Hyaluronic Acid-Based Hydrogels with Dynamic and Tunable Stiffness for Probing Breast Cancer Cell Response to Matrix Mechanics

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Epithelial-Mesenchymal Transition (EMT) is a dynamic multi-step process that is important during wound healing and organ development, and EMT can also contribute to fibrosis and cancer progression. During EMT, epithelial cells lose cell-cell interactions and exhibit increased cell motility and invasion. An increase in tissue stiffness due to mechanical and compositional changes of the extracellular matrix (ECM) is a hallmark of diseases such as fibrosis and cancer. Previous studies have used hydrogel materials with static mechanical properties to monitor cellular response to biophysical cues such as matrix stiffness. In general, hydrogels with dynamic control of stiffness can better mimic the cellular microenvironment. Here, we synthesized and characterized hyaluronic acid (HA)-based hydrogels with dynamic and tunable stiffnesses mimicking that of normal and tumorigenic mammary tissue. HA modified with methacrylic anhydride (MeHA) was cross-linked with the photo-initiator Irgacure in the presence of UV light to create hydrogels with static mechanical properties. For dynamic hydrogels, in addition to Irgacure, the tetrafunctional crosslinker PETMP, which can hydrolytically degrade, was also used to crosslink MeHA. MDA-MB-231 breast cancer cells, which exhibit a mesenchymal phenotype, underwent morphological changes with a gradual decrease in cell spread area and aspect ratio as the modulus of the MeHA-Irgacure-PETMP hydrogel decreased as a function of time. Immunofluorescence staining revealed that MDA-MB-231 cells began to express the epithelial marker E-cadherin and exhibited reorganization of vimentin intermediate filaments when cultured on soft and dynamically softening HA hydrogels. Thus, soft HA hydrogels promote the loss of mesenchymal features and acquisition of epithelial features in MDA-MB-231 cells. These findings suggest that targeting matrix mechanics may be a useful therapeutic approach for cancer.