How local changes of matrix curvature can direct collective cell migration through modulation of Erk signaling waves

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Collective migration is a key function of many epithelial tissues, both in physiological (wound healing) and pathological (cancerous metastases) processes. Recent evidence suggests that propagation waves of extracellular signal-regulated kinase (ERK) mitogen-activated protein kinase activation determine the direction of the collective cell migration. Interestingly, accumulative evidence shows that single cells respond to cell-scale curvature variations (curvotaxis). However, it remains elusive how local changes of curvature can modulate the propagation of ERK and be integrated to coordinate the collective movement. Here we use a photopolymerization method to form in soft hydrogels well-defined corrugation patterns of different wavelengths, as observed in many native epithelial tissues. Our results show that corrugations induce a uniaxial collective flow of MDCK cells in the direction of the corrugation axis, demonstrating a curvotaxis effect on collective migration. By combining Förster resonance energy transfer(FRET)-based biosensors in MDCK cells with long time-lapse experiments, our findings show that ERK protein activation spreads from cell to cell in a defined dynamic pattern (waves) during collective cell migration on flat hydrogels. We then investigate how the modulation of the local curvature can lead to a mechanical stretch at the single cell level, which can activate ERK through epidermal growth factor receptor (EGFR) activation, and ERK activation triggers cell contraction. The contraction of the activated cell pulls neighboring cells, evoking another round of ERK activation and contraction in the neighbors. Our study raises the question of the critical role of cellular response to external stimuli such as matrix curvature in intercellular signal transduction.

Dynamic state on corrugated hydrogels



Erk waves are activated by mechanical forces transmitted via cell-cell junctions













