Negative regulation of NOTCH4 signaling

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.

19/07/2019
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: 69

This document contains 1 pathway and 6 reactions (see Table of Contents)
NOTCH4 signaling can be negatively regulated at the level of nuclear translocation of the NOTCH4 intracellular domain fragment (NICD4). AKT-mediated phosphorylation of NICD4 promotes binding of NICD4 with 14-3-3-zeta (YWHAZ), leading to retention of NICD4 in the cytosol (Ramakrishnan et al. 2015).

The E3 ubiquitin ligase FBXW7, a component of the SCF ubiquitin ligase complex, binds to and ubiquitinates phosphorylated NICD4, targeting it for proteasome-mediated degradation (Wu et al. 2001). The level of NICD4 is significantly increased in Fbxw7 knockout mouse embryos, which die in utero and have impaired development of the vascular system (Tsunematsu et al. 2004).

Binding of NOTCH4 to ELOC (elongin C) is involved in proteasome-mediated degradation of NOTCH4, but the exact mechanism has not been elucidated (Cummins et al. 2011). MDM2, a TP53-induced ubiquitin ligase, was reported to ubiquitinate NICD4 and target it for degradation in response to TP53 activation (Sun et al. 2011).

NOTCH4 signaling is inhibited by binding of NICD4 to the transforming acidic coiled-coil protein-3, but the mechanism is not known (Bargo et al. 2010).

**Literature references**


### Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2018-04-06</td>
<td>Authored</td>
<td>Orlic-Milacic, M.</td>
</tr>
<tr>
<td>2018-05-01</td>
<td>Reviewed</td>
<td>Haw, R.</td>
</tr>
<tr>
<td>2018-05-09</td>
<td>Edited</td>
<td>Orlic-Milacic, M.</td>
</tr>
</tbody>
</table>
AKT1 phosphorylates NOTCH4

**Location:** Negative regulation of NOTCH4 signaling

**Stable identifier:** R-HSA-9604328

**Type:** transition

**Compartments:** cytosol

Recombinant human AKT1 phosphorylates recombinant human NICD4 on four AKT-target sites conserved in primates: S1495, S1847, S1865 and S1917 (Ramakrishnan et al. 2015).

**Followed by:** p-4S-NICD4 binds YWHAZ

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2018-04-06</td>
<td>Authored</td>
<td>Orlic-Milacic, M.</td>
</tr>
<tr>
<td>2018-05-01</td>
<td>Reviewed</td>
<td>Haw, R.</td>
</tr>
<tr>
<td>2018-05-09</td>
<td>Edited</td>
<td>Orlic-Milacic, M.</td>
</tr>
</tbody>
</table>
AKT1-mediated phosphorylation of NOTCH4 intracellular domain fragment NICD4 leads to binding of NICD4 to 14-3-3-zeta (YWHAZ). Binding to YWHAZ sequesters NICD4 to the cytosol, preventing its trafficking to the nucleus, and thus negatively regulates NOTCH4 signaling (Ramakrishnan et al. 2015).

**Preceded by:** AKT1 phosphorylates NOTCH4

**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2018-04-06</td>
<td>Authored</td>
<td>Orlic-Milacic, M.</td>
</tr>
<tr>
<td>2018-05-01</td>
<td>Reviewed</td>
<td>Haw, R.</td>
</tr>
<tr>
<td>2018-05-09</td>
<td>Edited</td>
<td>Orlic-Milacic, M.</td>
</tr>
</tbody>
</table>
**Unknown kinase phosphorylates NICD4**

**Location:** Negative regulation of NOTCH4 signaling

**Stable identifier:** R-HSA-9604606

**Type:** uncertain

**Compartments:** nucleoplasm

**Inferred from:** Unknown protein kinase phosphorylates mouse NICD4 (Mus musculus)

---

Unknown protein kinase phosphorylates the C-terminus of NICD4 (NOTCH4 intracellular domain fragment) (Wu et al. 2001).

**Followed by:** FBXW7 promotes ubiquitination of p-NICD4

---

**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2018-04-06</td>
<td>Authored</td>
<td>Orlic-Milacic, M.</td>
</tr>
<tr>
<td>2018-05-01</td>
<td>Reviewed</td>
<td>Haw, R.</td>
</tr>
<tr>
<td>2018-05-09</td>
<td>Edited</td>
<td>Orlic-Milacic, M.</td>
</tr>
</tbody>
</table>
FBXW7 promotes ubiquitination of p-NICD4

**Location:** Negative regulation of NOTCH4 signaling

**Stable identifier:** R-HSA-9604629

**Type:** transition

**Compartments:** nucleoplasm

**Inferred from:** FBXW7 promotes ubiquitination of mouse p-NICD4 (Homo sapiens)

The E3 ubiquitin ligase FBXW7, a component of the SCF ubiquitin ligase complex, binds to and ubiquitinates phosphorylated NICD4 (NOTCH4 intracellular domain fragment), targeting it for proteasome-mediated degradation (Wu et al. 2001). The level of NICD4 is significantly increased in Fbxw7 knockout mouse embryos, which die in utero and have impaired development of the vascular system (Tsunematsu et al. 2004). Notch4 level also increases when Fbxw7 is downregulated by RNA in mouse embryonic fibroblasts (Mao et al. 2004).

**Preceded by:** Unknown kinase phosphorylates NICD4

**Followed by:** Proteasome degrades ubiquitinated NICD4

**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2018-04-06</td>
<td>Authored</td>
<td>Orlic-Milacic, M.</td>
</tr>
<tr>
<td>2018-05-01</td>
<td>Reviewed</td>
<td>Haw, R.</td>
</tr>
<tr>
<td>2018-05-09</td>
<td>Edited</td>
<td>Orlic-Milacic, M.</td>
</tr>
</tbody>
</table>
Proteasome degrades ubiquitinated NICD4

Location: Negative regulation of NOTCH4 signaling

Stable identifier: R-HSA-9604642

Type: uncertain

Compartments: nucleoplasm

Inferred from: Proteasome degrades ubiquitinated mouse NICD4 (Homo sapiens)

FBXW7-mediated ubiquitination targets NICD4 (NOTCH4 intracellular domain fragment) for proteasome-mediated degradation (Wu et al. 2001).

Preceded by: FBXW7 promotes ubiquitination of p-NICD4

Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2018-04-06</td>
<td>Authored</td>
<td>Orlic-Milacic, M.</td>
</tr>
<tr>
<td>2018-05-01</td>
<td>Reviewed</td>
<td>Haw, R.</td>
</tr>
<tr>
<td>2018-05-09</td>
<td>Edited</td>
<td>Orlic-Milacic, M.</td>
</tr>
</tbody>
</table>
NICD4 binds to TACC3

**Location:** Negative regulation of NOTCH4 signaling

**Stable identifier:** R-HSA-9604675

**Type:** binding

**Compartments:** cytosol

**Inferred from:** NICD4 binds Tacc3 (Mus musculus)

Based on studies in mice, the intracellular domain of NOTCH4, NICD4, binds to transforming acidic coiled-coil protein-3 (TACC3). TACC3 is implicated as a negative regulator of NOTCH4 signaling and may compete with NICD4 binding to RBPJ (Bargo et al. 2010).

**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2018-04-06</td>
<td>Authored</td>
<td>Orlic-Milacic, M.</td>
</tr>
<tr>
<td>2018-05-01</td>
<td>Reviewed</td>
<td>Haw, R.</td>
</tr>
<tr>
<td>2018-05-09</td>
<td>Edited</td>
<td>Orlic-Milacic, M.</td>
</tr>
</tbody>
</table>
Table of Contents

Introduction 1

- Negative regulation of NOTCH4 signaling 2
  - AKT1 phosphorylates NOTCH4 4
  - p-4S-NICD4 binds YWHAZ 5
  - Unknown kinase phosphorylates NICD4 6
  - FBXW7 promotes ubiquitination of p-NICD4 7
  - Proteasome degrades ubiquitinated NICD4 8
  - NICD4 binds to TACC3 9

Table of Contents 10