Signaling by NOTCH1

D'Eustachio, P., Egan, SE., Haw, R., Orlic-Milacic, M.

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

The contents of this document may be freely copied and distributed in any media, provided the authors, plus the institutions, are credited, as stated under the terms of Creative Commons Attribution 4.0 International (CC BY 4.0) License. For more information see our license.

29/03/2019
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: 68

This document contains 3 pathways (see Table of Contents)

https://www.reactome.org
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.

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011-11-14</td>
<td>Authored</td>
<td>Egan, SE., Orlic-Milacic, M.</td>
</tr>
<tr>
<td>2012-02-06</td>
<td>Reviewed</td>
<td>Haw, R.</td>
</tr>
<tr>
<td>2012-02-07</td>
<td>Edited</td>
<td>D'Eustachio, P.</td>
</tr>
<tr>
<td>2012-02-11</td>
<td>Edited</td>
<td>Orlic-Milacic, M.</td>
</tr>
</tbody>
</table>
Activated NOTCH1 Transmits Signal to the Nucleus

Location: Signaling by NOTCH1

Stable identifier: R-HSA-2122948

Compartments: plasma membrane, cytosol, nucleoplasm

Mature NOTCH1 heterodimer on the cell surface is activated by one of its ligands: DLL1 (Cordle et al. 2008, Jarriault et al. 1998), DLL4 (Benedito et al. 2009), JAG1 (Li et al. 1998, Benedito et al. 2009) or JAG2 (Luo et al. 1997, Shimizu et al. 2000), expressed in trans on a neighboring cell. Thus, a ligand-expressing cell is a signal-sending cell, while the NOTCH1 expressing cell is a signal-receiving cell. If NOTCH1 has undergone Fringe modification in the Golgi, it is preferentially activated by Delta ligands (Yang et al. 2005), DLL1 and DLL4.

Upon binding to NOTCH1 on a neighboring cell, NOTCH ligands are ubiquitinated by Mindbomb (MIB1 and MIB2) and/or Neuralized (NEURL and NEURL1B) E3 ubiquitin ligases and endocytosed (Koo et al. 2007, Koo et al. 2005, Itoh et al. 2003, Lai et al. 2001, Koutelou et al. 2008, Song et al. 2006). Endocytosis of ubiquitinated ligands is thought to mechanically stretch the bound NOTCH1 receptor, exposing a cleavage site S2 that is recognized by ADAM10 and/or ADAM17 metalloprotease (van Tetering et al. 2009, Brou et al. 2000, Hartmann et al. 2002, Pan et al. 1997). S2 cleavage of NOTCH1 produces the NEXT1 fragment which is further cleaved at an S3 cleavage site by the gamma-secretase complex, resulting in release of the NOTCH1 intracellular domain (NICD1) into the cytosol (de Strooper et al. 1999, Schroeter et al. 1998, Huppert et al. 2000). NICD1 produced by activation of NOTCH1 in response to in trans presented Delta and Jagged ligands (DLL/JAG) traffics to the nucleus where it acts as a transcription regulator.

NOTCH1 signaling can also be activated by ligands other than DLL1, DLL4, JAG1 and JAG2.CNTN1 (Contactin-1), transiently expressed during central and peripheral nervous system development, activates NOTCH1 and NOTCH2 in trans, promoting oligodendrocyte maturation and myelination (Hu et al. 2003). DNER (Delta and Notch-like epidermal growth factor-related receptor) is a transmembrane protein spe-
specifically expressed in dendrites and cell bodies of postmitotic neurons. Activation of NOTCH1 by DNER in trans may play an important role in development of the central nervous system by influencing differentiation of astrocytes (Eiraku et al. 2005). Activation of NOTCH1 by both CNTN1 and DNER is Deltex (DTX)-dependent and results in gamma-secretase mediated release of NICD1. Three members of the Deltex protein family: DTX1, DTX2 and DTX4 possess a domain involved in binding cdc10/ankyrin repeats of NOTCH. DTX proteins are considered as positive regulators of NOTCH signaling, although the exact mechanism has not been elucidated (Matsuno et al. 1998, Kishi et al. 2001). In addition, DTX can mediate downregulation of NOTCH signaling by recruiting non-visual beta-arrestins to NOTCH (Mukherjee et al. 2005), thereby trigerring NOTCH ubiquitination. DTX proteins are negatively regulated by ITCH (AIP4) ubiquitin ligase (Chastagner et al. 2006).

NOTCH1 signaling in the signal-receiving cell can be turned off in cis by expression of NOTCH ligands DLL/JAG (Cordle et al. 2008, Sprinzak et al. 2010), as well as DLK1 (Baladron et al. 2005, Bray et al. 2008). Formation of NOTCH1:ligand complexes in cis prevents interaction of NOTCH1 with ligands expressed in trans, resulting in the inhibition of NOTCH signaling. In the signal-sending cell, NOTCH signaling can be negatively regulated by the protein NUMB, which is asymmetrically distributed during cell division (Rhyu et al. 1994). NUMB recruits ITCH ubiquitin ligase to NOTCH1 and promotes sorting of NOTCH1 through late endosomes for degradation (McGill et al. 2009, Chastagner et al. 2008).

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
<th>Editor</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011-11-14</td>
<td>Authored</td>
<td>Egan, SE.</td>
<td>Orlic-Milacic, M.</td>
</tr>
<tr>
<td>2012-02-06</td>
<td>Reviewed</td>
<td>Haw, R.</td>
<td></td>
</tr>
<tr>
<td>2012-02-07</td>
<td>Edited</td>
<td>D’Eustachio, P.</td>
<td></td>
</tr>
<tr>
<td>2012-02-11</td>
<td>Edited</td>
<td>Orlic-Milacic, M.</td>
<td></td>
</tr>
</tbody>
</table>
NICD1 produced by activation of NOTCH1 in response to Delta and Jagged ligands (DLL/JAG) presented in trans, traffics to the nucleus where it acts as a transcription regulator. In the nucleus, NICD1 displaces the NCOR corepressor complex from RBPJ (CSL). When bound to the co-repressor complex that includes NCOR proteins (NCOR1 and NCOR2) and HDAC histone deacetylases, RBPJ (CSL) represses transcription of NOTCH target genes (Kao et al. 1998, Zhou et al. 2000, Perissi et al. 2004, Perissi et al. 2008). Once the co-repressor complex is displaced, NICD1 recruits MAML (mastermind-like) to RBPJ, while MAML recruits histone acetyltransferases EP300 (p300) and PCAF, resulting in formation of the NOTCH coactivator complex that activates transcription from NOTCH regulatory elements. The minimal functional NOTCH coactivator complex that activates transcription from NOTCH regulatory elements is a heterotrimer composed of NICD, MAML and RBPJ (Fryer et al. 2002, Wallberg et al. 2002, Nam et al. 2006).


After NOTCH1 coactivator complex is assembled on a NOTCH-responsive promoter, MAML (mastermind-like) recruits CDK8 in complex with cyclin C, triggering phosphorylation of conserved serine
residues in TAD and PEST domains of NICD1 by CDK8. Phosphorylated NICD1 is recognized by the E3 ubiquitin ligase FBXW7 which ubiquitinates NICD1, leading to degradation of NICD1 and downregulation of NOTCH1 signaling. FBXW7-mediated ubiquitination and degradation of NOTCH1 depend on C-terminally located PEST domain sequences in NOTCH1 (Fryer et al. 2004, Oberg et al. 2001, Wu et al. 2001). The PEST domain of NOTCH1 and the substrate binding WD40 domain of FBXW7 are frequent targets of mutations in T-cell acute lymphoblastic leukemia - T-ALL (Welcker and Clurman 2008).

NICD1, which normally has a short half-life, can be stabilized by binding to the hypoxia-inducible factor 1-alpha (HIF1A) which accumulates in the nucleus when oxygen levels are low. This results in HIF1A-induced inhibition of cellular differentiation that is NOTCH-dependent (Gustafsson et al. 2005).

**Literature references**


# Table of Contents

- Introduction  
  - Signaling by NOTCH1  
    - Activated NOTCH1 Transmits Signal to the Nucleus  
    - NOTCH1 Intracellular Domain Regulates Transcription

Table of Contents