427b Interplay between Soluble and Membrane-Tethered Extracellular Signals Dictates Cell Patterning during Worm Development

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Cell patterning during development occurs when a soluble extracellular factor (morphogen) is released from a localized source and establishes a spatial gradient. As in the case of vulval development in the worm *C. elegans*, the morphogen often does not act alone. Six cells in a linear array communicate with their neighbors via a membrane-tethered receptor-ligand system. The soluble morphogen and the membrane-tethered lateral signal independently impart unique cell fates. Yet, in the natural system, they occur concurrently, and importantly, they cross-regulate each others' activity. The morphogen induces lateral signaling, while the inhibitory lateral signal attenuates perception of the morphogen. Thus, we asked how a robust pattern of distinct cell fates emerges from such an intricately coupled system. Using a mathematical model of a two-cell system, we show that lateral inhibition amplifies the perception of the morphogen gradient. Gradient amplification is maximized at an optimal strength of lateral inhibition. In other developmental contexts, lateral signaling is self-regulated via an intercellular positive feedback mechanism, a network design that is topologically distinct from that employed in vulval development. We show that introducing such a self-control scheme leads to fate misspecification for certain morphogen concentrations, reducing the robustness of the six-cell system to evolve into its characteristic pattern. Our results bring quantitative insight into the role of coupling membrane-tethered lateral and soluble morphogen signals to specify cell patterning. Since these pathways are highly conserved from flies to nematodes to mammals, our results will be useful in understanding the mechanisms guiding development of simple and complex organisms.