Notch Signaling

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The Notch pathway regulates cell proliferation, cell fate, differentiation, and cell death in all metazoans. Notch itself is a cell-surface receptor that transduces short-range signals by interacting with transmembrane ligands such as Delta (termed Delta-like in humans) and Serrate (termed Jagged in humans) on neighboring cells (Fig. 1). Some soluble ligands have also been identified in Caenorhabditis elegans, but these bind to Notch together with transmembrane adaptors (Komatsu et al. 2008). Ligand binding leads to cleavage and release of the Notch intracellular domain

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**Figure 1.** Notch signaling (simplified view).
(NICD), which then travels to the nucleus to regulate transcriptional complexes containing the DNA-binding protein CBF1/RBPjk/Su(H)/Lag1 (CSL).

Following their synthesis, Notch receptors are cleaved by protein convertases during exocytosis at site 1 (S1), which regulates their trafficking and signaling activity (Logeat et al. 1998; Gordon et al. 2009). During passage through the Golgi, they can be glycosylated by glycosyltransferases such as Fringe, which determines the subsequent response to different subfamilies of ligands. These and other posttranslational modifications of the receptors and ligands tune the amplitude and timing of Notch activity to generate context-specific signals. Several proteins, including E3 ubiquitin ligases (e.g., Deltex and Nedd4), Numb, and α-adaptin, regulate the steady-state levels of the Notch receptor at the cell surface. In signal-sending
Following ligand binding, signaling is initiated when endocytosis of ligand–receptor complexes induces unfolding of a juxtamembrane negative control region (NRR) unique to Notch proteins. Unfolding of the NRR allows gand activation (Fig. 2).

In addition to the canonical signals, mounting evidence indicates that CSL-independent activities of Notch also regulate vertebrate (Rangarajan et al. 2001; Demehri et al. 2008) and invertebrate (Ramain et al. 2001) development, but the biochemical details of this aspect of the pathway are yet to be uncovered. In the absence of ligand, Notch may also be involved in other cellular processes, such as regulating the stability of β-catenin (Sanders et al. 2009), a component of the Wnt signaling pathway (Nusse 2012).

Under most physiological conditions, unbound Notch receptors simply recycle or are targeted for lysosomal degradation. With one exception (Mukherjee et al. 2011), only pathological or experimental conditions are known to lead to receptor activation without ligand. These include mutations in the NRR domain (Weng et al. 2004), overexpression of Notch with ADAM proteases, and exposure to calcium chelators (Bozkulak and Weinmaster 2009; van Tetering et al. 2009), all of which expose Notch to shedding by ADAM17 (also known as TACE). Notch can also become activated when ESCRT components are mutated (Moberg et al. 2005; Thompson et al. 2005; Vaccari and Bilder 2005), which delays entry into the lysosome and permits ligand-independent activation. The frequent activation of Notch by mutations in T-cell acute lymphoblastic leukemia and its frequent inactivation in head and neck squamous cell carcinomas (Agrawal et al. 2011; Stransky et al. 2011) illustrate the importance of the pathway for control of cell fate and proliferation and the severe consequences of its dysregulation.

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REFERENCES

*A reference is also in this collection.


