# Impact of Viscosity on Human Hepatoma Spheroids in Soft Core–Shell Microcapsules


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## Abstract


The extracellular environment regulates the structures and functions of cells, from the molecular to the tissue level. However, the underlying mechanisms influencing the organization and adaptation of cancer in three-dimensional (3D) environments are not yet fully understood. In this study, the influence of the viscosity of the environment is investigated on the mechanical adaptability of human hepatoma cell (HepG2) spheroids in vitro, using 3D microcapsule reactors formed with droplet-based microfluidics. To mimic the environment with different mechanical properties, HepG2 cells are encapsulated in alginate core–shell reservoirs (i.e., microcapsules) with different core viscosities tuned by incorporating carboxymethylcellulose. The significant changes in cell and spheroid distribution, proliferation, and cytoskeleton are observed and quantified. Importantly, changes in the expression and distribution of F-actin and keratin 8 indicate the relation between spheroid stiffness and viscosity of the surrounding medium. The increase of F-actin levels in the viscous medium can indicate an enhanced ability of tumor cells to traverse dense tissue. These results demonstrate the ability of cancer cells to dynamically adapt to the changes in extracellular viscosity, which is an important physical cue regulating tumor development, and thus of relevance in cancer biology.