The Effect of ECM Stiffness and Topography on Breast Cancer Cell Migration

Kristin M Riching[1, 2], Kevin W Eliceiri[1, 2], and Patricia J Keely[1, 2]

***Short Abstract* — Physical and mechanical properties of the extracellular matrix can profoundly influence cell behavior, however, very little is known about how cells sense and respond to these changes. Matrix stiffness and organization affect breast cancer cell migration *in vitro*, and changes in matrix architecture associated with tumor progression *in vivo* lead to poor prognosis. A better understanding of cell-ECM mechanical interactions will enhance our knowledge of breast cancer progression and will potentially lead to better therapeutic targets for treatment.**

The extracellular matrix (ECM) has a profound effect on breast cancer progression. Increased mammographic breast tissue density, which corresponds to increased type I collagen deposition [1] and subsequent increased mechanical stiffness [2], has been linked to 4–6-fold increased risk for developing breast cancer [3]. In addition to increased collagen deposition, we have previously shown that the organization of collagen fibers also dramatically impacts cancer progression and metastasis in a mouse model. More specifically, we discovered that collagen surrounding mammary ducts is reorganized orthogonal to the epithelial-stromal boundary [4], and that this reorganization correlates with increased metastases to the lung [5]. Furthermore, in a histological study of human breast tumors, we found that patients with more orthogonally aligned collagen had reduced survival [6]. We recently developed an *in vitro* assay to study how cells create and respond to aligned collagen. With this assay, we determined that cells preferentially migrate within regions of aligned collagen and that this alignment requires Rho-mediated contractility [7]. We aim to further determine the mechanisms by which cells migrate within aligned collagen and, more specifically, to understand the changing physical and mechanical properties of the collagen matrix upon increasing fiber alignment. To do this, we used two different techniques to more reproducibly align collagen *in vitro* consisting of either flow of collagen molecules through microchannels or a device to induce alignment by mechanical strain. While these techniques differ in the method of aligning collagen, they both result in alignment similar to that seen generated by cells in our cell-mediated alignment assay. With the ability to independently align collagen *in vitro* and the ability to quantify this alignment, we seek to determine how mechanical properties such as elastic modulus differ between aligned and unaligned collagen. Furthermore, we are able to directly test how cells respond to and migrate within pre-aligned collagen matrices and provide a means by which to perturb signaling molecules associated with Rho-mediated contractility. Our preliminary findings suggest that both the stiffness and the organization of collagen matrices influence cell migration and metastasis. An understanding of the mechanisms whereby cells sense these physical and mechanical matrix cues can be used to generate models of cellular behavior in collagen gels, and will dramatically enhance our knowledge of breast cancer progression.

[1]Department of Biomedical Engineering, University of Wisconsin, Madison

[2]Laboratory for Optical and Computational Instrumentation, University of Wisconsin, Madison

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