Tissue Engineering Approaches to Model Breast Cancer Metastasis

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Metastasis is a leading cause of cancer-associated mortality with a 5-year survival rate of only 26% for metastatic breast cancer patients in the US. Despite recent advances in the detection, diagnosis, and treatment of primary tumors, treatment of metastases remains challenging. While animal models closely recapitulate the physiological environment, they are often difficult to implement to track cellular events occurring during metastasis with high spatial and temporal resolution and provide relatively low throughput for therapeutic discovery. Accordingly, there is an urgent need for *in vitro* devices that accurately recapitulate cellular events occurring during the metastatic cascade that could act as higher throughput platforms for therapeutic development.

Toward this goal we have developed fluidized, tissue engineered constructs that allow for monitoring of cellular events during metastatic progression over long term culture. We developed hydrogel formulations that provide direct control over breast cancer cell fate with respect to aggressive growth and dormancy.[1-3] We implemented 16 hydrogel formulations that systematically vary adhesivity and crosslinking density and have identified formulations that induce different phenotypes in the MDA-MB-231 triple negative breast cancer line. Certain hydrogels induce aggressive growth characterized by high proliferation, high metabolic activity, increased cell density, low apoptosis, and the formation of invasive cell clusters. Other formulations induce cellular dormancy characterized by low proliferation, low metabolic activity, no change in cell density, low apoptosis, and the cells residing as rounded solitary cells that show no invasive characteristics and do not form clusters. Other hydrogel formulations induce tumor mass dormancy characterized by a near perfect balance between proliferation and apoptosis where cell density remains constant over time. Cells residing in either dormant state display increased resistance to common chemotherapeutics compared to those undergoing aggressive growth. We also demonstrate the ability to reactivate cells undergoing dormancy to an active growth state through a dynamic increase in hydrogel adhesivity. After this dynamic switch, these once metabolically dormant cells become activated and begin forming invasive cell clusters similar to metastatic relapse. Additional efforts to model the metastatic cascade include the fabrication of vascularized tissue constructs[4-6] to monitor extravasation during metastasis and investigating the roles of inflammation in mediating extravasation efficiency. In summary, the ability to model crucial cellular events during metastasis using tissue engineered constructs may provide crucial insights for the development of new therapeutic strategies to prevent or eliminate metastatic cancer.

[1]Pradhan & Slater. *Biomaterials.* 2019. [2]Pradhan & Slater. *Data in Brief.* 2019. [3]Pradhan & Slater. *MethodsX*. 2020. [4]Guo et al. *Analytical Methods*. 2019. [5]Keller et al. *Journal of Visualized Experiments*. 2017. [6]Heintz et al. *Advanced Healthcare Materials*. 2016.