



POSTER #18

**LONG-RANGE INTERCELLULAR COMMUNICATION IN
COLLECTIVE CELL MIGRATION**

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Collective cell migration of cohesive groups involves intercellular mechanical communication transmitted between adjacent cells through cell-cell contacts to eventually drive long-range communication. We discovered how local mechanical fluctuations induce long-range communication and identified some potential molecular players driving this mechanism.

By designing and applying new analytical methods to migrating monolayers of epithelial cells, we find that cells at the front transmit mechanical cues by inducing normal and shear strains on neighboring follower cells. Accumulation and propagation of these mechanical cues over time and space create groups of cells that migrate and exert forces in a coordinated manner. Such motion patterns direct cells from within the monolayer toward the sites of shear-strain-induced motion at the monolayer front. These results provide a model of long-range mechanical communication between cells, in which local alignment of velocity and stress translates local mechanical fluctuations into globally collective migration (Figure 1).

Efficient collective migration depends on a balance between contractility, cytoskeletal rearrangements, and adhesions, all controlled by GTPases of the RHO family. Spatiotemporal analysis revealed a surprising role of the RHO GTPase RhoA in regulating long-range communication that was mirrored upon slight down-regulation of myosin-II contractility. A comprehensive screen uncovered a group of RhoA-activator guanine nucleotide exchange factors (GEFs) that are implicated in intercellular communication. Downregulation of these GEFs differentially enhanced propagation of guidance cues through the group, defining two functional clusters: RHOA-ARHGEF18 and ARHGEF3-ARHGEF28-ARHGEF11, with RHOC as an intermediate between them. We conclude that for effective collective migration the RhoA-GEFs/RhoA/C/actomyosin pathways must be optimally tuned to compromise between generation of motility forces and restriction of intercellular communication (Figure 2).

References:

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2. A Zaritsky*, Y Tseng*, MÁ Rabadán, M Overholtzer, Danuser G, A Hall. The Roles of Guanine Nucleotide Exchange Factors in Regulating Collective Cell Migration. Preprint @bioRxiv (2016), doi: <http://dx.doi.org/10.1101/076125>.

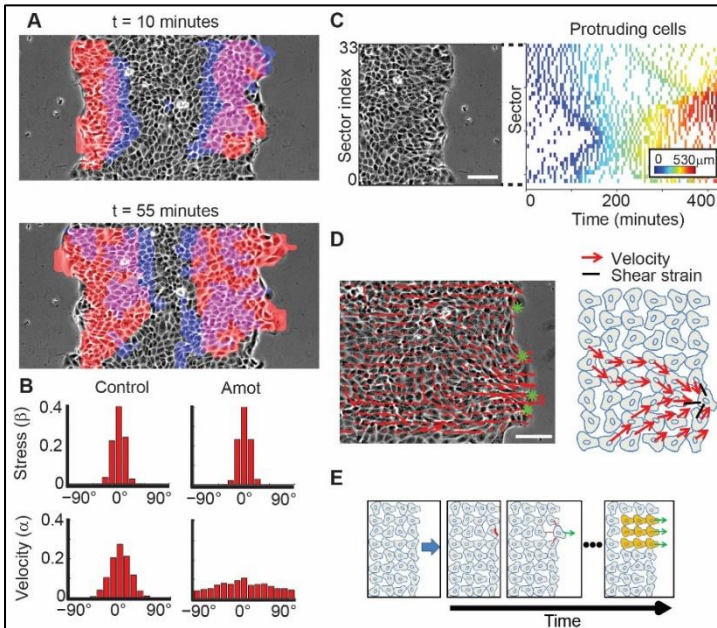


Figure 1. Long-range intercellular mechanical guidance. (A) Coordination in stress (blue) guides coordination in motion (red). (B) Tight junction associated proteins such as Angiomotin (not shown: Patj, Merlin and Claudin-1) are implicated in the transmission of aligned stress to aligned motion. (C) Lateral waves propagating along the monolayer edge. (D) Shear-strain events guide multicellular flow patterns. (E) Working model on how single cell fluctuations lead to group coordination.

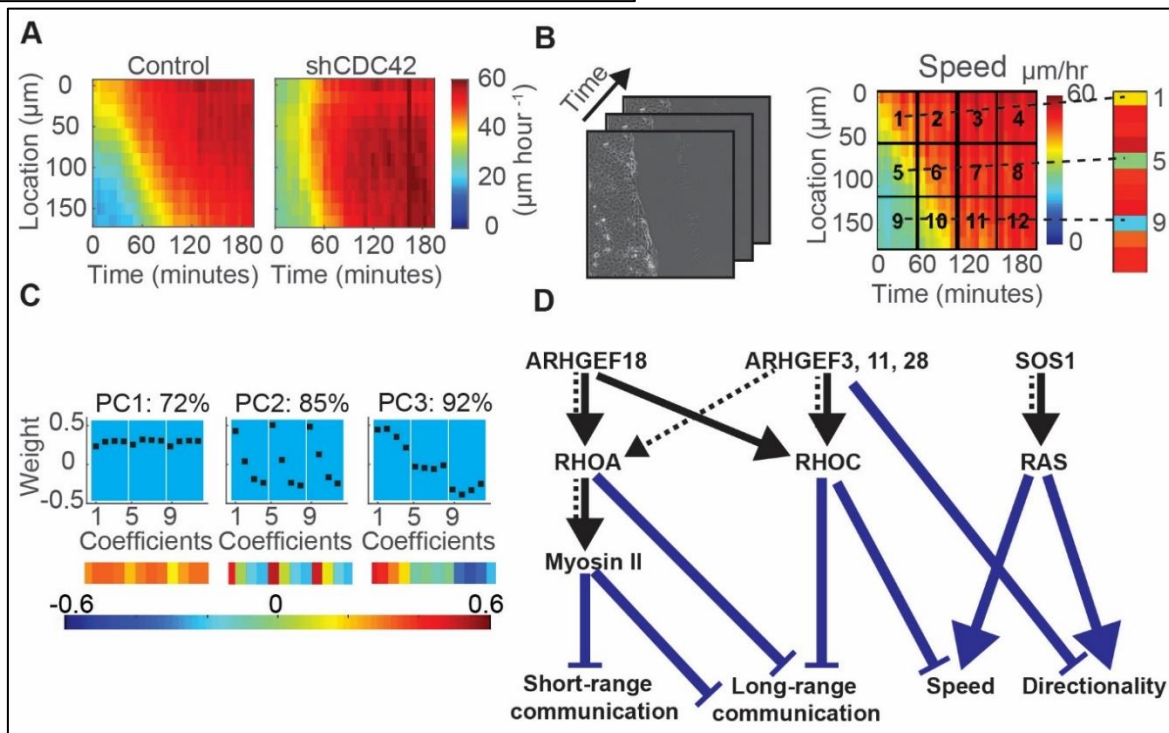


Figure 2. Diverse roles of guanine nucleotide exchange factors in regulating collective cell migration. (A) Speed kymographs showing the depletion of RhoA enhances front-to-back propagation. (B) Reducing a wound healing experiment to a 12-dimensional feature vector encoding spatiotemporal dynamics. (C) Reverse engineering the information encoded in an experiment: magnitude, temporal- and spatial-gradient. (D) Working model emerging from the phenotypic similarity (in the 9-dimensional feature space, full black arrows) and literature survey (Dotted black arrows) of GEFs and Rho-GTPases.