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 6 pathways (see Table of Contents)
Human NOTCH1 was cloned as a chromosome 9 gene, translocated to the T-cell beta receptor (TCBR) promoter on chromosome 7 in T-cell acute lymphoblastic leukemia (T-ALL) (Ellisen et al. 1991). This translocation, present in only a small percentage of T-ALL patients, results in the overexpression of a truncated NOTCH1 receptor, which lacks almost the entire extracellular domain, in T lymphocytes. Oncogenic NOTCH1 mutations were subsequently found to be present in >50% of T-ALL patients, with hot-spots in the heterodimerization domain (HD domain) and PEST domain of NOTCH1 (Weng et al. 2004).

Normal NOTCH1 becomes activated by binding DLL (DLL1 or DLL4) or JAG (JAG1 or JAG2) ligands expressed on the surface of a neighboring cell, which leads to proteolytic cleavage of NOTCH1 by ADAM10/17 and gamma-secretase, and release of the NOTCH1 intracellular domain (NICD1) which regulates expression of genes that play important roles in the development of T lymphocytes (Washburn et al. 1997, Radtke et al. 1999, Maillard et al. 2004, Sambandam et al. 2005, Tan et al. 2005). Mutations in the HD domain, responsible for association of NOTCH1 extracellular and transmembrane regions after furin-mediated cleavage of NOTCH1 precursor, as well as the truncation of the NOTCH1 extracellular domain by the rare T-ALL translocation, enable constitutive production of NICD1, in the absence of ligand binding (Malecki et al. 2006, Ellisen et al. 1991).

Mutations in the NOTCH1 PEST domain interfere with FBXW7 (FBW7)-mediated ubiquitination and degradation of NICD1, resulting in prolonged half-life and increased transcriptional activity of NICD1, which promotes growth and division of T-lymphocytes (Weng et al. 2004, Thompson et al. 2007, O'Neil et al. 2007).

Mutations in the HD domain and PEST domain of NOTCH1 are frequently found in cis in T-ALL. While HD mutations alone result in up to ~10-fold increase in NOTCH1 transcriptional activity and PEST domain mutations alone result in up to ~2-fold increase in NOTCH1 transcriptional activity, in cis mutations of HD and PEST domains act synergistically, increasing NOTCH1 transcriptional activity up to ~40-fold (Weng et al. 2004).
FBXW7 (FBW7), a component of the SCF (SKP1, CUL1, and F-box protein) ubiquitin ligase complex SCF-FBW7 involved in the degradation of NOTCH1 (Oberg et al. 2001, Wu et al. 2001, Fryer et al. 2004), is subject to loss of function mutations in T-ALL (Akhoondi et al. 2007, Thompson et al. 2007, O'Neil et al. 2007) which are mutually exclusive with NOTCH1 PEST domain mutations (Thompson et al. 2007, O'Neil et al. 2007).

Although gamma-secretase inhibitors (GSIs) are successfully used in vitro to inhibit NOTCH1 signaling in T-ALL cell lines, the gamma-secretase complex has many other substrates besides NOTCH. The specificity of GSIs is therefore limited and, as they are not considered to be particularly promising drugs for the clinical treatment of T-ALL (reviewed by Purow, 2012), they have not been annotated.

For a recent review of NOTCH1 signaling in cancer, please refer to Grabher et al. 2006.

**Literature references**


**Editions**

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Signaling by NOTCH1 t(7;9)(NOTCH1:M1580_K2555) Translocation Mutant

**Location:** Signaling by NOTCH1 in Cancer

**Stable identifier:** R-HSA-2660825

**Diseases:** cancer, T-cell leukemia

Human NOTCH1 was cloned as a chromosome 9 gene, translocated to the T-cell beta receptor (TCBR) promoter on chromosome 7 in T-cell acute lymphoblastic leukemia (T-ALL) (Ellisen et al. 1991). The translocated gene was found to be homologous to Drosophila Notch, and was initially named TAN-1 (translocation-associated Notch homolog). Although the translocation t(7;9)(q34;q34.3) is present in a small percentage of T-ALL patients, the mutant protein is highly oncogenic and its overexpression causes T-ALL-like illness in mice (Pear et al. 1996).

**Literature references**


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https://reactome.org
NOTCH1 heterodimerization domain mutations are frequently found in T-cell acute lymphoblastic leukemia (T-ALL) (Weng et al. 2004) and result in constitutive activity of NOTCH1 mutants (Malecki et al. 2006).

**Literature references**


NOTCH1 PEST domain mutations are frequently found in T-cell acute lymphoblastic leukemia (T-ALL). PEST domain mutations interfere with ubiquitination-mediated NOTCH1 downregulation and result in prolonged half-life of the intracellular NOTCH1 fragment, NICD1, and increased NICD1 transcriptional activity (Weng et al. 2004, Thompson et al. 2007, O'Neil et al. 2007).

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**Literature references**

FBXW7 Mutants and NOTCH1 in Cancer

Location: Signaling by NOTCH1 in Cancer

Stable identifier: R-HSA-2644605

Diseases: cancer

FBXW7 (FBW7) is a component of the SCF (SKP1, CUL1, and F-box protein) ubiquitin ligase complex SCF-FBW7 which is involved in the degradation of NOTCH1 (Oberg et al. 2001, Wu et al. 2001, Fryer et al. 2004). Loss of function mutations in FBXW7 are frequently found in T-cell acute lymphoblastic leukemia (Akhoondi et al. 2007, Thompson et al. 2007, O’Neil et al. 2007) and are mutually exclusive with NOTCH1 PEST domain mutations (Thompson et al. 2007, O’Neil et al. 2007).

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