Multistability in Notch-Jagged-Delta signaling pathway

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Short Abstract — Notch-Delta-Jagged signaling mechanism mediates cell fate determination during embryonic development, tumorigenesis and wound healing. This elaborated mechanism is activated when Notch of one cell interacts with Delta or Jagged of its neighboring cells. The Notch-Delta circuitry acts as an inter-cellular mutually inhibitory toggle-like two-way switch driving the two neighboring cells to select opposite fates — high Notch low Delta and vice versa. Using a new theoretical framework, we showed that when Jagged is incorporated, the circuit acts as a three-way switch with an additional state — (medium Notch, medium Delta), through which neighboring cells can adopt a similar cell fate.

Keywords — Notch signaling pathway, Jagged, Cell-cell communication, Multistability, Cell fate decision

Introduction

Understanding cell-fate decisions during metazoan development and tumorigenesis is a major research challenge in modern developmental and cancer biology. These decisions often depend on cell-cell interaction. Notch signaling pathway is an evolutionarily conserved mechanism that plays a crucial role in controlling cell fate differentiation during embryonic development and wound healing [1]. This embryonic-cell Notch signaling is often aberrantly activated in many cancers and controls stemness, proliferation, and survival of cancer cells [2].

Notch pathway is activated when Notch, the transmembrane protein that acts as the receptor for its transmembrane ligands Delta and Jagged, interacts with Delta and/or Jagged of the neighboring cells. Such trans-interaction cleaves the Notch receptor and releases Notch Intracellular Domain (NICD) that translocates to the nucleus and activates the target genes of Notch signaling pathway, including Delta and Jagged, which are indirectly repressed and activated respectively [1]. Notch can also interact with Delta and Jagged of the same cell, but this cis-interaction degrades both Notch and the ligand [1].

Notch-Delta signaling has been well-studied both experimentally and theoretically, and it usually diversifies the cell fate of two initially equivalent neighboring cells [3]. However, the role of Notch-Delta-Jagged signaling in cell fate determination remains unexplored. Here, we developed a novel theoretical framework that captures the role of both Jagged and Delta in Notch signaling system.

I. RESULTS

We devised a novel theoretical framework to explore the effects of Jagged in cell fate determination through Notch signaling. When considering only Notch and Delta, the system has two possible states: (1, 0) or (high Notch, low Delta) and (0, 1) or (low Notch, high Delta). In this case, each cell tends to have an opposite fate to its neighbor, which is consistent with previous theoretical and experimental studies [3]. When considering only Notch and Jagged, the system is monostable and the two cells tend to keep similar protein levels as that of its neighbor. When both Delta and Jagged are incorporated, the circuit acts as a three-way switch, which gives rise to additional intermediate state — (medium Notch, medium Delta) or (½, ½), in addition to the (1,0) and (0,1) states. The range of parameters for the existence of (½, ½) state increases when Jagged levels are increased, thereby suggesting that Jagged plays an important role in stabilizing this intermediate state. We also showed that this intermediate state allows interacting cells to adopt a similar cell phenotype.

II. CONCLUSION

We developed a new theoretical framework to study the effects of both Delta and Jagged on the Notch signaling. We showed that two cells that interact via Notch signaling can not only have the (high Notch, low Delta) and (low Notch, high Delta) states, but also an intermediate state (medium Notch, medium Delta). We hypothesize that this intermediate state stabilizes the hybrid epithelial/mesenchymal phenotype for cancer cells, and enable them to undergo collective cell migration during metastasis [4, 5].

REFERENCES