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A non-equilibrium thermodynamic model for tumor extracellular matrix with enzymatic degradation

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ABSTRACT

The extracellular matrix (ECM) of a solid tumor not only affords scaffolding to support tumor architecture and integrity but also plays an essential role in tumor growth, invasion, metastasis, and therapeutics. In this paper, a non-equilibrium thermodynamic theory is established to study the chemo-mechanical behaviors of tumor ECM, which is modeled as a poroelastic polyelectrolyte consisting of a collagen network and proteoglycans. By using the principle of maximum energy dissipation rate, we deduce a set of governing equations for drug transport and mechanosensitive enzymatic degradation in ECM. The results reveal that osmosis is primarily responsible for the compression resistance of ECM. It is suggested that a well-designed ECM degradation can effectively modify the tumor microenvironment for improved efficiency of cancer therapy. The theoretical predictions show a good agreement with relevant experimental observations. This study aimed to deepen our understanding of tumor ECM may be conducive to novel anticancer strategies.

1. Introduction

A solid tumor consists of cancer cells, host cells, and an extracellular matrix (ECM). The ECM not only provides a mechanical scaffold regulating the behaviors of all cells in the tumor but also plays a crucial role in the development, invasion, and metastasis of cancer. The physiological and pathological significance of tumor ECMs has been illustrated by a wide diversity of clinical syndromes (Frantz et al., 2010; Lu et al., 2012). In spite of their tissue-specific nature, the ECM can be considered as a polyelectrolyte gel primarily consisting of a collagen fibril network entangled with glycosaminoglycans (GAGs) (Fig. 1), which carry negative charges and imbibe water (Aukland, 1981; Levick, 1987; Swartz and Fleury, 2007; Provenzano et al., 2012; Stylianopoulos et al., 2012). Collagen fibers, constituting up to 90% of the ECM volume, are remarkably stiff in tension and endow the tumor tissues with a higher tensile strength (Frantz et al., 2010; Gilkes et al., 2014; Jain et al., 2014). By contrast, GAGs are responsible for the compressive resistance of tumors owing to their capacity to trap water (Frantz et al., 2010; DuFort et al., 2016). This gel-like structure confers elasticity, porosity, insolubility, and other physical properties on ECM, and determines its role in scaffolding to sustain mechanical stresses and transport fluids.

Since anticancer drugs need to penetrate through the vessel wall and ECM to reach the target cancer cells, the mechanical and transport properties of the ECM play a vital role in drug-based cancer treatment (Jain and Stylianopoulos, 2010; Miao et al., 2015). However, the differential growth of tumors commonly elicits compressive stresses in the surrounding ECM as a

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Nomenclature

Force and deformation

$\mathbf{P}$	First Piola–Kirchhoff stress tensor
$\boldsymbol{\sigma}(\sigma_i)$	Cauchy stress tensor (and its principal components)
$\sigma_c'(\sigma_c)$	Applied uniaxial compressive stress (and its absolute value)
Λ	Overall fluid pressure
Π	Osmotic pressure
Φ	Electric potential
f	Force along collagen fibril
p	Fluid pressure in external solution
$\mathbf{F}(\lambda_i)$	Deformation gradient tensor (and its principal components)
$\mathbf{C}$	Right Cauchy–Green tensor
J	Volumetric ratio of deformation

Energy

E	Internal energy of ECM per unit volume in reference configuration
h_α	Enthalpy per fluid particle of constituent α
η	Entropy per unit volume in reference configuration
η_α	Entropy per fluid particle of constituent α
W	Helmholtz free energy per unit volume in reference configuration
μ_α	Gibbs free energy (i.e. chemical potential) per fluid particle of constituent α
ς	Energy dissipation rate per unit volume in reference configuration

Physical property

C_α, c_α	Nominal concentrations of fluid constituent α in reference and current configurations
$\mathbf{Q}_\alpha$, $\mathbf{q}_\alpha$	Mass fluxes of fluid constituent α
$\mathbf{V}_\alpha$, $\mathbf{v}_\alpha$	Relative velocities of fluid constituents
$h_{\alpha s}$, $h_{\alpha\beta}$	Diffusive drag coefficients of fluid constituents
ξ_α	Generation rate of fluid constituent α
φ_m, $\hat{\varphi}_m$	Volume fractions of solid component m in reference and current configurations
ν_α, ν_m	Volumes of a fluid particle of constituent α and a solid fibril (chain)
r_α, r_m	Radii of a spherical fluid particle of constituent α and cross-section of a solid fibril (chain)
z_α, z_2	Electric charges of a fluid particle of constituent α and a GAG chain
d_m	Degradation factor pertaining to solid component m
k_m^e	Enzymatic degradation rate
γ_m	Mechanosensitive factor
E_1	Tensile elastic modulus of collagen fibril
D_a, D_{a0}	Diffusivities in the ECM and free solution
k	Permeability of the ECM
η_{vis}	Viscosity of water
χ	Dimensionless measure of enthalpy of mixing
k_B	Boltzmann constant
T	Temperature

result of the rapid proliferation of cancer cells. High compressive stresses can convert fibroblasts into contractile myofibroblasts that are capable of producing new ECM, which further increases the stresses in and stiffens the tumor. The accumulated stresses and the enhanced stiffness may compress the blood vessels embedded in the ECM, impeding perfusion and delivery of anticancer drugs (Jain et al., 2014). In addition, experimental measurements and histological examination have revealed that the ECM in solid tumors is distinctly different from that in normal tissues. Generally, tumor interstitium is featured by higher collagen contents, and a lower diffusive coefficient (Jain, 1987). The dense ECM tends to block the diffusion of therapeutic particles (e.g., nanomedicines) and confine them in the vicinity of the blood vessels (Chauhan and Jain, 2013). These facts suggest that the tumor ECM can pose a physical barrier for the delivery of anticancer agents such as nanomedicines containing macromolecular drug particles. Therefore, the normalization or degradation of tumor ECM has been suggested as an effective strategy to improve the efficacy of therapeutic drugs (Jain and Stylianopoulos, 2010; Jain, 2013). Degrading the ECM components can help alleviate stress levels, improve tumor perfusion, and increase the accessible volume for accommodating mobile drug particles. To this end, enzyme molecules, hormone relaxin, transforming growth factor-β blockade, and tumor penetrating peptide have been shown to facilitate delivery of nanotherapeutics in solid tumors by enhancing interstitial transport (Mckee et al., 2006; Mok et al., 2007; Perentes et al., 2009; Liu et al., 2012; Sugahara et al., 2010).