

A Brief Summary of Canonical Notch Signalling

Notch is translated as a large, 300kDa protein that must be cleaved at three sites (S1, S2, and S3) in order to activate its downstream targets. It is a cell membrane-bound receptor and its ligands include the membrane-bound proteins Delta and Serrate (in *Drosophila*), or Delta-like and Jagged (in Mammals).

Modifications

The Notch extracellular segment contains many small EGF-like repeat domains which can be modified by the addition of sugars. Multiple enzymes such as POFUT1 glycosylate these domains and are essential for Notch signaling function. Three Fringe proteins, Lunatic Fringe, Manic Fringe, and Radical Fringe add GlcNac groups to Notch, leading to greatly increased signalling of Notch in the presence of the Delta ligand.

Cleavages

The S1 cleavage occurs during the secretory pathway and yields a larger fragment containing most of the extracellular portion and a smaller fragment containing an intracellular domain connected to a short extracellular portion. The two components are non-covalently bound at the cell surface, constituting the inactive repressor. The S2 cleavage occurs in the extracellular region of the membrane-bound component, and depends on extracellular ligand binding. Following this, the entire complex is endocytosed and the S3 cleavage occurs constitutively. The S3 cleavage releases the intracellular Notch domain (NIC), and is dependent on γ -secretase, a macromolecular complex that is well-known for also cleaving the Alzheimer's-related amyloid precursor protein (APP).

Transcriptional Control

The NIC product is transported to the nucleus, where it binds a transcription factor, Suppressor of Hairless (Su(H)) or the vertebrate CBF1. In the absence of NIC, Su(H) represses targets via a histone deacetylase. Binding of NIC downregulates this transcriptional repression and recruits other proteins to a complex that acts as a transcriptional activator. There is evidence that this complex also targets NIC for ubiquitination and subsequent proteasome degradation, providing a built-in check on Notch signalling activation. There is also evidence for a Su(H)-independent pathway that involves the protein Deltex instead. The targets of Notch signalling are quite diverse and context-dependent, as Notch regulates multiple developmental processes and cell fate decisions throughout developmental time.

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AEHVPERLAAGTLVLVLL-PPDQLRNNSFHFLELRELSHVLHTNVVFKRDAQQQMIFFYYGH-BEELRKHPI-KRSTVGWATSSL N1
ASDQPENLAEGTLIIIVLL-PPEQLQDSRSFRLRALGTLTLLHTNLRKQDSQGALMVYPYFGEKSAAMKKQKMTRRS----- N2
ASEVPALLARGVLVLTLL-PPEELLRSADFLQRLSAILRTSLRFRILDARGQAMVFPYHRP----- N3
RPEGEDSEGRPSLALLVLRPPA-LDQQLLALARVLSLTLRVGLWVRKDSSEGRNMVFPYPTRAKEELSGARDSSSWERQAP--- N4
ENKTKSPVLAEGAMSVVMLMNVAFREIQAQFLRNMSHMLRTTVRLKFDALGHDIINWKDNVRVPEIE----- DN

S1 ↓ S2 ↓

LPGTSGGRQRRELDPMDIRGSIIVYLEIDNRQCVQSSSQCFQSA-TDVAAFL--GALASLGSL-NIPYKIEAVKSEFVEPPLPSQL N1
LPEEQEQEQ-----EVIGSKI FLEIDNRQCVQSDSDQCFKN--TDAANAAL---LASHAIQGTLSY--PLVSVFSELESPRNAQ N2
SPG-SESRVRELGP-EVIGSVVMLEIDNRLCLQSAENDHCFPDQAQSAADYL-GALSAVERL-DFPYPLRDVVRGEPLAEPQSV N3
FTQPLKGETESLGAGFVVVMGVDLRRCGPEHPASRCFWDGSLLLRFLAAMAAVGALEPLLPG--PLLAHPQAGTRPPANQLPWP N4
DTDFARKNKILYTOQVHTGIQIYLEIDNRKCTECFTHAVEAA-EFLAATAAKHQLRNDPFQIHSVRGIKNPGDEDNGEFP-ANVK DN

S3 ↓

HLMYVAAAFAVLLFFVCGVLLSRKRR... N1
LLYLLAVAVVILFFILLGVIMAKRKQ... N2
LLPLLAVAGAVLLIIFILGVMVARRRK... N3
ILCSPVGVLLLALGALLVQLIRRRR... N4
YVITGIILVIALAFFGMVLSTQRKRA... DN

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Figure 1: Amino acid alignment of Notch paralogs 1-4 in mouse, and Drosophila (DN). The positions of the three cleavage points, S1-S3, are marked. Taken from Baron 2003.

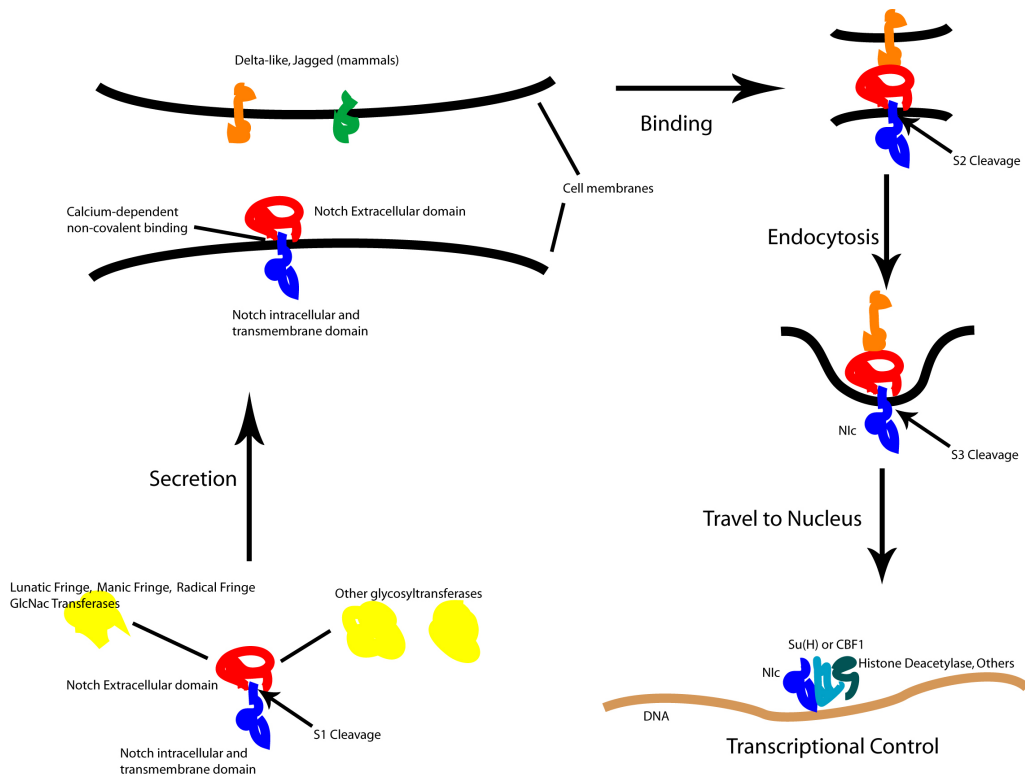


Figure 2: Simplified diagram of Notch signaling mechanism.

Sources

Martin Baron, An overview of the Notch signalling pathway, *Seminars in Cell and Developmental Biology*, Volume 14, Issue 2, Notch Signalling in the Immune System, April 2003, Pages 113-119.

Spyros Artavanis-Tsakonas, Matthew D. Rand, and Robert J. Lake, Notch Signaling: Cell Fate Control and Signal Integration in Development, 30 April 1999 *Science* 284 (5415), 770.

Jeffrey S. Mumm and Raphael Kopan, Notch Signaling: From the Outside In, *Developmental Biology*, Volume 228, Issue 2, 15 December 2000, Pages 151-165.