Pre-NOTCH Processing in Golgi

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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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Literature references


Reactome database release: 72

This document contains 1 pathway and 8 reactions (see Table of Contents)

Processing of mammalian NOTCH precursors in the Golgi typically involves the cleavage by FURIN convertase. Pre-NOTCH is a ~300 kDa protein, and cleavage by FURIN produces two fragments with approximate sizes of 110 kDa and 180 kDa. The 110 kDa fragment contains the transmembrane and intracellular domains of NOTCH and is known as NTM or NTMICD. The 189 kDa fragment contains NOTCH extracellular sequence and is known as NEC or NECD. The NTM and NEC fragments heterodimerize (Blaumueller et al. 1997, Logeat et al. 1998, Chan et al. 1998) and are held together by disulfide bonds and calcium ions (Rand et al. 2000, Gordon et al. 2009).

An optional step in Pre-NOTCH processing in the Golgi is modification by fringe enzymes. Fringe enzymes are glycosyl transferases that initiate elongation of O-linked fucose on fucosylated peptides by addition of a beta 1,3 N-acetylg glucosaminyl group, resulting in formation of disaccharide chains on NOTCH EGF repeats (GlcNAc-beta1,3-fucitol). Three fringe enzymes are known in mammals: LFNG (lunatic fringe), MFNG (manic fringe) and RFNG (radical fringe). LFNG shows the highest catalytic activity in
modifying NOTCH (Bruckner et al. 2000, Moloney et al. 2000). Fringe-created disaccharide chains on NOTCH EGF repeats are further extended by B4GALT1 (beta-1,4-galactosyltransferase 1), which adds galactose to the N-acetylgalcosaminyl group, resulting in formation of trisaccharide Gal-beta1,4-GlcNAc-beta1,3-fucitol chains (Moloney et al. 2000, Chen et al. 2001). Formation of trisaccharide chains is the minimum requirement for fringe-mediated modulation of NOTCH signaling, although fringe-modified NOTCH expressed on the cell surface predominantly contains tetrasaccharide chains on EGF repeats. The tetrasaccharide chains are formed by sialyltransferase(s) that add sialic acid to galactose, resulting in formation of Sia-alpha2,3-Gal-beta1,4-GlcNAc-beta1,3-fucitol (Moloney et al. 2000). Three known Golgi membrane sialyltransferases could be performing this function: ST3GAL3, ST3GAL4 and ST3GAL6 (Harduin-Lepers et al. 2001). The modification of NOTCH by fringe enzymes modulates NOTCH-signaling by increasing the affinity of NOTCH receptors for delta-like ligands, DLL1 and DLL4, while decreasing affinity for jagged ligands, JAG1 and JAG2.

**Literature references**


**Editions**

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Transport of NOTCH precursor to Golgi

Location: Pre-NOTCH Processing in Golgi

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