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Analysis of Tumor as an Inverse Problem Provides a Novel Theoretical Framework for Understanding Tumor Biology and Therapy

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Abstract—We use a novel "inverse problem" technique to construct a basic mathematical model of the interacting populations at the tumor-host interface. This approach assumes that invasive cancer is a solution to the set of state equations that govern the interactions of transformed and normal cells. By considering the invading tumor edge as a traveling wave, the general form of the state equations can be inferred. The stability of this traveling wave solution imposes constraints on key biological quantities which appear as parameters in the model equations. Based on these constraints, we demonstrate the limitations of traditional therapeutic strategies in clinical oncology that focus solely on killing tumor cells or reducing their rate of proliferation. The results provide insights into fundamental mechanisms that may prevent these approaches from successfully eradicating most common cancers despite several decades of research. Alternative therapies directed at modifying the key parameters in the state equations to destabilize the propagating solution are proposed.

Keywords—Mathematical modeling, Tumor host interaction, Tumor invasion, Tumor therapy.

INTRODUCTION

The tumor-host interface is a highly complex, dynamical structure dominated by nonlinear processes for which there is no clear theoretical framework of understanding [1]. Experience in other areas of science has demonstrated that such systems require mathematical formulation to concisely express the underlying dynamics and interactions, to elicit a clear understanding of the outcome of the interactions, and to investigate the potential effects of manipulation of the system. However, clinical medicine has not generally integrated theoretical analysis into its understanding of tumor biology. We submit that this has impeded progress in clinical oncology because the vast amounts of data generated by molecular biology and other new technologies have not been synthesized into a coherent, comprehensive paradigm. Furthermore, because of the absence of a sound theoretical framework, design and the evaluation of therapeutic approaches remain

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empiric and generally focused on cytoreductive strategies despite limited results in most solid tumors even after several decades of intense research. This is well summarized by the authors of [2]: "In general ... progress with the vexing problem of anticancer selectivity has been slow—a matter of trial and error and guesswork as much as rational calculation. In the search for better ways of curbing the survival, proliferation, and spread of cancer cells, it is important to examine more closely the strategies by which they thrive and multiply."

The purpose of this paper is not to develop a comprehensive model of the tumor-host interface, but rather to provide the simplest possible mathematical framework which encompasses the critical behavior of this interface, namely, the advance of tumor tissue into the surrounding host tissue, and to elucidate key biological parameters controlling this behavior. Within the context of this framework we show that we can understand the effectiveness of various treatment approaches as well as suggest new therapeutic strategies.

We believe that this analysis provides insight into tumor biology and treatment not available by other means and illustrates the potentially critical role of mathematical analysis in successfully understanding and treating tumor invasion.

METHODS

In developing the model, we use an "inverse problem" approach. That is, we assume that the known behaviors of the tumor-host interface represent the potential solutions of state equations governing the system. By examining the constraints imposed by the solutions, we can determine the general form of the state equations and examine critical parameters that control the behavior of the system.

First, we propose that, mathematically, the tumor-host interface of an invasive cancer is morphologically a traveling wave in which the tumor edge represents the wave front propagating into and replacing the surrounding normal tissue. This is based on extensive clinical observation of tumor growth demonstrating tumor volume increases by Gompertizian or logistic functions with the tumor edge invading into adjacent normal tissue at a regular rate [3–6]. We have discussed this more extensively in other publications [7]. Therefore, we infer that a mathematical description of tumor invasion must be a system of equations that can exhibit traveling wave solutions.

Furthermore, since observable, untreated cancers propagate into normal tissue, this mathematical system must also yield solutions in which the tumor state and the normal tissue state are stable in isolation but the latter is unstable in the presence of tumor and will therefore inevitably be invaded by tumor. That is, when tumor is present in normal tissue the governing system must result in a traveling wave representing the transition from an unstable steady state (normal tissue) to a stable steady state (tumor).

If we denote by $N(x,t)$ and $T(x,t)$ normal and tumor cell density, respectively, at time t and spatial position x, then the existence of a constant speed traveling wave indicates that the solution of the state equations must be written in the general form

$$\begin{aligned} N(x,t) &= N(x \pm ct), \\ T(x,t) &= T(x \pm ct), \end{aligned} \tag{1}$$

where c is the wave speed. Such a solution is a constant profile traveling wave moving in the positive (with $-c$) or negative (with $+c$) x direction. The wave boundary is a transition region from normal tissue to malignant tissue with the tumor front propagating into normal tissue at speed c. Note that for equation (1) to be valid, we are assuming that the tumor front is approximately a plane-wave, i.e., the radius of curvature of the entire tumor is much greater than any length scales characterizing the tumor-host interface. In such a case, which is generally true for late-time growth, the direction x is along any line perpendicular to the tumor surface.

In a mixture of populations competing for space and substrate, the governing system that will give rise to a traveling wave solution typically takes the form [8]

$$\frac{\partial \mathbf{n}}{\partial t} = \mathbf{f}[\mathbf{n}] + D\frac{\partial^2 \mathbf{n}}{\partial x^2}, \tag{2}$$

where $\mathbf{n}$ is the vector whose components represent the population densities, $\mathbf{f}$ is the nonlinear population kinetics function, and D is a diagonal matrix of diffusion coefficients presumed to be greater than zero. The simplest conceptualization of the tumor-host interface is that derived from a population ecology picture in which populations of tumor cells and normal cells compete for the same spatial volume and nutritive substrate and interact with one another through a variety of potentially complex mechanisms. Each population initially grows according to a Malthusian growth law but is limited to some maximum carrying capacity, with the growth rates and carrying capacities possibly being different for each population.

It is reasonable to assume that a variety of interactions between the cellular populations have adverse effects on each population and can be included in lumped, phenomenological competition terms. The simplest and most widely used of these models is of the Lotka-Volterra type. There are a variety of other mathematical models of tumor growth kinetics (see, e.g., [9, Chapter 3]) which provide equal or perhaps greater quantitative fidelity to growth rates observed *in vitro* than does the Lotka-Volterra model. However, because all such models, including Lotka-Volterra, predict the same qualitative behavior, we have employed the one that is both simple to analyze mathematically and which effectively illustrates our point [10,11]. For simplicity, we write the Lotka-Volterra equations for (2) with one dominant tumor population, T, interacting with one dominant native (normal) cell population, N:

$$\frac{\partial N}{\partial t} = r_N N\left(1 - \frac{N}{K_N} - \frac{b_{NT}T}{K_N}\right) + D_N\frac{\partial^2 N}{\partial x^2} \tag{3}$$

and

$$\frac{\partial T}{\partial t} = r_T T\left(1 - \frac{T}{K_T} - \frac{b_{TN}N}{K_T}\right) + D_T\frac{\partial^2 T}{\partial x^2}, \tag{4}$$

where r_N and r_T are maximum growth rates of normal cells and tumor cells (i.e., the net result of tumor cell doubling minus tumor cell loss from apoptosis or necrosis); K_N and K_T denote the maximal normal and tumor cell densities; b_{NT} and b_{TN} are the lumped competition terms; D_N and D_T are cellular diffusion (i.e., migration or invasion) coefficients. The biological significance of the competition terms should be clarified: b_{TN} is a lumped, phenomenological term which includes a variety of host defenses including the immune response, and b_{NT} is the negative effects of tumor on normal tissue such as tumor-induced extracellular matrix breakdown and microenvironmental changes. It can be shown that the results of the analysis of these equations remain valid even when multiple subpopulations of tumor and normal cells are considered [12].

RESULTS AND DISCUSSION

This system in equations (3) and (4) fulfills the above criterion that, in the absence of tumor cells, normal tissue achieves a stable, nonzero, steady state. Furthermore, it can exhibit solutions of the form in equation (1) in which one population can invade the other. Specifically, the model yields the following final steady states [8]:

I $N = 0$, $T = 0$: this trivial solution is an unconditionally unstable state and hence is biologically irrelevant.

II $N = K_N$, $T = 0$: this corresponds to normal, healthy tissue with no tumor cells present. Regardless of the starting point, the system always evolves to this state if both $b_{TN}K_N/K_T > 1$ and $b_{NT}K_T/K_N < 1$. If the starting point is sufficiently close to $N = K_N$, $T = 0$ (as would occur in early tumor development), only the former condition need be satisfied.

III $N = 0$, $T = K_T$: this corresponds to complete tumor invasion with total destruction of adjacent normal tissue. Regardless of the starting point, the system always evolves to this state if both $b_{NT}K_T/K_N > 1$ and $b_{TN}K_N/K_T < 1$. If the starting point is sufficiently close to $N = 0$, $T = K_T$ (as would occur when tumor treatment is initiated), only the former condition need be satisfied.

IV $N = (K_N - b_{NT}K_T)/(1 - b_{NT}b_{TN})$, $T = (K_T - b_{TN}K_N)/(1 - b_{NT}b_{TN})$: this corresponds to tissue composed of tumor and normal cells, for example, desmoplastic tumor. The system evolves to this state if both $b_{NT}K_T/K_N < 1$ and $b_{TN}K_N/K_T < 1$. One limitation of this model is that if the carrying capacities K_N and K_T are limited only by available space, this state of coexistence is biologically unphysical because it violates the spatial constraint sum-rule that $N/K_N + T/K_T \leq 1$. There are, however, models more elaborate than Lotka-Volterra having a state of coexistence not violating this spatial constraint sum-rule [13].

The case of an invasive cancer with the tumor edge advancing as a propagating wave into normal tissue would correspond to a transition to a stable steady state containing tumor (**III** or **IV**) with or without normal tissue. From the above, it is clear that an invasive cancer which initially arises from one or a small number of transformed cells (i.e., $N = (1-\varepsilon)K_N$ and $T = \varepsilon K_T$, with $\varepsilon < 1$) must satisfy both inequalities in **III**.

Using marginal stability analysis [12], it can be shown that the propagation speed of state **III** into state **II** (i.e., the tumor wave front into the normal host tissue) is given by

$$c_{T\to N} \geq 2\sqrt{r_T D_T \left(1 - \frac{b_{TN}K_N}{K_T}\right)}. \tag{5}$$

Furthermore, making the biologically plausible assumption that carrying capacities for normal and tumor cells are not substantially different, the inequalities required for state **III** stability will hold only if b_{NT} is large, and b_{TN} is small, i.e., the presence of tumor has a significantly adverse effect on the normal cell population but not vice versa. The most obvious contribution to b_{NT} comes from the fact that tumor cells consume much more resources than do normal cells [14,15].

Equation (5) is in the form of an inequality because the marginal stability analysis provides only a minimum velocity. The actual velocity is dynamically selected by the system based on the width of the tumor interface at the initial time, i.e., $T(x, t = 0)$. If the tumor drops off faster than $\exp[-\sqrt{r_T/D_T}\,x]$ as it progresses into the normal tissue, the minimal c in equation (5) will be selected [15]. Recent numerical work by Hosono [16] has indicated that the front propagation velocity given by the approximation (5) holds except for the case when interspecific competition is stronger than intraspecific competition (i.e., $b_{NT}b_{TN} > 1$). In that case, the velocity is sensitive to all parameters within the model. However, because the relaxation to the asymptotic velocity is algebraically slow [17], numerical simulations may be biased by early-time transients or an insufficiently steep initial profile.

Another possible significant contribution to b_{NT} is the acidic intercellular pH in tumors that results from their preferential reliance on glycolytic metabolic pathways. We have previously shown that excess H^+ ions will diffuse away from the tumor producing an unfavorable microenvironment for the normal cells at the tumor-host interface [7]. Other factors contributing to b_{NT} include extracellular matrix breakdown by tumor produced proteinases and normal cell crowding by increased interstitial pressure in tumors.

Fully successful tumor therapy requires the system parameters be changed to yield steady state **II** instead of **III** or **IV**. This will essentially reverse the traveling wave so that normal tissue (which in this case becomes the stable steady state) will propagate into tumor (now the unstable steady state) causing the latter to completely regress. Assuming that tumor has already developed as a traveling wave, successful therapy will at minimum, require that

$$\frac{b_{TN}K_N}{K_T} > 1. \tag{6}$$

Ensuring the complete eradication of the tumor will require that the state $N = K_N$, $T = 0$ be *globally* stable so that, in addition to (6), the condition for state **II** global stability must be met as well

$$\frac{b_{NT}K_T}{K_N} < 1. \tag{7}$$

If conditions (6) and (7) are met, the normal tissue would recover at a speed [7] given by

$$c_{N\to T} \geq 2\sqrt{r_N D_N \left(1 - \frac{b_{NT}k_T}{K_N}\right)}. \tag{8}$$

By "recovery of normal tissue", we do not mean to imply that the segment of organ destroyed by the invading malignancy will regenerate to its initial state. In fact, the reverse traveling wave will almost certainly not contain the original epithelial cell populations of the tissue since these are typically terminally differentiated with proliferative potential maintained in only a small number of stem cells. Rather, we expect the wave of normal tissue will typically contain fibroblasts and other mesenchymal cells similar to the ingrowth of normal tissue in the wound healing process. This would result in the residual fibrosis that is in fact observed to a variable degree in the sites of tumors that have regressed completely following therapy [18].

Two clinically relevant insights are immediately clear from this analysis.

1. Cytotoxic therapies will transiently reduce tumor size by reducing T but do not alter the basic system dynamics. Therefore, the model predicts that cytotoxic approaches will invariably fail because the tumor population will recover (i.e., $\frac{\partial T}{\partial t}$ remains > 0) unless therapy reduces T to zero (i.e., all tumor cells are destroyed).
2. Therapies aimed at reducing the tumor proliferation rate (r_T) will never eradicate the tumor because r_T does not appear in the critical terms determining the steady state to be reached by the system. The model predicts that such therapies may slow invasion (see equation (5)) but will never alter the final outcome.

In considering successful therapeutic strategies, the above mathematical model of tumor-host interaction focuses attention on four critical parameters: b_{TN} and K_T, the competition term and carrying capacity of tumor, and b_{NT} and K_N, the competition term and carrying capacity of the normal tissue surrounding the tumor. The model explicitly demonstrates that any therapy must be viewed in a context that includes measurements of effects on tumor and adjacent normal cells.

Therapeutic strategies, therefore, should include the following.

1. *Reduce K_T.* A clear method for reducing the carrying capacity for the tumor population is decreasing vascularity. This indicates that recent interest in anti-angiogenic drugs is well founded [14]. Two caveats, however, must be added. First, if the reduction in angiogenesis also affects normal tissue, then the therapy may also reduce K_N and the inequalities in equation (6) or (7) may not be satisfied. Second, if $b_{NT} \ll 1$, then a several-fold reduction in K_T may be insufficient to suitably alter the stability of the steady states.
2. *Reduce b_{NT} and increase b_{TN}.* This demonstrates the need for experimental data that quantifies the relative contribution of various mechanisms (e.g., tumor acid or protease production) to the lumped competition term b_{NT} *in vivo*. Similar quantification of components of b_{TN} (e.g., immunological response) is also required. If we can estimate the value of b_{NT}, both the identification of potential therapeutic approaches and quantifications of their expected effect on the propagating wave of tumor invasion can be obtained. For example, therapy could be directed toward decreasing the uptake and utilization of substrate by tumor cells, increasing the avidity of substrate uptake by normal cells or reduction of tumor acid and protease production. The role of each of these therapeutic strategies, however, must be understood in the context of the mathematical models. Empiric therapy should be replaced by explicit measurement of the expected effect of the

therapy on b_{NT} and b_{TN} so that the degree to which the therapy must change the targeted mechanism to alter the overall system dynamics is known prior to initiation of treatment.

3. *Increase* K_N. This is tumor therapy directed explicitly towards normal cells. Presumably, the maximum density of normal cells is ordinarily dependent on cell-cell interactions rather than substrate limitation. The mathematical model predicts that therapy that decreases contact inhibition in normal cells by increasing K_N could reverse the inequality in (5), possibly resulting in tumor regression.

CONCLUSION

We use an "inverse problem" approach to develop a simple phenomenological mathematical model of tumor invasion sufficiently robust to encompass the observed behavior of the tumor-host interface. By examining the resulting state equations, we are able to identify critical parameters that must be altered for successful therapy. Our goal in this study was to present a general overview of the dynamics of the tumor-host interface and of possible related cancer therapeutic strategies. The model employed was therefore deliberately chosen for simplicity using lumped interactive terms rather than a more comprehensive model explicitly including all possible mechanisms affecting the tumor-host interface. For this reason, only very general conclusions can be obtained with limited predictive information regarding specific cancer therapies. However, it does seem clear even from this approach that traditional cancer treatment with systemic chemotherapy should be reconsidered. Specifically, we show that cytoreductive agents will invariably fail to cure cancer unless they reduce tumor population density to zero. Since most transformed populations are heterogeneous and capable of evolving into drug resistant phenotypes, complete eradication by cytotoxic agents is generally unlikely. The flaw in this approach is the failure to alter the key parameters in the state equations leaving $\frac{\partial T}{\partial t} > 0$ whenever $T > 0$. We propose that therapies directed at changing these parameters (as outlined above) in conjunction with cytoreductive agents will yield results that are far more positive.

Despite their limitations, we believe that mathematical models are essential to gain clinical understanding of the complex, nonlinear processes that govern tumor invasion and may be used to understand the strengths and weaknesses of existing cancer therapies and to predict new treatment strategies.

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