Signaling by NOTCH3

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This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the Reactome Textbook.

12/11/2022


**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**


Reactome database release: 82

This document contains 3 pathways (see Table of Contents)
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 epithelial to mesenchymal 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).

**Literature references**


**Editions**

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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).

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In the nucleus, NICD3 forms a complex with RBPJ (CBF1, CSL) and MAML (mastermind) proteins MAML1, MAML2 or MAML3 (possibly also MAMLD1). NICD3:RBPJ:MAML complex, also known as the NOTCH3 coactivator complex, activates transcription from RBPJ-binding promoter elements (Lin et al. 2002). While NOTCH1 prefers paired RBPJ binding sites, NOTCH3 preferentially binds to single RBPJ binding sites (Ong et al. 2006).


NOTCH3 positively regulates transcription of the pre-T-cell receptor alpha chain (PTCRA, commonly known as pT-alpha or pre-TCRalpha) (Talora et al. 2003, Bellavia et al. 2007). IK1, splicing isoform of the transcription factor Ikaros (IKZF1), competes with RBPJ for binding to the PTCRA promoter and inhibits PTCRA transcription. NOTCH3, through pre-TCR signaling, stimulates expression of the RNA binding protein HuD, which promotes splicing of IKZF1 into dominant negative isoforms. These dominant negative isoforms of IKZF1 heterodimerize with IK1, preventing its binding to target DNA sequences and thus contributing to sustained transcription of PTCRA (Bellavia et al. 2007, reviewed by Bellavia, Mecarrozzi, Campese, Grazioli, Gulino and Screpanti 2007).

NOTCH3-triggered pre-TCR-signaling downregulates the activity of the transcription factor TCF3 (E2A), through ERK-dependent induction of ID1. Inhibition of TCF3-mediated transcription downstream of NOTCH3 contributes to development of T-cell lymphomas in transgenic mice expressing NICD3 (Talora...
et al. 2003). Activation of ERKs downstream of NOTCH3-stimulated pre-TCR signaling leads to phosphorylation of the transcription factor TAL1, formation of the TAL1:SP1 complex, and activation of cyclin D1 (CCND1) transcription, which stimulates cell division (Talora et al. 2006).

NOTCH3 signaling can activate NF-kappaB (NFKB)-mediate transcription either indirectly, through activation of pre-TCR signaling, or directly, through association of NOTCH3 with IKKα. NFKB is constitutively active in T lymphoma cells derived from NOTCH3 transgenic mice (Vacca et al. 2006).

Transcription of the PLXND1 gene, encoding the semaphorin receptor Plexin D1, is directly stimulated by NOTCH1 and NOTCH3 coactivator complexes. PLXND1 is involved in neuronal migration and cancer cell invasiveness (Rehman et al. 2016). Expression of FABP7 (BLBP) in radial glia is positively regulated by NOTCH1 and NOTCH3 during neuronal migration (Anthony et al. 2005, Keilani and Sugaya 2008).

NOTCH3 gene is frequently amplified in ovarian cancer (Park et al. 2006). NOTCH3 coactivator complex directly stimulates DLGAP5 transcription. DLGAP5 is involved in G2/M transition and is overexpressed in ovarian cancer cells. (Chen et al. 2012). Another gene overexpressed in ovarian cancer whose transcription is directly stimulated by NOTCH3 is PBX1 (Park et al. 2008). The NOTCH3 coactivator complex directly stimulates WWC1 gene transcription. WWC1 gene encodes protein Kibra, involved in Hippo signaling. NOTCH3-mediated induction of WWC1 positively regulates Hippo signaling and inhibits epithelial-to-mesenchymal transition (EMT) in triple negative breast cancer cells (Zhang et al. 2016).

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