Applied Mathematics and Computation 321 (2018) 700–720

Contents lists available at ScienceDirect

Applied Mathematics and Computation

journal homepage: www.elsevier.com/locate/amc

Dynamics of tumor–CD4$^+$–cytokine–host cells interactions with treatments

Xiaochuan Hu, Sophia R.-J. Jang*

Department of Mathematics and Statistics, Texas Tech University, Lubbock, TX 79409-1042, USA

ARTICLE INFO

MSC:
92D25
92B05

Keywords:
Tumor
Immunotherapy
Cytokine
Ordinary differential equations
Global stability
Bistability

ABSTRACT

Mathematical models of interactions between tumor cells, CD4$^+$ T cells, cytokines, and host cells are proposed to investigate the role of CD4$^+$ on tumor regression. Our results suggest that host cells along with the mechanism of production of CD4$^+$ T cells play important roles in driving tumor dynamics. Cancer cells can be eradicated if the tumor has a small growth rate and is also not competitive. Treatments by either CD4$^+$, cytokines, or a combination of the two are applied to study their effectiveness. It is concluded that doses of treatments along with the tumor size are critical in determining the fate of the tumor. Tumor cells can be eliminated completely if doses of treatments by cytokine are large. The treatments are in general more effective if the tumor size is smaller. Bistability is observed in all of the models with or without the treatment strategies indicating that there is a window of opportunity for clearing off the tumor cells.

1. Introduction

Cancer is a leading cause of death worldwide. It is a broad group of diseases involved with unregulated cell growth. It is well accepted that cancer cells have defects in regulatory circuits that govern normal cell proliferation and homeostasis, and the growth signaling pathways suffer deregulation in all human tumors [34]. In cancer, cells divide and grow uncontrollably, forming malignant tumors and invading even the distant parts of the body [34]. Many tumors express antigens that can be recognized by the adaptive immune system and therefore can be used to induce an anti-tumor immune response. The Tumor Immuno-Surveillance Hypothesis formulated in 1957 indicates that the immune system is capable of inhibiting the growth of very small tumors and eliminating them before they become clinically evident [11].

Cancer immunotherapy is the use of the immune system to treat cancer. It frequently involves adopted cellular transfers of T cells and/or cytokines. Cancer immunotherapies have focused much on the antitumor activities of white blood cells, especially T cells (usually CD8$^+$ T cells), natural killer (NK) cells, and macrophages [28]. Experiments have shown that these immune cells can lyse tumor cells very effectively [30,31]. The major histocompatibility complex (MHC) is a set of cell surface molecules encoded by a large gene family in all vertebrates. It mediates interactions of immune cells with other leukocytes or body cells [34]. The MHC gene family is divided into three subgroups: classes I–III. Most cancer immunotherapies are based on the generation of cytotoxic T lymphocyte (CTL) such as CD8$^+$ T cells that recognize tumor antigens in association with MHC class I molecules on tumor cells [24].

Many tumors, however, have evolved to evade recognitions by the white blood cells [24]. For example, it is found that certain cancer cells do not express MHC class I antigens on the cell surface [24]. Traditionally, CD4$^+$ T cells have been

* Corresponding author.
E-mail address: sophia.jang@ttu.edu (S.R.-J. Jang).

https://doi.org/10.1016/j.amc.2017.11.009
0096-3003/

assumed to have only a helper role by activating $CD8^+$ T cells to kill cancer cells. Recent experiments have shown that $CD4^+$ T cells actually play a more direct role in killing the cancer cells [24,27,36]. Indeed, these $CD4^+$ T cells appear to have an effector role through the cytokines and chemokines that they produce [24,36]. Consequently, $CD4^+$ T cells can kill cancer cells even in the absence of $CD8^+$ T cells and NK cells. In these cases, tumor eradication may be mediated by tumoricidal myeloid cells recruited into the tumors or by anti-angiogenic cytokine, such as IL-4 secreted by $CD4^+$ T cells [24,36].

The interactions between tumor cells and other components of the tumor microenvironment are very complex and continuously changing. Consequently, devising cancer immunotherapies to treat or to cure cancer has proven a very challenging task. Mathematical modeling provides a valuable tool for understanding the complicated interactions among the many components of the tumor microenvironment [7,14,20,21]. In the following, we briefly review several mathematical models of tumor–immune interactions.

The research by Kirschner and Panetta [18] can be considered as the pioneer work in this area. Their model consists of three variables, the tumor cells T, the generic effector cells E such as $CD8^+$ T cells, macrophages or NK cells, and the IL-2 cytokine denoted by I, and is described by the following system

$$\begin{cases} T' = r_2 T(1-bT) - \dfrac{aET}{g_2+T} \\ E' = cT + \dfrac{p_1 ET}{g_1+T} - \mu_2 E + s_1 \\ I' = \dfrac{p_2 ET}{g_3+T} - \mu_3 I + s_2, \end{cases} \tag{1.1}$$

where all of the parameters are positive except possibly for s_1 and s_2 which are nonnegative. Parameters s_1 and s_2 denote continuous treatments of effector cells and IL-2, respectively. In particular, the tumor grows logistically in the absence of the effector cells and the tumor killing rate by the effector cells is modeled by the Michaelis–Menten kinetics. The production of the effector cells and cytokines is also modeled by a Michaelis–Menten term. Using tumor's antigenicity c as the bifurcation parameter, Kirschner and Panetta [18] provide a one-parameter bifurcation diagram when $s_1 = s_2 = 0$ to study the effects of c on model dynamics. Treatments by the effector cells ($s_1 > 0$, $s_2 = 0$), cytokines ($s_1 = 0$, $s_2 > 0$) or both ($s_i > 0$, $i = 1, 2$) are considered. Through numerical investigations, they conclude that treatment by the effector cells can clear off the tumor if c is not too small and the treatment dose is above a critical threshold. This critical dose is determined from local stability of the boundary steady state with the absence of tumor. However, treatment by IL-2 alone does not give a satisfactory outcome. Immunotherapy of effector cells or a combination of the effector cells and IL-2 gives promise outcome for controlling the tumor.

de Vladar and González [8] investigate the following model of tumor–immune interaction with treatments

$$\begin{cases} x' = -\mu_c x \log\dfrac{x}{x_\infty} - \gamma xy \\ y' = \mu_2(x - \beta x^2)y - \delta y + k, \end{cases} \tag{1.2}$$

where x denotes tumor volume and y is the density of effector cells. The parameter x_∞ is the tumor's carrying capacity and k is the constant treatment. Notice that the tumor's growth is modeled by the Gompertzian law which implicitly assumes that the tumor tends to grow when it is near zero. The production of effector cells stimulated by the cancer is modeled by the term $x - \beta x^2 = x(1-\beta x)$ and the killing of the tumor is modeled by a simple mass action. These assumptions are different from those used by Kirschner and Panetta [18]. The system has a unique interior equilibrium and two boundary equilibria of either no tumor or no immune cells. Their model predicts that the theory on immune surveillance is plausible and the constant dose therapies are not able to induce complete remission of the tumor if the treatment is stopped due to the Gompertzian law of tumor growth.

To study the impact of anti-immune activity by tumor on the outcome of immunotherapy, Forys et al. [13] propose the following model of two-dimensional ordinary differential equations :

$$\begin{cases} X' = w - uX + aF(X,Y)X - bXY \\ Y' = rY - cXY, \end{cases} \tag{1.3}$$

where X and Y are the sizes of specific anti-tumor immunity and tumor, respectively. The tumor is assumed to grow exponentially and the killing of tumor is modeled by a simple mass action. The parameters w and u are the constant production rate and loss rate of the immune cells respectively. The stimulation of the immune cells by tumor is assumed either of the form $F(X,Y) = F_1(X,Y) = \frac{(Y/X)^\alpha}{k_1^\alpha + (Y/X)^\alpha}$ so that the stimulation depends on the amount of signal molecules per cell, or of the form $F(X,Y) = F_2(X,Y) = \frac{Y^\alpha}{k_2^\alpha + Y^\alpha}$ where the stimulation is antigen dependent only. All of the parameters are positive except $b \geq 0$. $b > 0$ denotes anti-immunity by tumor since the immune cells are lost due to interaction with the tumor. If $b = 0$, then there is no anti-immunity by tumor. The model exhibits six different types of phase portraits with no limit cycles as analyzed by Forys et al. [13] and the patterns of asymptotic behavior of the system do not depend on the type of the stimulation function F_1 or F_2. It is concluded that weak immunity results in unrestricted tumor growth and the immune system has no control over the growth of large tumor even if there is no anti-immunity by tumor.

The above models focus on the effector roles of $CD8^+$ T cells or any generic effector cells such as NK cells, etc. Since the effector roles of $CD4^+$ have only been discovered very recently, there are two mathematical models that appeared in the