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How tumor growth can be influenced by delayed interactions between cancer cells and the microenvironment?

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ABSTRACT

Although recent advances in oncology emphasized the role of microenvironment in tumor growth, the role of delays for modeling tumor growth is still uncertain. In this paper, we considered a model, describing the interactions of tumor cells with their microenvironment made of immune cells and host cells, in which we inserted, as suggested by the clinicians, two time delays, one in the interactions between tumor cells and immune cells and, one in the action of immune cells on tumor cells. We showed analytically that the singular point associated with the co-existence of the three cell populations loses its stability *via* a Hopf bifurcation. We analytically calculated a range of the delays over which tumor cells are inhibited by immune cells and over which a period-1 limit cycle induced by this Hopf bifurcation is observed. By using a global modeling technique, we investigated how the dynamics observed with two delays can be reproduced by a similar model without delays. The effects of these two delays were thus interpreted in terms of interactions between the cell populations.

1. Introduction

Cancer or malignant tumor is a world-wide problem, mainly because the underlying mechanism of tumor growth is not well understood and, consequently, is quite unpredictable and challenging to control it (Schuch et al., 2002; Laurent et al., 2005; Chew et al., 2012; Norrby, 2014). The malignant tumor invades surrounding tissues and primarily grows in the mesenchyme; it has the capability to grow in distant organs once the angiogenic switch occurred, leading to the formation of metastases. Interactions between tumors and their environments not only induce genetic instability of cancer cells but also governs their proliferation (Sun et al., 2012). The tumor growth is not always very fast: an initial tumor may remain confined to a very limited size below a detectable threshold for a long time by routine imaging; this is designated as "tumor dormancy" (Wheelock et al., 1981). Indeed, the sole presence of mutant cells does not necessarily induce a quick proliferation of tumor cells leading to a deleterious cancer. Interactions of tumor cells with immune cells and host cells play an important role in cancer proliferation (Bissell and Hines, 2011) which remains to be clarified. Most of the past mathematical studies were devoted to the role of the immune system (Eftimie and Bramson, 2011; d'Onofrio, 2005) and the action of some chemotherapy, surgery, radiotherapy or hormonotherapy on tumor growth (Kuznetsov et al., 1994; Kirschner and Panetta, 1998; Chaplain, 1999; Galach, 2003; Pillis and Radunskaya, 2003; de Pillis et al., 2006; Reppas et al., 2016). The role of the proximal environment — the healthy (host) cells — of the tumor was more rarely considered (Pillis and Radunskaya, 2003; Itik and Banks, 2010; Letellier et al., 2013; Viger et al., 2014). In these last studies, the key point was that the role of host cells was taken into account as clinically suggested (Folkman, 1995; Merlo et al., 2006; Malanchi et al., 2012). Such an approach still needs further attention.

When delays in the interactions between tumor cells and their environment were considered in models, most often they corresponded to delays between the phases of the cell cycle affecting cells productions, proliferation and differentiation (Galach, 2003;

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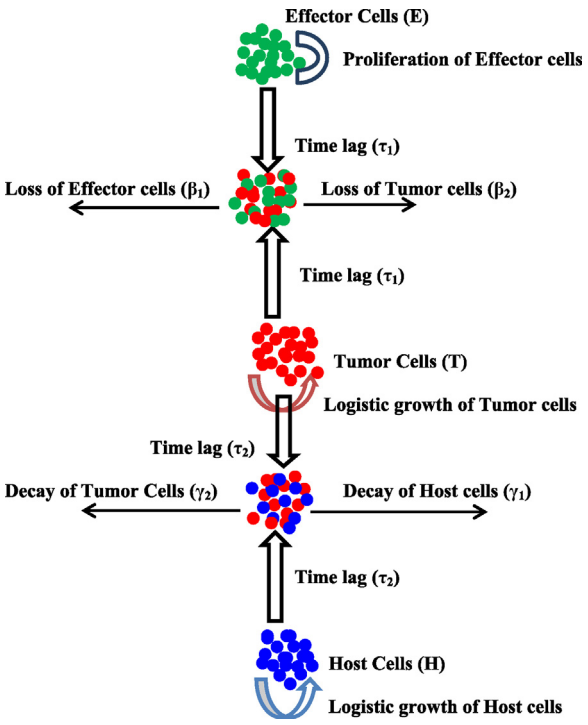

Fig. 1. Schematic diagram of model (1) where effector, tumor and host cells are in green (gray), red (light black) and blue (black), respectively. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

Mayer et al., 1995; Byrne, 1997; Villasana and Radunskaya, 2003; Yu and Wei, 2009; d'Onofrio and Gandolfi, 2004; Bi and Ruan, 2013; Bi et al., 2014; Khajanchi and Banerjee, 2014). For instance, it was shown that a delay, introduced in the tumor cells response to changes in their environment, affects proliferation of the former: shorter the delay, stronger the tumor (Byrne, 1997). Although it is not certain if the delay actually plays any significant role from the clinical point of view, it helps to understand that tumor cells are difficult to eradicate due to the speed with which they can respond to any change in their environment, including therapies (Sun et al., 2012; Merlo et al., 2006; Malanchi et al., 2012; Garcia-Barros et al., 2003; Bochet et al., 2011). This paper deals with the interactions between tumor cells and their surrounding microenvironment (including the immune system), mainly emphasizing the role of host cells and considering the effect of delays in these interaction processes. We started from the model developed by Pillis and Radunskaya (2003) which can produce chaotic behaviors (Itik and Banks, 2010; Letellier et al., 2013). The sensitivity to initial conditions of such behaviors easily matches with clinical observations. Our objective is not to investigate a model describing in a quite exhaustive way all phenomena at the cell level but rather a qualitative model working at the tissue level. However, in the original model (Pillis and Radunskaya, 2003; Itik and Banks, 2010; Letellier et al., 2013), the immune system was assumed to respond instantaneously to the presence of tumor cells. Since there is an obvious delay in the response to the presence of tumor cells, as suggested by clinical evidence that antitumor or activity by immunotherapy is not observed instantaneously but 2–10 weeks later after the initiation of a treatment (Topalian et al., 2012), we modified the original model (Pillis and Radunskaya, 2003) by adding two time delays in the action of tumor cells on immune cells and, of immune cells on tumor cells. The presence of delays in nonlinear dynamical systems always affects the stability of the singular (equilibrium) points and, in particular, affecting the Hopf bifurcation (d'Onofrio et al., 2010; Piotrowska, 2016) observed before more complex dynamics such as chaos (Mayer et al., 1995; Hale and Lunel, 1993; Hale and Sternberg, 1988; Wiggins, 1990).

The subsequent part of this paper is organized as follows. Section 2 is devoted to a brief presentation of the delay differential equations governing the interactions between host, immune and tumor cells that we investigated. In Section 3, an analytical study of the model is performed (stability of the singular points, persistence of limit cycle, etc.) and a numerical validation of our analytical results is discussed. In Section 4, we numerically investigated how this cancer dynamics is affected by our two time delays. In Section 5, we employ the technique of global modeling to study the equivalence of the model without delay. Section 6 provides a discussion of our results.

2. The model

Over the last few decades many models have been proposed for understanding the dynamics of cancer-immune interactions but a very few of them includes the host (healthy) cells. In their model, Pillis and Radunskaya (2003) considered that the immune and the tumor cells were also interacting with the host cells (Fig. 1). However, they assumed that all the interactions were instantaneous. As suggested by some clinical evidences of delayed interactions (Brahmer et al., 2012, 2015), we introduced two time delays, one in the action of tumor cells on effector cells and one, in the action of effector cells on tumor cells. The model as proposed in Pillis and Radunskaya (2003) is thus modified in the set of three delay differential equations

$$\begin{cases} \dot{E} = \dfrac{\rho TE}{g+T} - \beta_1 T(t-\tau_1)E(t-\tau_1) - \delta E, \\ \dot{H} = \alpha H\left(1 - \dfrac{H}{k_1}\right) - \gamma_1 TH, \\ \dot{T} = aT\left(1 - \dfrac{T}{k_2}\right) - \beta_2 T(t-\tau_2)E(t-\tau_2) - \gamma_2 TH, \end{cases} \tag{1}$$

where $E(t)$, $H(t)$ and $T(t)$ designate the population of activated effector cells, host cells and tumor cells at any time t, respectively. In the first equation of system (1), the first term describes the proliferation enhancement of tumor-specific effector cells by tumor cells using a Michaelis–Menten type saturation of the immune system where ρ is the rate of proliferation and g is the value at which the growth rate of effector immune cells is half its maximum value. The term $-\beta_1 T(t-\tau_1)E(t-\tau_1)$ corresponds to the inhibition of immune effector cells by tumor cells at rate β_1. The third term represents the effector cell natural death with a corresponding mean half-life $1/\delta$. The second equation in system (1) represents the dynamics of host cells where the first term designates the logistic growth of host cells in which α is the intrinsic growth rate and k_1 the biotic capacity. The competition between tumor and host cells obeys the law of mass action, here described as $\gamma_1 TH$ where γ_1 is the inhibition rate. The third equation of system (1) represents the rate of change in tumor cells where the first term is the logistic growth of tumor cells $aT(1-(T/k_2))$, in the absence of immune action depending on a growth rate a and the environmental carrying capacity k_2. Interactions between tumor and effector cells are described by the degradation term $-\beta_2 T(t-\tau_2)E(t-\tau_2)$ of the formers by the latter at rate β_2. The last term $\gamma_2 TH$ represents the competition between tumor cells and host cells. The role of vascularization could have been taken into account as in Hatzikirou et al. (2015) and Viger et al. (2014) but this would have increased the dimensionality of the model under consideration (since endothelial cells would have to be included as in Viger et al. (2014)). Our mathematical investigations would have been overcomplicated in an undue way since our objective is to investigate the role of delays in tumor growth and,