

Lay Abstract

The leading cause of cancer-related mortality is not the primary tumor, but the metastatic spread of cancer cells into other tissues of the body. This is particularly true for breast cancer, where survival drops almost 75% if the tumor has metastasized. A defining characteristic of metastasis is the ability of the tumor cells to remodel distant tissues well before the arrival of the invading metastatic cells. These changes are akin to preparing a guest room for a visitor, making the tissue more conducive for colonization of the tumor cells once they arrive. As such, the unique features of the newly invaded tissue dictate if the metastatic cell will enter a state of growth arrest, limiting disease progression, or enter an active proliferative state to form overt metastatic tumors. There is a **critical need** to determine what features of the local tissue microenvironment at the metastatic location dictate the metastatic cancer cell fate.

The two most common sites of metastasis are the bones and lungs, which are mechanically active tissues that undergo frequent cycles of compression and stretching. When tumor cells move from the source location to invade these tissues, they are exposed to a vastly different environment of extracellular matrix (ECM) proteins and physiologic mechanical loading conditions. However, the effects of mechanical loading on the growth cycle of invading tumor cells cannot be readily evaluated using animal models. To investigate the role of recurrent stretching within the metastatic microenvironment, our group recently developed a novel microscale test platform that allows us to grow a 3D network of cancer cells and apply a realistic mechanical stimulus to mimic the constant motion of lung tissue within a relevant ECM protein network. Our results clearly indicate that cyclic stretching mimicking the cyclic stretching of the alveoli in the lungs induces growth arrest in otherwise highly proliferative breast cancer cells. Interestingly, our analysis of the ECM composition of the metastatic niche demonstrates that during metastasis the newly invaded tissue undergoes a dynamic biochemical transition, resulting in an increase in specific matrix proteins associated with stiffness. Furthermore, our modeling data indicates that an increase in the stiffness of the metastatic tissue matrix would reduce the strains experienced by individual cancer cells within the tumor.

Given these advances, we seek to address the **central hypothesis** that patterns of cyclical strain such as those that occur during breathing function to suppress metastatic tumor growth, and that changes in the biochemical composition of the niche act to stiffen the tissue, shielding tumor cells from the cyclic strains and allowing for tumor outgrowth. In this proposal we will work to disentangle the role of matrix biology and stress shielding within the metastatic niche, separating out the effects of biochemical and mechanical signaling to reveal the role of tissue motion in tumor suppression. Ultimately, these studies will take advantage of the tumor suppressive effects of cyclic strain to develop novel therapies designed to specifically target metastatic disease.