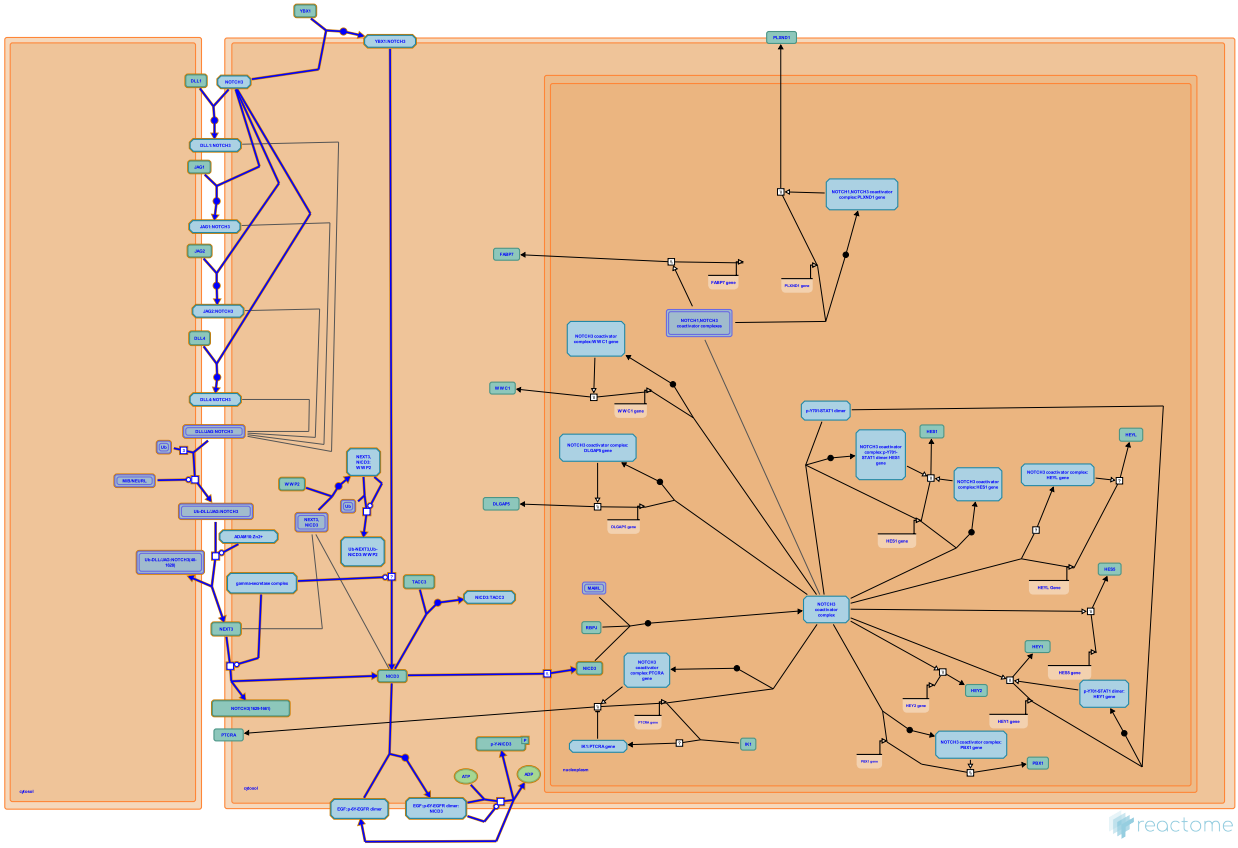
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

NOTCH3 Activation and Transmission of Signal to the Nucleus ↗

Stable identifier: R-HSA-9013507



NOTCH3 receptor can be activated by DLL/JAG ligands DLL1, JAG1, and JAG2 (Shimizu et al. 2000), as well as DLL4 (Claxton and Fruttiger 2004, Indraccolo et al. 2009). Ligand binding induces a conformational change in NOTCH3, which exposes the S2 site in the extracellular region of NOTCH3. The S2 site is cleaved by ADAM10 metalloprotease, generating the membrane anchored NOTCH3 fragment NEXT3. The NEXT3 fragment of NOTCH3 is further cleaved at the S3 site by the gamma secretase complex, releasing the intracellular domain NICD3 into the cytosol (Groot et al. 2014). Besides DLL/JAG ligands, NOTCH3 signaling can also be activated by binding of NOTCH3 to YBX1 (YB 1) (Rauen et al. 2009). NICD3 traffics to the nucleus where it acts as a transcription factor. WWP2, an E3 ubiquitin ligase, negatively regulates NOTCH3 signaling by ubiquitinating NEXT3 and NICD3 in the cytosol and targeting them for lysosome-mediated degradation (Jung et al. 2014). NOTCH3 signaling is also negatively regulated by binding to TACC3 (Bargo et al. 2010) and by EGFR-mediated phosphorylation (Arasada et al. 2014).

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. ↗

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. ↗

Djudjaj, S., Mühlenberg, PJ., Raffetseder, U., Frye, BC., Eitner, F., Bernhagen, J. et al. (2009). YB-1 acts as a ligand for Notch-3 receptors and modulates receptor activation. *J. Biol. Chem., 284*, 26928-40. ↗

Claxton, S., Fruttiger, M. (2004). Periodic Delta-like 4 expression in developing retinal arteries. *Gene Expr Patterns, 5*, 123-7. ↗

Pusceddu, I., Mecarozzi, M., Indraccolo, S., Amadori, A., Masiero, M., Minuzzo, S. et al. (2009). Cross-talk between tumor and endothelial cells involving the Notch3-Dll4 interaction marks escape from tumor dormancy. *Cancer Res, 69*, 1314-23. ↗

Editions

2017-09-20	Authored	Orlic-Milacic, M.
2017-10-30	Reviewed	Haw, R.
2017-11-02	Edited	Orlic-Milacic, M.

NOTCH3 binds DLL1 ↗

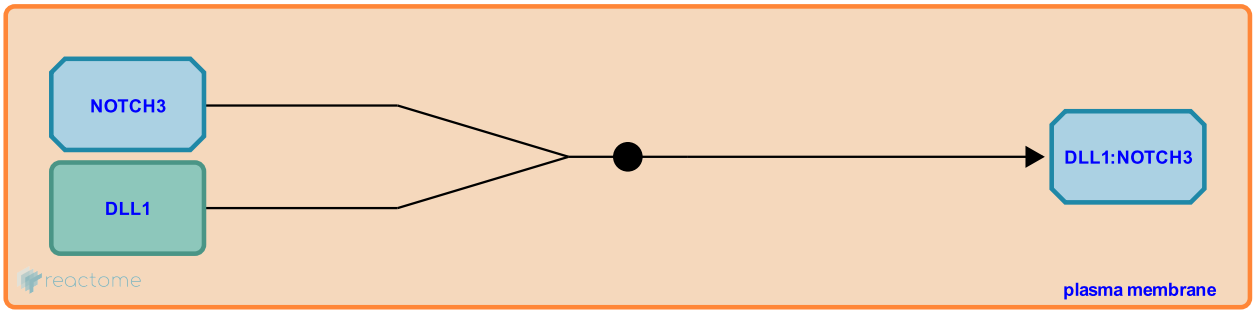
Location: NOTCH3 Activation and Transmission of Signal to the Nucleus

Stable identifier: R-HSA-157145

Type: binding

Compartments: plasma membrane, extracellular region

Inferred from: Notch3 binds Dll1 (Mus musculus)



Based on a study with mouse proteins, NOTCH3 receptor binds to DLL1 ligand (Shimizu et al. 2000). The interaction of DLL1 and NOTCH3 is implicated in functional differentiation of activated CD4+ T lymphocytes into type 1 helper T cells (Th1) (Maekawa et al. 2003). The effect of Fringe-mediated modification of NOTCH3 on its interaction with DLL1 is poorly studied (Hou et al. 2012).

Followed by: Ubiquitination of DLL/JAG ligands upon binding to NOTCH3

Editions

2017-09-20	Authored	Orlic-Milacic, M.
2017-10-30	Reviewed	Haw, R.
2017-11-02	Edited	Orlic-Milacic, M.

NOTCH3 binds JAG1 ↗

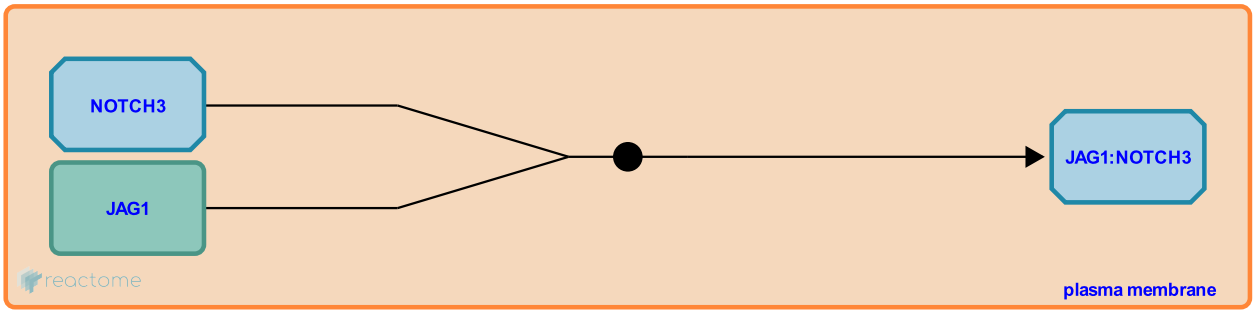
Location: NOTCH3 Activation and Transmission of Signal to the Nucleus

Stable identifier: R-HSA-157100

Type: binding

Compartments: plasma membrane, extracellular region

Inferred from: Notch3 binds Jag1 (Mus musculus)



Based on a study with mouse proteins, NOTCH3 receptor binds to JAG1 (Jagged1) ligand (Shimizu et al. 1999).

Followed by: Ubiquitination of DLL/JAG ligands upon binding to NOTCH3

Literature references

Gray, GE., Ish-Horowitz, D., Leiman, J., Carcangiu, ML., Banks, A., Mitsiadis, E. et al. (1999). Human ligands of the Notch receptor. *Am J Pathol, 154*, 785-94. ↗

Editions

2017-09-20	Authored	Orlic-Milacic, M.
2017-10-30	Reviewed	Haw, R.
2017-11-02	Edited	Orlic-Milacic, M.

NOTCH3 binds JAG2 ↗

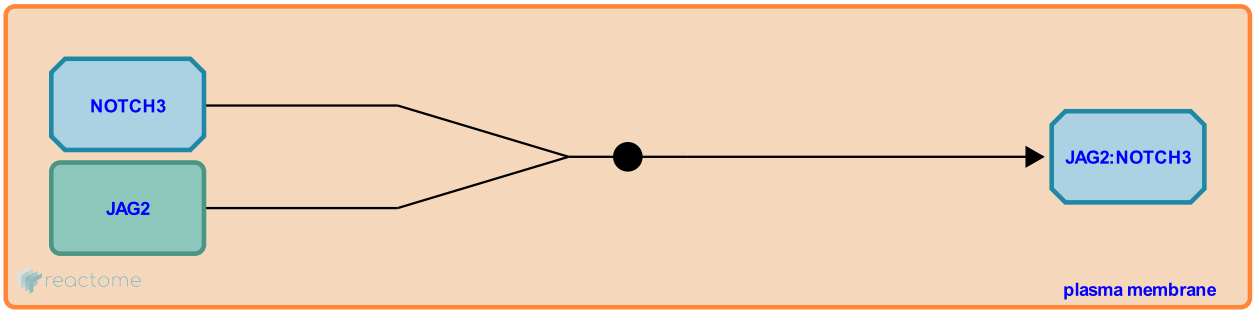
Location: NOTCH3 Activation and Transmission of Signal to the Nucleus

Stable identifier: R-HSA-157124

Type: binding

Compartments: plasma membrane, extracellular region

Inferred from: Notch3 binds Jag2 (Mus musculus)



Based on a study with mouse NOTCH3 and presumably mouse JAG2 (Jagged2), JAG2 ligand binds to NOTCH3 receptor (Shimizu et al. 2000).

Followed by: Ubiquitination of DLL/JAG ligands upon binding to NOTCH3

Editions

2017-09-20	Authored	Orlic-Milacic, M.
2017-10-30	Reviewed	Haw, R.
2017-11-02	Edited	Orlic-Milacic, M.

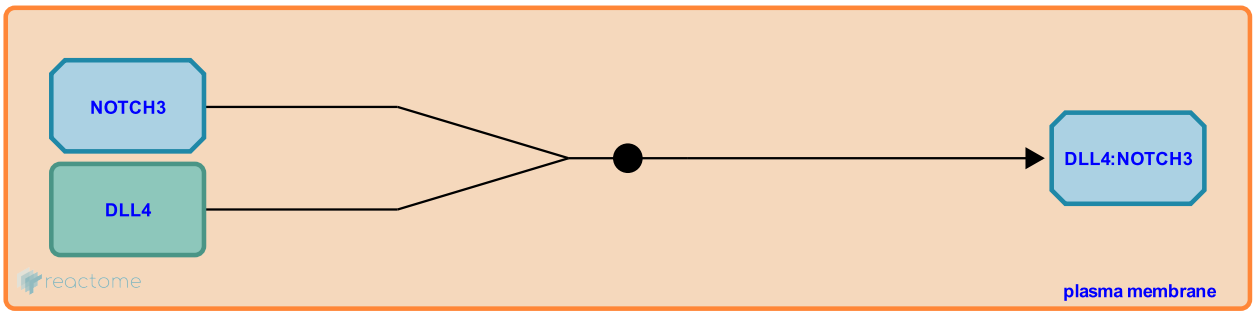
NOTCH3 binds DLL4 ↗

Location: NOTCH3 Activation and Transmission of Signal to the Nucleus

Stable identifier: R-HSA-2168136

Type: binding

Compartments: plasma membrane



Binding of NOTCH3 receptor to DLL4 ligand has not been directly demonstrated. DLL4 and NOTCH3 are expressed on neighboring cells in retina (Claxton and Fruttiger 2004) and in endothelium/blood (Indraccolo et al. 2009), and DLL4 significantly and specifically increases NOTCH3 signaling (Indraccolo et al. 2009).

Followed by: Ubiquitination of DLL/JAG ligands upon binding to NOTCH3

Literature references

Claxton, S., Fruttiger, M. (2004). Periodic Delta-like 4 expression in developing retinal arteries. *Gene Expr Patterns, 5*, 123-7. ↗

Pusceddu, I., Mecarozzi, M., Indraccolo, S., Amadori, A., Masiero, M., Minuzzo, S. et al. (2009). Cross-talk between tumor and endothelial cells involving the Notch3-Dll4 interaction marks escape from tumor dormancy. *Cancer Res, 69*, 1314-23. ↗

Editions

2017-09-20	Authored	Orlic-Milacic, M.
2017-10-30	Reviewed	Haw, R.
2017-11-02	Edited	Orlic-Milacic, M.

Ubiquitination of DLL/JAG ligands upon binding to NOTCH3 ↗

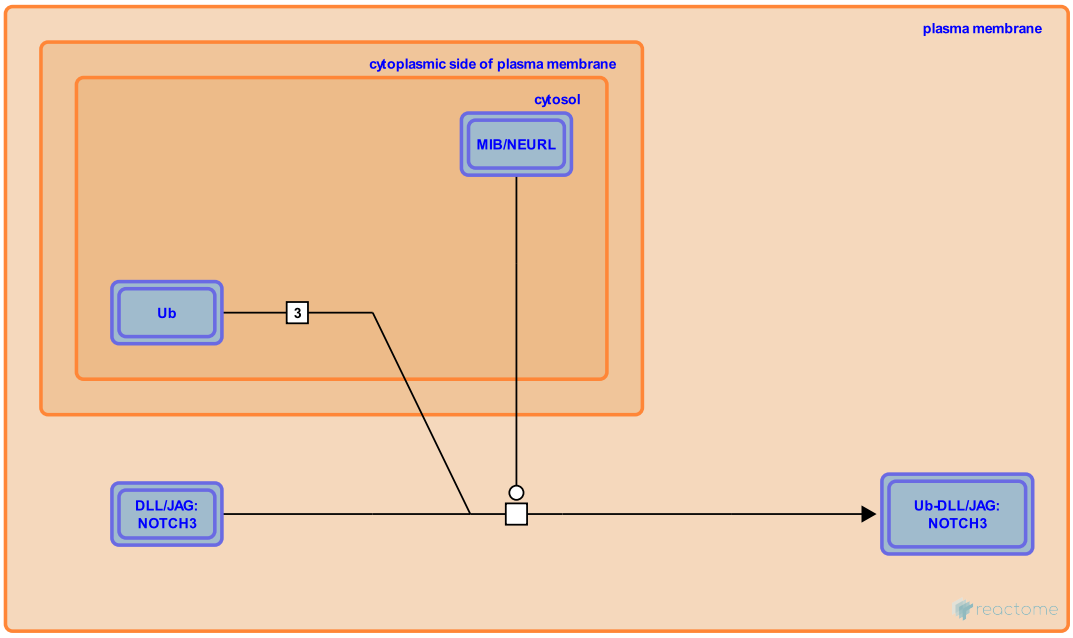
Location: NOTCH3 Activation and Transmission of Signal to the Nucleus

Stable identifier: R-HSA-9013069

Type: transition

Compartments: plasma membrane

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



Based on an analogy with NOTCH1 and NOTCH2, and on studies of Drosophila Notch, NOTCH ligands DLL1, DLL4, JAG1 and JAG2 are assumed to undergo ubiquitination and endocytosis after binding to NOTCH3 in trans. Ubiquitination of DLL/JAG ligands in mammals is performed by orthologues of Drosophila Mindbomb, MIB1, possibly MIB2, and possibly orthologues of Drosophila Neuralized, NEURL and NEURL1B.

Preceded by: NOTCH3 binds JAG1, NOTCH3 binds DLL1, NOTCH3 binds DLL4, NOTCH3 binds JAG2

Followed by: NOTCH3-ligand complex is cleaved to produce NEXT3

Editions

2017-09-20	Authored	Orlic-Milacic, M.
2017-10-30	Reviewed	Haw, R.
2017-11-02	Edited	Orlic-Milacic, M.

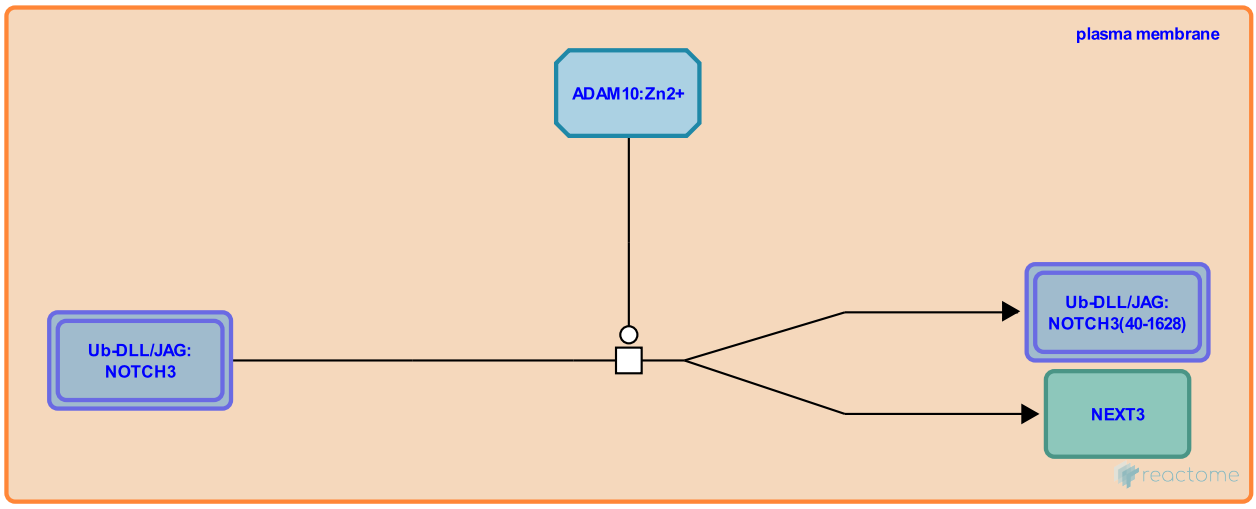
NOTCH3-ligand complex is cleaved to produce NEXT3 ↗

Location: NOTCH3 Activation and Transmission of Signal to the Nucleus

Stable identifier: R-HSA-9013284

Type: transition

Compartments: plasma membrane, extracellular region



Ligand binding induces a conformational change in NOTCH3, probably through mechanical pulling of NOTCH3 triggered by endocytosis of the receptor-attached ubiquitinated ligand. This conformational change exposes the S2 site in the extracellular region of NOTCH3 and triggers cleavage of NOTCH3 by ADAM10 metalloprotease, generating the membrane-anchored NOTCH3 fragment NEXT3 (Groot et al. 2014). The extracellular NOTCH3 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 NOTCH3

Followed by: NOTCH3 binds WWP2, NEXT3 is cleaved to produce NICD3

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. ↗

Editions

2017-09-20	Authored	Orlic-Milacic, M.
2017-10-30	Reviewed	Haw, R.
2017-11-02	Edited	Orlic-Milacic, M.

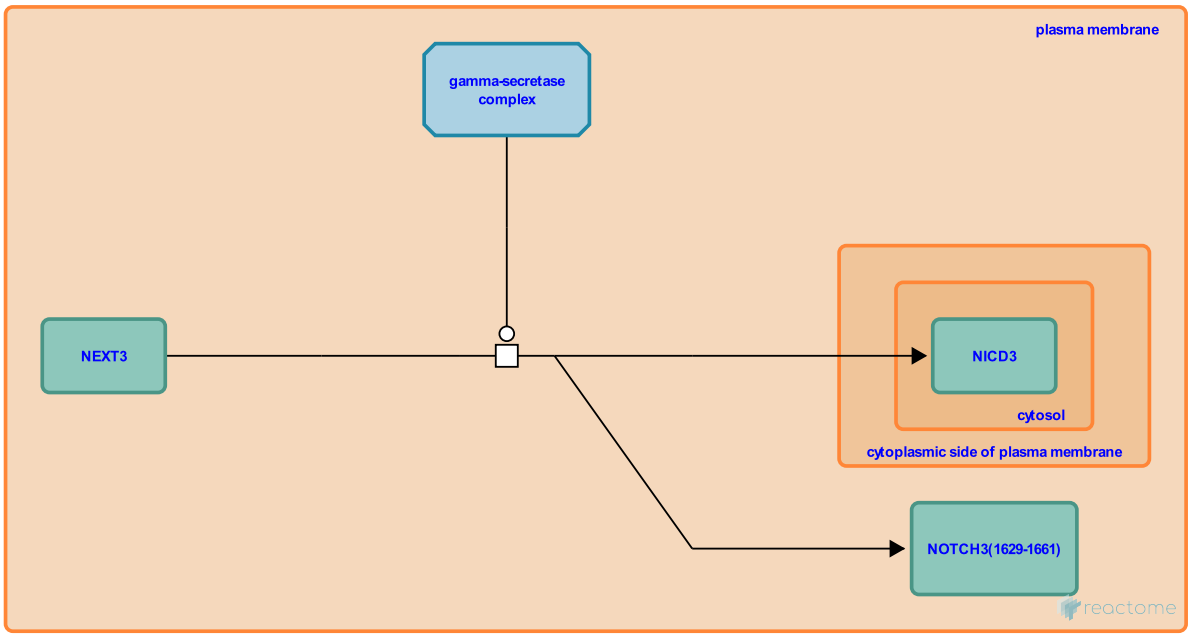
NEXT3 is cleaved to produce NICD3 ↗

Location: NOTCH3 Activation and Transmission of Signal to the Nucleus

Stable identifier: R-HSA-9013361

Type: transition

Compartments: plasma membrane, cytosol



NEXT3 fragment of NOTCH3 is further cleaved at the S3 site by the gamma-secretase complex, containing either PSEN1 (presenilin-1) or PSEN2 (presenilin-2) as the catalytic subunit, which releases the intracellular domain NICD3 into the cytosol (Groot et al. 2014).

Preceded by: NOTCH3-ligand complex is cleaved to produce NEXT3

Followed by: NOTCH3 binds WWP2, NICD3 binds to TACC3, NOTCH3 binds activated EGFR, NICD3 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. ↗

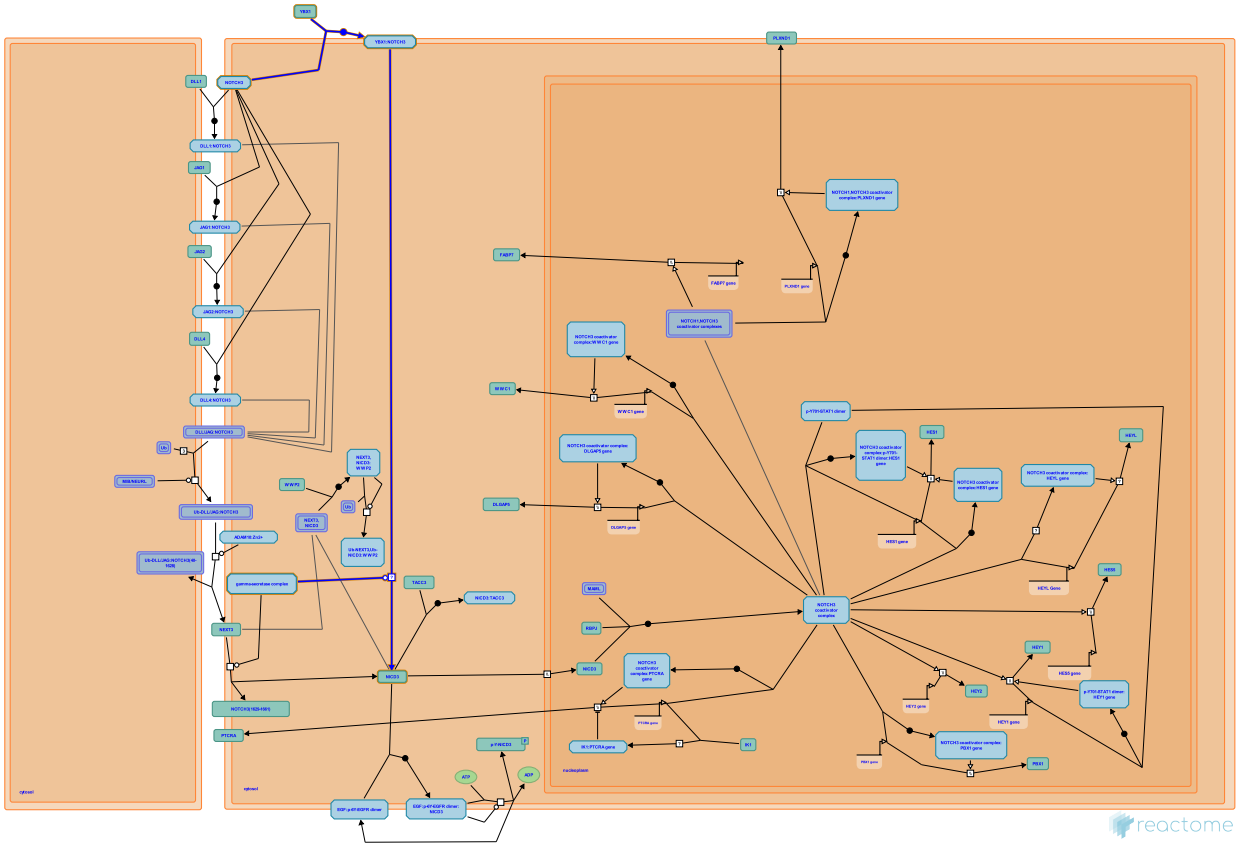
Editions

2017-09-20	Authored	Orlic-Milacic, M.
2017-10-30	Reviewed	Haw, R.
2017-11-02	Edited	Orlic-Milacic, M.

Noncanonical activation of NOTCH3 ↗

Location: NOTCH3 Activation and Transmission of Signal to the Nucleus

Stable identifier: R-HSA-9017802



Besides DLL/JAG ligands, NOTCH3 signaling can also be activated by binding of NOTCH3 to YBX1 (YB 1) (Rauen et al. 2009). YBX1, a protein involved in mRNA processing, is secreted by mesangial cells and monocytes during inflammation and acts as an extracellular mitogen (Frye et al. 2009). YBX1 triggers the gamma secretase complex mediated cleavage of NOTCH3, resulting in release of NOTCH3 intracellular domain (NICD3) and activation of NOTCH3 target genes (Rauen et al. 2009).

Literature references

Djudjaj, S., Muehlenberg, P., En-Nia, A., Raffetseder, U., Halfter, S., Frye, BC. et al. (2009). Y-box protein-1 is actively secreted through a non-classical pathway and acts as an extracellular mitogen. *EMBO Rep., 10*, 783-9. ↗

Djudjaj, S., Mühlenberg, PJ., Raffetseder, U., Frye, BC., Eitner, F., Bernhagen, J. et al. (2009). YB-1 acts as a ligand for Notch-3 receptors and modulates receptor activation. *J. Biol. Chem., 284*, 26928-40. ↗

Editions

2017-09-20	Authored	Orlic-Milacic, M.
2017-10-30	Reviewed	Haw, R.
2017-11-02	Edited	Orlic-Milacic, M.

NICD3 binds to TACC3 ↗

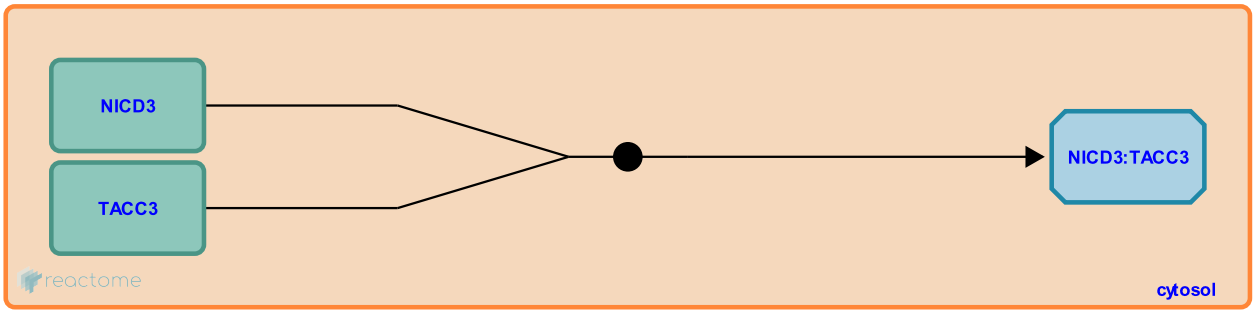
Location: NOTCH3 Activation and Transmission of Signal to the Nucleus

Stable identifier: R-HSA-9017855

Type: binding

Compartments: cytosol

Inferred from: NICD3 binds to Tacc3 (Mus musculus)



Based on studies in mice, the intracellular domain of NOTCH3, NICD3, binds to transforming acidic coiled-coil protein-3 (TACC3). The interaction involves the ankyrin repeats of NOTCH3. The two proteins co-localize in the cytosol and possibly in the nucleus. TACC3 is implicated as a negative regulator of NOTCH signaling and may compete with NOTCH binding to RPBJ (Bargo et al. 2010).

Preceded by: NEXT3 is cleaved to produce NICD3

Editions

2017-09-20	Authored	Orlic-Milacic, M.
2017-10-30	Reviewed	Haw, R.
2017-11-02	Edited	Orlic-Milacic, M.

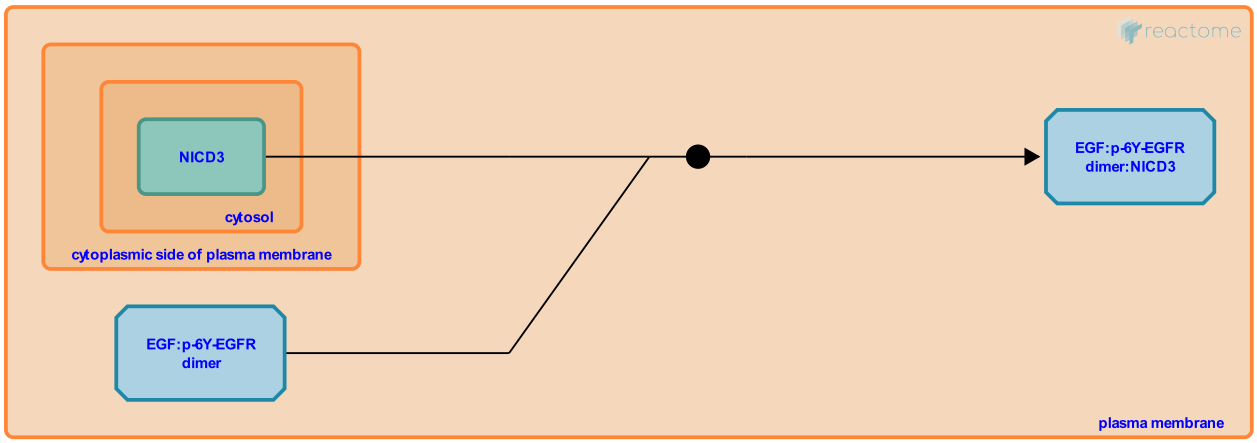
NOTCH3 binds activated EGFR ↗

Location: NOTCH3 Activation and Transmission of Signal to the Nucleus

Stable identifier: R-HSA-9018573

Type: binding

Compartments: plasma membrane



The intracellular domain of NOTCH3 (NICD3) co-immunoprecipitates with ligand activated, autophosphorylated EGFR. Binding of NOTCH3 to EGFR is inhibited by erlotinib treatment, which prevents EGFR activation (Arasada et al. 2014).

Preceded by: NEXT3 is cleaved to produce NICD3

Followed by: EGFR phosphorylates NOTCH3

Literature references

Huppert, SS., Carbone, DP., Arasada, RR., Rahman, MA., Amann, JM. (2014). EGFR blockade enriches for lung cancer stem-like cells through Notch3-dependent signaling. *Cancer Res., 74*, 5572-84. ↗

Editions

2017-09-20	Authored	Orlic-Milacic, M.
2017-10-30	Reviewed	Haw, R.
2017-11-02	Edited	Orlic-Milacic, M.

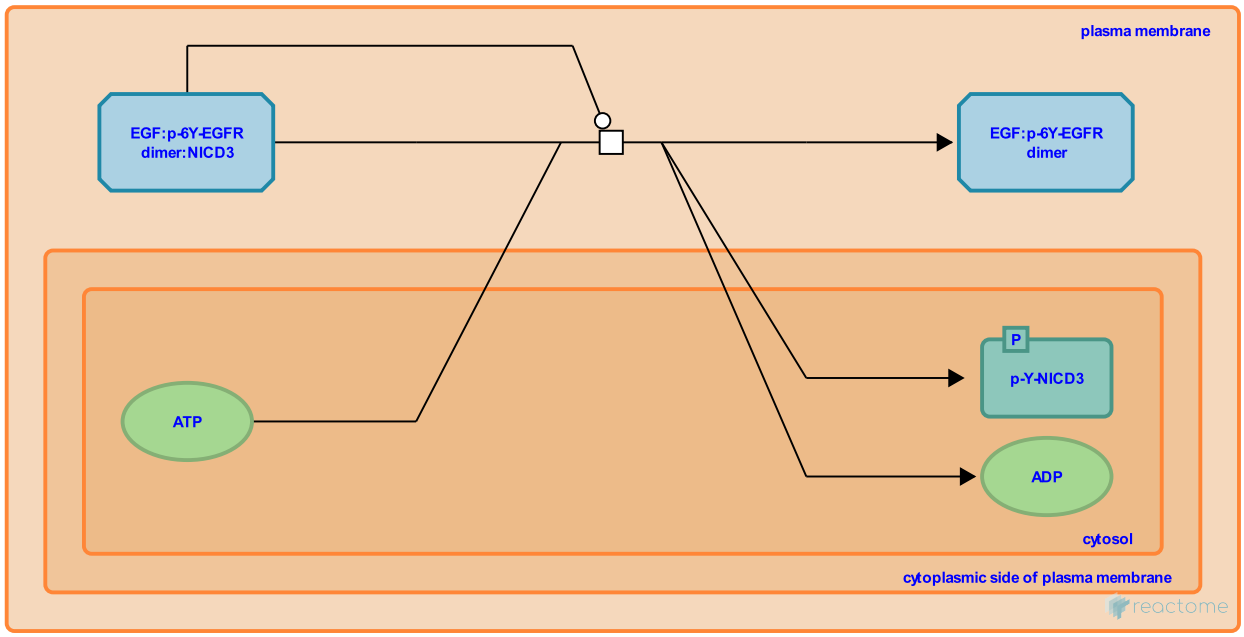
EGFR phosphorylates NOTCH3 ↗

Location: NOTCH3 Activation and Transmission of Signal to the Nucleus

Stable identifier: R-HSA-9018572

Type: transition

Compartments: plasma membrane



EGFR phosphorylates intracellular domain of NOTCH3 (NICD3) on an unknown tyrosine residue. EGFR signaling inhibits NICD3-mediated transcription. It is not known whether EGFR-mediated phosphorylation of NICD3 affects NICD3 nuclear translocation or the formation of the NOTCH3 coactivator complex. Erlotinib treatment, which inhibits EGFR activation, results in increased NOTCH3 signaling and induction of stem-like phenotype in treated cells (Arasada et al. 2014).

Preceded by: NOTCH3 binds activated EGFR

Literature references

Huppert, SS., Carbone, DP., Arasada, RR., Rahman, MA., Amann, JM. (2014). EGFR blockade enriches for lung cancer stem-like cells through Notch3-dependent signaling. *Cancer Res., 74*, 5572-84. ↗

Editions

2017-09-20	Authored	Orlic-Milacic, M.
2017-10-30	Reviewed	Haw, R.
2017-11-02	Edited	Orlic-Milacic, M.

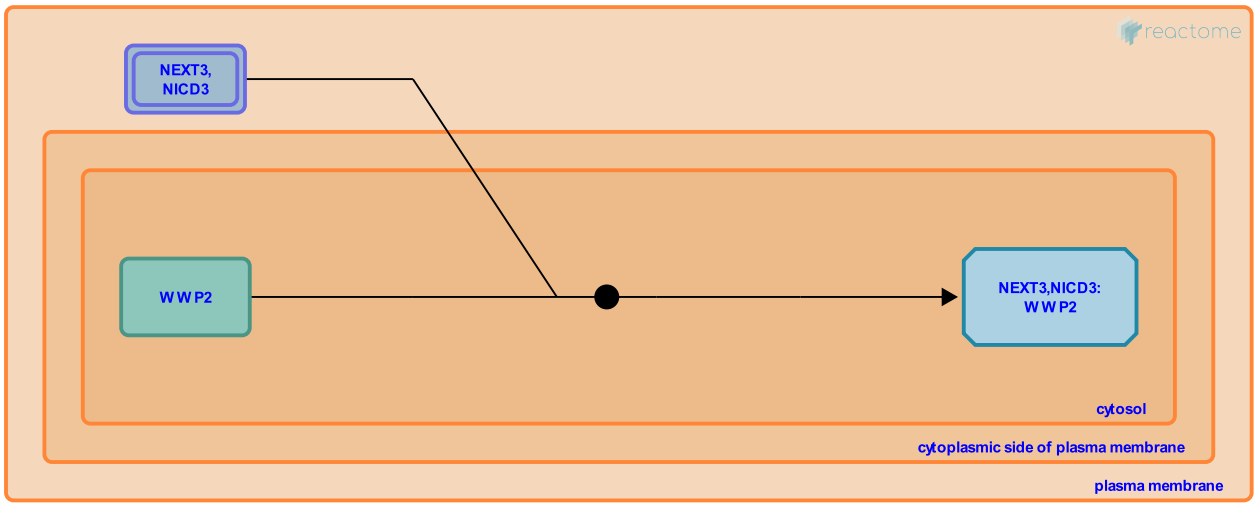
NOTCH3 binds WWP2

Location: NOTCH3 Activation and Transmission of Signal to the Nucleus

Stable identifier: R-HSA-9021520

Type: binding

Compartments: cytosol



WWP2, an E3 ubiquitin ligase, can interact with NOTCH3 cleavage products NEXT3 and NICD3 in the cytosol. The interaction involves the PPPY motif in the PEST domain of NOTCH3 (Jung et al. 2014).

Preceded by: NOTCH3-ligand complex is cleaved to produce NEXT3, NEXT3 is cleaved to produce NICD3

Followed by: WWP2 ubiquitinates NOTCH3

Literature references

Wu, RC., Guan, B., Blackshaw, S., Wang, TL., Zhu, H., Stoeck, A. et al. (2014). Notch3 interactome analysis identified WWP2 as a negative regulator of Notch3 signaling in ovarian cancer. *PLoS Genet., 10*, e1004751.

Editions

2017-09-20	Authored	Orlic-Milacic, M.
2017-10-30	Reviewed	Haw, R.
2017-11-02	Edited	Orlic-Milacic, M.

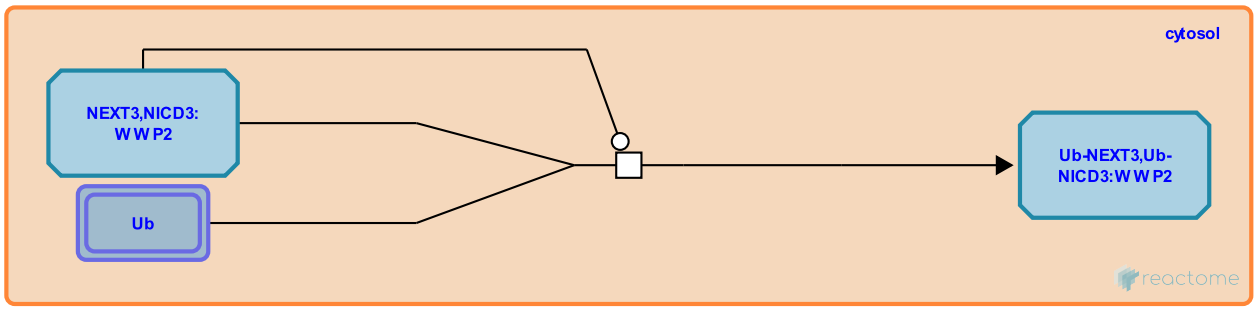
WWP2 ubiquitinates NOTCH3 ↗

Location: NOTCH3 Activation and Transmission of Signal to the Nucleus

Stable identifier: R-HSA-9021523

Type: transition

Compartments: cytosol



WWP2, an E3 ubiquitin ligase, ubiquitinates NOTCH3 cleavage fragments NEXT3 and NICD3 in the cytosol, targeting them for lysosome-mediated degradation. WWP2 thus negatively regulates NOTCH3 signaling. WWP2 is a putative tumor suppressor whose deletions have been reported in the majority of ovarian carcinomas (Jung et al. 2014).

Preceded by: NOTCH3 binds WWP2

Literature references

Wu, RC., Guan, B., Blackshaw, S., Wang, TL., Zhu, H., Stoeck, A. et al. (2014). Notch3 interactome analysis identified WWP2 as a negative regulator of Notch3 signaling in ovarian cancer. *PLoS Genet., 10*, e1004751. ↗

Editions

2017-09-20	Authored	Orlic-Milacic, M.
2017-10-30	Reviewed	Haw, R.
2017-11-02	Edited	Orlic-Milacic, M.

NICD3 traffics to the nucleus ↗

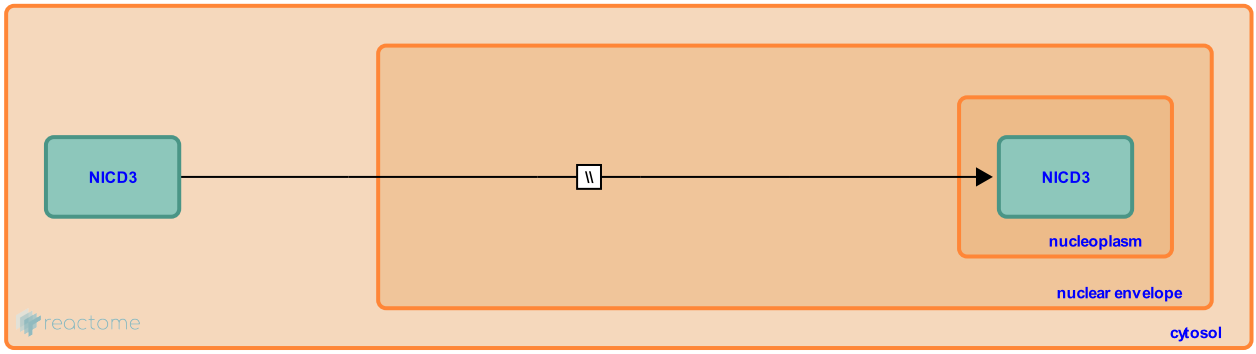
Location: NOTCH3 Activation and Transmission of Signal to the Nucleus

Stable identifier: R-HSA-157937

Type: omitted

Compartments: nuclear envelope

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



Based on an analogy with Drosophila Notch and its intracellular cleavage product NICD, it is believed that the cytosolic NICD3 translocates to the nucleus (Lecourtois and Schweisguth 1998, Struhl and Adachi 1998).

Preceded by: NEXT3 is cleaved to produce NICD3

Editions

2005-01-10	Authored	Jassal, B.
2017-10-30	Reviewed	Haw, R.
2017-11-02	Edited	Orlic-Milacic, M.

Table of Contents