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Tumor Gompertzian growth by cellular energetic balance

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Abstract

A macroscopic approach to the tumor Gompertzian growth is proposed and successfully applied to the multicellular tumor spheroid data. It is based on the energetic balance among the different cell activities, related to the growth inhibitor factors. The main results can also be described by methods of statistical mechanics.

Keywords: Tumor growth; Gompertz law; Multicellular tumor; Spheroids

1. Introduction

A microscopic model of tumor growth in vivo is still an open problem. It requires a detailed description of cellular interactions and a control on the large variety of in situ conditions related to the distributions of nutrient, oxygen, growth inhibitors, blood vessels and capillarity and to the mechanical effects due to tissue elasticity and heterogeneity. On the other hand, in spite of the previous large set of potential parameters, tumors have a peculiar growth pattern that is generally described by a Gompertzian curve [1], often considered as a pure phenomenological fit to the data. More precisely there is an initial exponential growth (until 1–3 mm in diameter) followed by the vascular Gompertzian phase [2]. Then it seems reasonable to think that cancer growth follows a general pattern that one can hope to describe by macroscopic variables, constrained by a set of environmental conditions crucial to understand the fundamental features of the growth as, for example, the shape and the maximum possible size of the tumor and the onset of the tissue invasion and metastasis. Following this line of research, for example, the universal model proposed in Ref. [3] has been recently applied to cancer [4].

In this paper, we consider a macroscopic approach to the tumor growth that: (i) gives an energetic basis to the Gompertzian law; (ii) clearly distinguishes among the general evolution patterns, which include feedback effects and external constraints; (iii) can give indications on the different tumor phases during its evolution. The proposed macroscopic approach is not in competition with microscopic models [5], but it is a complementary description of the tumor growth based on the slow time evolution of a subsystem A (the tumor) embedded in a larger system B (the body), where the energetic balance plays a crucial role. Indeed, the

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analogy between thermodynamics and evolution is well known [6] and our model suggests that, by correctly interpreting the various contributions to the energy of the subsystem A, one can give an energetic basis to the Gompertzian growth and obtain interesting indications on the different tumor phases during its evolution.

The Gompertzian curve is solution of the equation [7]

$$\frac{\mathrm{d}N}{\mathrm{d}t} = N\gamma \ln\left(\frac{N_\infty}{N}\right), \tag{1}$$

where $N(t)$ is the cell number at time t (t is a dimensionless variable given in some specific units; e.g. in months), γ is a constant and N_∞ is the theoretical saturation value for $t \to \infty$ which depends on external environmental constraints.

It is quite natural to identify the right hand side of Eq. (1) as the number of proliferating cells at time t and then to consider $f_p(N) = \gamma \ln(N_\infty/N)$ as the fraction of proliferating cells and $1 - f_p(N) = f_{np}$ as the fraction of non-proliferating cells. Here, we observe the difference with respect to an exponential growth that corresponds to a N independent specific proliferation rate, typical of a system of independent cells. Instead, the logarithmic dependence observed in the Gompertzian law, can be regarded as a sort of feedback mechanism, such that the system, at any time, rearranges the growth rate and the fraction of proliferating cells according to the logarithm of the total number of cells $N(t)$.

Living tumor cells consume an amount of energy, in the form of nutrient and oxygen, which is recovered from the environment (which will be addressed in the following as B), represented by a living body (in vivo) or an external solution (in vitro). B, as already mentioned, has also a mechanical action that can be responsible of compression, increase of pressure and density and change of shape of the tumor (addressed in the following as A).

Starting from these observations and by taking into account some crucial biological indications, we intend to describe the tumor growth on an energetic basis. Section 2 contains a general, model independent, discussion of the interplay between the biological aspects and their energetic counterparts, entirely based on the translation of the effect of the growth inhibitor factors into an increase of the duplication energy. To support the general considerations of Section 2, in Section 3 a thermodynamical model is briefly outlined. The phenomenological consequences of the general approach of Section 2 are compared with the experimental data on multicellular tumor spheroids (MTS). In Section 5, we present our conclusions.

2. Energetic description of biological effects: general aspects

Let us first consider the problem at fixed time and recall the first law of thermodynamics. A change of the energy content of a system has three possible origins, namely mechanical work performed on or by the system, variation of the number of elementary constituents (particles), heat exchange with the environment. Accordingly, the internal energy of the system is expressed as the sum of three terms, respectively, $-PV$ (minus the product of pressure times volume), μN (where μ, the chemical potential, is the change in energy when the number of particles N is increased by one unit), S/β (heat content, where S is the entropy, $\beta = 1/T$ is the typical inverse temperature scale, with the Boltzmann constant $\kappa = 1$).

Let us consider an energy balance law for the tumor in the same spirit of the first law of thermodynamics.

In fact, at some fixed time t one can regard the available energy for the tumor, U, as the sum of three pieces, $U = \Omega + \mu N + E_M$, where $\Omega = -PV$ is associated to the mechanical work necessary to counteract the external pressure and to cause a change of shape, μN is proportional to the number of cells N of A and μ represents the variation in energy related to a change in N (note, for the sake of clarity, that the mechanical work related to the change in volume of A due to the increasing number of cells is taken into account in Ω) and finally E_M, which represents the energy spent for metabolic activities (it should be clear that the previous variables that we used to describe our system are not exactly those introduced in thermodynamics).

Since the change in the number of cells in the tumor is due to biological proliferation and by recalling the above definition of μN, it is natural to associate μ to the energy that A needs to generate one new cell, i.e., the energy necessary for proliferation, that has to be distinguished from the energy associated to all the other metabolic processes which is addressed as E_M and the biomechanical work (if any), called Ω.