Developmental Biology

Volume 241, Issue 2, 15 January 2002, Pages 313-326

Regular Article

Intracellular Cell-Autonomous Association of Notch and Its Ligands: A Novel Mechanism of Notch Signal Modification

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https://doi.org/10.1006/dbio.2001.0517

Abstract

Notch (*N*) and its ligands, Delta (*Dl*) and Serrate (*Ser*), are membrane-spanning proteins with EGF repeats. They play an essential role in mediating proliferation and segregated differentiation of stem cells. One of the prominent features of *N* signal system is that its ligands are anchored to the plasma membrane, which allows the ligand/receptor association only between the neighboring cells. Various lines of evidences have verified this intercellular signal transmission, but there also have been implications that expression of *Dl* or *Ser* interferes cell-autonomously with the ability of the cell to receive *N* signal, implying that *N* and its ligands may interact in the same cell. Here, we demonstrate that *N*, *Dl*, and *Ser* cell-autonomously form homomeric or heteromeric complexes. The cell-autonomous heteromeric complexes are not present on the cell surface, implying that the association occurs in the endoreticulum or Golgi apparatus. Expression of *Dl* or *Ser* cell-autonomously reduces the *N*-mediated *HES-5* promoter activity, indicating that the cell-autonomous association alters the N signal receptivity. Intracellular deletion of *Dl* shows elevated activity of this dominant-negative effect. *In vivo* overexpression study suggests that the cell-autonomous function of *Dl* and *Ser* is independent of the ligand specificity and may be modulated by Fringe (*Fg*), which inhibits the formation of the cell-autonomous *Dl*/*N* or *Ser*/*N* complex.

Keywords

cell-autonomous; association; Notch; Delta; Serrate

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