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Modeling of Immune Response to Tumor Cancer

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Abstract: In this paper, we present a new mathematical model that describes tumor-immune interactions, focusing on the role of Natural Killer (NK) and CD8+T cells in tumor. And also we present non-dimensional analysis of the proposed model by using scaling, equilibrium points and their existence which is the basic tools for qualitative analysis of any mathematical model. Several closely related results are also considered.

Key words: Cancer model · Acquired immunity · Immune response · Steady states · NK cell · CD8+T cell

INTRODUCTION

Cancer is the uncontrolled growth of abnormal cells in the body [1, 2]. These three malignant properties of cancer differentiate malignant tumors from benign tumors, which do not grow uncontrollably, directly invade locally, or metastasize to regional lymph nodes or distant body sites like brain, bone, liver, or other organs [1].

The Cancer Research Institute reports that in 1995, an estimated 1, 252, 000 cases were diagnosed, with 547, 000 deaths in the United States alone. With new techniques for detection and treatment of cancer, the relative survival rate has now risen to 54 percent [3]. Cancer causes 1 in 8 deaths worldwide and is rapidly becoming a global pandemic. According to the International Agency for Research on Cancer, there were 12.7 million new cancer cases in 2008. If rates don't change, the global cancer burden is expected to nearly double to 21.4 million cases and 13.5 million deaths by 2030 [4]. It is significant to explore new treatment techniques, in order to reduce the rate of mortality due to cancer in the future.

This model is based upon and validated by recently experiment studied by [5] in which mouse tumor cell lines are modified to express higher levels of immune stimulating NKG2D ligands. The experimental result shows that sufficiently high levels of ligand expression create a significant barrier to tumor establishment in the mouse. Another study [6] shows human with metastatic melanoma are treated with immune cells that are highly specific towards tumor cells. The patients in this study receive these specific immune cells only after being subjected to immune depleting chemotherapy which is thought to disrupt the regulations of the immune system and increase the efficacy of the treatment.

The strength of the immune response greatly impacts success or failure of the immune systems attack on tumor. More recently, [7] have proposed the model of anti-tumor immune response where individual equations were suggested for the description of mechanisms of natural immunological defense presented by NK cells and specific immune response presented by $CD8^+$ T cells.

Mathematical Model

Biological Assumption: For the sake of completeness, we outline the assumptions of the original model [7, 8, 9, 10] here:

- Tumor grows logistically in the absence of an immune response.
- Both NK cells and CD8+T cells can kill tumor cells.
- The tumor cells grow logistically in the absence of immune response.
- Both NK cells and $CD8^+$ T cells are activated by tumor cells.
- Natural Killer (NK) cells being part of the immune system are always present even no tumor cells exist.
- As part of specific immunity, tumor specific $CD8^+$ T cells are recruited once tumor cells are presented.
- Each of the NK and CD8+T cells become inactive after some number of encounters with the tumor cells

Model Populations:

In the equations, we denote the three cell populations by:

- T (t), tumor cell population at time t
- N(t), total level of natural killer cell effectiveness at time t

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- L(t), total level of tumor specific CD8+T cell effectiveness at time t

Besides considering assumptions and populations our model carries the four types of actions which are described below.

- Natural growth
- Natural decay
- Recruitment

Using the list of assumptions from above, we describe the system as three coupled differential equations, where each equation gives the rate of change of the particular cell population in terms of growth and death, cell-cell kill, cell recruitment.

Immune recruitment terms are generally assumed to be of a Michaelis- Menten form, (see, e.g., [11] in which Michaelis-Menten dynamics are derived for immune cell recruitment by cancer cells). In the case of the CD8+T cells, in addition to being recruited by interactions with T-cell processed tumor cells through a Michaelis-Menten dynamic, additional CD8+T cells are stimulated by the interaction of NK cells with tumor cells. This NK stimulation is represented by the rNT term in equation (3). The term rNT, representing a fraction of the number of interactions between NK cells and tumor cells, is the vehicle through which we model the fact that the specific immune response of the CD8+T cells is activated only after the activation of the earlier response of innate immunity. The fractional cell kill term for the NK cells was assumed to be proportional to the size of the NK cell population. This assumption was consistent with all the data we examined. However, the same assumption was not consistent with the data for tumor-specific CD8+T cells. Substituting specific mathematical forms for each of the growth, death, recruitment and inactivation terms yields the following system of equations:

$$\begin{cases} \dfrac{dT}{dt} = aT(1-bT) - cNT - dLT \\ \dfrac{dN}{dt} = e + \dfrac{gNT}{h+T} - fN - pNT \\ \dfrac{dL}{dt} = \dfrac{kLT}{h+T} - mL - qLT + rNT \end{cases} \tag{1}$$

where T, N and L represent tumor density, NK cells density and tumor specific CD8+T cell effectiveness at time t respectively. *a* and *b* are growth rate and natural death rate tumor respectively, *c* represents cells killed by NK cells, *d* is fraction of tumor cells killed by CD8+T cells, *e* is constant source of NK cells, *g* denotes maximum NK cells recruitment rate by tumor cells, *f* represents the loss of NK cells naturally s, *p* stands for NK cells inactivation rate by tumor cells, *k* is Maximum CD8+ cells recruitment rate by tumor cells *m* stand for death rate of CD8+ T cells, *h* is Michaels-Menten recruitment constant for both NK cells and CD8+T cells, *q* is CD8+T cells inactivation rate by tumor cells, *r* represent rate at which specific CD8+T cells are stimulated to produce as a result of tumor killed by NK cells.

Non-Dimensionalization and Analysis

Scaling: For convenience let us introduce dimensionless variables as

$$\bar{T} = \frac{f}{q}, \bar{N} = \frac{e}{f}, \bar{L} = \frac{f}{d}, \text{ and } \bar{t} = \frac{1}{f}$$

Dropping primes for notational clarity, equations (1) take the following form in normalized units:

$$\begin{cases} \dfrac{dT}{dt} = u_1(1-u_2T)T - u_3NT - LT \\ \dfrac{dN}{dt} = 1 + u_4\left(\dfrac{T}{u_5+T}\right)N - N - u_6NT \\ \dfrac{dL}{dt} = u_7\left(\dfrac{T}{u_5+T}\right) - u_8L - LT + u_9NT \end{cases} \tag{2}$$

where

$$u_1 = \frac{a}{f}, u_2 = \frac{bf}{q}, u_3 = \frac{ce}{f^2}, u_4 = \frac{g}{f}, u_5 = \frac{hq}{f},$$
$$u_6 = \frac{p}{q}, u_7 = \frac{k}{f}, u_7 = \frac{k}{f}, u_8 = \frac{m}{f}, \text{ and } u_9 = \frac{erd}{qf^2}$$

Steady States: In order to find the steady states or equilibria of system (2), we put all the equations simultaneously equal to zero [9, 12, 13].

$$\left.\begin{array}{l} u_1(1-u_2T)T - u_3NT - LT = 0 \\ 1 + u_4\left(\dfrac{T}{u_5+T}\right)N - N - u_6NT = 0 \\ u_7\left(\dfrac{T}{u_5+T}\right) - u_8L - LT + u_9NT = 0 \end{array}\right\} \tag{3}$$

The dynamical system (2) has two equilibria: tumor-free (healthy) equilibrium E_1 = (0, 1, 0) and endemic equilibrium $E_e = (T^*, N^*, L^*)$ which is obtained by making $T = 0$ and $T \neq 0$ and also by rearranging terms respectively in system (3). Where derivation of the endemic equilibrium is as follows:

$$T = \frac{u_1 - u_3 N - L}{u_1 u_2} \tag{4}$$

$$N = \frac{u_5 + T}{\alpha} \tag{5}$$

$$L = \frac{u_9 (u_5 + T)^2 T}{\alpha\beta} \tag{6}$$

where $\alpha = (u_5 + T)(u_6 T + 1) - u_4 T$ and $\beta = (u_5 + T)(u_8 + T) - u_7 T$

Using (4) - (6), we obtain:

$$u_1\alpha\beta(u_2 T - 1) + u_3(u_5 + T)\beta + u_9 T(u_5 + T)^2 = 0 \tag{7}$$

Putting expressions for α and β, we obtain a polynomial equation of degree five in terms of QUOTE T.

That is

$$a_5 T^5 + a_4 T^4 + a_3 T^3 + a_2 T^2 + a_1 T + a_0 = 0 \tag{8}$$

where

$$a_5 = u_1 u_2 u_6$$
$$a_4 = u_1(u_2 d_1 - u_6)$$
$$a_3 = u_1 u_2 d_2 + u_9 + u_3 - u_1 d_1$$
$$a_2 = u_1 u_2 d_3 - u_1 d_2 + u_3(2u_5 + u_8 - u_7) + 2u_5 u_9$$
$$a_1 = u_1 u_2 d_4 - u_1 d_3 + u_3 u_5(u_5 + 2u_8 - u_7) + u_5^2 u_9$$
$$a_0 = u_3 u_5^2 u_8 - u_1 d_4 = u_5^2 u_8(u_3 - u_1)$$

and

$$d_1 = u_6(u_5 + u_8 - u_7) + (u_5 u_6 + 1 - u_4)$$
$$d_2 = u_5 u_6 u_8 + (u_5 u_6 + 1 - u_4)(u_5 + u_8 - u_7) + u_5$$
$$d_3 = u_5[u_8(u_5 u_6 + 1 - u_4) + (u_5 + u_8 - u_7)]$$
$$d_4 = u_5^2 u_8$$

Solutions of practical interest should have non-negative population T, N, and L. However, it is hard to find a closed analytical solution for (8), but one can see that it has positive solution T^*, and substituting this value of T in (5) and (6) we obtain corresponding value of N^*, and L^*.

Proposition 1: Tumor - free equilibrium always exists.

Proposition 2: Endemic equilibrium point exists if and only the following three conditions hold:

- $u_1 > 3u_3 N + L$
- $(u_6 T + 1)(u_5 + T) > u_4 T$
- $(u_8 T + T)(u_5 + T) > u_7 T$

CONCLUSIONS

The equilibrium points and their existence conditions are obtained. Our result indicates that the most promising research for treatment of tumor should be those that affect the two significant parameters growth and death rates of tumor cells. Here we simply present method of scaling and equilibrium points with their existence. For the future work, we extend it by analyzing its stability analysis and also qualitative analysis. We therefore suggest that the future work better considers these factors to have better result on developing mathematical modeling of immune response to tumor cancer.

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