

Understanding and Exploiting Cancer Mechanobiology

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Abstract

Epithelial cells are classically known to respond to differences in extracellular matrix (ECM) stiffness by transitioning to a malignant, non-polarized state on stiffer ECM, i.e. Epithelial-Mesenchymal Transition (EMT). While this is akin to stiff tumors that one can detect with manual palpation, cancer fibrosis is dynamic and stiffening occurs over months to years. I will describe our efforts to mimic the onset of tumor-associated fibrosis using dynamic methacrylated-hyaluronic acid (MeHA) hydrogels. Contrary to previous observations, we find that collective decisions by mammary epithelial cells in 3D aggregates—called acini—indicate partial protection from the stiffened niche via molecular mechanisms that interpret stiffness. After cells leave this niche, however, mechanical changes can be remembered. In a parallel story, I will share our results on oral cancer, where cells that disseminate from the niche exhibit “mechanical memory” of their surroundings, and that memory can be used to “educate” their neighboring epithelial cells. I will conclude my presentation with the discovery of a physical marker—adhesion strength—that predicts both metastatic potential and survival rates. Cells disseminating from mammary tumors are weakly adherent, and when presorted by adhesion, primary tumors created from strongly adherent cells exhibit fewer lung metastases than weakly adherent cells or unsorted populations. Admixed cancer lines can be separated by label-free adhesive signatures using a next-generation flow chamber. When applied to metastatic tumors, the chamber retrospectively predicted metastatic disease from stromal samples with 100% specificity, 85% sensitivity, and AUC of 0.94. The chamber can also differentiate more weakly adherent human metastatic mammary tumors, e.g., invasive ductal carcinoma (IDC) or invasive lobular carcinoma (ILC), from non-invasive tumors, e.g., ductal carcinoma in situ (DCIS). These results together suggest how, unlike other senescent cells, metastatic cancer cells use weak adhesion to navigate against stiffness gradients and how we can use this to our advantage to assess metastatic potential of patient tumors.