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Mathematical Modeling of Avascular Tumor Growth and Invasion

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Abstract : Cancer has been recognized as one of the most challenging problems in biology and medicine. Aggressive tumors are a lethal type of cancers characterized by high genomic instability, rapid progression, invasiveness, and therapeutic resistance. Their behavior involves complicated molecular biology and consequential dynamics. Although tremendous effort has been devoted to developing therapeutic approaches, there is still a huge need for new insights into the dark aspects of tumors. As one of the key requirements in better understanding the complex behavior of tumors, mathematical modeling and continuum physics, in particular, play a pivotal role. Mathematical modeling can provide a quantitative prediction on biological processes and help interpret complicated physiological interactions in tumors microenvironment. The pathophysiology of aggressive tumors is strongly affected by the extracellular cues such as stresses produced by mechanical forces between the tumor and the host tissue. During the tumor progression, the growing mass displaces the surrounding extracellular matrix (ECM), and due to the level of tissue stiffness, stress accumulates inside the tumor. The produced stress can influence the tumor by breaking adherent junctions. During this process, the tumor stops the rapid proliferation and begins to remodel its shape to preserve the homeostatic equilibrium state. To reach this, the tumor, in turn, upregulates epithelial to mesenchymal transit-inducing transcription factors (EMT-TFs). These EMT-TFs are involved in various signaling cascades, which are often associated with tumor invasiveness and malignancy. In this work, we modeled the tumor as a growing hyperplastic mass and investigated the effects of mechanical stress from surrounding ECM on tumor invasion. The invasion is modeled as volume-preserving inelastic evolution. In this framework, principal balance laws are considered for tumor mass, linear momentum, and diffusion of nutrients. Also, mechanical interactions between the tumor and ECM is modeled using Ciarlet constitutive strain energy function, and dissipation inequality is utilized to model the volumetric growth rate. System parameters, such as rate of nutrient uptake and cell proliferation, are obtained experimentally. To validate the model, human Glioblastoma multiforme (hGBM) tumor spheroids were incorporated inside Matrigel/Alginate composite hydrogel and was injected into a microfluidic chip to mimic the tumor’s natural microenvironment. The invasion structure was analyzed by imaging the spheroid over time. Also, the expression of transcriptional factors involved in invasion was measured by immune-staining the tumor. The volumetric growth, stress distribution, and inelastic evolution of tumors were predicted by the model. Results showed that the level of invasion is in direct correlation with the level of predicted stress within the tumor. Moreover, the invasion length measured by fluorescent imaging was shown to be related to the inelastic evolution of tumors obtained by the model.

Keywords : cancer, invasion, mathematical modeling, microfluidic chip, tumor spheroids
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