NOTCH2 Activation and Transmission of Signal to the Nucleus

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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.

31/10/2022
**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**


Reactome database release: 82

This document contains 1 pathway and 11 reactions (see Table of Contents)
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**


**Editions**

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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**


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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-NOTCH2 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


## Editions

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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

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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

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)