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Sci. STKE **2006** (364), cm7. [DOI: 10.1126/stke.3642006cm7]

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Notch Signaling Pathway

Matthias Ehebauer, Penelope Hayward, Alfonso Martinez-Arias*

(Published 5 December 2006)

Notch is a receptor that mediates intercellular signaling through a pathway conserved across the metazoa. It is involved in cell fate assignation and pattern formation during development. The receptor acts as a membrane-tethered transcription factor and is activated by members of the Delta, Serrate, Lag-2 family of Notch ligands, which trigger two successive proteolytic cleavages of the receptor. The second cleavage releases the intracellular domain of Notch, which translocates to the nucleus, where it interacts with the CSL family of transcriptional regulators and forms part of a Notch target gene–activating complex. In the absence of signaling, CSL [CBF1, Su(H), Lag-1] regulators repress Notch target genes through interactions with several transcriptional co-repressors that recruit histone deacetylases and other chromatin-modifying enzymes. After forming, the transcription-activating binary Notch intracellular domain–CSL complex recruits several proteins that facilitate transcription, among them the coactivator MAM and histone acetylases. Transcription of target genes is terminated when the Notch intracellular domain is degraded in a proteasome-dependent manner.

This record contains general information about the Notch Signaling Pathway collected across species.

The family of Notch receptors mediates short-range cell interactions primarily involved in binary cell fate decisions during the development of all metazoa. These cell fate decisions can be of two kinds. In one instance, which is similar to a stem cell mode, a cell can adopt a new fate or remain in its original state; in the other instance, which is usually associated with differentiative cell division, the daughter cells can adopt one of two fates. In both instances, Notch activation favors one fate over the other [reviewed in (*1*, *2*)]. This strategy of selection of alternative fates is central to the process generically known as "lateral inhibition," in which a population of cells share a developmental potential but only some of these cells achieve that fate. Cells that adopt the fate activate Notch in surrounding cells to suppress those cells from adopting the same fate.

Notch signaling is also important for boundary induction [reviewed in (*1*, *3*)] and vertebrate segmentation (*4*). In these instances, Notch signaling is used to induce new cell fates rather than to select from two alternative ones. In addition to these activities, Notch displays functional interactions with Wnt signaling in sequential cell fate assignations (*5*). Given the widespread role of Notch in development, it is not surprising that several diseases are associated with mutations in genes encoding Notch receptors and Notch ligand [reviewed in (*6*–*9*)].

Department of Genetics, University of Cambridge, Cambridge CB2 3EH, UK.

*Corresponding author. E-mail, ama11@hermes.cam.ac.uk

The Notch receptor family comprises a group of type I transmembrane proteins with a similar architecture and modular arrangement of domains. A "canonical" Notch receptor consists of a large extracellular domain (NECD) and a somewhat smaller intracellular domain (NICD). The NECD is composed of up to 36 tandemly arranged epidermal growth factor (EGF)–like repeats, followed by three similarly arranged Lin12-Notch (LN) repeats, which are unique to the Notch receptor family. The NICD contains the RBPJk-associated molecule (RAM) region in the juxtamembrane region, followed by seven ankyrin repeats (ANK), a putative transactivating domain (*10*), and a C-terminal PEST motif. The EGF-like repeats contain the receptor's ligand-binding sites (*11*–*13*), whereas the LN repeats are involved in preventing ligand-independent signaling (*14*–*16*). The entire intracellular part of the receptor, the NICD, is involved in relaying signal to the nucleus (*17*–*19*).

Ligands for Notch are members of the DSL (Delta, Serrate, Lag-2) family of transmembrane proteins. All are type I transmembrane proteins containing an N-terminal DSL domain as well as several EGF-like repeats in the extracellular domain, plus a short intracellular domain. Genetic analyses have identified several regions in the Notch extracellular domain that can bind ligand. The best characterized is the Delta- and Serrate-binding site consisting of the Notch EGF-like repeats 11 and 12. These repeats seem sufficient for the interaction with Delta and Serrate (*12*). There is evidence for the existence of another ligand-binding site at EGF repeats 24 to 26 (*13*, *15*).

The Connections Map illustrates the events involved in Notch receptor processing, as well as those involved in transmitting the signal from the receptor to the nucleus to control gene expression (Fig. 1). Notch is translated as a single polypeptide, but upon entering the secretory pathway it is proteolyzed at a site designated S1 by a furin-like protein in trans-Golgi vesicles (*20*, *21*). This produces two polypeptide fragments, one containing most of the extracellular domain and the other containing the small remaining fragment of NECD and the membrane-tethered intracellular domain. These fragments remain noncovalently associated in a Ca^{2+}-dependent manner (*22*). A conserved region C-terminal to the LN repeats and N-terminal to the transmembrane helix seems sufficient for this interaction (*16*).

In addition to this cleavage event, the receptor is glycosylated during its transit through the Golgi, and this modification has important consequences for its signaling competence [reviewed in (*23*)]. Many of Notch's EGF repeats are fucosylated at serine or threonine residues by *O*-fucosyltransferase 1 (O-FucT-1). These fucosylated residues can be further modified by other glycosyltransferases. Fringe is the first of three glycosyltransferases that catalyze the addition of monosaccharides to the fucose moieties on Notch, thus forming longer glycans. These posttranslational modifications have modulatory effects on Notch receptor–Notch ligand interactions. Indeed, Fringe inhibits Notch interactions with Serrate but potentiates interactions with Delta [reviewed in (*23*)]. In vertebrates, most of

the cell surface Notch is the noncovalently associated glycosylated form. In *Drosophila*, cleavage of Notch by furin is not required for function (*24*).

Upon ligand binding, the Notch receptor is sequentially cleaved by two different proteases at sites designated S2 and S3, resulting in the release of the intracellular domain NICD. The cleavage that releases the intracellular domain S3 takes place at a site inside the transmembrane helix and is an event that is analogous to the processing of the amyloid precursor protein (APP), which is associated with Alzheimer's disease and for which regulated intramembrane proteolysis has been demonstrated [reviewed in (*25*)]. The first of the two sequential cleavage steps occurs at the S2 site and is catalyzed by a metalloprotease of the ADAM/TACE/Kuzbanian family (*26–28*). Cleavage at the S2 site releases the extracellular domain from the receptor, leaving behind only the membrane-tethered intracellular domain, and this leads to a ligand-independent cleavage at S3. The second cleavage at S3, in the transmembrane helix, is catalyzed by the γ-secretase activity of the presenilin-nicastrin-Aph1-Pen2 protein complex [reviewed in (*25*)]. This event results in the release of NICD, which can then enter the nucleus, where it interacts directly with members of the CSL [CBF1, Su(H), Lag-1] family of transcription factors and participates in transcription activation [reviewed in (*29*)].

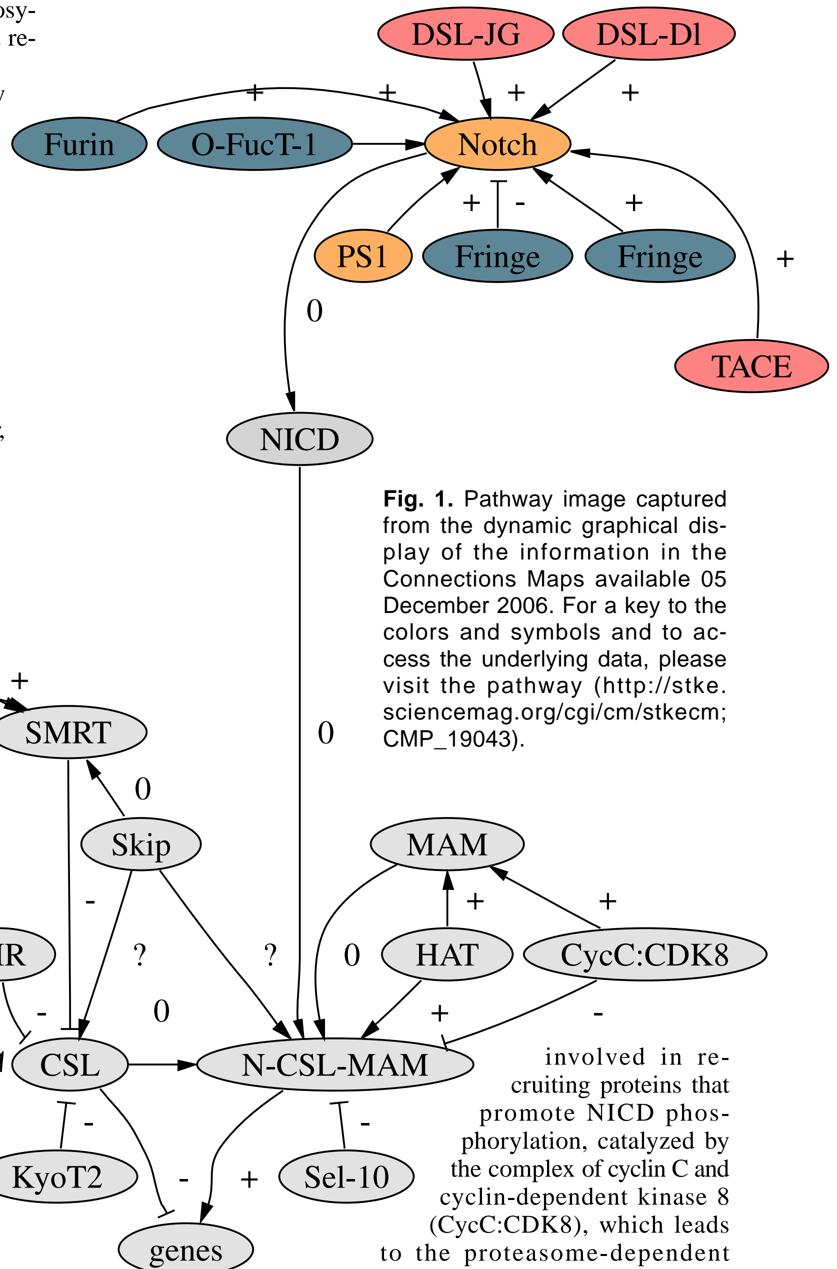

Fig. 1. Pathway image captured from the dynamic graphical display of the information in the Connections Maps available 05 December 2006. For a key to the colors and symbols and to access the underlying data, please visit the pathway (http://stke.sciencemag.org/cgi/cm/stkecm;CMP_19043).

The transcriptional regulator CSL is a constitutive repressor of Notch target genes that acts through its association with the transcriptional co-repressors SMRT, NcoR, CIR, SHARP, KyoT2, and Skip (*30–34*). Several of these co-repressors, SMRT, CIR, and SHARP, are directly implicated in recruiting histone deacetylases (HDACs) or components of chromatin-modifying protein complexes, such as SAP30, to Notch target genes. Others, such as NcoR, have been shown to associate with similar chromatin-modifying proteins (*35*); however, this has not been demonstrated to be relevant to Notch signaling. Upon entering the nucleus, NICD displaces these co-repressors and their associated chromatin-modifying proteins from CSL and forms a transcription-activating complex (*36–39*).

The binding of NICD to CSL recruits other proteins to the complex, in particular MAM (MAML1, Mastermind) (*40–43*). MAM plays an important role as a coactivator of the NICD-CSL complex by recruiting histone acetylases (HATs). It is also involved in recruiting proteins that promote NICD phosphorylation, catalyzed by the complex of cyclin C and cyclin-dependent kinase 8 (CycC:CDK8), which leads to the proteasome-dependent degradation of NICD, mediated by the E3-ubiquitin ligase Sel-10 [(*44*, *45*); reviewed in (*46*)]. Thus, MAM couples transcriptional activation with Notch turnover. Both NICD and MAM have been implicated in recruiting HATs (*44*, *47*, *48*). The protein Skip has been characterized as a transcriptional co-repressor when bound to CSL [reviewed in (*29*)], but chromatin immunoprecipitation experiments indicate that Skip remains associated with Notch target gene promoters during Notch signaling, implying that it remains associated with the transcription-activating complex (*45*). The precise role of Skip in Notch target gene activation remains unclear.

Structures for all the domain types in the Notch receptor have been reported. The structure of EGF-like repeats 11 to 13 [PDB entry 1TOZ (http://www.rcsb.org/pdb/explore.do?structureId=1TOZ) (*49*)] and of the first LN repeat of human Notch

1 were solved by nuclear magnetic resonance spectroscopy [PDB entry 1PB5 (http://www.rcsb.org/pdb/explore.do?structureId=1PB5) (*50*)]. Moreover, three crystal structures of the ANK domain have been published: the near-complete ANK domains of *Drosophila* Notch [PDB entry 1ot8 (www.rcsb.org/pdb/explore.do?structureId=1OT8) (*51*)] and human Notch 1 [PDB entry 1YYH (http://www.rcsb.org/pdb/explore. do?structureId=1YYH) (*52*)] and a partial ANK domain structure for mouse Notch 1 [PDB entry 1YMP (http://www.rcsb.org/ pdb/explore.do?structureId=1YMP) (*53*)]. Additionally, the crystal structure of CSL bound to DNA [(PDB entry 1TTU (http://www.rcsb.orgpdb/explore.do?structureId=1TTU) (*54*)] has been described, as have two crystal structures of the Notch target gene-activating complex [PDB entry 2F8X (http://www.rcsb.org/pdb/explore.do?structureId=2F8X) (*55*); PDB entry 2FO1 (http://www.rcsb.org/pdb/explore.do?structureId=2FO1) (*56*)].

Analysis of the structure of CSL bound to DNA and the structures of the Notch target gene-activating complexes has led to a mechanistic hypothesis of Notch target gene activation. The structures reveal the binding sites, located by mutagenesis studies, of CSL co-repressors (*54*, *56*). During Notch signaling, these binding sites are masked in part by the binding of the RAM region of NICD. This, together with possible conformational changes caused by the binding of RAM to CSL (*56*, *57*), likely leads to the dissociation of CSL's co-repressors and the subsequent activation of Notch target genes.

Pathway Details

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Scope: Canonical

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Citation: M. Ehebauer, P. Hayward, A. Martinez-Arias, Notch signaling pathway. *Sci. STKE* **2006**, cm7 (2006).