Biological Systems: Open Access

Bellouquid A et.al., Biol syst Open Access 2015, 4:1
DOI: 10.4172/2329-6577.1000132

Mini Review Open Access

New Perspectives in Mathematical Modeling Focusing on the Type of the Immune Response and Cancer Eradication

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Received date: Mar 03, 2015, **Accepted date:** Apr 07, 2015, **Published date:** Apr **15**, 2015

Abstract

Tumor progression is characterized by the interaction between the tumor and immune system cells in a particular microenvironment. Recently, the involvement of immune cells either favorably or unfavorably was confirmed; and it seems that much would depend on the type of the immune response generated for each individual patient. This note deals with the perspective of modeling of the onset and the progression of cancer, depending on the nature of the patient's immune response, using tools of kinetic theory for active particle, developed recently to overcome the complexity of biological systems. Mathematical models can act, once validated, as in silico laboratories. This approach would result in a less expensive design of new treatments, based on specific stimulation of the patient's efficient type of the immune response against tumors.

Keywords: Biological systems; Cancer; Immune response; Mathematical models; Kinetic theory

Introduction

Cancer can be viewed as a complex disease where cells of the same genotype generate, during cell cycle progression, daughter cells characterized by the acquisition of new hallmarks. While healthy cells finely control proliferation-triggering signals that instruct entry into cell division cycle, cancer cells progressively acquire new traits involving deregulation of these signals [1]. During progression of the disease, other cellular processes such as cell survival are also deregulated [1]. Conceptual progress in the field has, however, extended the biology of tumors beyond this simple notion of uncontrolled cell division. Progress in cancer research made it clear that the pathology encompass the contribution of other factors grouped in the "tumor microenvironment" [2]. Cells of the immune system constitute one major actor within this microenvironment [2]. In fact, tumor progression is characterized by interaction between the tumor and various cells of the immune system in this complex and intriguing microenvironment. In the last decade, the ability of cancer cells to escape recognition by immune cells has been added to main hallmarks that allow cancer cells to sustain their ability to survive and eventually evolve towards metastatic stages [1].

A mathematical theory exploring how evolution can be constructive and how natural selection can lead from lower to higher levels of organization is presented in [3]. This deals with a study of evolutionary game theory in a setting where individuals learn from each other. This biological framework is transferred into a general mathematical framework [4], where the modeling of the dynamics, at the cellular scale, is developed by methods of statistical dynamics and game theory. This approach was initiated [5] and subsequently developed by various authors [6-13]. It has been developed to describe the dynamics of large systems of interacting cells, called active particles [6], with their states called activity. This corresponds to genotype-phenotype expression, also called expression [12], and it is summarized by a scalar variable, ranging in a domain.$D_u \subseteq \mathbb{R}$.. The individuals corresponding to the same expression are grouped into functional subsystems or subpopulations, where the common tract is viewed as a functional expression that aims at survivance. The activity within subpopulation is the micro-state, which is heterogeneously distributed, while the overall state of the system is described by suitable distribution functions $f_i(t,u) : [0,\ T]\times D_u \to \mathbb{R}^+$over the activity$u$, where$0 < T \leq +\infty$. The quantity $f_i(t,u)du$ represents the (infinitesimal) number of active particles of the ith subsystem having at time an activity comprised in the (infinitesimal) interval $[u;\ u+du]$. Under suitable integrality conditions, the quantities

$v_i(t) = \int_{D_u} f_i(t,u)du$ and $A_i(t) = \int_{D_u} f_i(t,u)du$ represent respectively the size and the activation in the ith subsystem at time . Consequently, it is fascinating to understand the behavior of theses quantities over time.

Pair interactions between active particles generate birth-death processes and, with relative small probability, modification of their expression, which amounts to the generation of a new subpopulation. The evolution of the system may depend not only on the interactions between living entities, but also on the interactions between living entities and the external surrounding environment. In more details, interactions involve three kinds of particles: candidate, test, and field [6]. The interaction rule is as follows: candidate particles can acquire, in probability, the state of the test particles, after an interaction with field particles, while test particles lose that state after interactions.

Let $f = (f_1, \ldots,\ f_n)$the set of distributions functions. The structure, to be used as paradigm for the derivation of our model, is: $\partial_t f_i(t,u) = J_i[f](t,u) = C_i[f](t,u) + P_i[f](t,u) - \lambda_i[f_i]\left(f_i - \tilde{f}_i\right)(t,u)$,

for, $i = 1, \ldots, n$.Following the recent paper [13], the dynamics of distributions functions is obtained by a balance of particles due to the inlet and outlet flows in the elementary volume $[u;\ u + du]$ of the space of micro-state . The said fluxes are determined by the dynamics of interactions, which involve candidate, field and test particles. More specifically, two types of interactions are considered, conservative interactions (modeled by $C_i[f]$), when particles modify only their microscopic state, corresponding to an early stage of competition, and non-conservative interactions modeled by$P_i[f]$, when interactions generate proliferation or destruction of particles in their microscopic state. $\lambda_i[f_i]$ refers to the natural decay of each subpopulation towards a level distribution $\tilde{f}_i$, or to a death process of the ith particle due to their natural extinction, where death occurs only within same subpopulation and state of the candidate particle. The reader interested on more details on the modeling approach is addressed to our previous works [13]. This provides a mathematical structure suitable to include a variety of specific biological dynamics such as the immune response in the presence of mutations and selection.

Now, we refer to biological systems involving the competition between cancer cells, carrier of the pathology, and effector immune cells. Cells of the immune system evolve and differentiate in time in order to acquire the ability of recognizing non-self-substances and learning to identify new pathogen agents or new dangers not previously encountered. The specialization of cells of the immune system plays a central role in coordinating the immune response to different categories of pathogens or other dangers including cancer cells. This specialization is manifested by the presence of different subpopulations of T cells that produce specific cytokines and display distinct functions. For example, the control of pathogens that are found in phagocytic cells requires the involvement of CD4+ T cells secreting IFNγ to activate antimicrobial mechanisms of the phagocyte [14]. These cells are generally referred to as Th1 “T helper type 1” cells [14]. However, the Th2 lymphocytes which produce IL-4, IL-5 and IL-13, are important in the control of extracellular parasites [14]. Another subpopulation of CD4+ T cells was identified and named Th17. These are characterized by the production of IL-17 [15], IL-17F, IL-21 and IL-22 [16-18], Th17 type cells were found to be key drivers of inflammation and tissue damage [19,20].

In the tumoral microenvironment, it appears that immune cells play a role in the prevention from the occurrence and progression of tumors [21]. In addition, it has been reported that the presence of T cells infiltrating the tumors is associated with improved survival in patients with colorectal [22], breast [23,24] and lung [25-28] cancers. However, the immune system, through the inflammatory process, could also be associated with tumor development [29,30].

More recently, it has been reported that the type of tumor infiltrating T lymphocytes and their density would be crucial [31]. Indeed, high densities of memory T cells in the intratumoral environment would correlate with decreasing incidence of early metastasis and would prevent remissions in patients with colorectal cancer [32]. In another study, the role of different subpopulations of T cells in colorectal cancer has been studied and it has been shown that patients with high expression of genes related to Th17 response exhibit a poor prognosis [32]. In contrast, patients with high expression of genes related to Th1 response had significantly prolonged survival [32]. However, the genes associated with Th2 and T regulatory type responses have no effect on disease progression [32]. Increased expression of IL-23 (a growth promoting cytokine of Th17 cells) but not of IL-12 (cytokine involved in Th1 differentiation), was also reported in human tumors. Whereas IL-12 promotes the infiltration of cytotoxic T cells, IL-23 promotes inflammatory responses and increases angiogenesis, but reduces the infiltration of cytotoxic T cells [33]. In addition, the suppression of IL-23 in vivo in mice leads to increased infiltration of cytotoxic T cells in the tumor tissue, thereby promoting a protective effect against carcinogenesis. Furthermore, transplanted tumors also exhibit restricted growth in mice deficient in IL-23 or its receptor [33]. Altogether, these data indicate that the Th17 immune response promotes the growth of tumors; while cytotoxic T lymphocyte and Th1 type immune responses promote survival of cancer patients. Thus the type of the immune response developed within the tumor microenvironment is crucial and could, if it is the appropriate one, contribute to the eradication of the tumor. Therefore, attempts to develop mathematical models, whose consistency was verified via asymptotic behavior developed for solution and by numerical simulations, encompassing these immune findings would help in the prediction of cancer cell evolution and eventually eradication.

Acknowledgments

This work has been supported by Hassan II Academy of Sciences and Technology (Morocco), project "Méthodes mathématiques et outils de modélisation et simulation pour le cancer".

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