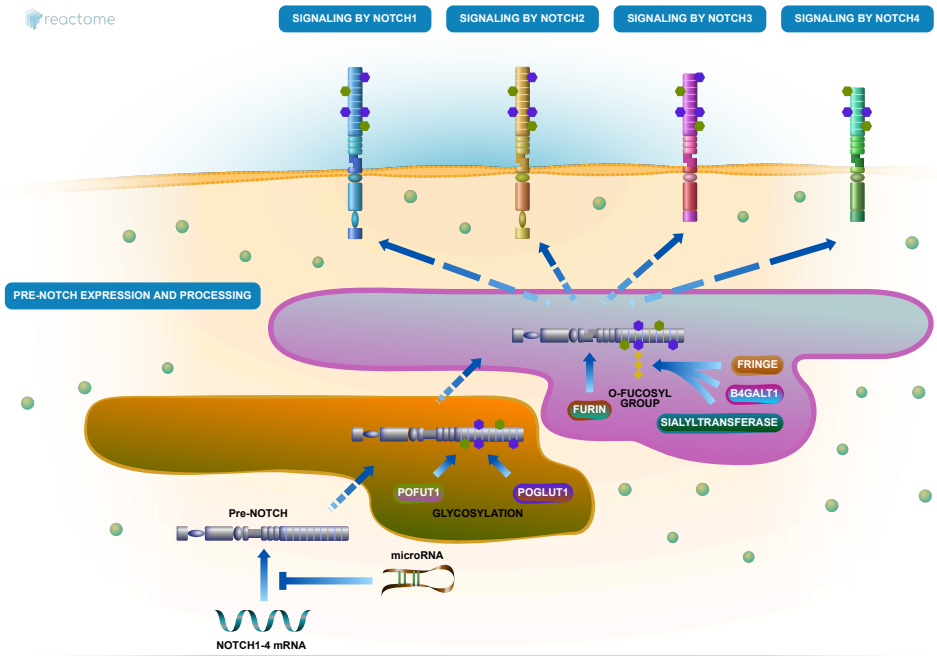
Signaling by NOTCH



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

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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

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

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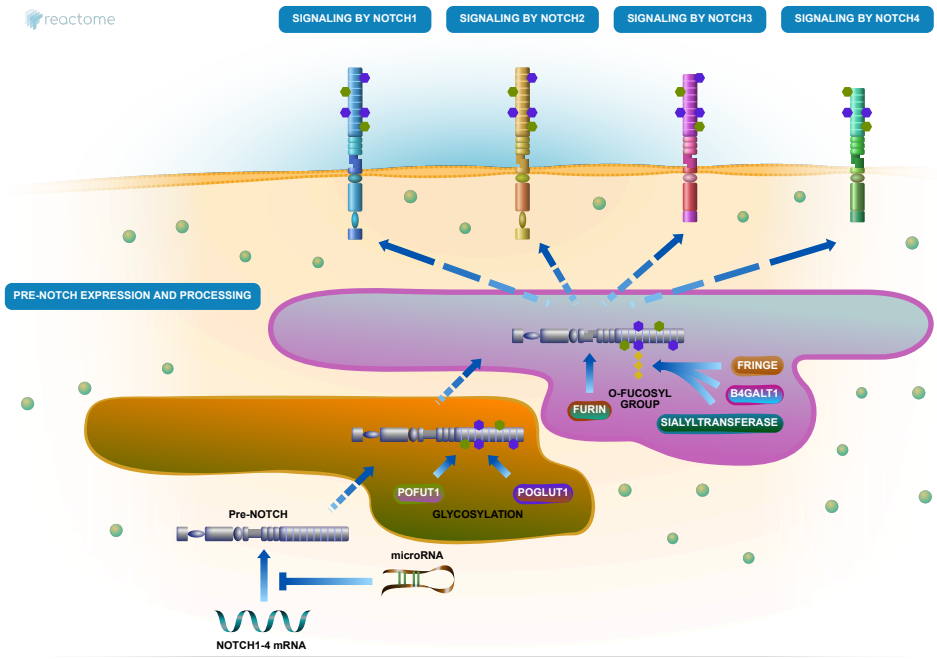
Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Reactome database release: 88

This document contains 6 pathways (see Table of Contents)

Signaling by NOTCH ↗

Stable identifier: R-HSA-157118



The Notch Signaling Pathway (NSP) is a highly conserved pathway for cell-cell communication. NSP is involved in the regulation of cellular differentiation, proliferation, and specification. For example, it is utilised by continually renewing adult tissues such as blood, skin, and gut epithelium not only to maintain stem cells in a proliferative, pluripotent, and undifferentiated state but also to direct the cellular progeny to adopt different developmental cell fates. Analogously, it is used during embryonic development to create fine-grained patterns of differentiated cells, notably during neurogenesis where the NSP controls patches such as that of the vertebrate inner ear where individual hair cells are surrounded by supporting cells.
This process is known as lateral inhibition: a molecular mechanism whereby individual cells within a field are stochastically selected to adopt particular cell fates and the NSP inhibits their direct neighbours from doing the same. The NSP has been adopted by several other biological systems for binary cell fate choice. In addition, the NSP is also used during vertebrate segmentation to divide the growing embryo into regular blocks called somites which eventually form the vertebrae. The core of this process relies on regular pulses of Notch signaling generated from a molecular oscillator in the presomatic mesoderm.
The Notch receptor is synthesized in the rough endoplasmic reticulum as a single polypeptide precursor. Newly synthesized Notch receptor is proteolytically cleaved in the trans-golgi network, creating a heterodimeric mature receptor comprising of non-covalently associated extracellular and transmembrane subunits. This assembly travels to the cell surface ready to interact with specific ligands. Following ligand activation and further proteolytic cleavage, an intracellular domain is released and translocates to the nucleus where it regulates gene expression.

Editions

2004-12-15	Authored	Jassal, B.
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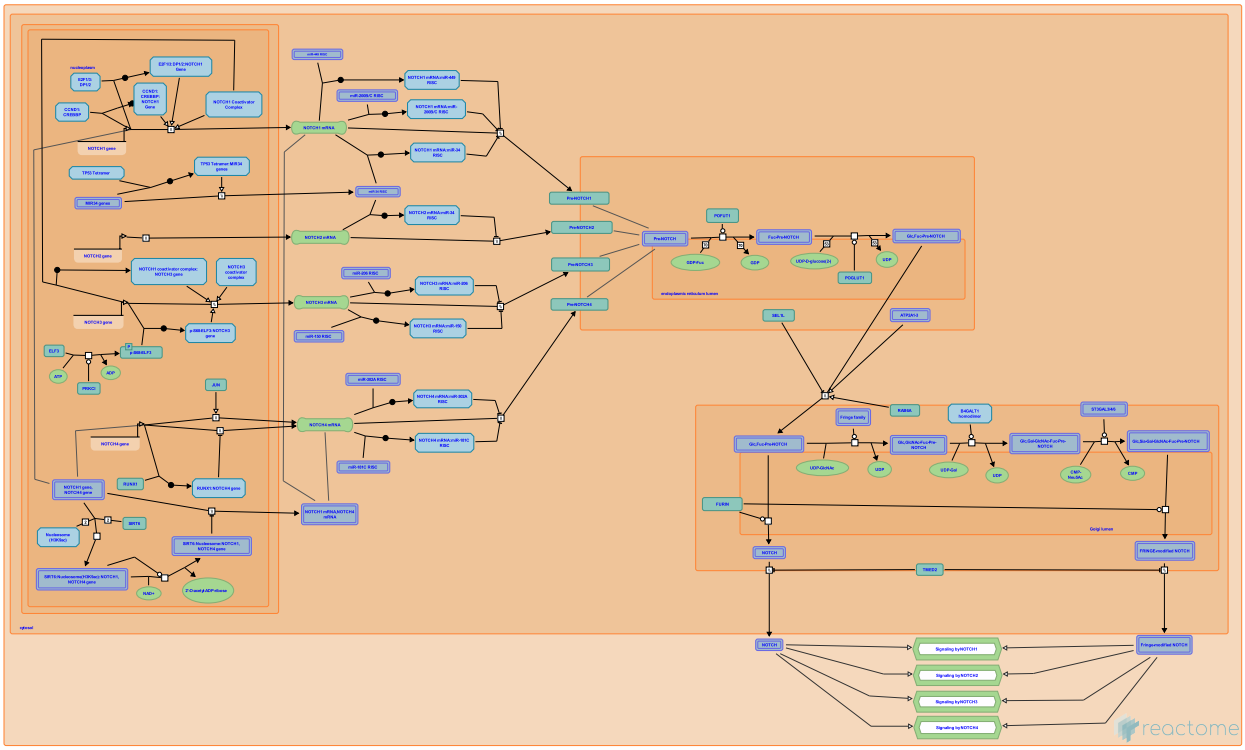
Pre-NOTCH Expression and Processing ↗

Location: Signaling by NOTCH

Stable identifier: R-HSA-1912422

Compartments: cytosol, endoplasmic reticulum lumen, Golgi membrane, Golgi lumen, nucleoplasm, plasma membrane, endoplasmic reticulum membrane



In humans and other mammals the NOTCH gene family has four members, NOTCH1, NOTCH2, NOTCH3 and NOTCH4, encoded on four different chromosomes. Their transcription is developmentally regulated and tissue specific, but very little information exists on molecular mechanisms of transcriptional regulation. Translation of NOTCH mRNAs is negatively regulated by a number of recently discovered microRNAs (Li et al. 2009, Pang et al.2010, Ji et al. 2009, Kong et al. 2010, Marcet et al. 2011, Ghisi et al. 2011, Song et al. 2009, Hashimoto et al. 2010, Costa et al. 2009).

The nascent forms of NOTCH precursors, Pre-NOTCH1, Pre-NOTCH2, Pre-NOTCH3 and Pre-NOTCH4, undergo extensive posttranslational modifications in the endoplasmic reticulum and Golgi apparatus to become functional. In the endoplasmic reticulum, conserved serine and threonine residues in the EGF repeats of NOTCH extracellular domain are fucosylated and glucosylated by POFUT1 and POGLUT1, respectively (Yao et al. 2011, Stahl et al. 2008, Wang et al. 2001, Shao et al. 2003, Acar et al. 2008, Fernandez Valdivia et al. 2011).

In the Golgi apparatus, fucose groups attached to NOTCH EGF repeats can be elongated by additional glycosylation steps initiated by fringe enzymes (Bruckner et al. 2000, Moloney et al. 2000, Cohen et al. 1997, Johnston et al. 1997, Chen et al. 2001). Fringe-mediated modification modulates NOTCH signaling but is not an obligatory step in Pre-NOTCH processing. Typically, processing of Pre-NOTCH in the Golgi involves cleavage by FURIN convertase (Blaumueller et al. 1997, Logeat et al. 1998, Gordon et al. 2009, Rand et al. 2000, Chan et al. 1998). The cleavage of NOTCH results in formation of mature NOTCH heterodimers that consist of NOTCH extracellular domain (NEC i.e. NECD) and NOTCH transmembrane and intracellular domain (NTM i.e. NTMICD). NOTCH heterodimers translocate to the cell surface where they function in cell to cell signaling.

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Editions

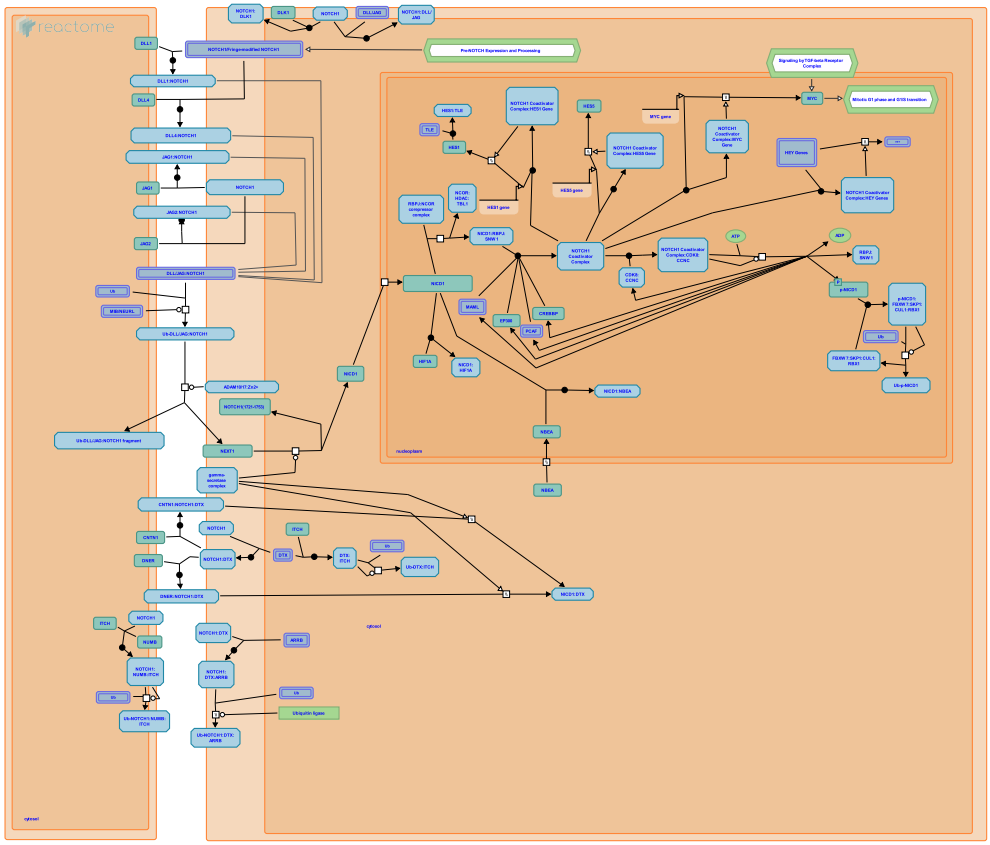
2011-11-14	Authored	Egan, SE., Orlic-Milacic, M.
2012-02-06	Reviewed	Haw, R.
2012-02-07	Edited	D'Eustachio, P.
2012-02-11	Edited	Orlic-Milacic, M.

Signaling by NOTCH1 ↗

Location: Signaling by NOTCH

Stable identifier: R-HSA-1980143

Compartments: cytosol, plasma membrane, nucleoplasm



NOTCH1 functions as both a transmembrane receptor presented on the cell surface and as a transcriptional regulator in the nucleus.

NOTCH1 receptor presented on the plasma membrane is activated by a membrane bound ligand expressed in trans on the surface of a neighboring cell. In trans, ligand binding triggers proteolytic cleavage of NOTCH1 and results in release of the NOTCH1 intracellular domain, NICD1, into the cytosol.

NICD1 translocates to the nucleus where it associates with RBPJ (also known as CSL or CBF) and mastermind-like (MAML) proteins (MAML1, MAML2 or MAML3; possibly also MAMLD1) to form NOTCH1 coactivator complex. NOTCH1 coactivator complex activates transcription of genes that possess RBPJ binding sites in their promoters.

Literature references

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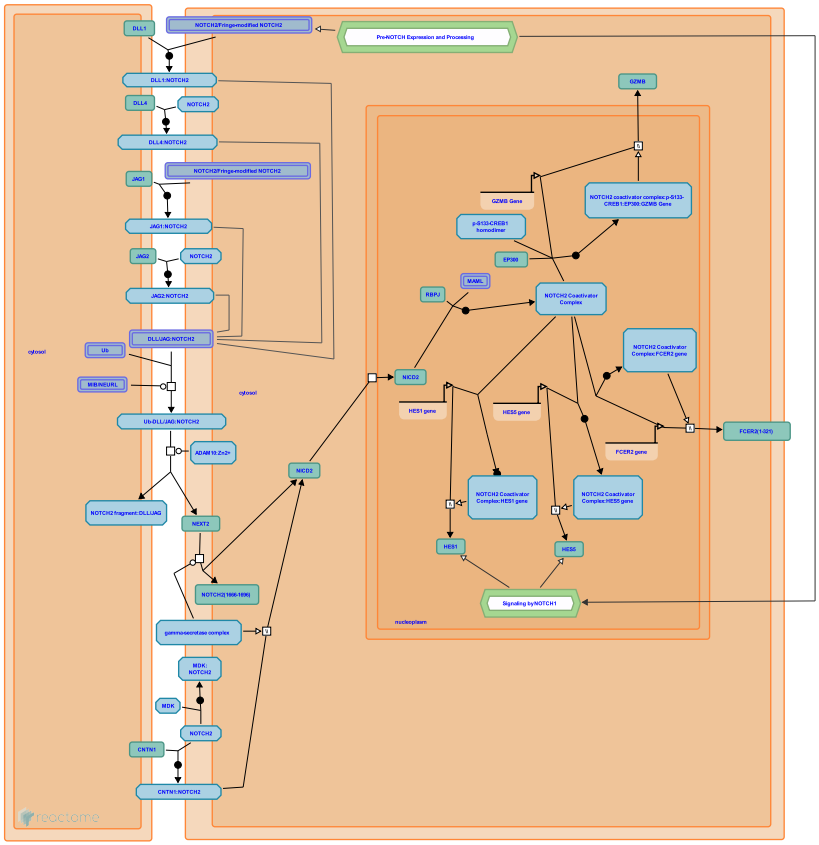
Signaling by NOTCH2 ↗

Location: Signaling by NOTCH

Stable identifier: R-HSA-1980145

Compartments: nucleoplasm, plasma membrane, cytosol



NOTCH2 is activated by binding Delta-like and Jagged ligands (DLL/JAG) expressed in trans on neighboring cells (Shimizu et al. 1999, Shimizu et al. 2000, Hicks et al. 2000, Ji et al. 2004). In trans ligand-receptor binding is followed by ADAM10 mediated (Gibb et al. 2010, Shimizu et al. 2000) and gamma secretase complex mediated cleavage of NOTCH2 (Saxena et al. 2001, De Strooper et al. 1999), resulting in the release of the intracellular domain of NOTCH2, NICD2, into the cytosol. NICD2 traffics to the nucleus where it acts as a transcriptional regulator. For a recent review of the cannonical NOTCH signaling, please refer to Kopan and Ilagan 2009, D'Souza et al. 2010, Kovall and Blacklow 2010. CNTN1 (contactin 1), a protein involved in oligodendrocyte maturation (Hu et al. 2003) and MDK (midkine) (Huang et al. 2008, Gungor et al. 2011), which plays an important role in epithelial-to-mesenchymal transition, can also bind NOTCH2 and activate NOTCH2 signaling.

In the nucleus, NICD2 forms a complex with RBPJ (CBF1, CSL) and MAML (mastermind). The NICD2:RBPJ:MAML complex activates transcription from RBPJ binding promoter elements (RBEs) (Wu et al. 2000). NOTCH2 coactivator complexes directly stimulate transcription of HES1 and HES5 genes (Shimizu et al. 2002), both of which are known NOTCH1 targets. NOTCH2 but not NOTCH1 coactivator complexes, stimulate FCER2 transcription. Overexpression of FCER2 (CD23A) is a hallmark of B-cell chronic lymphocytic leukemia (B-CLL) and correlates with the malfunction of apoptosis, which is thought be an underlying mechanism of B-CLL development (Hubmann et al. 2002). NOTCH2 coactivator complexes together with CREBP1 and EP300 stimulate transcription of GZMB (granzyme B), which is important for the cytotoxic function of CD8+ T cells (Maekawa et al. 2008).

NOTCH2 gene expression is differentially regulated during human B-cell development, with NOTCH2 transcripts appearing at late developmental stages (Bertrand et al. 2000).

NOTCH2 mutations are a rare cause of Alagille syndrome (AGS). AGS is a dominant congenital multisystem disorder characterized mainly by hepatic bile duct abnormalities. Craniofacial, heart and kidney abnormalities are also frequently observed in the Alagille spectrum (Alagille et al. 1975). AGS is predominantly caused by mutations in JAG1, a NOTCH2 ligand (Oda et al. 1997, Li et al. 1997), but it can also be caused by mutations in NOTCH2 (McDaniell et al. 2006).

Hajdu-Cheney syndrome, an autosomal dominant disorder characterized by severe and progressive bone loss, is caused by NOTCH2 mutations that result in premature C-terminal NOTCH2 truncation, probably leading to increased NOTCH2 signaling (Simpson et al. 2011, Isidor et al. 2011, Majewski et al. 2011).

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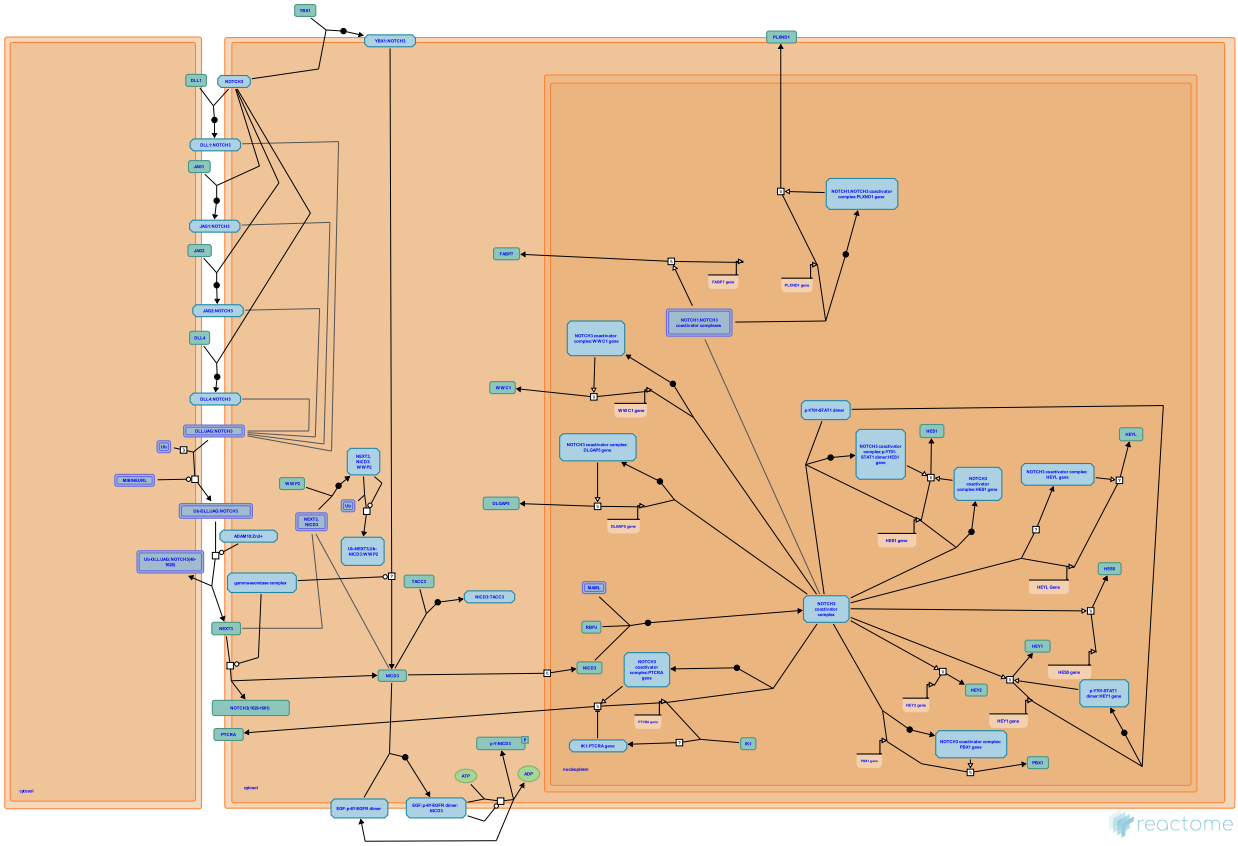
Editions

2004-12-15	Authored	Jassal, B.
2004-12-15	Reviewed	Joutel, A.
2012-02-11	Edited	Orlic-Milacic, M.
2013-01-11	Revised	Orlic-Milacic, M.
2013-04-25	Reviewed	Ilagan, MXG., Boyle, S.

Signaling by NOTCH3 ↗

Location: Signaling by NOTCH

Stable identifier: R-HSA-9012852



Similar to NOTCH1, NOTCH3 is activated by delta-like and jagged ligands (DLL/JAG) expressed in trans on a neighboring cell. The activation triggers cleavage of NOTCH3, first by ADAM10 at the S2 cleavage site, then by gamma-secretase at the S3 cleavage site, resulting in the release of the intracellular domain of NOTCH3, NICD3, into the cytosol. NICD3 subsequently traffics to the nucleus where it acts as a transcriptional regulator. NOTCH3 expression pattern is more restricted than the expression patterns of NOTCH1 and NOTCH2, with predominant expression of NOTCH3 in vascular smooth muscle cells, lymphocytes and the nervous system (reviewed by Bellavia et al. 2008). Based on the study of Notch3 knockout mice, Notch3 is not essential for embryonic development or fertility (Krebs et al. 2003).

Germline gain-of-function NOTCH3 mutations are an underlying cause of the CADASIL syndrome - cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. CADASIL is characterized by degeneration and loss of vascular smooth muscle cells from the arterial wall, predisposing affected individuals to an early onset stroke (Storkebaum et al. 2011). NOTCH3 promotes survival of vascular smooth muscle cells at least in part by induction of CFLAR (c FLIP), an inhibitor of FASLG activated death receptor signaling. The mechanism of NOTCH3 mediated upregulation of CFLAR is unknown; it is independent of the NOTCH3 coactivator complex and involves an unelucidated crosstalk with the RAS/RAF/MAPK pathway (Wang et al. 2002).

In rat brain, NOTCH3 and NOTCH1 are expressed at sites of adult neurogenesis, such as the dentate gyrus (Irvin et al. 2001). NOTCH3, similar to NOTCH1, promotes differentiation of the rat adult hippocampus derived multipotent neuronal progenitors into astroglia (Tanigaki et al. 2001). NOTCH1, NOTCH2, NOTCH3, and their ligand DLL1 are expressed in neuroepithelial precursor cells in the neural tube of mouse embryos. Together, they signal to inhibit neuronal differentiation of neuroepithelial precursors. Expression of NOTCH3 in mouse neuroepithelial precursors is stimulated by growth factors BMP2, FGF2, Xenopus TGF beta5 - homologous to TGFB1, LIF, and NTF3 (Faux et al. 2001).

In mouse telencephalon, NOTCH3, similar to NOTCH1, promotes radial glia and neuronal progenitor phenotype. This can, at least in part be attributed to NOTCH mediated activation of RBPJ-dependent and HES5-dependent transcription (Dang et al. 2006).

In mouse spinal cord, Notch3 is involved in neuronal differentiation and maturation. Notch3 knockout mice have a

decreased number of mature inhibitory interneurons in the spinal cord, which may be involved in chronic pain conditions (Rusanescu and Mao 2014).

NOTCH3 amplification was reported in breast cancer, where NOTCH3 promotes proliferation and survival of ERBB2 negative breast cancer cells (Yamaguchi et al. 2008), and it has also been reported in ovarian cancer (Park et al. 2006). NOTCH3 signaling is involved in TGF beta (TGFB1) signaling-induced eptihelial to mesenchimal transition (EMT) (Ohashi et al. 2011, Liu et al. 2014)

NOTCH3 indirectly promotes development of regulatory T cells (Tregs). NOTCH3 signaling activates pre-TCR-dependent and PKC-theta (PRKCQ)-dependent NF-kappaB (NFKB) activation, resulting in induction of FOXP3 expression (Barbarulo et al. 2011). Deregulated NOTCH3 and pre-TCR signaling contributes to development of leukemia and lymphoma (Bellavia et al. 2000, Bellavia et al. 2002).

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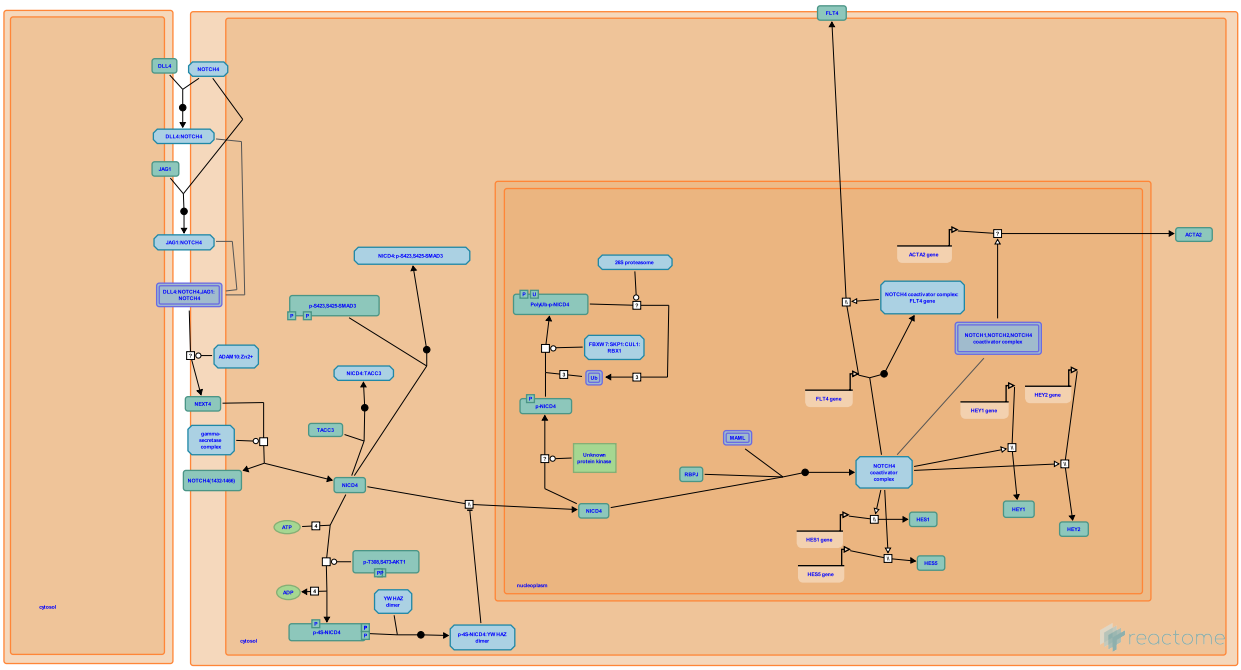
Editions

2004-12-15	Authored	Jassal, B.
2004-12-15	Reviewed	Joutel, A.
2017-09-20	Authored, Revised	Orlic-Milacic, M.
2017-10-30	Reviewed	Haw, R.
2017-11-02	Edited	Orlic-Milacic, M.

Signaling by NOTCH4 ↗

Location: Signaling by NOTCH

Stable identifier: R-HSA-9013694



The NOTCH4 gene locus was discovered as a frequent site of insertion for the proviral genome of the mouse mammary tumor virus (MMTV) (Gallahan and Callahan 1987). MMTV-insertion results in aberrant expression of the mouse mammary tumor gene int-3, which was subsequently discovered to represent the intracellular domain of Notch4 (Robbins et al. 1992, Uyttendaele et al. 1996).

NOTCH4 is prevalently expressed in endothelial cells (Uyttendaele et al. 1996). DLL4 and JAG1 act as ligands for NOTCH4 in human endothelial cells (Shawber et al. 2003, Shawber et al. 2007), but DLL4- and JAG1-mediated activation of NOTCH4 have not been confirmed in all cell types tested (Aste-Amezaga et al. 2010, James et al. 2014). The gamma secretase complex cleaves activated NOTCH4 receptor to release the intracellular domain fragment (NICD4) (Saxena et al. 2001, Das et al. 2004). NICD4 traffics to the nucleus where it acts as a transcription factor and stimulates expression of NOTCH target genes HES1, HES5, HEY1 and HEY2, as well as VEGFR3 and ACTA2 (Lin et al. 2002, Raafat et al.2004, Tsunematsu et al. 2004, Shawber et al. 2007, Tang et al. 2008, Bargo et al. 2010). NOTCH4 signaling can be downregulated by AKT1 phosphorylation-induced cytoplasmic retention (Ramakrishnan et al. 2015) as well as proteasome-dependent degradation upon FBXW7-mediated ubiquitination (Wu et al. 2001, Tsunematsu et al. 2004).

NOTCH4 was reported to inhibit NOTCH1 signaling in-cis, by binding to NOTCH1 and interfering with the S1 cleavage of NOTCH1, thus preventing production of functional NOTCH1 heterodimers at the cell surface (James et al. 2014).

NOTCH4 is involved in development of the vascular system. Overexpression of constitutively active Notch4 in mouse embryonic vasculature results in abnormal vessel structure and patterning (Uyttendaele et al. 2001). NOTCH4 may act to inhibit apoptosis of endothelial cells (MacKenzie et al. 2004).

Expression of int-3 interferes with normal mammary gland development in mice and promotes tumorigenesis. The phenotype of mice expressing int-3 in mammary glands is dependent on the presence of Rbpj (Raafat et al. 2009). JAG1 and NOTCH4 are upregulated in human ER+ breast cancers resistant to anti-estrogen therapy, which correlates with elevated expression of NOTCH target genes HES1, HEY1 and HEY2, and is associated with increased population of breast cancer stem cells and distant metastases (Simoes et al. 2015). Development of int-3-induced mammary tumours in mice depends on Kit and Pdgfra signaling (Raafat et al. 2006) and on int-3-induced activaton of NFKB signaling (Raafat et al. 2017). In head and neck squamous cell carcinoma (HNSCC), high NOTCH4 expression correlates with elevated HEY1 levels, increased cell proliferation and survival, epithelial-to-mesenchymal transition (EMT) phenotype and cisplatin resistance (Fukusumi et al. 2018). In melanoma, however, exogenous NOTCH4 expression correlates with mesenchymal-to-epithelial-like transition and reduced invasiveness (Bonyadi Rad et al. 2016). NOTCH4 is frequently overexpressed in gastric cancer. Increased NOTCH4 levels correlate with activation of WNT signaling and gastric cancer progression (Qian et al. 2015).

NOTCH4 is expressed in adipocytes and may promote adipocyte differentiation (Lai et al. 2013).

During Dengue virus infection, DLL1, DLL4, NOTCH4 and HES1 are upregulated in interferon-beta (INFB) dependent manner (Li et al. 2015). NOTCH4 signaling may be affected by Epstein-Barr virus (EBV) infection, as the EBV protein BARF0 binds to NOTCH4 (Kusano and Raab-Traub 2001).

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Rossant, J., Kitajewski, J., Uyttendaele, H., Ho, J. (2001). Vascular patterning defects associated with expression of activated Notch4 in embryonic endothelium. *Proc. Natl. Acad. Sci. U.S.A., 98*, 5643-8.

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Editions

2004-12-15	Authored	Jassal, B.
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