Development of Pre-Clinical Models to Study How Biophysical Forces Alter Metastatic Breast Cancer

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Human cells experience various biophysical forces in vivo that significantly influence biological processes and cellular phenotype. One such force, cellular deformation, occurs during trans endothelial migration or passage through narrow capillaries and plays a crucial role in cancer metastasis. While deformation-induced biophysical changes have been well-documented, the resulting phenotypic changes driving pro- survival behavior remain underexplored. This study developed a modular microfluidic platform to deform cells through a constriction channel and collect them for single-cell immunostaining using fluorescence microscopy. Two breast cancer subtypes, estrogen receptor-positive (ER+) and triple-negative breast cancer (TNBC), were examined due to their distinct deformation characteristics during metastasis. Approximately 94% of cells successfully deformed, with MDA-MB-231 (TNBC) cells deforming at 98.17 cells/min and MCF-7 (ER+) cells at 6.696 cells/min. Analysis revealed increased p-AKT phosphorylation in deformed MCF-7 cells and non-deformed MDA-MB-231 cells, suggesting subtype-specific biochemical responses. Additionally, this study explored the role of fluid shear stress (FSS)—a force cancer cells experience in the bloodstream—by developing a microfluidic system to mimic the tumor microenvironment (TME). Using microfluidic devices, cells were exposed to FSS, which immediately induced enhanced proliferation. To assess whether these changes were sustained, 3D spheroids were cultured for seven days using a droplet microfluidic trapping array, confirming prolonged phenotypic alterations. By successfully integrating shear exposure with 3D culture, this study demonstrates that biophysical forces drive biochemical changes that enhance metastatic potential.

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