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An extended mathematical model of tumor growth and its interaction with the immune system, to be used for developing an optimized immunotherapy treatment protocol

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ABSTRACT

Background: Chemotherapy is usually known as the main modality for cancer treatment. Nevertheless, most of chronic cancers could not be treated with chemotherapy alone. Immunotherapy is a new modality for cancer treatment that is effective for early stages of cancer and it has fewer side effects compared to chemotherapy, specifically for those types of cancer that are resistant to it.
Method: This work presents an extended mathematical model to depict interactions between cancerous and adaptive immune system in mouse. We called the model an extended model, because we embedded all those compartments that have important roles in response to tumor in one model. The model includes tumor cells, natural killers, naïve and mature cytotoxic T cells, naïve and mature helper T cells, regulatory T cells, dendritic cells and interleukin 2 cytokine. Whole cycle of cell division program of immune cells is also considered in the model. We also optimized protocol of immunotherapy with DC vaccine based on the proposed mathematical model.
Result: Simulation results of the proposed model are in conformity with the experimental data recorded from mouse in immunology department of Tehran University of Medical Science as well as what has been explained in the literature. Our results explain dynamics of the immune cells from the first day of cancer growth and progression. Simulation result shows that reducing intervals between immunotherapy injections, efficacy of the treatment will be increased because CD8+ cells are boosted more rapidly. Optimized protocol for immunotherapy suggests that if the effect of DC vaccines on increasing number of anti-tumor immune cells be just before the maximum number of CD8+ cells, the effect of treatment will be maximized.

1. Introduction

There are several common modalities for cancer treatment such as chemotherapy, radiotherapy, immunotherapy, and surgery. Among these types of cancer treatments chemotherapy is a systematic therapy that fights and kills both the residual cancer cells in tumor site and the migrated tumor cells in other parts of the body [1]. The principle of chemotherapy is to attack rapidly proliferating cells [2]. Consequently, this mechanism also damages normal proliferating cells. On the other hand, chemotherapy is not effective for some types of cancers like melanoma. It has been observed that in these cases, immunotherapy can be more successful in cancer treatment. This modality of cancer treatment stimulates adaptive or acquired immune system to react against tumor and therefore, has less side effects compared to simple chemotherapy. There are different types of immunotherapy, including adoptive cell transfer, cytokines, dendritic cell (DC) vaccines, monoclonal antibodies and adjuvant therapies [3,4]. In DC vaccines, patient's dendritic cells are extracted from his/her body, and then, are grown in more numbers and are activated with specific cancer antigens and finally are injected into the patient's body [5].

Helper T (Th) cells are a type of T-cells that are critical for coordinating activity of the immune response. Type one helper T-cells (Th1) and regulatory T-cells (Treg cells) play important roles in organization of the immune response. Th1 cells orchestrate development of the immune response by activating antigen specific effec-

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tor cells [6] Regulatory T-cells are known as suppression lymphocytes, and are crucial for maintaining self-tolerance by enforcing a dominant negative regulation on other immune cells, such as cytotoxic T-lymphocytes [7]. It has been shown that Treg cells are the main cause of immunotherapy failures in cancer treatments [8]. Antigen presenting cells and specifically Dendritic cells (DCs) are defined as natural adjuvant for antigen delivery. So, DCs are essential target for cancer immunotherapy. Clinical results demonstrate that generation of protective anti-tumor immunity depends on presentation of tumor antigen by dendritic cells [9].

According to the functions of DCs, Th1 and Treg cells, it is imperative to consider their role in the model, this can help the model to produce more realistic results and predictions. In this case, it can be expected that the predictions of the model agree more significantly with the recorded clinical results.

Different models have been developed to describe immune-tumor interaction [10]. In most of the mathematical models, for the sake of simplicity, not all interactions of the immune system with the tumor are described (modeled), whereas some of the ignored compartments play important roles in interactions with the tumor cells and define important features of the immune response. These models are able to show only some aspects of the experimental results and sometimes they even predict non-realistic responses. As examples, we can mention those works that do not consider either the dynamics of the helper T-cells or that of dendritic cells [10–16]. More specifically, Yang et al. [10], De Pillis et al. [13], and Kirschner et al. [15] have not considered the role of DCs in their models. On the other hand, Treg cells are one of the important parts of the immune system that are responsible for regulating and suppressing anti-tumor cells. De Pillis et al. [11], Castiglione et al. [12], Castillo-montiel [17] and De Pillis et al. [18] present models in which they do not consider Treg cells and therefore, cannot show the suppression effect.

De Pillis and colleagues introduced a model that presents interaction between tumor and the immune system in [13] that is a popular model. They have developed an ordinary differential equation (ODE) point model to describe tumor growth and its interactions with the immune system. Immune cells that are described in their model, are natural killers (NK), cluster of differentiation 8 (CD8), circulating lymphocytes and interleukin 2 (IL-2). Their proposed model does not consider helper T-cells, DCs and Treg cells. It does not consider the role of Treg cells and thereby, it cannot predict the result of anti-tumor immune cells suppression. Experimental studies show that with increasing size of tumor, suppression effect on anti-tumor immune cells increases and thereby, the number of anti-tumor cells decreases [19]. But, in [13] when the size of tumor increases the number of CD8+ increases also; this observation is not in accordance with clinical results.

Kim et al. [20] and Wilson et al. [21] developed models using delayed differential equations to describe interaction of different kinds of the immune cells with an infection and its corresponding antigens. However, the results of Kim et al. [20] and Wilson and Levy [21] are not in accordance with the experimental results for cancer specified antigen presenting for a long time. Tessi et al. [19] and [22] developed a set of ordinary differential equations including immune suppressing Treg cells and cytokines and immune promoting cells. These works have considered all compartments of the immune system related to the tumor response. The results reported in [19] show the response of the tumor to immune system, under different values for the antigenicity and growth rate of the tumor. Accordingly, they suggested an optimum antigenicity based on the different growth rates. In addition, their results predicted the important role of the Treg cells on suppression of anti-tumor immune cells. In [22] the results present the effect of chemotherapy and immunotherapy on control of the tumor growth. Moreover, an optimal fractionizing treatment schedule for a fixed dose of chemotherapy is predicted. However, the parameters of the proposed model have been obtained from different types of cancer in human and mouse; so, the consistency of the model is under question and it may not be able to show correct dynamics of the immune cells [19].

Finally, there are various drugs that affect on different parts of the immune system. Considering different compartments of immune system will help to predict effect of drugs with the same mechanism. It is also possible to investigate combination therapy of drugs, like immunotherapy together with DC vaccine and Treg cells depletion. Too simplified models cannot predict these dynamics.

With regards to all points mentioned above, we would like to develop a model that includes important agents and therefore, functions of the immune system to be able to predict the behavior of the tumor under immunotherapy more realistically.

In the present work, our first goal is to build a mathematical model to investigate the role and function of the immune cells in interaction with cancerous cells. The mathematical model will express reaction of immune T cells to tumor cells, and it includes those parts that play key-roles in determining immune system response against tumor. In this work we describe for the first time functions of the naïve and mature helper T-cells, DCs, NK, naïve and mature CD8+, IL-2 and Treg cells with the cycle of cell division, all in one model. This model can be used to analyze dynamics of different parts of the immune system during interaction with tumor. Our second goal is to use the model to develop a suitable strategy using optimal control theory for immunotherapy of mouse against tumor growth, while maximizing the efficacy of the treatment and minimizing its side effects.

Organization of the rest of the paper is as follows. Section II presents a mathematical model that describes tumor growth and its interaction with the immune cells. In section III, we will explain experimental data that are used in the work to estimate model parameters. Section IV presents the results of numerical simulations of the proposed model. We used these results to validate the model. Section V formulates the optimal control problem for cancer therapy based on the proposed model, and in section VI, a conclusion about the whole work will be presented.

2. Mathematical model

In general, mathematical models for the immune system and cancerous cells describe growth and death of each agent and its interactions with other agents. In this work we use delayed differential equations (DDE) to explain temporal development of this interaction in a point model, that is, no spatial aspect is considered in this model. The proposed model includes tumor growth and the immune system response to the presence of tumor cells.

Biological agents of the model are represented by the following variables:

T: Total cancer cell populations
N: Natural killer (NK) cell populations
L_n: Naïve CD8+ T-lymphocyte populations
L: Mature CD8+ T-lymphocyte populations
D: Dendritic cell populations
I_2: Interleukin 2(IL-2) cytokines
T_{reg}: Regulatory T-cell populations
Th_n: Naïve helper T-cells
Th_1: type one helper T-cells

Fig. 1 demonstrates detailed interactions of most significant agents of the immune system with each other and with the tumor cells. The biological processes that have been considered in order to build the model are as follows [3]: