Collective migration is essential during development, repair, and disease progression. The tissue-scale cooperation of cells to collectively migrate likely requires the integration of long-range multi-cellular physical signals. Cellular unjamming may be the mesoscale link that predicts emergent collective behavior. This phenomenon proposes that each cells’ energy within an epithelium is a function of three contributions: bulk cell elasticity, active contractility of the actomyosin cortex, and the interfacial tension or competition between cortical tension and cell-cell adhesive forces. The interfacial line tension between cells is either negative or positive, as decreasing actomyosin contractility or increasing cell-cell adhesion is predicted to either shorten or elongate the interfacial region (Fig1A). These physical properties compete to generate a preferred cell shape: \[ \text{Shape Index} = \frac{\text{Perimeter}}{\sqrt{\text{Area}}} \] (Fig1B). Interestingly, a critical energy drop is found at 3.81 where cells may elongate and unjam become fluid-like or collectively migrate (Fig1C). The theory of cellular unjamming in its current form, however, does not yet incorporate cell-matrix adhesive forces and how these forces might affect a cells’ shape and motility.

We use tumor-conditioned (TC-) MCF10A epithelial spheroids spreading on polyacrylamide gels as a model system of collective migration. Cell shapes measured within spreading TC-MCF10A spheroids indicate a wider range of cell shape configurations compared with cells within normal MCF10A spheroids that adhered but did not spread (Fig1D,E,F). In addition to the cells collectively migrating out of TC-MCF10A spheroids exploring a wider range of cell shapes, these cells exerted increased traction forces (Fig1G). Time-lapse microscopy imaging of MCF10A spheroids depict a supracellular actin cable that is maintained at the boundary and cells that are immobilized or jammed (Fig 1H), however within TC-MCF10A spheroids, cells are actively reorganizing their actin cytoskeleton as they unjam and coordinate their persistent collective migration outward (Fig 1I).

These studies suggest that coordinated actin reorganization, cell shape changes, and enhanced tractions drive groups of cells to undergo an unjamming transition and collectively migrate out of epithelial spheroids. The results are broadly applicable and could have exciting applications across the diverse fields of developmental biology, tissue repair, and disease progression.