Engineered Environments to Understand Breast Cancer Spread and Drug Resistance

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Metastasis is the leading cause of fatality for women diagnosed with breast cancer. The most common anatomical sites of distant tumor growth include the brain, lung, liver, and bone, and it is well known that this metastatic spread in breast cancer is not random. Rather, different clinical subtypes of breast cancer exhibit unique patterns of metastatic site preference, called tissue tropism. Given the physical and chemical diversity of these secondary tissue sites, my lab hypothesizes that there is a relationship between the biophysical and biochemical properties of the tissue, and the ability of cells within a particular subtype of breast cancer to adhere, migrate, grow, and respond to chemotherapeutics at these secondary sites.

To quantify this relationship, we have created biomaterial microenvironments, which capture the integrin-binding, stiffness, and stem-cell recruitment properties of the secondary site tissues often recipient of breast cancer spread (brain, lung, and bone), and quantified cell adhesion, polarization, motility, and response to chemotherapeutics. This platform consists of a new class of hydrogels with an extremely wide range of mechanical properties that combine poly(ethylene glycol) (PEG), and phosphorylcholine (PC) zwitterions. Cell response to EGF and integrin antibodies was tissue specific, and, excitingly, this “tissue mimic sensitivity” reflects the known clinical site-specificity in human patients.

Separately, we have observed that tissue stiffening increases the resistance of carcinoma cells to sorafenib by nearly three-fold. Toward rational identification of combinatorial treatments, we used a bead-based ELISA (MAGPix, Luminex) and have identified JNK as a promising phospho-protein target, which provided survival signals during substrate stiffening. Dosing carcinoma cells with JNK inhibitor and sorafenib was the one combination, which eliminated stiffness sensitive resistance. We propose that these types of biomaterial environments can be used to predict tissue-specific spread, and may serve as a system that pharmaceutical companies can use to rule out false positives and potentially save billions of dollars in the drug development pipeline.