

Physical Modeling of Cancer Tumor Growth: A Preliminary Review

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Abstract: A biological insight into cancer disease is presented. A general view to the cause of cancer at cellular level is given to the reader. Various stages of cancer tumor growth and spread are studied and the physical-biological parameters which might be considered in development of a physical model of cancer tumor are presented. It is concluded that at prevascular stage of tumor growth, the general rule of conservation of energy leads to the same growth curve as many other living organisms.

Key words: Cancer cell, metastasis, angiogenesis, Mathematical model, Tumor growth

INTRODUCTION

Cancer Cell:

It has long been appreciated that somatic cells have a finite proliferative capacity, termed the "Hayflick Limit" (Gewirtz, D.A., S.E. Holt, 2008). The mortal state of each cell is controlled by an "internal clock". During normal life, cells progress through a cell cycle which can be decomposed into a proliferative cycle, in which cells duplicate DNA and divide, and a quiescent phase where cells rest and wait for proliferative signals. Production of a Cancer cell is the outcome of a long and complex process that involves the accumulation of mutations in the genes that control cell replication and death. Due to several genetic mutations, cancer cells acquire the ability to produce growth signals while becoming less sensitive to anti-growth signals. Thus cancer cell possess the ability to escape from death processes and replicate indefinitely. It means cancer cell proliferation is mainly limited by the environmental supply of nutrients (Ribbaa, B., O. Sautb, 2006).

In early stages, cancer organizes itself as an invasive and adaptive network in a proliferation-invasion-proliferation sequence. It is known that proliferative cells can proceed to quiescence in the presence of anti-growth signals such as hypoxia, i.e. lack of oxygen, and/or nutrient deprivation. However, quiescent cells can return the proliferative cycle if growth signals appear.

Tumor Invasion and Cancer Cell Migration:

The formation of a tumor begins with the emergence of cellular heterogeneity called multicellular tumor spheroids (MTS). The initial failure in DNA replication occurs at a molecular level in the cell nucleus and accumulation of such cell leads to MTS. The process of tumor evolution involves many different inter-related biochemical and cellular processes at various spatial and temporal scales. Specifically, it is possible to distinguish three main scales in development of cancer: the sub-cellular, the cellular and the macroscopic scale (Bellomo, N., E. De Angelis, 2003). The growth of solid tumors occurs in two distinct phases: the initial growth being referred to as the relatively harmless avascular phase and the later growth as the vascular phase. During the early avascular stage of solid tumor growth there may be an immune response to the cancer from the host, with cells of the immune system, most notably T-lymphocytes, responding to and attacking the cancer cells (Gerischa, A., M.A.J. Chaplain, 2008). The ability to invade tissue is the main characteristic of cancer, an ability produced by indefinite replication of cells. Invasion of tissue by the cancer cells is the key component in metastasis, whereby cancer cells spread to distant parts of the host and initiate the growth of secondary tumors. Cancer cell migration through the extracellular matrix (ECM) is facilitated by production and emission of degradative enzymes. Other effects of these enzymes include cell proliferation, loss of cell-cell adhesion and enhanced cell-matrix adhesion which lead to active migration of cancer. Cells can deform their

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cytoplasm enabling them to anchor to neighboring locations in the tissue and detach earlier bonds, thus enabling them to move and therefore migrate in a specified direction. Invasion of surrounding tissue normally occurs after the tumor has reached a certain size and the peripheral rim of cells has started to disaggregate. Culture studies, which simulate a prevascular carcinoma have revealed that benign tumors are finite-sized and inhomogeneous assembly of cancer cells which appear in a bound spheroid form (Gewirtz, D.A., S.E. Holt, 2008; Ribbaa, B., O. Sautb, 2006; Bellomo, N., 2003). Genetic mutations, chemo-attractant gradients or a lack of nutrients in their current location can stimulate cell mobility and cause them to migrate.

Tumor Compactness:

Loss of compactness is the most crucial requisite for the tumor to invade distant organs in the body. This dictates that cell-cell bonds must be able to detach. In many tumors mutations leads to genetic changes related to the cells' adhesive system (Zacharaki, E.I., G.S. Stamatakos, 2004; Biswas, P.K., M.T.T. Pacheco, 2005). Being the hallmarks of metastasis, all the invasion and migration processes are characterized by a loss of compactness at the tumor surface. This loss of compactness is the difference between malignant and benign tumors and seems to be a biological process where a well organized and bipolar layer of cells becomes more diffuse and semidetached (Ramis-Conde, I., M.A.J. Chaplain, 2008). Even if increased cell mobility and proliferation contribute greatly to the invasive ability of the tumor, in order for metastasis to occur the detachment of intercellular bonds is necessary. Cancer cells employ different methods of invasion both individually and in combination to allow tumors to grow. Before a tumor becomes invasive, the roughness of its surface is caused by variations in how groups of peripheral cells degrade the ECM they are in contact with (McDougalla, S.R., A.R.A. Andersonb, 2006).

Interaction of cancer cells with the environment appears in a two-scale, physical-chemical framework. At the cellular level, dynamics have in general a much longer space scale and a slower time scale than events at the molecular level. For example, a reaction such as the enzymatic degradation of ECM can occur in milliseconds whereas the replication of a cell can take about one day. This difference in space and time scales is evident at the edge of a cancerous cell mass as it tries to penetrate the (ECM) and thereby invade surrounding territory or spread to other locations. Cancer-induced degradation leads to the reorganization of the protein network that forms the ECM and, in many cases, to the production of chemicals that promote cell migration and proliferation (Ramis-Conde, I., M.A.J. Chaplain, 2008).

Once the ECM has been degraded, the new configuration of its protein network can interact with the cells. This interaction results in mitosis, via the cells absorbing the growth factors present in the degraded medium, as well as migration. Cell migration occurs because of the chemotactic gradients that arise in the degraded ECM. At a molecular level cells need to produce those reactions that facilitate their migration through the ECM, a process which often involves the degradation of this matrix (Gewirtz, D.A., S.E. Holt, 2008; Ribbaa, B., O. Sautb, 2006).

Angiogenesis:

Tumors become especially dangerous after they induce blood vessel growth. Angiogenesis, the growth of a network of blood vessels, is a crucial component of solid tumor growth, linking the relatively harmless avascular growth phase and the potentially fatal vascular growth phase. The new blood vessels can not only carry oxygen and nutrition that further facilitate tumor growth but also act as passages for tumor cells to spread to other sites of the body. Thus tumor growth can be divided into two phases: avascular and vascular growth. As a process, angiogenesis is a well-orchestrated sequence of events involving endothelial cell migration, proliferation; degradation of tissue; new capillary vessel (sprout) formation; loop formation (anastomosis) and, crucially, blood flow through the cancer-generated network. Once there is blood flow associated with the budding network, the subsequent growth of the network evolves both temporally and spatially in response to the combined effects of angiogenic factors.

The three-dimensional tumor culture data (Gewirtz, D.A., S.E. Holt, 2008) reveals some oscillatory pattern for the proliferating cell count consisting of an intricate feature of partial collapse and re-growth. Although the collapse may be attributed to the start of a necrotic process (Gerischa, A., M.A.J. Chaplain, 2008), During an avascular growth or its in-vitro simulation, the diffusion of nutrition attenuates in the central region with the increasing size of the tumor. Consequently, the cells in this region loose proliferation speed and some enter a quiescent phase where they do not proliferate any more. With further increase in size and consequent less supply of nutrition, some of the quiescent cells enter a necrotic phase and the tumor develop a central necrotic core (McDougalla, S.R., A.R.A. Andersonb, 2006). As the necrotic contribution increases, the avascular tumors enter a dormant phase striking a balance between the mitosis and necrosis rates. Experimentally, it has been

found that before entering the dormant phase, the cell count shows a great deal of fluctuations (Delsantoa, P.P., C.A. Condatc, 2008).

MATERIALS AND METHODS

Cancer Modeling:

Cancer is a highly complex, nonlinear dynamic system. Tumor growth has become a paradigmatic example of multidisciplinary research, where biology and mathematics have met each other to deal with a multi-scale problem. A better understanding of tumor growth and spread may ultimately lead to treatments being developed which can localize cancer and prevent metastasis. Modeling aspects of cancer growth has been approached using a wide range of mathematical models (Ramis-Conde, I., M.A.J. Chaplain, 2008).

To model the cells, one might consider them as free particles, existing in two-dimensional space, that interact with one another. To describe cell-cell adhesion, adhesive bonds on the cells' surfaces are introduced by including a potential function. In this model, two cells interact via the potential function if they are separated by a distance that is approximately less than double the radius of an average cancer cell.

Modeling of tumors has been the subject of numerous studies to understand their rich proliferation dynamics and immunological aspects. Mathematical models of cancer have been extensively developed with the aim of predicting tumor growth and efficacy of therapeutic strategies. Mathematical modeling has helped us to understand the immunogenic response to a tumor (Biswas, P.K., M.T.T. Pacheco, 2005; Evangelia, I. Zachar akia, 2004; Paolo Castorina and Dario Zappal'a, 2004), but the descriptions are usually zero-dimensional and only the total amounts of the various populations, but not their anatomical distribution, are considered. To help in the formulation of effective therapies it is therefore convenient to develop a spatio-temporal model to describe the competitive evolution of two or more cancer cell subspecies and to apply this model to investigate the interaction between the tumor and the therapeutic agent.

Cancer growth models may be divided into macroscopic models, which describe the tumor as a single entity, and microscopic ones, which consider the tumor as a complex system whose behavior emerges from the local dynamics of its basic components, the neoplastic cells. Mesoscopic models are based on the local interaction simulation approach where the cell and matrix densities are functions of time, space, and orientation. Due to their inherent complexity, it is necessary to analyze their growth at different scales. In a macroscopic approach, we consider the tumor as single entities, whose behavior can be predicted in terms of their global interaction with the environment and a few internal parameters (Delsantoa, P.P., C.A. Condatc, 2008).

Tumor growth computer simulation models aim at three-dimensionally predicting and visualizing both the growth and the response of tumors to therapeutic schemes with respect to time. Such a model can provide an efficient platform for gaining insight into the radiobiological mechanisms involved in tumor growth *in vitro* as well as during the avascular stages of *in vivo* tumor evolution. Optimization of dose fractionation during radiation therapy by performing *in silico* experiments before the actual delivery of the radiation dose to the patient is the main practical target. A further application might be the partial replacement of current expensive (in terms of both time and money) *in vitro* oncologic experiments by computer simulations.

A proposed approach is based on a discrete time cell cycle model, which is applied to each one of the cells constituting the tumor. The discrete time and space character of such a model allows the imposition of arbitrary boundary conditions such as the spatial profile of the oxygen and glucose supply. Therefore, this kind of model can be easily extended to the *in vivo* case (Stamatakis, G.S., D.D. Dionysiou, 2002), where the presence of different tissues producing variable elastic and nutrient supply profiles in the vicinity of a tumor can greatly affect the growth pattern and its contour shape. Moreover, all apparently possible pathways in the cellular level leading to cell death have been incorporated including interphase cell death via either spontaneous or radiation induced apoptosis, as well as mitotic cell death through either necrosis or apoptosis. (Zacharaki, E.I., G.S. Stamatakis, 2004)

In-vivo tumor growth is often well predicted by the Gompertz model (Brunton, G.F. and T.E. Wheldon, 1980). At the beginning of the growth process, a large number of cells cycle go through the proliferative phases, which results in exponential growth. As the number of cells increases, the local environment cannot supply cells with sufficient space, nutrients, and oxygen, and some cells shift to quiescence. Precisely there is an initial exponential growth up to 1-3 mm in diameter followed by the vascular Gompertzian phase (Ribbaa, B., O. Sautb, 2006). Then it seems reasonable to think that cancer growth follows a general pattern that one can hope to be described by macroscopic variables.

From mathematical point of view, the simplest tumor model uses ordinary first-order differential equation in an empirical form and simulate the number or volume growth by execution of various mitosis and necrosis

rates and immunological reactions (Ramis-Conde, I., M.A.J. Chaplain, 2008; McDougalla, S.R., A.R.A. Andersonb, 2006). Such models do not consider any of the physical interactions playing in the cell aggregate. The second type of studies employ spatio-temporal (diffusion-type) equations (Delsantoa, P.P., C.A. Condatc, 2008; Zacharaki, E.I., G.S. Stamatakos, 2004; Biswas, P.K., M.T.T. Pacheco, 2005) which, in effect, include the cell mobility or the kinetic factor. Specific models of cancer cell invasion have been both discrete, where cells are considered as individual identities (Gerischa, A., M.A.J. Chaplain, 2008; Stamatakos, G.S., D.D. Dionysiou, 2002), continuum using reaction diffusion equations, or hybrid models, and have been used to explain the diverse aspects of tumor growth dynamics.

Advantages of Modeling Approach:

With the aim of inhibiting cancer growth and reducing the risk of metastasis, pharmaceutical companies in the early 1990s developed anti-metastatic agents called inhibitors of metalloproteinases (MMPi). Despite the promising results obtained in pre-clinical studies, results of Phase III trials have been somewhat disappointing for late stage cancer patients. With the aim of mathematically investigating this therapeutic failure, a mechanical based model was developed which integrates cell cycle regulation and macroscopic tumor dynamics. By simulating the model, the efficacy of MMPi therapy was evaluated. Simulation results predict the lack of efficacy of MMPi in advanced cancer patients. The theoretical model may aid in evaluating the efficacy of anti-metastatic therapies, thus benefiting the design of prospective clinical trials (Gerischa, A., M.A.J. Chaplain, 2008). The followed spurt in the growth do not have any explanation from the existing mathematical models and biological information, since in an in-vitro growth the angiogenesis or vascularization is out of question (Biswas, P.K., M.T.T. Pacheco, 2005).

Multicellular tumor spheroids are characterized by the emergence of cellular heterogeneity and can constitute a satisfactory in vitro model of solid tumors. Therefore, a substantial volume of experimental work on tumor spheroids investigating basic biological mechanisms, such as metabolism and proliferation, regulation of growth saturation, differentiation and development of necrosis has been performed during the last decades (Evangelia, I. Zachar akia, 2004).

A theory should retain all relevant features from the lower to the higher scale. From the point of view of the mathematical modeling, this means that the problem requires different approaches, because mathematical models related to cellular phenomena are generally stated in terms of ordinary differential equations and deal with the behavior of a single cell, while integro-differential kinetic equations are used for collective phenomena. On the other hand, macroscopic behaviors are generally described by non-linear partial differential equations that should lead to mathematical problems stated as moving boundary problems.

Then it seems reasonable to think that cancer growth follows a general pattern that one can hope to be described by macroscopic variables and following this line of research, for example, the proposed universal model has been recently applied to cancer (Paolo Castorina and Dario Zappal'a, 2004).

In a rational model it is assumed that the invasion process is triggered by contact between peripheral cancer cells and the ECM [1–3]. Parameters such as ECM density and the contact surface between cancer cells and ECM are important in development rate of cancer.

It was first proposed by West, Brown and Enquist (WBE) (West, G.B., J.H. Brown, 2001) that tumors follow the general model of growth which might be valid for all living organisms, from mammals to plants. This simple model is based on energy conservation law and takes benefits from scaling arguments. They start with the assumption that the energy intake, supplied by ingested nutrients, is spent partly to support the metabolic functions of the organism's existing cells and partly for cell replication, i.e. to reproduce new cells.

RESULTS AND DISCUSSIONS

Development of Physics-based Model:

The WBE theory is critically dependent on the relation between the metabolic rate B of energy flow and the organism mass m . Although this relation is generally considered as:

$$B(m) \propto m^p, \quad p \leq 1 \tag{1}$$

The precise value of the exponent p is the object of ongoing debates and its value must be experimentally ascertained (West et al. assume $p = 3/4$).

To carry on further in modeling, for simplicity, it is assumed that metabolism and growth are the same for all the cells of a given individual and constant throughout its lifespan. Let B be the resting metabolic

energy expenditure of an organism. Then, at any time t and for any discrete short time interval Δt , the law of energy conservation leads to:

$$B\Delta t = N\beta\Delta t + \varepsilon\Delta N \quad (2)$$

Where:

N = total number of cells in the organism

β = metabolic rate for a single cell

ε = energy required to create a new cell.

μ = mass of a single cell

$m = N\mu$, mass of the whole organism

Re-arranging equations 1 and 2 leads to:

$$\frac{dm}{dt} = am^p - bm \quad (3)$$

Where:

$$b = \frac{\beta}{\varepsilon}$$

$$a = \frac{\mu B}{\varepsilon}$$

The parameters \mathbf{a} and \mathbf{b} represent the rates of metabolism and nutrients intake, respectively. The metabolic rate is assumed fixed, $a \equiv \bar{a}$, implying that, in its original version, there is no slow down in metabolism typically attributed to an emerging necrotic tumor core. We are aware that a tumor's metabolic rate in vivo is variable.

Impact of Mechanical Stress on MTS Growth:

It has been suggested that tumor growth and metastasis may be influenced by mechanical stress produced by the surrounding tissue. In particular, increasing local stress leads to a higher cell density ρ . In fact, while ρ is normally assumed to be constant throughout the entire growth process, it might be shown that the cell density may increase as a result of increasing mechanical stress within the microenvironment. Correspondingly, there are experimental evidence that cells in the internal MTS layers experience a size reduction by up to a factor of three

The stress-induced growth inhibition of plateau-phase spheroids was accompanied, at the cellular level, by decreased apoptosis with no significant changes in proliferation. A concomitant increase in the cellular packing density observed, which may prevent cells from undergoing apoptosis via a cell-volume or cell-shape transduction mechanism. These results suggest that solid stress controls tumor growth at both the macroscopic and cellular levels, and thus influences tumor progression and delivery of therapeutic agents.

Discussion:

The sequential steps of the evolution of cancer disease may be roughly summarized as follows (Bellomo, N., E. De Angelis, 2003):

1. Genetic changes, distortion in the cell cycle and loss of apoptosis.
2. Interaction and competition at the cellular level with immune and environmental cells.
3. Condensation of tumor cells into solid forms, macroscopic diffusion and angiogenesis.
4. Detachment of metastases and invasion.

The first two steps are mainly related to cellular phenomena; the last two need macroscopic descriptions although cellular phenomena cannot be neglected as they are always the entities generating the macroscopic behavior.

In future works, special emphasis is placed on the adjustment of the model output to experimental data and more detailed computations on time-varying differential equations will be considered.

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