Magnetically Actuated Cancer Metastasis Model (MACMM)

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Statement of Purpose: Uncontrolled cell growth and spread to distant organs is the underlying driving force for cancer, which is the second leading cause of death worldwide. Mechanical factors in the tumor microenvironment contribute to cancer behavior [1]. Stress in the tumor surroundings influences the transport of therapeutic agents to the tumor. The alignment and concentration of extracellular matrix, directed in part by strain, may influence tumor growth and matrix invasion. However, the sensitivity of individual cancer cells to local extracellular matrix strain and altered microstructure is not well understood. A better knowledge of this sensitivity could lead to therapies designed to disrupt pathological states of the tumor mechanical microenvironment. The ability to encapsulate and direct the properties of MNPs within cancer tissue constructs can play a key role in control the in vitro microenvironment around cancer cells, including extracellular matrix stress, strain, and alignment [2]. Studies have shown several techniques that have been developed to integrate micro-mechanical loading on the extracellular matrix (ECM) to study cancer cell behavior [3]. However, experimentally flexible, robust, and easily controllable force loading on in vitro tissues remains to be demonstrated. Two challenges to achieving such control over the mechanical microenvironment are accurately applying directed forces on a local scale over hundreds of microns to several millimeters, and accurately measuring the resulting local displacement, strain, and microstructural alterations experienced by cancer cells.

Methods: Millimeter-scale Alginate-Chitosan beads loaded with MNPs and coated with glutaraldehyde cross-linked chitosan were fabricated and embedded in collagen hydrogels, polymerized at 1.5 and 3 mg/ml in a custom-designed PDMS culture chamber. An adjacent holder for a N52 Neodymium magnet was designed to provide local micro-actuation under an external magnetic field. The response of human breast cancer cells was assessed in the magnetically actuated tissue constructs. The MNPs were characterized for size distribution, aggregation state, composition, and magnetization using transmission electron microscopy (TEM), x-ray dispersive spectroscopy (EDX), scanning electron microscopy (SEM), and with a physical property measurement system (PPMS), respectively. Magnetic alginate-chitosan (MAC) beads were characterized for size, shape, surface topography, magnetic properties, and swelling using brightfield microscopy, SEM, a novel micropipette aspiration technique, and swelling tests, respectively [3]. Phase contrast microscopy and quantitative polarized light microscopy was used to reveal the anisotropy in collagen fiber microstructure resulting from the force loading by the magnetic beads. Time-lapse images were captured to determine the migration and morphology of breast cancer cells (MDA-MB-231) cultured on magnetically actuated tissue constructs. Cancer cell viability was assessed using live-dead fluorescence staining and the MTT colorimetric assay.

Results: Magnetic actuation of collagen hydrogels controls the magnitude and direction of applied force. This is similar to forces found in the tumor stroma, a controllable tissue culture platform. Cancer cells within the tissue construct experienced strain gradients from 0-10% without significant loss of cell viability over more than two days culture. Cancer cells of the highly invasive MDA-MB-231 cell line had lower rates of migration near (<850 micron) magnetic beads than far away (<1.5 mm), where the applied strain was minimal. Microstructural alignment in the region of elevated strain near the bead was higher, with a parallelism index of 0.40 ± 0.07, versus 0.17 ± 0.01 near beads not exposed to an external magnet.

Conclusions: The technique of magnetic actuation of tissue constructs is suitable; i) to enable precise control over dynamic extracellular matrix displacement, strain, and applied load, ii) to align collagen fiber network microstructure, and iii) to precisely assess cancer cell responses to defined load, strain, and microstructural profiles.

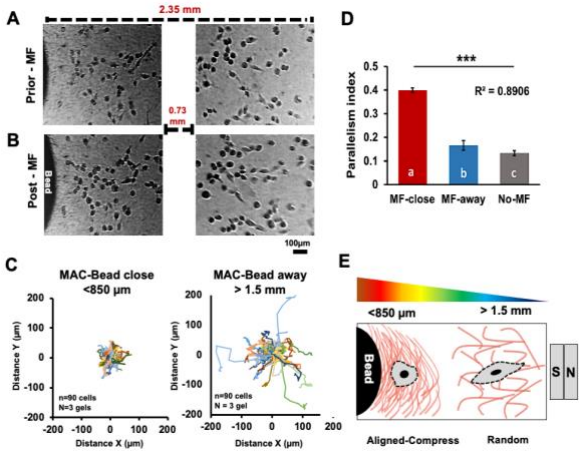

Figure 1: MDA-MB-231 cells cultured on 1.5 mg/ml collagen gel embedded with MAC bead. (A) Original image before exposure to a static magnetic field, (B) after 24h of exposure to a static magnetic field, (C) Migration trajectories of MDA-MB-231 located close to magnetic alginate bead (< 850 micron) and away (> 1.5 mm) from the bead, (D) parallelism index (PI), and (E) Schematic of magnetic micro-actuation displaced the microstructure of collagen fiber network in two regions, close the bead and in distance from the bead. Data are mean ± SE, n = 3 gels/group. scale bars is 100 µm.

References:

[1] Cheng, G., et al., 2009; 4 e4632
[2] Alshehri. A.M, et al., 2017. 159: 945-955
[3] Libring, S. et al., 2021.13: 13174440