Mechanisms of cell-cell signal integration during epithelial morphogenesis

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Cell-cell communication during organ development relies on regulating the spatiotemporal dynamics of key signal transduction integrators such as calcium ions. However, how calcium signaling dynamics are integrated and contribute to the morphogenesis of non-neural tissues is still poorly understood. Here, we report new methods to reverse-engineer multiscale signal integration using the \textit{Drosophila} wing disc, an established system for delineating biophysical mechanisms of morphogenesis. We built a geometrically-accurate computational model of multicellular calcium signaling. The computational model predicts the regulation of the main classes of calcium signaling dynamics observed in vivo: single-cell calcium spikes, multicellular transient bursts, global intercellular calcium waves, and global fluttering. Further, the spatial extent of signaling dynamics from single cells to global waves is a function of global stimulation strength and specific mode of stimulation. The generation of global waves depends on the subdivision of the cell population into a small fraction of initiator cells surrounded by a large fraction of standby cells connected by gap junctions. Further, we performed a RNAi-based screen of candidate upstream regulators that control the distinct spatiotemporal classes of calcium signaling. This quantitative screen employed a deep learning-based bioimage platform to identify neuropeptide GPCRs as key regulators of calcium signaling during epithelial morphogenesis. We also have performed additional validation assays of candidate hits from the screen to assess roles in proper patterning and growth. This study proposes a parsimonious mechanistic explanation for the regulation of multicellular calcium signaling dynamics in epithelial systems and defines the high-dimensional mapping of signaling dynamics to morphological phenotypes.