A Is For . . .

Notch

Notch *— A group of transmembrane receptor and ligand proteins that regulate cell-fate decisions during development via cell–cell contact.*

The development of an organism from a single cell to a multicellular, three-dimensional structure of characteristic size and shape depends on the coordinated action of genes to direct the fate of individual cells. Neighboring cells also exchange signals to coordinate their respective behaviors and fates.

Notch signaling is one of several signaling pathways, and possibly the most prevalent, used by metazoans to control cell fates through local cell–cell interactions. Signals transmitted through Notch, in combination with other cellular factors, influence differentiation, proliferation, and apoptotic events at all stages of organogenesis and development. Adjacent cells become distinguished from one another depending on whether they predominantly send or receive Notch signals. As one cell commits to a particular fate, it expresses ligands that signal through Notch receptors to inhibit similar differentiation in adjacent cells (i.e., lateral inhibition).

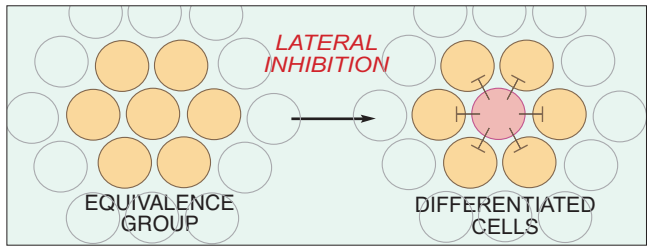
The genetic effect of the Notch receptor was first identified in 1917, described in mutant *Drosophila* flies that developed "notches" in their wing margins (due to haploinsufficiency). Notch has since been found to be present in all metazoans, from worms to humans. The gene was cloned in the mid-1980s.

Notch receptors are type-1, hetereodimeric, transmembrane proteins. Humans have four Notch receptors, numbered 1 to 4. The receptors are synthesized as single-chain precursors and cleaved in the trans-Golgi into an extracellular and an intracellular subunit. The extracellular subunit consist of a series of epidermal growth factor (EGF)-like repeats and three Lin/Notch repeats. The intracellular subunit includes a transmembrane region, followed by a RAM23 motif and seven ankyrin repeats involved in nuclear signaling, and a PEST sequence that modulates receptor degradation.

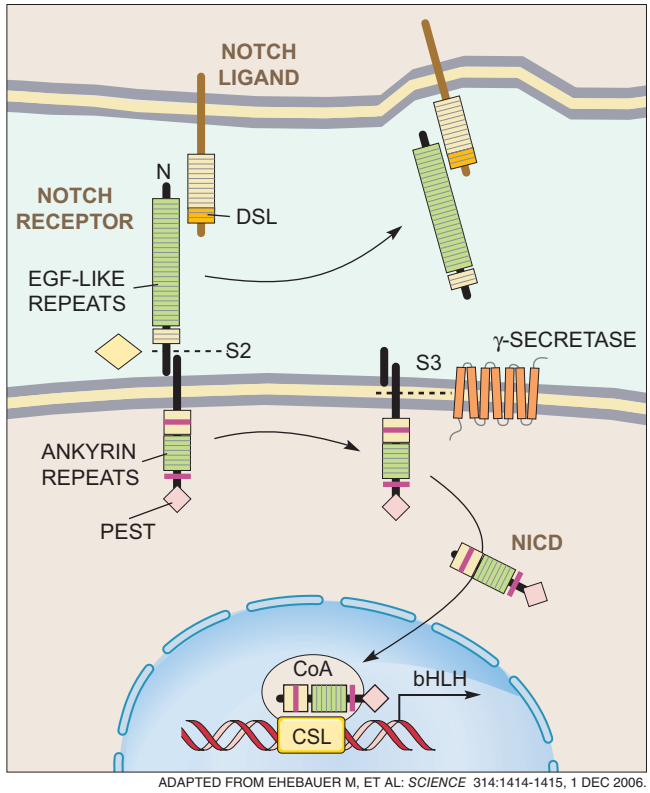
Notch ligands, like the Notch receptors, are type-1 membrane-bound, transmembrane proteins. They contain a series of EGF-like repeats and a DSL (Delta, Serrate, Lag-2) domain important for receptor binding. The ligand family has five members in mammals: Delta-like 1, 3, and 4 and Jagged 1 and 2.

Binding of Notch ligand to the receptor induces a conformational change in the receptor extracellular domain that exposes an S2 cleavage site. Following cleavage by a metalloprotease (ADAM, TACE, etc.), Notch undergoes a second cleavage at the transmembrane site S3, catalyzed by the γ-secretase (presenilin) complex. This frees the Notch intracellular domain (NICD) to translocate to the nucleus, where it interacts with the CSL transcription factors [CBF1/Su(H)-/Lag1].

[cont on pg 207]



In developing tissue, neighboring cells express similar levels of Notch and its ligand (equivalence group). As one cell commits to a new fate or differentiation due to intrinsic or extrinsic signals, Notch receptors in adjacent cells are activated to suppress this change in those cells, a process termed lateral inhibition.



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Binding of Notch by its DSL ligand induces two sequential cleavages that frees the intracellular domain of Notch (NICD) to translocate to the nucleus. There, it interacts with the CSL transcription factors, replacing a corepressor complex with a co-activator (CoA) one to initiate transcription of bHLH proteins.

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CSL is typically associated with a corepressor complex, but binding of NICD displaces it with a coactivator (CoA) complex that completes transcription of bHLH (basic helix-loop-helix) genes.

Notch signaling plays an integral role in the specification, proliferation, and differentiation of many cell lineages. Notch receptors and ligands are widely expressed during organogenesis, where they function in the development of tissues from all three primary germ layers (endoderm, mesoderm, and ectoderm).

In addition, Notch signaling also controls fetal and postnatal tissue development, as well as the development and maturation of adult tissues. In adults, Notch receptors and ligands can be found differentially expressed in many tissues. Notch signaling is implicated in cell-fate decisions such as self-renewal in adult stem cells and differentiation of progenitor cells along a particular lineage, regulating hematopoiesis, neovascularization, neurogenesis (including learning and memory), and tissue renewal and homeostasis.

Aberrant Notch signaling has been identified as a causative factors in several human cancers. In particular, it was first demonstrated in T-cell acute lymphoblastic leukemia (T-ALL), where a t(7;9) translocation results in constitutively active Notch1 protein in T cells, which promotes their proliferation and survival. Deregulated expression of Notch receptors, ligands, and targets also is seen in solid tumors, including those of the cervix, colon, lung, pancreas, prostate, breast, skin, and brain.

The molecular basis for oncogenic activity by Notch remains unclear, but it is believed that Notch may contribute to tumorigenesis by inhibiting apoptosis (through inhibition of proapoptotic transcription factors and upregulation of antiapoptotic proteins) and by accelerating cell proliferation (by enhancing CDK2 and cyclin activity).

Kevin G. Leong and Aly Karsan: Recent insights into the role of Notch signaling in tumorigenesis. *Blood* 107:2223-2233, 15 Mar 2006.

Eric C. Lai: Notch signaling: control of cell communication and cell fate. *Development* 131:965-973, Mar 2004.

Matthias Ehebauer, Penelope Hayward, and Alfonso Martinez Arias: Notch, a universal arbiter of cell fate decisions. *Science* 314:1414-1415, 1 Dec 2006.