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Mechanics and Malignancy: Biophysical Approaches for Investigating the Tumor Microenvironment

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Despite huge advances in the molecular regulators of cancer growth and metastasis, patient survival rates have largely stagnated, with over 90% of cancer-related deaths due to metastasis. The majority of cancer drugs target cancer cells in the primary tumor, which doesn't prevent the development of metastatic tumors from cells dormant in the tissues. Bone marrow derived mesenchymal stem cells (MSCs) that accumulate in the primary tumor due to their natural tropism for inflammatory tissues may also enhance the metastatic potential of tumor cells through direct interactions or paracrine signaling. A series of recent studies have highlighted that in addition to molecular changes, cancer cells also undergo biophysical changes. Though emerging work highlights the importance of tumor stromal cells and microenvironment in cancer progression, the interplay of these factors has not been fully investigated. My research combines molecular and gene expression analysis with quantitative biophysical analysis using sensitive mechanical tools (such as time-lapsed cell tracking, traction force microscopy, and particle tracking microrheology) to provide genetic and mechanical profiles of tumor and stromal cells in conditions that more closely mimic the tumor microenvironment. This approach has recently been used to demonstrate that ovarian cancer cells, which metastasize to the soft omentum fat pad, preferentially engraft on adipose-mimetic substrates or MSCs differentiated into soft adipocytes. Moreover, after engrafting they display a gene expression signature characteristic of epithelial-mesenchymal transition with corresponding increases in motility, proliferation, and chemoresistance. Though this preference for soft matrices is in contrast to what has been documented in breast and other cancers, our studies have confirmed that an increased malignant phenotype is still associated with higher traction forces. Work from my lab has also shown that both murine and human MSCs undergo dramatic cytoskeletal stiffening in response to pro-migratory molecules in the tumor microenvironment, including a cocktail of molecules released by tumor cells in culture and individual molecules like TGF-β1 and PDGF. The degree of stiffening is a key differentiating factor between MSCs and their less migratory fibroblast counterparts and even predictive of decreased MSC function with extended culture.