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Regulation of Cellular Patterning through the Extracellular Matrix

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Mechanical stress of the cellular microenvironment governs tissue homeostasis through mechanically-sensitive gene regulatory networks. Molecularly and mechanically interlaced stimuli establish spatial gradients, ultimately defining cellular patterning. We observe the cellular propensity for durotactic, haptotactic, and chemotactic gradients as cellular phenomena such as migration, division, and differentiation. Commonly observed is the tendency for boundary cells to undergo the phenotypic transition, epithelial-mesenchymal transition (EMT), to maintain normal tissue homeostasis. Previous work has demonstrated an upregulation of EMT markers in the boundary population of a spatially confined epithelial monolayer relative to the confluent population, possibly due to disproportionate cell-cell contacts and isometric tension. To further understand the role of intercellular tension in EMT-driven spatial patterning of epithelial sheets, we developed a multicellular computational model of interfacial cellular forces. Thermodynamically constrained cells defined by an energy function, the Hamiltonian, migrate on a finite element substrate to minimize the total energy of the system. Abutted neighboring cells form intercellular adhesions – representative of E-cadherin junctions – to transmit traction forces across the cell-cell junctions. Forces across cell-cell adhesions balance substrate forces thereby producing a stable epithelial monolayer. As a result, the largest mechanical stresses are observed at the boundary of the epithelial monolayer when compared to the center. However, cell-cell junctional forces remain isotropic across the entire monolayer. Simulating transforming growth factor beta 1 (TGF-β)-induced EMT disrupts the intercellular adhesion force isotropy and introduces a gradient of intercellular adhesion forces that are largest in the boundary population. These predictions were validated *in vitro* using FRET analysis of spatially constrained epithelial cells treated with TGF-β to induce EMT. Furthermore, assembly of the extracellular matrix protein fibronectin corresponds to regions of larger mechanical stress. Inhibiting fibronectin assembly eliminates TGF-β localization and subsequent EMT spatial patterning. These findings suggest that mechanical gradients produce cellular patterning through extracellular matrix remodeling, and the spatial information is communicated across the epithelial sheet as intercellular tension. Future work will investigate mechanisms of manipulating EMT spatial patterning as a means to control physiological and aberrant cellular processes.