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Tumor growth in complex, evolving microenvironmental geometries: A diffuse domain approach

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HIGHLIGHTS

- We study tumor growth in complex dynamic domains with elastic, deformable membranes.
- Tumor size and cell–basement membrane (BM) adhesion are positively correlated.
- Tumor size and BM stiffness are negatively correlated during tumor progression.
- Elevated BM stiffness promotes tumor invasion of the stroma.
- We develop an efficient numerical method, independent of space dimension and geometry.

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ABSTRACT

We develop a mathematical model of tumor growth in complex, dynamic microenvironments with active, deformable membranes. Using a diffuse domain approach, the complex domain is captured implicitly using an auxiliary function and the governing equations are appropriately modified, extended and solved in a larger, regular domain. The diffuse domain method enables us to develop an efficient numerical implementation that does not depend on the space dimension or the microenvironmental geometry. We model homotypic cell–cell adhesion and heterotypic cell–basement membrane (BM) adhesion with the latter being implemented via a membrane energy that models cell–BM interactions. We incorporate simple models of elastic forces and the degradation of the BM and ECM by tumor-secreted matrix degrading enzymes. We investigate tumor progression and BM response as a function of cell–BM adhesion and the stiffness of the BM. We find tumor sizes tend to be positively correlated with cell–BM adhesion since increasing cell–BM adhesion results in thinner, more elongated tumors. Prior to invasion of the tumor into the stroma, we find a negative correlation between tumor size and BM stiffness as the elastic restoring forces tend to inhibit tumor growth. In order to model tumor invasion of the stroma, we find it necessary to downregulate cell–BM adhesiveness, which is consistent with experimental observations. A stiff BM promotes invasiveness because at early stages the opening in the BM created by MDE degradation from tumor cells tends to be narrower when the BM is stiffer. This requires invading cells to squeeze through the narrow opening and thus promotes fragmentation that then leads to enhanced growth and invasion. In three dimensions, the opening in the BM was found to increase in size even when the BM is stiff because of pressure induced by growing tumor clusters. A larger opening in the BM can increase the potential for further invasiveness by increasing the possibility that additional tumor cells could invade the stroma.

1. Introduction

The tumor microenvironment (TME) is a dynamic structure with varying composition and distribution. The TME is composed of extracellular matrix and stromal cells and plays a crucial role on tumor progression and suppression (e.g., Tlsty and Coussens, 2006; Albini and Sporn, 2007; Place et al., 2011; Pickup et al., 2013). Changing the tissue geometry alters tension gradients, sites of mechanotransduction and the location of the proliferating, migrating and differentiating cells within a tissue. Even small local changes in cell–cell or cell–ECM interaction can have dramatic consequences for global tissue structure and function (DuFort et al., 2011). The mechanisms of communication between

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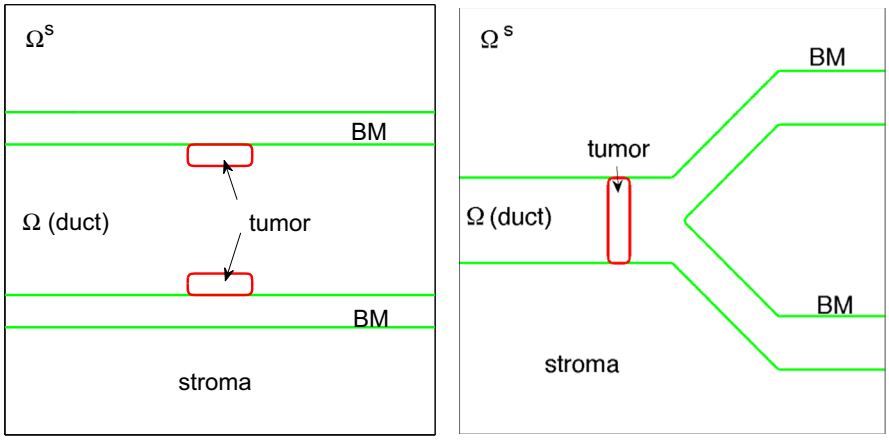

Fig. 1. The initial shape of tumor clusters (red; $\phi_T = 0.5$ contours) and basement membranes (green; $\psi = 0.5$ contours) in the 2D simulations. Left: simple duct; Right: branched duct. Note that in the simple duct, the membrane thickness is explicitly modeled by introducing the inner and outer membrane boundaries. (For interpretation of the references to color in this figure caption, the reader is referred to the web version of this paper.)

Table 1
Nondimensional parameters in the two dimensional numerical simulations.

ϵ	0.05	$\tilde{\epsilon}$	0.05
M	20.0	$\tilde{M}$	20.0
γ	0.2	ν_U	1.0
ν_p^H	0.2	ν_p^T	0.0
n_c	1.0	λ_M	1.0
λ_A	0.0	λ_N	3.0
λ_{dc}	1.0	λ_{deg}	20.0
λ_{prod}	200.0	λ_{decay}	10.0
$\lambda_{dm\psi}$	1.0	λ_{dmE}	1.0
λ_{mE}	0.0	λ_{vE}	0.0
D_m	0.1	χ_E	0.1
m_{mot}	1.0		

Table 2
Nondimensional parameters in the three dimensional numerical simulations.

ϵ	0.1	$\tilde{\epsilon}$	0.1
M	10.0	$\tilde{M}$	10.0
γ	0.2	ν_U	1.0
ν_p^H	0.2	ν_p^T	0.0
n_c	1.0	λ_M	1.0
λ_A	0.0	λ_N	3.0
λ_{dc}	1.0	λ_{deg}	1.0
λ_{prod}	100.0	λ_{decay}	20.0
$\lambda_{dm\psi}$	1.0	λ_{dmE}	1.0
λ_{mE}	0.0	λ_{vE}	0.0
D_m	0.1	χ_E	0.1
m_{mot}	1.0		

tumor cells and the TME are complex but fall into two main categories: contact-dependent mechanisms that involve cell–cell and cell–ECM adhesion and contact-independent mechanisms in which soluble molecules such as growth factors, chemokines and cytokines, and soluble subcellular organelles including microvesicles and exosomes play an essential role (Fang and DeClerck, 2013). The interaction between cancer cells and their microenvironment can largely determine the phenotype of the tumor (Mueller and Fusenig, 2004). Recently it has been shown that not only can the microenvironment enhance growth of the primary cancer but also facilitate its metastatic dissemination to distant organs (Joyce and Pollard, 2009; H. Li et al., 2007; X. Li et al., 2007).

Because tumor progression is difficult to approach by experimental methods alone, mathematical models and sophisticated computer simulations can help explain experimental and clinical observations and aid in assessing effective cancer treatment strategies. As a consequence, a keen interest in the mathematical modeling of cancer and numerical simulation of the tumor growth has persisted amongst mathematicians in recent years. A variety of modeling strategies are now available for investigating one or more aspects of cancer. For instance, in discrete cell-based approaches such as cellular automata and agent-based models the behavior of individual cells is simulated according to biological rules. Continuum models such as single-phase and multiphase mixture models treat tumors as a collection of cells at larger scales and principles from continuum mechanics such as mass and momentum conservation are used to construct partial differential equations and integro-differential equations governing the motion of cell densities, or volume fractions, stresses and cell velocities. See, for example, the recent reviews (Ribba et al., 2004; Quaranta et al., 2005; Hatzikirou et al., 2005; Nagy, 2005; Wodarz and Komarova, 2005; Byrne et al., 2006; Fasano et al., 2006; van Leeuwen et al., 2007; Roose et al., 2007; Graziano and Preziosi, 2007; Harpold et al., 2007; Drasdo and Höhme, 2007; Friedman et al., 2007; Sanga et al., 2007; Anderson and Quaranta, 2008; Bellomo et al., 2008; Cristini et al., 2008; Deisboeck et al., 2009, 2011; Byrne, 2010; Rejniak and McCawley, 2010; Cristini and Lowengrub, 2010; Lowengrub et al., 2010; Frieboes et al., 2011; Kim et al., 2011; Kam et al., 2012; Hatzikirou et al., 2012; Szabó and Merks, 2013; Baldock et al., 2013; Katira et al., 2013) for a collection of recent results.

There are a number of models that focus on different aspects of cell–cell and cell–ECM mechanical interactions on solid tumor progression. For example, the interaction of multiple tumor cell species has been modeled by multiphase mixture models (Ward and King, 1997, 1999; Please et al., 1998, 1999; Ambrosi and Presiosi, 2002; Breward et al., 2002, 2003; Byrne et al., 2003; Byrne and Preziosi, 2003; Franks et al., 2003a,b; Roose et al., 2003; Cristini et al., 2003, 2009; Araujo and McElwain, 2005a,b; Zheng et al., 2005; Chaplain et al., 2006; H. Li et al., 2007; X. Li et al., 2007; Macklin and Lowengrub, 2007; Tosin, 2008; Wise et al., 2008; Ambrosi and Preziosi, 2009; Ambrosi et al., 2009; Preziosi and Tosin, 2009a,b; Armstrong et al., 2009; Tracqui, 2009; Macklin et al., 2009; Frieboes et al., 2010; Preziosi and Vitale, 2011; Hawkins-Daarud et al., 2012). In these models, the mechanical effects of the stroma, the extracellular matrix, the basement membrane and the connective tissue were either neglected or highly idealized. Recently, Bresch et al. (2010) used the immersed interface boundary method to study the interactions of a growing tumor and a