Modifying Substrate Mechanics to Bioengineer an in vitro Tumor Microenvironment

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Pancreatic cancer (PC) remains resistant to most chemotherapy and radiation techniques. Consequently, its five-year survival rate is less than 6%. Most current studies elucidate how cell pathways or enzymes impact PC. This paper asserts that substrate mechanics and the tumor microenvironment (TME) dictate whether cancer metastasizes. Patient tissues were resected in surgery under approved protocols. The tumor xenografts were grown in immunodeficient mice, and pancreatic tumor cells (PTCs) were extracted via cardiac puncture. Tumorous, pancreatitis, and healthy tissues were indented using a custom multi-scale indention system (MSI) to determine their elastic moduli. Then polyacrylamide hydrogels were used to mimic the viscoelastic characteristics of the tissues. The hydrogels were coated in collagen proteins, and PTCs were cultured on the hydrogels. Cell viability assays (CVA) were performed to determine how rigidity impacts cell growth. Phalloidin actin stains and DAPI nuclear stains were conducted to determine cell area. Alamar blue assays were conducted to quantify enzymatic activity. It was found that PC tumors are approximately 10 times stiffer than the normal pancreas, and it was determined that PA hydrogel chemistry yields gels in the same range. CVAs revealed that PTCs grown on stiffer substrates proliferated more rapidly, approximately a 2-fold increase. PTCs had increased cell area on stiffer substrates and more enzymatic activity, approximately 30% more. Thus, PTCs are mechanosensitive, and petri dishes are inaccurate vessels to test cells in. Gemcitabine, a chemotherapy drug, will be cultured with PTCs. Cell proliferation assays will be performed to determine how the rigidity of the TME impacts chemoresistance.

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