Journal of Theoretical Biology 433 (2017) 49–56

Contents lists available at ScienceDirect

Journal of Theoretical Biology

journal homepage: www.elsevier.com/locate/jtbi

A nonlinear poroelastic theory of solid tumors with glycosaminoglycan swelling

Shi-Lei Xue, Shao-Zhen Lin, Bo Li*, Xi-Qiao Feng*

Institute of Biomechanics and Medical Engineering, Department of Engineering Mechanics, Tsinghua University, Beijing, 100084, P R China

ARTICLE INFO

Article history:
Received 26 April 2017
Revised 12 July 2017
Accepted 26 August 2017
Available online 30 August 2017

Keywords:
Tumor mechanobiology
Mechanical property
Poroelasticity
Compression resistance
Glycosaminoglycan swelling

ABSTRACT

Mechanics plays a crucial role in the growth, development, and therapeutics of tumors. In this paper, a nonlinear poroelastic theory is established to describe the mechanical behaviors of solid tumors. The free-swollen state of a tumor is chosen as the reference state, which enables us to avoid pursuing a dry and stress-free state that is hard to achieve for living tissues. Our results reveal that the compression resistance of a tumor is primarily attributed to glycosaminoglycan (GAG) swelling, and the compactness of cell aggregates is found to affect tumor consolidation. Over-expressed GAGs and dense cell aggregates can stiffen the tumor, a remodeling mechanism that makes the tumor with higher elastic modulus than its surrounding host tissues. Glycosaminoglycan chains also influence the transient mechanical response of the tumor by modulating the tissue permeability. The theoretical results show good agreement with relevant experimental observations. This study may not only deepen our understanding of tumorigenesis but also provide cues for developing novel anticancer strategies.

1. Introduction

Tumor development is often accompanied with the change in mechanical properties (e.g., stiffness). Experiments showed that solid tumors undergo stiffening and are in general stiffer than the surrounding healthy tissues (Paszek et al., 2005). On one hand, this feature has been harnessed to detect cancer (Sinkus et al., 2000). On the other hand, tumor rigidity may compromise efficacy of chemotherapy (Netti et al., 2000) and promote tumor metastasis (Levental et al., 2009). In addition, by enhancing the compression resistance of solid tumor, this stiffening mechanism contributes to the growth-induced compressive stresses and elevates the interstitial fluid pressure, both of which are hallmarks of the mechanical microenvironment of cancers (Jain et al., 2014). For example, compressive stresses in tumors can inhibit the proliferation of cancer cells, increase their invasive potential, and collapse the blood vessels (Helmlinger et al., 1997; Tse et al., 2012; Padera et al., 2004; Stylianopoulos et al., 2012).

Although solid tumors usually exhibit higher stiffness than their host tissues, tumor cells generally have lower elastic moduli than the corresponding normal cells (Fritsch et al., 2010; Plodinec et al., 2012). This apparent contradiction can be mainly attributed to the mechanical resistance capacity of tumor extracellular matrix (ECM) (Butcher et al., 2009; Levental et al., 2009). ECM is primarily composed of collagen fibrils and glycosaminoglycan (GAG) chains, both of which contribute to the mechanical property of the ECM (Frantz et al., 2010). The collagen network maintains the mechanical integrity of the ECM, and the excess deposition and crosslinking of collagen fibrils can promote tumor stiffening (Levental et al., 2009). Interspersed in the collagen network, GAG chains imbibe water, resulting in a gel-like phase that contributes to the compression resistance of tumors (Provenzano et al., 2012; DuFort et al., 2016; Voutouri et al., 2016).

Due to their relevance to tumor growth, metastasis and therapeutics, it is of importance to understand the mechanical properties of tumors (Stylianopoulos et al., 2013; Voutouri et al., 2014). A solid tumor can be treated as a multi-phase material consisting of a solid organic matrix, which is composed of cell aggregates and ECM, and an interstitial fluid phase, which is predominantly water (Jain, 1987; Chatelain et al., 2011). The traditional mixture theory proposed by Trusesdell (1957) is often applied to model soft tissues consisting of multiple phases (Trusesdell and Noll, 2004). For example, the swelling and deformation of articular cartilage have been elucidated by considering it as a mixture of solid matrix, water, and the ionic species (Lai et al., 1991). In the mixture theory, each specie is controlled by balance equations (for mass and linear momentum) and thermodynamic laws, and the overall responses of the whole system are determined by the rule-of-mixture relations (Humphery and Rajagopal, 2002; Byrne and Preziosi, 2003; Giverso and Preziosi, 2012; Wise et al., 2008; Ciarletta et al., 2011; Sciumè et al., 2014; Mascheroni et al., 2016). The mixture theory invokes various constitutive

* Corresponding authors.
E-mail addresses: libome@tsinghua.edu.cn (B. Li), fengxq@tsinghua.edu.cn (X.-Q. Feng).

http://dx.doi.org/10.1016/j.jtbi.2017.08.021
0022-5193/

relations and a number of associated parameters and, therefore, it is difficult to be solved. As an alternative, we here employ the poroelastic theory developed by Biot (1941) to describe the mechanical behaviors of tumors. In the poroelastic theory, the multiphase system is homogenized as a continuum with a solid skeleton and pore fluids. Thereby, the tissues can be studied in the framework of continuum mechanics. The solid and fluids follow distinct kinematics, and the interaction of solid and fluids are also taken into consideration (Coussy, 2004). The poroelastic theory can well describe the basic features of multiphase systems and account for the complex chemomechanical coupling phenomena of solid tumors (Roose et al., 2003; Garikipati et al., 2004; Loret and Simões, 2005; Grillo et al., 2012; Xue et al., 2016, 2017; Ambrosi et al., 2017). However, the mechanical characteristics and relevant biochemical mechanisms of solid tumors remain unclear as yet.

In the present paper, a nonlinear poroelastic theory considering GAG swelling is formulated to capture the mechanical responses of a solid tumor. We choose the free-swollen state of the tumor as the reference state, and decompose the overall tissue deformation into a swelling part and an elastic deformation part. By considering the specific features of tumor tissues, we establish the free-energy function and the kinetic law of solid tumors. As an example, the steady state and the transient response of a tumor undergoing confined compression are analyzed. Our theoretical results are validated by experiments in the literature.

2. Theoretical model

Since solid tumors are basically composed of the solid skeleton (i.e., cells and collagen fibrils) and the interstitial space filled with GAG chains and physiological solutions, the theory of poroelasticity is suitable to capture the macroscopic mechanics of solid tumors. For a porous soft tissue without externally applied loads, the skeleton is stretched due to the swelling of GAG chains. Therefore, the total deformation of the skeleton consists of two portions arising from GAG swelling and mechanical loading. In this theory, the swollen, homogenous, and stress-free state is chosen as the reference state (Lucantonio et al., 2013; Vernerey, 2016), which is close to the physiological state of living tissues and the initial state of samples in the experimental environment (Mow et al., 1984; Netti et al., 2000). This enables us to directly compare the theoretical prediction with the experimental results, such as the stresses (and strains) measured by compression tests and the contents of collagen and GAGs estimated by biochemical analysis (Netti et al., 2000).

The positions of a representative material point in the reference and current deformed configurations are described by $\mathbf{X}$ and $\mathbf{x}$, respectively. Let $\mathbf{F}=\partial\mathbf{x}/\partial\mathbf{X}$ denote the deformation gradient of the tumor. To account for the swelling-induced skeleton deformation, we further introduce a dry configuration of the skeleton, which is actually the initial state of the skeleton before any deformation. The deformation gradient $\mathbf{F}_0=\partial\mathbf{X}/\partial\tilde{\mathbf{X}}$ maps an infinitesimal element in the dry configuration to the reference configuration, where $\tilde{\mathbf{X}}$ labels the material point in the dry skeleton. For the case when the solid skeleton is homogeneous and isotropic, we have $\mathbf{F}_0=\lambda_0\mathbf{I}$, with λ_0 being the initial skeleton stretch due to GAG swelling. Consequently, the total deformation gradient of the skeleton, $\tilde{\mathbf{F}}=\partial\mathbf{x}/\partial\tilde{\mathbf{X}}$, can be described by $\tilde{\mathbf{F}}=\mathbf{F}\cdot\mathbf{F}_0$.

We use the following compressible and isotropic Neo–Hookean strain energy density function to characterize the skeleton in the dry configuration

$$\tilde{W}_{\mathrm{sk}}=\frac{1}{2}\tilde{\varphi}_{\mathrm{sk}}\mu_{\mathrm{sk}}\left(\tilde{I}_1-3-2\ln\tilde{J}\right), \tag{1}$$

where $\tilde{\varphi}_{\mathrm{sk}}$ is the volume fraction of the skeleton in the dry configuration, μ_{sk} is the initial shear modulus of the skeleton, $\tilde{I}_1=\mathrm{tr}(\tilde{\mathbf{F}}^{\mathrm{T}}\cdot\tilde{\mathbf{F}})$, and $\tilde{J}=\det(\tilde{\mathbf{F}})$ is the volumetric ratio. From $\tilde{\mathbf{F}}=\mathbf{F}\cdot\mathbf{F}_0$ and $\mathbf{F}_0=\lambda_0\mathbf{I}$, we have $\tilde{I}_1=\lambda_0^2 I_1$, and $\tilde{J}=J_0 J$, where $I_1=\mathrm{tr}(\mathbf{F}^{\mathrm{T}}\cdot\mathbf{F})$, $J=\det(\mathbf{F})$, and $J_0=\det(\mathbf{F}_0)=\lambda_0^3$. Letting W_{sk} and φ_{sk} denote the free energy and volume fraction of the solid skeleton in the reference configuration, respectively, we have $W_{\mathrm{sk}}=\tilde{W}_{\mathrm{sk}}/J_0$ and $\varphi_{\mathrm{sk}}=\tilde{\varphi}_{\mathrm{sk}}/J_0$. Hence, W_{sk} can be written as

$$W_{\mathrm{sk}}=\frac{1}{2}\varphi_{\mathrm{sk}}\mu_{\mathrm{sk}}\left(\lambda_0^2 I_1-3-2\ln J-6\ln\lambda_0\right), \tag{2}$$

where λ_0 can be determined from the case of free-swelling (i.e., $\mathbf{F}=\mathbf{I}$).

The GAGs immersed in the ECM are short chains that carry negative charges and capable of imbibing water (Auckland and Nicolaysen, 1981; Swartz and Fleury, 2007). GAG chains bind to a protein core and form macromolecules, such as proteoglycans and hyaluronan. By using the Flory-Huggins theory, the free energy W_{sol} resulting from mixing the GAGs and water molecules can be estimated as (Flory, 1942; Huggins, 1942)

$$W_{\mathrm{sol}}=k_{\mathrm{B}}TC_{\mathrm{w}}\left(\ln\frac{\nu_{\mathrm{w}}C_{\mathrm{w}}}{\varphi_{\mathrm{G}}+\nu_{\mathrm{w}}C_{\mathrm{w}}}+\frac{\chi\varphi_{\mathrm{G}}}{\varphi_{\mathrm{G}}+\nu_{\mathrm{w}}C_{\mathrm{w}}}\right), \tag{3}$$

where C_{w} and φ_{G} are the concentration of the solvent and the volume fraction of GAG chains in the reference configuration, respectively; ν_{w} the volume of a water molecule, k_{B} the Boltzmann constant, T the absolute temperature, and χ a dimensionless parameter characterizing the enthalpy of mixing.

Besides, the interstitial fluid are solutions composed of water molecules and free ions. Hence, mixing the fluid constituents also contributes to the free energy as (Hong et al., 2010)

$$W_{\mathrm{ion}}=k_{\mathrm{B}}T\sum_b C_b\left(\ln\frac{C_b}{\nu_{\mathrm{w}}C_{\mathrm{w}}c_b^{\mathrm{ref}}}-1\right), \tag{4}$$

where C_b is the concentration of solute b in the reference configuration and c_b^{ref} the reference concentration of solute b.

In addition, we introduce two constraint conditions. The first is the saturation constraint, that is, the sum of the volumes of the solid skeleton, GAG chains and water molecules equals the total volume of the tumor tissue. The backward Piola transformation of this constraint can be written as (Hong et al., 2010; Xue et al., 2017)

$$\varphi_{\mathrm{G}}+\varphi_{\mathrm{sk}}+\nu_{\mathrm{w}}C_{\mathrm{w}}=J. \tag{5}$$

For soft tissues, the porosity n can be defined as the volume fraction of the interstitial space, that is, $n=\nu_{\mathrm{w}}C_{\mathrm{w}}$. Using Eq. (5), we further have $n=J-\varphi_{\mathrm{sk}}-\varphi_{\mathrm{G}}$. Both the solid and fluid constituents of the tumor are assumed incompressible.

The second constraint condition is the electroneutrality, that is, the net charge everywhere in the tissue vanishes (Gu et al., 1998; Cheng et al., 2015). In tumors, charges prevailingly come from the GAG chains and free ions in the interstitial fluid. The electroneutrality condition can be expressed as

$$\sum_\beta ez_\beta C_\beta+ez_{\mathrm{G}}\frac{\varphi_{\mathrm{G}}}{\nu_{\mathrm{G}}}=0, \tag{6}$$

where e is the elementary charge, z_β the valence of fluid constituent β, z_{G} the charge carried by each GAG chain, and ν_{G} the volume per GAG chain.

Taken together, the Helmholtz free energy density of solid tumors involves the contributions from stretching the skeleton W_{sk}, mixing the GAG chains and the solvent W_{sol}, and mixing the solvent and solutes W_{ion}. Combining Eqs. (5) and (6), the free energy density finally reads

$$W=W_{\mathrm{sk}}+W_{\mathrm{sol}}+W_{\mathrm{ion}}+\Lambda\left(\varphi_{\mathrm{G}}+\varphi_{\mathrm{sk}}+\nu_{\mathrm{w}}C_{\mathrm{w}}-J\right)+\Phi\left[\sum_\beta ez_\beta C_\beta+ez_{\mathrm{G}}\frac{\varphi_{\mathrm{G}}}{\nu_{\mathrm{G}}}\right], \tag{7}$$