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Mathematical modeling and simulation for a coupled communication system of immune cells ⋆

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Abstract: Immune cells play a central role in preventing the invasion of several types of antigens, including bacteria, viruses, and foreign proteins. CD4 positive T cells belong to a subset of immune cells that facilitate adaptive immune responses by promoting activation of other immune cell types. The population of CD4 positive T cells is further classified into subsets, known as helper T (Th) cells, according to the behavior of cells. Th1 cells produce cytokines that reduce viral infection, while Th2 cells mainly facilitate an allergic response against parasites. The process of commitment to one of these subsets is determined by numerous complicated events. Communication via cytokine is one major factor that determines the commitment of naive Th cells to Th1 or Th2 cells. Mutual inhibition among these subsets is known at the transcriptional regulation of associated genes that characterize the behavior of each subset. Although an adequate control of the balance between two subsets is essential, the mechanistic description toward control for the commitment process has not yet been fully investigated.
We construct a mathematical model that describes interactions between these two subsets via secretion of cytokines. We incorporate reciprocal inhibition into our model to describe the exclusive commitment of cells as a decision making process. The main system contains positive feedback loops. The dominant state of one subset can be observed, representing adequate recognition for the type of antigen. Extensive numerical simulations suggest that the switch of dominance can occur with external perturbation. The model can serve as a guideline to control the balance of subset constitution to adequately promote immune response.

Keywords: mathematical model, population dynamics, immunotherapy, cancer, cellular and humoral immunity

1. INTRODUCTION

1.1 A brief introduction to immunology

Immune cells play a central role in preventing the invasion of several types of antigens, including bacteria, viruses, and foreign proteins. T lymphocytes play diverse and relevant roles in the adaptive immune response. They are classified into several different phenotypes, including CD4 positive T cells (helper T cells), CD8 positive T cells, and CD4+CD25+ T cells (regulatory T cells: Treg). We can further subdivide helper T cells (Th) into several functionally distinct phenotypes according to the pattern of cytokine secretion. One of two major subpopulations, Th1 cells, is characterized by secreting cytokines interferon-γ (IFN-γ), IL-2, and IL-12. The other is Th2 cells, which are characterized by secreting cytokines IL-4, IL-5, and IL-13. Th1 cells are associated with helping cell-mediated immunity (CMI), which elicits phagocytotic activity, inflammatory response, and apoptosis to virally infected cells or tumors. Th2 cells, however, mediate humoral immunity (HI) by interacting with B cells to promote the maturation of a B cell into a plasma cell that is capable of secreting antigen-specific antibodies (Kindt et al. (2006)).

1.2 Positive feedback activation and cross-regulation

Cytokines promote the development of naive helper cells into effector cells, which can determine the eventual CMI/HI balance (Kapsenberg (2003)). IL-12 produced by macrophages induces Th1 differentiation from naive T cells. IFN-γ secreted by Th1 cells subsequently promotes the production of IL-12 by up-regulating macrophages, which in turn induce further Th1 differentiation. Hence, interactions between macrophages and Th1 cells in a positive feedback manner mediate Th1 cell differentiation and activation. IL-4 secreted by Th2 cells itself promotes Th2 differentiation as an autocrine manner. Thus, a positive feedback mechanism mediates Th2 cell differentiation and activation (see Kidd (2003), Kindt et al. (2006)). Recent studies have identified molecular level evidence for the existence of cross-regulation (mutual inhibition) between

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Th1 and Th2 subsets. IFN-γ secreted by Th1 cells inhibits the differentiation and proliferation of Th2 cells, whereas, IL-4 plays an equivalent role in Th1 differentiation and proliferation. The transcription factor T-bet is known to be essential for the development of Th1 cells, whereas GATA-3 is a transcription factor that plays an equivalent role in Th2 development. Cross-regulation occurs between T-bet and GATA-3 such that T-bet inhibits IL-4 production while GATA-3 inhibits IFN-γ production (Hwang et al. (2005)).

1.3 Deleterious effects induced by imbalanced immune responses

The balance between Th1 and Th2 subsets (CMI/HI balance) in the development of the adaptive immune response can determine disease outcomes. For example, progression of diseases caused by infection from Leishmania major, HIV, and the infection with Epstein-Barr virus might depend on the balance between Th1 and Th2 subsets (Kindt et al. (2006)). Moreover, accumulating evidence indicates that humoral immunity can promote carcinogenesis and malignancy. For example, activation of humoral immune responses can lead to chronic activation of innate immune cells that support tumor development by increasing the survival of tumors (de Visser et al. (2006), Tan and Coussens (2007)). These findings suggest that we need to consider control mechanisms underlying the complex interplay among different subsets of Th cells in tumor-immune interactions.

1.4 Previous our study and the purpose

In previous papers, the author constructed mathematical models describing the dynamics of tumor elimination by cell-mediated and humoral immune responses. In previous works, qualitative dynamical behaviors of tumor-immune interactions are classified on the basis of two types of thresholds: activation and elimination Nakaoka (2015). On the basis of these thresholds, a mathematical condition for tumor persistence has been proven. Although mathematical analyses have already been extensively performed, numerical computations are not abundant in the previous papers.

In this paper, we perform numerical computations to investigate how changing parameter values maintain the balance between cell-mediated and humoral immune responses. We focus on the tumor as an antigen, and investigate the outcome of polarized HI for tumor persistence. The organization of the present paper is as follows. In Section 2, we formulate a main mathematical model. In Section 3, we perform numerical computations and draw diagrams. In Section 4, numerical computation results are discussed with biological interpretations.

2. MODEL FORMULATION

In this section, we consider a mathematical model describing the dynamics of tumor elimination by cell-mediated and humoral immune responses. We denote the density of tumors by x. Let y_1 and y_2 denote the magnitude of cell-mediated and humoral immune responses, respectively. Let $g(x)$ denote the per capita growth rate of the tumor population. By $E_j(y_j)$ $(j = 1, 2)$, we denote the per capita elimination rate of the tumor by cell mediated and humoral immune responses. Each $A_j(x)$ $(j = 1, 2)$ represents the per capita activation rate of cell-mediated or humoral immune response via tumor associated antigenic stimulation. As mentioned in Section 1, Th1 and Th2 subtypes undergo positive feedback proliferation via IFN-γ or IL-4, respectively. By $P_j(y_j)$ $(j = 1, 2)$, we denote the rate of positive feedback proliferation that is independent of tumor associated antigenic stimulation. As mentioned in Section 1, IFN-γ secreted by Th1 cells inhibits the population growth of Th2 cells, whereas, IL-4 plays an equivalent role in the growth of the Th1 population. By $S_j(y_i)$ $(i \neq j$, $i, j = 1, 2)$, we denote the effect of cross-regulation between Th1 and Th2 subsets. Let $D_j(y_j)$ $(j = 1, 2)$ denote the per capita inactivation rate of effector helper T cells, including cell death and anergy. The general form of equations is given by

$$\begin{cases} x' = g(x)x - E_1(y_1)x - E_2(y_2)x, \\ y_1' = \{A_1(x) + P_1(y_1)\}S_1(y_2)y_1 - D_1(y_1)y_1, \\ y_2' = \{A_2(x) + P_2(y_2)\}S_2(y_1)y_2 - D_2(y_2)y_2 \end{cases} \tag{1}$$

with the initial condition

$$x(0) = x^0, \quad y_1(0) = y_1^0, \quad y_2(0) = y_2^0. \tag{2}$$

Hereafter we call the value of x^0 *initial tumor size*. Note that we have assumed a functionally symmetric structure in the equations for Th1 and Th2 subsets. Model (1) can represent heterogeneity between cell-mediated and humoral immune responses by assuming different values for parameters and initial conditions.

There are eight types of equilibrium, whether or tumors, cell-mediated or humoral immune responses are present (see also Table 1). One category represents elimination of tumors in which tumors are eradicated completely (E_1, E_2, E_{12}). Another category is tumor persistence in which tumors survive (marked with "*": E^*, E_1^*, E_2^*, E_{12}^*). CMI-dominance represents the presence of CMI without HI (E_1, E_1^*). In the same manner, HI-dominance is defined as having no CMI but having HI (E_2, E_2^*). CMI-HI coexistence represents the coexistence of cell-mediated and humoral immune responses (E_{12}, E_{12}^*). No immune response under the persistence of tumors E^* is called an anergy state.

$E_0 = (0, 0, 0)$	No tumor, CMI and HI (naive)
$E_1 = (0, \bar{y}_1, 0)$	No tumor and HI (CMI-dominant, clearance)
$E_2 = (0, 0, \bar{y}_2)$	No tumor and CMI (HI-dominant, clearance)
$E_{12} = (0, y_1^c, y_2^c)$	No tumor (CMI-HI coexistent, clearance)
$E_1^* = (\bar{x}_1^*, \bar{y}_1^*, 0)$	No HI (CMI dominant, persistence)
$E_2^* = (\bar{x}_2^*, 0, \bar{y}_2^*)$	No CMI (HI dominant, persistence)
$E_{12}^* = (x^*, y_1^*, y_2^*)$	All present (CMI-HI coexistent, persistence)
$E^* = (K, 0, 0)$	No CMI and HI (anergy)

Table 1. Eight types of possible equilibria of (1). Each type is classified into one of two categories, whether the tumor is eliminated or not. Each category is further classified whether one of immunity is dominant or coexisting.

Let us specify the functional form of each component in model (1) for numerical computations. The dynamics of tumors without immune response is assumed to follow the logistic law: