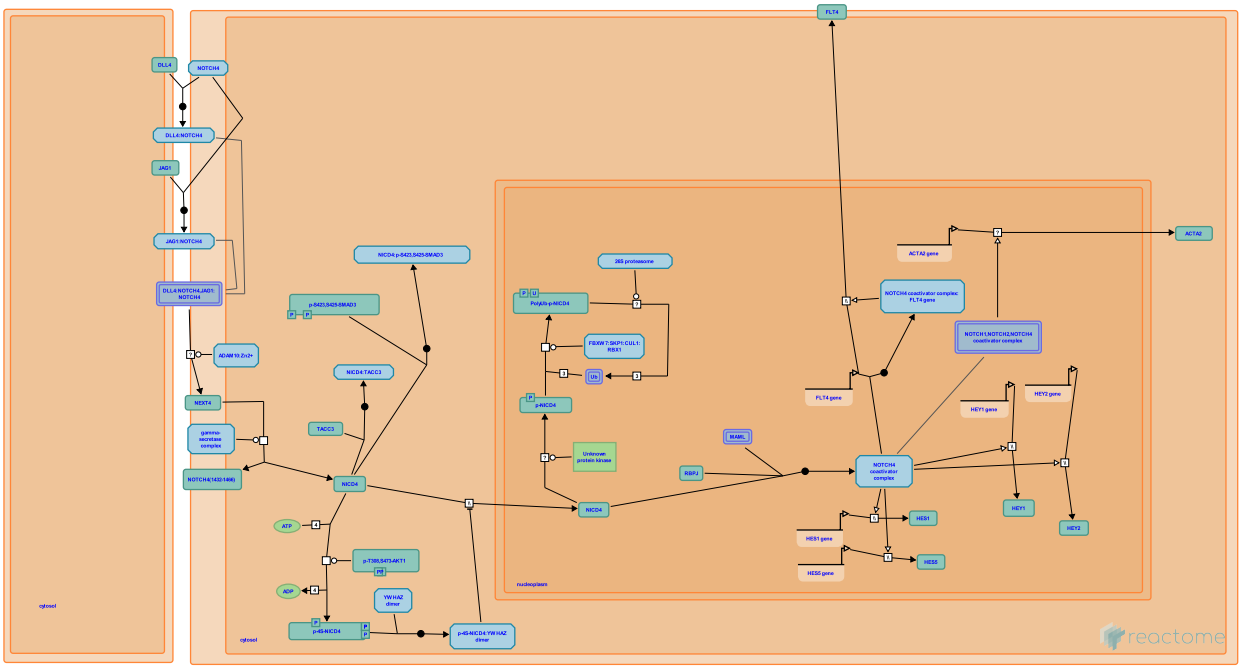
Signaling by NOTCH4



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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.

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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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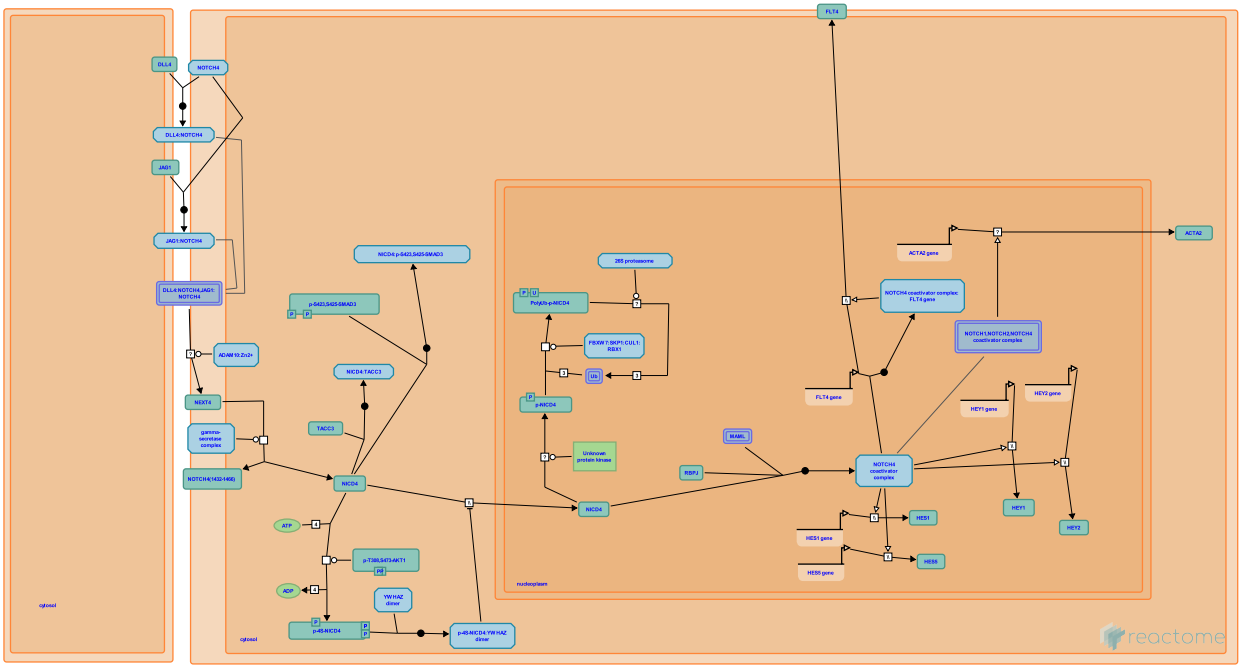
Signaling by NOTCH4 ↗

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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Editions

2004-12-15	Authored	Jassal, B.
2004-12-15	Reviewed	Joutel, A.
2012-02-11	Edited	Orlic-Milacic, M.
2018-04-05	Authored, Revised	Orlic-Milacic, M.
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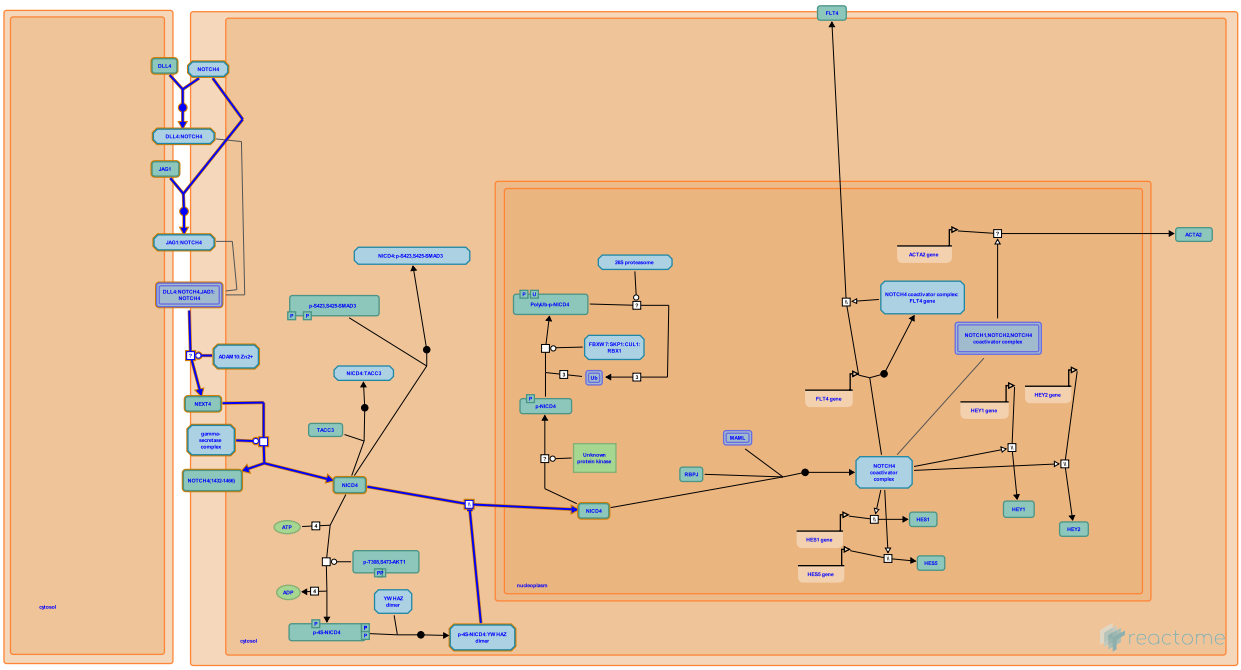
NOTCH4 Activation and Transmission of Signal to the Nucleus ↗

Location: Signaling by NOTCH4

Stable identifier: R-HSA-9013700



NOTCH4 is co-expressed with DLL4 (Delta-4) and JAG1 (Jagged-1) in the vascular system (Shutter et al. 2000, Uyttendaele et al. 2000). NOTCH4 can be activated by DLL4 and JAG1 when HMVECd cells (human primary endothelial cell line derived from neonatal dermal microvasculature) or HUVEC cells (human umbilical venous endothelial cell line) expressing recombinant mouse Notch4 are co-cultured with HMVECd or HUVEC cells expressing recombinant human or mouse DLL4 (Shawber et al. 2003, Shawber et al. 2007) or mouse Jag1 (Shawber et al. 2007). Activation of NOTCH4 by DLL4 and JAG1 could not be reproduced when the mouse fibroblast cell line NIH 3T3 or human embryonic kidney cell line HEK293 was transduced with Notch4- or either Dll4- or Jag1-expressing vectors and used in co-culture experiments (Aste-Amezaga et al. 2010, James et al. 2014).

Signaling by NOTCH4, similar to other NOTCH family proteins, involves proteolytic cleavage of the membrane-bound NOTCH4 receptor and release of the NOTCH4 intracellular domain fragment (NICD4) into the cytosol (Saxena et al. 2001, Das et al. 2004). NICD4 traffics from the cytosol to the nucleus, where it acts as a transcription factor (Lin et al. 2002).

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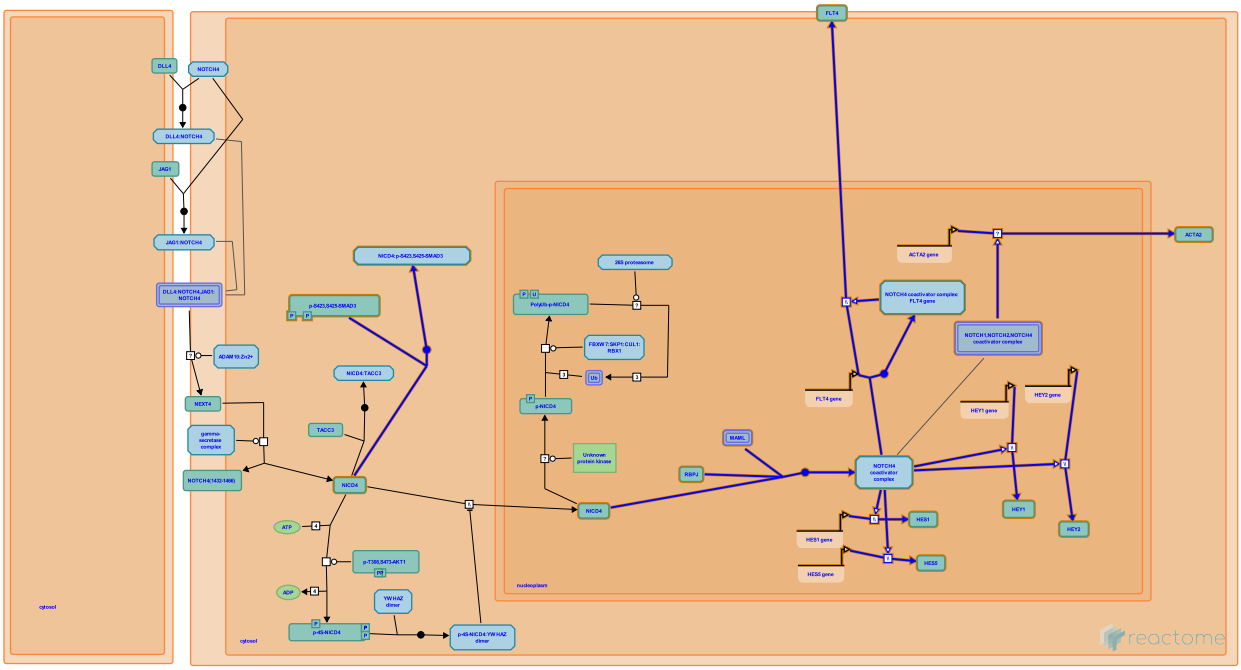
NOTCH4 Intracellular Domain Regulates Transcription ↗

Location: Signaling by NOTCH4

Stable identifier: R-HSA-9013695



In the nucleus, NOTCH4 intracellular domain fragment (NICD4) binds transcription factors RBPJ (CSL) and mastermind family members (MAML1, MAML2 or MAML3) to form the NOTCH4 co-activator complex (Lin et al. 2002). The NOTCH4 coactivator complex stimulates transcription of well-established NOTCH targets HES1, HES5, HEY1 and HEY2 in a cellular context-dependent manner (Lin et al. 2002, Raafat et al.2004, Tsunematsu et al. 2004, Bargo et al. 2010). NOTCH4 also stimulates transcription of the FLT4 (VEGFR3) gene, encoding vascular endothelial growth factor receptor-3 (Shawber et al. 2007) and ACTA2 gene, encoding smooth muscle alpha actin (Tang et al. 2008).

NICD4 inhibits TGF-beta-induced SMAD-mediated transcription via binding of NICD4 to TGF-beta activated SMAD3 (Sun et al. 2005, Grabias and Konstantopoulos 2013).

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Negative regulation of NOTCH4 signaling ↗

Location: Signaling by NOTCH4

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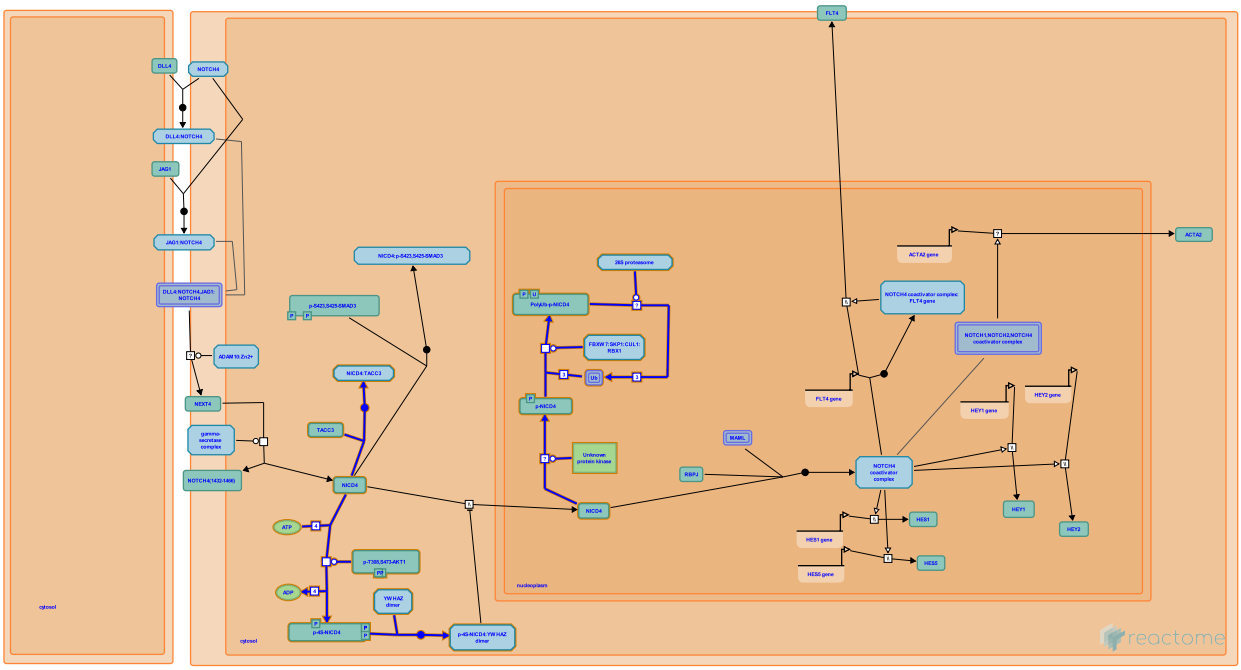

NOTCH4 signaling can be negatively regulated at the level of nuclear translocation of the NOTCH4 intracellular domain fragment (NICD4). AKT-mediated phosphorylation of NICD4 promotes binding of NICD4 with 14-3-3-zeta (YWHAZ), leading to retention of NICD4 in the cytosol (Ramakrishnan et al. 2015).

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 he mechanism is not known (Bargo et al. 2010).

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Table of Contents