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Origins and evolution of cell phenotypes in breast tumors

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Abstract

This study presents a stochastic model that correlates genomic instability with tumor formation. The model describes the time- and space-variant volumetric concentrations of cancer cells of various phenotypes in a breast tumor. The cells of epithelial origin in the cancerous breast tissue are classified into four different phenotypes, normal epithelial cells and the grade 1, grade 2 and grade 3 cancer cell types with increasing potential for growth and invasion. Equations governing the time course of volumetric concentrations of cell phenotypes are derived by using the principle of conservation of mass. Cell migration into and from the stroma is taken into account. The transformations between cell phenotypes are due to genetic inheritance and chromosome aberrations. These transformations are assumed to be stochastic functions of the local cell concentration. The simulations of the model for planar geometry replicate the shapes of human breast tumors and capture the time history of tumor growth in animal models. Simulations point to transformation of tumor cell population from heterogeneous compositions to a single phenotype at advanced stages of invasive tumors. Systematic variations of model parameters in the computations indicate the important roles the migration capacity, proliferation rate, and phenotype transition probability play in tumor growth. The model developed provides realistic simulations for standard breast cancer therapies and can be used in the optimization studies of chemotherapy, radiotherapy, hormone therapy and emerging individualized therapies for cancer.

Keywords: Stochastic; Model; Tumor; Growth; Heterogeneous; Breast

1. Introduction

Breast tissue is a composite of breast glandular epithelial cells lining the breast ducts, other cells, and the surrounding collagen-rich matrix called stroma containing blood vessels and lymph vessels (Going et al., 1988). The epithelial cells lining the breast ducts are highly differentiated cells that are responsive to hormonal stimulation (Rubin et al., 1999). It is from these cells that cancerous cells emerge during cycles of cell division. The cancer in breast tissue follows a well-recognized pathway from non-proliferating lesions to invasive cancers (Page and Rodgers, 1992; Querzoli et al., 1995). As the breast disease progresses, the well ordered architecture of the breast in the form of mammary glands is disrupted (Debnath et al., 2002). Another important structural change concerns the formation of new blood vessels induced by the tumor (Ahmed et al., 2001). Breast tumors must create their own blood supply in order to grow and as a byproduct of this imperfect vasculature, the interstitial pressure increases within the tumor (Jain, 2001). The presence of nutrients, the composition of surrounding cells, and the interstitial pressure in the tumor all affect the growth of cancer cells in a tumor.

Cell division cycle events fundamental to all cells, including DNA repair and recombination, checkpoint control of cell cycle, and transcription, are altered in cancer cells (Tyson et al., 2002). Factors such as age, child-bearing history, genetic predisposition and environmental factors including radiation effects in some cases speed up the time course of emergence of

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genetically unstable cells (Sachs et al., 1999; Ahmad et al., 2001; Wrensch et al., 2003). Genetic instability is characterized by an elevated rate at which cell genomes acquire changes. Large scale genomic changes such as chromosome aberrations perpetuate and even amplify with cycles of cell division (Lengauer, 1998; Bissell and Radisky, 2001; De la Torre et al., 2003). Chromosome aberrations associated with breast cancer are numerous and involve duplications, deletions as well as translocations (Mitelman et al., 2003).

Although a multitude of genetically altered cell types might emerge transiently at any point of time in a breast tumor as a result of cell division, only a few cell phenotypes will have the capacity to adapt to the environment and continue to survive to make up the tumor tissue (Heppner, 1984). Cancer cells in a tumor can be classified into a finite number of distinct phenotypes based on their cell division rates, altered adhesion properties, migration capacity, ability to induce blood vessel growth, and resistance to chemotherapy (Heppner, 1984; Chen et al., 1992). Using this observation as a premise, in this study, we have developed a mathematical model in order to explore by numerical simulation the effects of the biophysical properties of emerging cell phenotypes on the time course of tumor growth. In the model, heterogeneous cell population in the tumor is classified into finite number of cell phenotypes based on their potential for growth and invasion. Despite of multitude of external signals imposed on cells during the course of their lives, the repertoire of response (output phenotypes) is rather limited. The cells may migrate, divide, die (apoptosis/necrosis), differentiate or produce secretive molecules destined to influence neighboring or distant cells. Transition from one phenotype to another during cell division may depend on the local cell phenotype composition.

Discrete equations for local growth of cells of various phenotypes are obtained using the principle of mass conservation on migrating cell populations over a control volume. Numerical simulation of the model equations brings insights into the mechanisms of tumor growth by considering one at a time or in combination the effects of such factors as rate of apoptosis, transition rate to increasing levels of genomic instability, altered adhesion and motility, and angiogenesis. Our mathematical simulations also have the potential for developing optimization methods for delivery of chemotherapy, hormonal therapy, and recently emerging individualized therapies. As such, it stands to complement the recent bioinformatics studies investigating associations between gene expressions in breast cancer and patient survival (DeRisi et al., 1997; Sorlie et al., 2001; Jenssen et al., 2002).

The model presented in this article departs from earlier time-dependent growth models such as that of Hahnfeldt et al. (1999) and Sachs et al. (2001) in that it considers explicitly the spatial composition of the tumor mass at each point of the tumor during the entire time course of tumor growth. The earlier models emphasized overall tumor behavior in response to imposed medical interventions and had given priority to being minimally parameterized. Recent tumor growth models based on cellular automata (Patel et al., 2001) capture spatial variation of tumor growth at its early stages of growth, at a tumor size that would typically not detectible in the human. The model presented in this article complements these studies with its predictive capabilities of tumor composition during the time course of the growth of the tumor, even for large tumors.

2. Conceptual model

Our simulations begin with normal breast glandular cells occupying a well-defined region of the breast tissue. Cells with altered cell adhesion and growth regulation properties emerge from normal epithelial cells as a result of acquisition of genetic perturbations during many cycles of cell division. The resulting tumor tissue contains the following components: (i) solute, representing normal and cancer cells of various levels of metastasis potential, (ii) solvent, representing stroma, and (iii) base level normal cells including blood cells and those lining the micro blood vessels and lymph vessels. The tissue will grow and remodel and any change in the amount and spatial position of cancer cells will be compensated by a change in stroma and blood and lymph vessels.

Growing tumors manifest cellular phenotypes with distinctly different cell cycle rates and capacity for migration (Heppner, 1984). In the model, cells of epithelial origin in a breast tumor are classified into four categories as follows: normal breast epithelial cells (A_0) and cancerous cells of three distinct categories with increasing metastasis potential (A_1, A_2, A_3). Altered cells in A_1 category are assumed to differ from normal cells in terms of reduced cell–cell adhesion strength and ability to migrate into the surrounding stroma. Cells in the A_1 category respond to estrogen and progesterone, much like normal breast cells. Cancer cells of phenotype A_2 are assumed to represent a more aggressive phenotype than the cell population in A_1. These cells have little need to adhere to cells of the same tissue type for their growth. A_2 cells have greater proliferation rates and greater propensity to migrate than A_1 cells. A_3 cells represent the most aggressive phenotype. This phenotype has developed multiple drug resistance capability (Szachowicz-Petelska et al., 2001). A_3 cell phenotype is assumed to have the additional property of releasing peptides and other factors that stimulate the growth of micro-vessels (Tanaka et al., 2003).