

What Can Be Learned from A Phase Transitions in Tumor Growth?

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Introduction

The thermodynamics formalism of irreversible processes [1], systems biology [2] and complex systems theory [3] offer a theoretical framework appropriate for the characterization of the emergence and evolution of cancer. In such a sense, in a previous work [4] we presented a conceptual definition of the cancer, such as: Cancer is a generic name given to a complex network of interactions of malignant cells, which have lost their specialization and control over normal growth. This network of malignant cells could be considered as a nonlinear dynamical system, self-organized in time and space, far from thermodynamic equilibrium, exhibiting high complexity [5], robustness [6] and adaptability [7].

In spite of achievements in molecular biology and genomics, the growth mechanism for tumor cells and the nature of its robustness is still greatly unknown. Tumor cell robustness enables a system to maintain its functionality in the face of various external and internal perturbations [4]. Tumor cells exhibit two aspects of robustness: functional redundancy, which appears in cellular heterogeneity, and feedback-control systems [4]. Controlling cell robustness by reducing heterogeneity is a potential strategy for the development of drugs and therapies.

It is known that the evolution of cancer can pass through three basic stages [8]: avascular, vascular and metastasis. In the avascular stage, the tumor grows to a state known as “dormant” state [9] with a microscopic nature (~1 mm diameter). This latency stage can remain silent for a long time and is not macroscopically perceptible. Hence, as we postulated in previous works [10,11] this process resembles a phase transition “second order”, whose biological implication is clear: the difficulty of early detection of cancer.

Phenomena far from thermodynamic equilibrium have their causes in processes of bifurcations and correlations. In our case, they may have relevance to the macroscopic evolution of the tumor. It is well known that, bifurcations in dynamical systems play a similar role to phase transitions in the vicinity of thermodynamic equilibrium. These behaviors emerge from the amplification of microscopic fluctuations to macroscopic level. As established by [12], the above mentioned mechanism is the main device of self-organization, and consequently, of the emergence of complexity at the macroscopic level

For reasons still unknown [13] the tumor leaves the dormant

state and begins a process of angiogenesis, vascular growth. We conjectured about it, in a previous work [14], where apparent fluctuations related to the joint action of the host and immune system on tumor cells may cause an adverse outcome causing a type of stochastic resonance effect. This leads to a change in the geometrical fractal properties of the interface of the tumor, to be more precise, a change in the fractal dimension. Consequently, a certain number of active cells in tumor located at the interface could escape, leading to a vascular growth.

This could be an acceptable explanation of why a tumor in a latent phase, stationary state [15], can go to a critical state, reach

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macroscopic dimensions, vascular phase, and subsequently invade distant organs, metastasis, despite actions of the immune system and the host [16,17].

Is very relevant to our discussion the fact that, although in a first approximation it is possible to predict when tumors reach latency. As has been established in [18], it is virtually impossible to predict when metastasis begins, given the strong random character of the action of the immune system and the host.

In the vascular phase, the tumor acquires macroscopic dimensions, invading much of the host and adjacent organs, that is to say, self-organized tumor system, far from equilibrium, self-organizes to a higher level of hierarchy in a way apparently robust as it is known that in most cases after surgical removal thereof, micro-metastasis is found [19].

The process of metastasis [20] appears abruptly as a consequence of first order transitions, diminishing the chances of survival compared to the previous stages, thus exhibiting a higher robustness and a higher level of hierarchy. The tumor now competes with the different levels of hierarchical and functional organization of the body (those which play vital roles), so it is considered like a cancer tumor, given its ability to metastasize [21].

Our models suggest [22,23] that the development of a primary tumor from a microscopic level, avascular growth, to a macroscopic level, vascular phase and the subsequent appearance of metastasis, is not simply the accumulation of malignant cells, but it is a dynamic non-linear, self-organized process, far from thermodynamic equilibrium, which exhibits a high degree of robustness, complexity and hierarchy [23] and that in turn leads to the creation of new information and learning ability.

The information created during the evolutionary process of cancer cannot be destroyed [24], which is manifested by clinical recurrence (relapse) of cancer after a while that has apparently been “removed”, for example: tumor progression in prostate cancer following radical prostatectomy occurs in 20%–40% of

patients; approximately 40% of patients who undergo surgical resection of non-small cell lung cancer without overt metastases relapse within 24 months after surgery; for breast cancer, 20% of clinically disease-free patients relapse 7–25 years after mastectomy [9,19].

Hence the tactic in the treatment of cancer must not only be based on their physical elimination, also must to be focused in to change the created information. A recent study [25] has shown that pancreatic cancer cells can be forced to return to normal cells by introducing a protein called E47. As is well known, the protein E47 binds to specific DNA sequences and controls genes involved in growth and differentiation. “For the first time, we have shown that over expression of a single gene can reduce the tumor-promoting potential of pancreatic adenocarcinoma cells and reprogram them toward their original cell type. Thus, pancreatic cancer cells retain a genetic memory which we hope to exploit”.

The thermodynamics formalism previously developed [10,22,23,26,27,28] suggests that the tumor that exhibit a greater value of the entropy production rate have an increased invasive ability and so they have more aggressive capacity. As a matter of fact, the entropy production rate can be the useful tool to quantify the robustness and it may be used as a quantitative index of the metastatic potential of tumors.

As far as the authors are aware, a theoretical framework fully developed in this chapter has not been previously exposed. We hope to provide a better understanding of the growth dynamics of cancerous tumors, resulting in better and more effective therapies

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