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Stiffness and Modulus and Independent Controllers of Breast Cancer Metastasis

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Abstract
One out of eight women in the United States will develop breast cancer during their lifetime. Ninety percent of cancer related deaths are due to metastasis. Metastasis is the biological process where individual or aggregate cancerous cells break away from the primary tumor site and colonize distant, non-adjacent locations throughout the body. It is my objectives to study how mechanical, topographical and biochemical cues affect metastatic breast cancer metastasis at an early developmental stage. ECM components have previously been shown to affect cell motility via ligand-receptor interactions, and physical cues, such as matrix stiffness and protein density. The primary tumor site significantly stiffens during tumor progression. The ability cells have to sense and respond to these matrix features influences and facilitates cell invasion. It is now widely accepted that mechanical properties of the ECM can regulate cell migration; however, presently, tissue *modulus* and *stiffness* have been used interchangeably. It is unknown if cell responses are sensitive to a

bulk tissue modulus or stiffness on the geometric length scale of the cell. It is my objective to create tunable biomaterials from known materials to independently parse the roles of stiffness and modulus upon the migration of breast cancer cells.

I have created a variety of tunable biomaterials which I can parse the roles of mechanical properties and observe their affect upon cell mechanosensing. All systems were coated with collagen I, which is the most abundant ECM protein during tumor development. I was able to quantify the migration along with other parameters of the metastatic breast cancer cell line MDA-MB-231. My results show that the highly metastatic MDA-MB-231 is stiffness sensitive among all biomaterial models. Cells maximum cell speeds are at high concentrations of collagen I on the polymer microlenses and show a biphasic response dependent on stiffness. On poly (ethylene glycol)- 2-Methacryloyloxyethyl phosphorylcholine (PEG-PC) hydrogels cells favor intermediate modulus and show stiffness dependency at low protein concentrations. Cells on Cd/Se and polydimethylsiloxane (PDMS) samples are influenced by the topographical cue more so than the stiffness or modulus of the material. By controlling mechanosensing via force transduction signaling pathways, and determining the appropriate length-scale by which mechanical properties regulate cancer metastasis, I hope to eventually uncover novel therapeutics to block cell invasion.

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