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Evolution of osmotic pressure in solid tumors

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ABSTRACT

The mechanical microenvironment of solid tumors includes both fluid and solid stresses. These stresses play a crucial role in cancer progression and treatment and have been analyzed rigorously both mathematically and experimentally. The magnitude and spatial distribution of osmotic pressures in tumors, however, cannot be measured experimentally and to our knowledge there is no mathematical model to calculate osmotic pressures in the tumor interstitial space. In this study, we developed a triphasic biomechanical model of tumor growth taking into account not only the solid and fluid phase of a tumor, but also the transport of cations and anions, as well as the fixed charges at the surface of the glycosaminoglycan chains. Our model predicts that the osmotic pressure is negligible compared to the interstitial fluid pressure for values of glycosaminoglycans (GAGs) taken from the literature for sarcomas, melanomas and adenocarcinomas. Furthermore, our results suggest that an increase in the hydraulic conductivity of the tumor, increases considerably the intratumoral concentration of free ions and thus, the osmotic pressure but it does not reach the levels of the interstitial fluid pressure.

1. Introduction

Generation and accumulation of physical forces during growth play a crucial role in tumor progression and response to treatment (Jain et al., 2014). Physical forces stem from both the fluid and the solid phase of a tumor (Stylianopoulos et al., 2013). The forces of the fluid phase correspond to the hydrostatic fluid pressure of the tumor interstitial space, the osmotic pressure owing to the transport of positive and negative ions and the existence of fixed charges in the tumor microenvironment, and also include the vascular pressure and the fluid shear stress on the luminal side of the tumor blood vessel wall (Koumoutsakos et al., 2013). The forces of the solid phase of tumors are divided into two types: the residual stresses developed due to mechanical interactions between solid constituents of the tumor microenvironment and particularly interactions between the collagen fibers, glycosaminoglycans (GAGs: hyaluronic acid, heparin sulfate, chondroitin sulfate and keratin sulfate) and cells (Stylianopoulos et al., 2012), and the stresses exerted on the entire tumor by the surrounding normal tissue, which resists to tumor expansion.

Solid stresses in the interior of tumors are compressive and when applied directly to cancer cells reduce their proliferation rate, induce apoptosis and increase their metastatic and invasive potential (Cheng et al., 2009; Helmlinger et al., 1997; Tse et al., 2012). These stresses are also applied to intratumoral blood vessels causing their compression (Padera et al., 2004; Stylianopoulos et al., 2013). Vessel compression, in turn, reduces perfusion and as a result hinders the delivery of blood-borne therapeutic agents. Cancer and stromal cells, collagen and hyaluronic acid contribute to the generation of solid stresses, while solid stress alleviation by selective depletion of any of these components decompresses tumor blood vessels and improves perfusion and drug delivery (Chauhan et al., 2013; Stylianopoulos et al., 2012).

Interstitial fluid pressure (IFP) in the interior of the tumor is uniformly elevated and can be as high as the vascular pressure (Boucher and Jain, 1992). This eliminates pressure gradients across the tumor vessel wall, and hinders the transvascular transport of macromolecules and nanomedicines (Jain and Stylianopoulos, 2010). Significant progress has been also made on the role of microvascular fluid flow and vessel wall shear stress in tumor progression, metastasis and response to treatment (Jain et al., 2014; Koumoutsakos et al., 2013). Little work has been performed, however, on the effect of the osmotic pressure in the tumor microenvironment. The high negative charge density of GAGs attracts cations and establishes a Donnan distribution of diffusible species that is responsible for the osmotic pressure. Many tumors are rich in hyaluronic acid as well as in other GAGs and recently researchers hypothesized that the osmotic pressure might contribute to the compression of intratumoral blood vessels in a way similar to solid stress (Provenzano et al., 2012; Provenzano and Hingorani, 2013). The magnitude and distribution of osmotic pressures in tumors, however, cannot be measured experimentally and to our knowledge there is no mathematical model to calculate osmotic pressures in the interstitial space of tumors.

In this study, we extended our biomechanical model of tumor growth (Stylianopoulos et al., 2013) to account for the transport of free ions and fixed charges in the tumor microenvironment.

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We correlated the concentration of fixed charges to the amount of GAGs in the tumor interior and calculated the levels of osmotic pressure for different concentrations of GAGs, using values from the literature. Our model suggests that for physiologically relevant GAG concentrations for tumors (i.e., on the order of 0.4 mg/g wet tissue), osmotic pressures are relatively low and should not contribute to the compression of intratumoral blood vessels. Furthermore, model predictions elucidate the dependence of the concentration of free ions and the levels of osmotic pressure on the hydraulic conductivity of the tumor interstitial space.

2. Methods

2.1. Multiplicative decomposition of the deformation gradient tensor

A detailed description of the methodology can be found in the Supplementary material. Tumor growth is modeled using the multiplicative decomposition of the deformation gradient tensor, **F** (Ambrosi and Mollica, 2002; Rodriguez et al., 1994). The tensor, **F** is decomposed to three independent motions: the growth of the tumor, $\mathbf{F}_g$, the generation of residual stresses, $\mathbf{F}_r$, and the elastic mechanical interactions, $\mathbf{F}_e$ (Fig. 1d in (Skalak et al., 1996)). Therefore, the final expression of **F** becomes,

$$\mathbf{F}=\mathbf{F}_e\mathbf{F}_g\mathbf{F}_r. \tag{1}$$

We considered $\mathbf{F}_r$ to be an isotropic tensor, i.e., $\mathbf{F}_r=\lambda_r\mathbf{I}$, and the value of the residual stretch ratio λ_r was calculated by a bi-exponential expression as a function of the volume of the tumor based on previous research (Stylianopoulos et al., 2013).

Tumor growth was also taken to be isotropic, i.e., $\mathbf{F}_g=\lambda_g\mathbf{I}$, where the growth stretch ratio, λ_g was calculated as a function of the oxygen concentration in the tissue according to (MacLaurin et al., 2012; Roose et al., 2003) (details in Supplementary material). The elastic component of the deformation gradient tensor was calculated as $\mathbf{F}_e=\mathbf{F}(\mathbf{F}_r\mathbf{F}_g)^{-1}$.

The tumor was taken to be isotropic and governed by the compressible neo-Hookean constitutive equation with strain energy density function given by

$$W=0.5\mu(-3+I_1)+0.5\kappa(-1+J_e)^2, \tag{2}$$

where μ is the shear modulus, κ is the bulk modulus, J_e is the determinant of the elastic deformation gradient tensor $\mathbf{F}_e$, $II_1=I_1J_e^{-2/3}$, and I_1 is the first invariant of the right Cauchy–Green deformation tensor, evaluated from $\mathbf{F}_e$.

2.2. Implementation of Triphasic theory

The equations for solid and fluid phase conservation are:

$$\frac{d\varphi^s}{dt}+\nabla\cdot(\mathbf{v}^s\varphi^s)=S^s \tag{3}$$

$$\frac{d\varphi^w}{dt}+\nabla\cdot(\mathbf{v}^w\varphi^w)=Q \tag{4}$$

where φ^s and φ^w are the volume fractions of the solid and fluid phase, respectively and $\mathbf{v}^s$ and $\mathbf{v}^w$ are the corresponding solid and fluid velocities. S^s is the creation/degradation of the solid phase and Q describes the fluid entering the tissue from the vasculature and exiting the tissue through the lymphatics.

The quantity S^s in Eq. (3) was calculated as (Roose et al., 2003):

$$S^s=\frac{\lambda_c c_{ox}}{k_c+c_{ox}}F\varphi^s(1-\varphi^s) \tag{5}$$

where c_{ox} is the oxygen concentration, F is a parameter, which accounts for the inhibitory effect of solid stress on tumor growth and λ_c and k_c are constant parameters derived from experimental data (Casciari et al., 1992a; Casciari et al., 1992b) (details in Supplementary material).

The quantity Q in Eq. (4) was calculated from Starling's approximation (Baxter and Jain, 1989):

$$Q=\frac{L_pS}{V}(p_v-p)-\frac{L_{pl}S_l}{V_l}(p-p_l), \tag{6}$$

where p_v, L_p and (S/V) are the micro-vascular pressure, hydraulic conductivity and vascular density of the blood vessels, respectively, and p_l, L_{pl} and $(S/V)_l$ are the corresponding quantities for the lymphatics.

The momentum balance equations for a triphasic medium are (Lu et al., 2010; Sun et al., 1999):

$$\nabla\cdot(\boldsymbol{\sigma}^s-p\mathbf{I})=\mathbf{0}, \tag{7}$$

$$-k\nabla^2p+\nabla\cdot\mathbf{v}^s=Q+S^s+k\left[F_cc^f\nabla^2\Psi+F_c\nabla c^f\nabla\Psi-RT(\varphi-1)\nabla^2c^k\right], \tag{8}$$

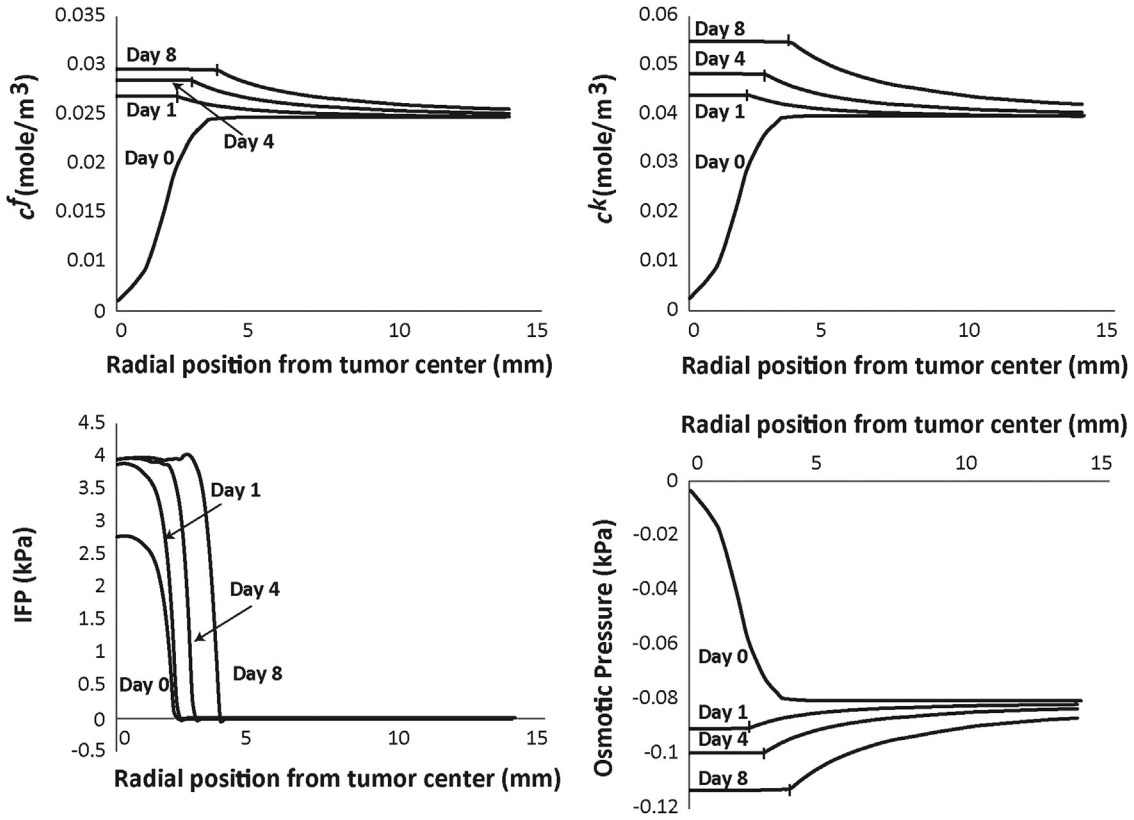

Fig. 1. Spatial distribution of the concentration of fixed, c^f, and free, c^k, ions, of the interstitial fluid pressure (IFP) and the osmotic pressure in the tumor and the surrounding normal tissue. The GAG content of the tumor varied from zero to 0.4 mg/g wet wt at day 8. The GAG content of the normal tissue was set to 4.5 mg/g wet wt. Vertical lines on the plot depict the interface of tumor and normal tissue.