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Quantifying Heterogeneity of Cell-ECM Interactions Through Integrated Biophysical Analyses

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Abstract: Cell-extracellular matrix (ECM) interactions are critical modulators of repair and regeneration. However, variability within individual cells of the same cell type and within the ECM microenvironment can lead to heterogeneous outcomes that may limit the reliable application of cell-biomaterial constructs in regenerative medicine. Understanding the origins of heterogeneity is critical to overcoming this challenge and requires measurement of cell-ECM interactions at the single cell level. There are four core biophysical modules that cells employ to interact with their surrounding ECM: protrusion, adhesion, contractility, and matrix remodeling. Conventional approaches measure these interactions in separate experiments on separate cells, resulting in bulk comparisons that mask the details of individual cell behaviors. Measuring these four modules simultaneously in individual cells is expected to improve our understanding of how phenotypic heterogeneity arises within and across cells and ECM conditions, as well as how the spatial and temporal dynamics of cell-ECM interactions integrate to give rise to emergent behaviors like migration and differentiation. Here, we present an integrated approach to measure the four core modules: timelapse z-stack imaging of mCherry expressing cells is conducted while traction force microscopy (TFM) of matrix-embedded beads and fluorescence of cleaved dye quenched (DQ) collagen as well as reflection confocal imaging of the collagen matrix are acquired. Application of this integrated imaging technique revealed relationships among the four core modules of cell-ECM interaction within single cells, lending new insight into the state-space of cell-ECM interactions and enabling a more holistic understanding of the organization of the processes underlying emergent phenotypes.

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