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CELL-MEDIATED IMMUNE PROCESSES AND CONTROL OF CANCER

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ABSTRACT

Cell kinetics and the chemical mass action principle formulate the basis of immune system dynamics which may be synthesized mathematically as cascades of bilinear systems which are connected by nonlinear nondynamical terms. In this manner, a model for cell-mediated immune response (CMI) to tumor antigens and debris is developed. We also consider parametric control variables relevant to the latest experimental data, i.e., sigmoidal dose-response relationship and Michaelis-Menten dynamics.

The preliminary results show that the parametric control variable is important in the destruction of tumors. As well as that, the exacerbation theory is a good method for tumor treatment. Finally, tumor control as an application of immunotherapy is analyzed from the basis established above.

INTRODUCTION

The principal aim of all forms of cancer therapy is to remove or destroy the tumor without serious damage to the host. This can be achieved by surgery, radiotherapy, chemotherapy, immunotherapy, or by a combination of these methods of intervention. In comparison to the alternative methods of control, immunotherapy is the preferred and most efficient therapy since immune effector cells kill the target cells without the accompanying destruction of normal neighborhood cells. Potential methods of tumor immunotherapy can be classified in two broad categories: 1) active immunotherapy, in which a state of immune responsiveness to tumors is induced in the host, and 2) passive (adoptive) immunotherapy, in which immunologically active reagents that mediate an antitumor response are transferred directly to the host [1].

Mathematical modeling of the interactions between tumor cells and the immune system have been under serious consideration for the last two decades. Rescigno and Delisi [2] and Grossman and Berke [3] have presented simple models for the interaction of tumor cells and cytotoxic (killer) T-lymphocytes. Lefever and Garay [4] analyzed the cell-mediated cytotoxic reactions against transformed cells and their negative regulation by blocking factors. Merrill [5] proposed and analyzed a model of immune surveillance mediated by NK cells. However, it is generally accepted that the immune response to a tumor involves several effector cells, e.g., T-lymphocytes, B-lymphocytes, and macrophages, and simple kinetic models of the anti-tumor immune response can describe only one aspect of this complex phenomenon. Therefore, these models have not provided a comprehensive explanation of all of the complexities of the immune response to tumors.

More recently, De Boer, Hogeweg, and their associates [6,7] have presented a model of the macrophage T-lymphocyte interactions that generate an antitumor immune response. However, these methods have not included consideration of tumor escape mechanisms and natural killer activity.

In this paper, a detailed, knowledge-based mathematical model of the effector mechanism used by the immune system to attack tumor cells, or the process of cell-mediated immunity (CMI), is presented. In addition, control of the dynamics of immune surveillance, which is the ultimate goal of tumor immunology, is also considered.

CELLULAR-MOLECULAR STRUCTURE

Based on the existing knowledge of tumor immunology, a mathematical model of the anti-tumor immune response due to cellular kinetics can be developed. These cellular kinetics have been well-defined in conservation equations and from principles of chemical mass-action [8,9]. In general, the cellular population (or concentration), x_i, of the i^{th} class may be described by

dx_i/dt = (source rate - death rate + division rate + rate differentiation to - rate differentiation from) for the i^{th} class, or

$$dx_i/dt = v_i(t) - x_i/\tau_i + p_i(\cdot)x_i + \sum_{j\neq i} 2p_j(\cdot)p_{ji}(\cdot)x_j - \sum_{k\neq i} 2p_k(\cdot)p_{ik}(\cdot)x_k \quad (1)$$

where $v_i(t)$ is a source term (from bone marrow via blood); τ_i is a death time constant; and $p_i(\cdot)$, $p_{ji}(\cdot)$, $p_{ik}(\cdot)$ are appropriate growth coefficients (including probabilities of stimulation and differentiation from one class to the other).

These coefficients (or probabilities) represent parametric feedback control in the immune system of a very complex nature. Indeed, contemporary immunological research is to a considerable extent focused upon these terms, i.e., the manner in which cell production is activated and controlled, principally by molecularly regulated substances. Consequently, $p_i(\cdot)$, $p_{ji}(\cdot)$, $p_{ik}(\cdot)$ are primarily functions of molecular concentrations, which may be deterministic functions or random processes, dependent upon the approximations used.

Here i refers to different cell types; e.g. this might refer to B-cell, T-cell, and macrophage cell lineages, such as resting cells, excited cells, cytotoxic cells, suppressors, helpers, memory cells, and plasma cells (which generate antibody, Ab). Also, other killer cells and mast cells could be included.

As same manner, the molecular concentrations of the m^{th} class can be described. These molecules, such as Ab, Ag (antigen), appropriate cell receptor, appropriate lymphokine, IFN (interferon), etc., could be included.

TUMOR IMMUNOLOGY

It has been hypothesized that immune reactions may either prevent the initial appearance of tumors (immunosurveillance) or could occur following tumor initiation and be involved in limiting their development.

Immunologic surveillance against malignant cells are based on the antigenicity. A weak antigenic tumor evokes a weak immune response, and the tumor load has become too large to control by the time a sufficient number effector cells are generated. The debris of these tumor cells is phagocytosed by antigen presenting cells (APC), that subsequently present antigens in an Ia-restricted fashion to T cells to initiate cell mediated immunity. The stimulation of T_h cells requires at least two signals, i.e., antigen and interleukin-1 (IL-1). A major function of interleukin-2 (IL-2) is to induce the growth of activated T cells and natural killer cell activity [10]. It is known that IL-2 induces lymphocytes to produce interferon-γ and this IFN type is particulary efficient in inducing tumor cell resistance to NK cell-mediated lysis [11]. Large granular lymphocytes (LGL) are assumed to include NK cells. Both IL-2 and IFN have been shown to stimulate the growth and activity of LGL cells. Macrophages may become highly cytotoxic when they become activated by MAF (= γ-IFN). The target cells are also specifically destroyed by lymphotoxins (LT) of cytotoxic T (T_C) cells. Regulation of CMI response is governed by a series of + and - signals by T_h and T_s cells, respectively.

Fig. 1 provides a functional description of our model.

Based on the latest knowledge of tumor immunology, we can make a mathematical model of the anti-tumor immune response due to cell kinetics. Our model is composed of 12 states nonlinear differential equations. Each of the states include; each T-precursor cells, T_C, T_S, T_h, LGL precursor cell, LGL, macrophage, activated macrophage, tumor, and tumor debris.

Each of the states can be modelled as bilinear. However, the coupled systems by parametric feedback control make the total system highly nonlinear. The parametric control variable takes the form of sigmoidal dose-response curves. This might include IL-2, IFN, effector cell cytotoxicity, inflammatory reaction, and suppression. It is these terms upon which much of immunological research is currently focused.

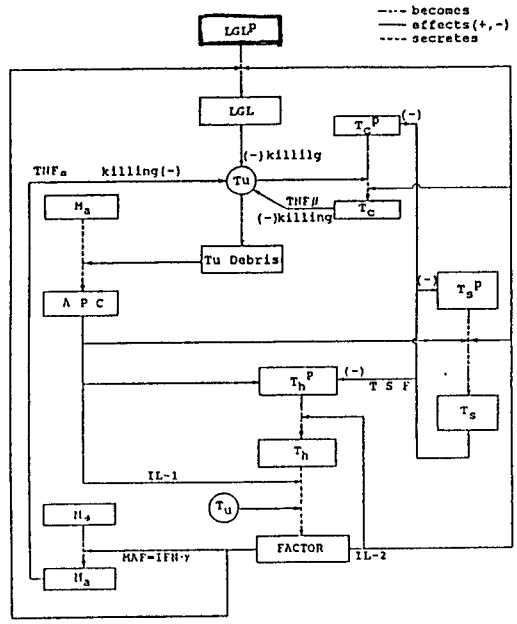

Fig. 1 Schematic representation of anti-tumor immune response.

SIMULATION AND RESULTS

We have investigated the effects of antigenicity of tumors. As mentioned earlier, higher antigenic tumors stimulate the T_h cells, that produce enough IL-2 to make necessary effector cells to remove target cells (Fig. 2a). In case of lower antigenicity, there is not sufficient IL-2 and the concentrations of effector cells are the same as the healthy state (Fig. 2b). IFN is also very important in removing the tumor cells. Fig. 2c shows that the tumor grows progressively when no IFN is produced. The population of M_a decreases exponentially in this case.

Among several methods of immunotherapy, exacerbation theory is good for treating tumor. Fig. 2d shows the tumor regression due to increase of effector cells at first. During the decrease of effector cells, the tumor was reoccurred and reached the equilibrium state. At 66 days, 10^3 tumor cells are injected for 2 weeks. This higher tumor concentration evokes the stimulation of effector cells and tumor is destroyed completely (Fig. 2e).

IDEALISTIC IMMUNOTHERAPY

Generally, cancer patients are treated according to discrete IL-2 dosage schedule (e.g., three times a day) [12]. When administered intravenously, IL-2 has a very short half-life. When IL-2 is administered at 100,000 units per kg body weight, there is a very rapid fall-off, with an estimated distribution half-life of 7 to 10 minutes and a clearance half-life of approximately 30 to 60 minutes [13]. Moreover, a number of clinical studies of continuous delivery of anti-cancer drugs have been reported, and the use of therapeutic devices to provide continuous delivery is increasing in chemotherapy [14]. Experimental results have also shown that IL-2 induced lymphocytosis is higher with continuous intravenous administration than for administration each eight hours [12]. Therefore, continuous delivery of IL-2 was assumed for this analysis.

When a system, for an animal, for instance, is in a cancerous state, the question is how can appropriate optimal therapeutic treatment be administered so that the organism can resume functioning with its normal attributes? Therefore, the issue of optimal therapeutic treatment is explored for this analysis.

The objective of administering IL-2 is to minimize the size of the tumor cell population at the terminal time of treatment. The performance functional J is selected to include the size of the tumor cell population at a selected terminal time of treatment T, as well as to penalize the excessive use of IL-2. Let the cost criterion be the integral square of the deviation of actual tumor size from the desired tumor level with an integral term added to limit control

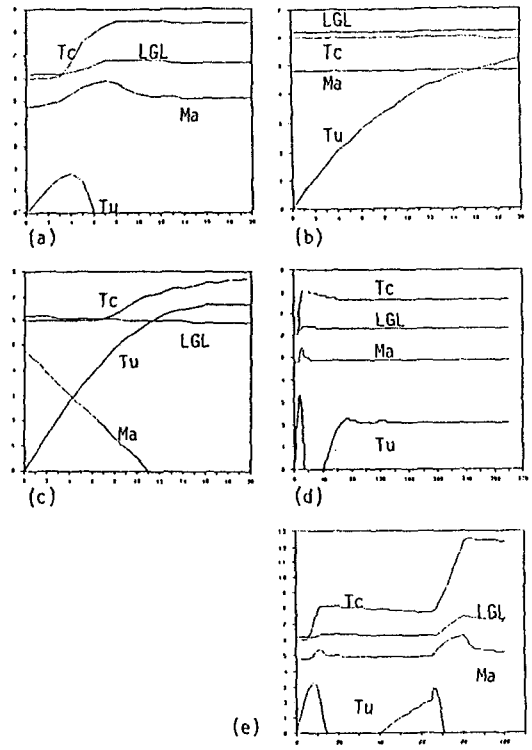

Fig. 2 Tumor dynamics.

input and a final term added to insure the proper final state. The two "costs" may well be different units, i.e. they are not directly comparable. A parameter W_1 is then introduced, which enables the weighting of one type of cost. Thus, a performance criterion of the form

$$J = \int_0^T [(x-x_d)^2 + W_1 u^2(t)]dt + W_2(x(T)-x_d)^2 \qquad (2)$$

is considered, where x is tumor size (cell population), u(t) is the input level of IL-2, and T is the length of a selected treatment interval. The quantity of IL-2 is a time-dependent control variable, representing the actual size of the IL-2 level used for stimulation of the effector cells at the tumor site. However, the assumption is made that the IL-2 is approximated to be identical to the amount of IL-2 infused. x_d, which is the maximum allowable tumor size without threatening the life of the patient, is a safe tumor size (i.e., the desired level). The constant W_2 is chosen to weight the terminal condition as desired. Since the purpose of an optimal IL-2 regimen is to minimize J, which corresponds to the achievement of a low-total final population while restricting the amount of IL-2 in use, there is a trade-off between the final population and the

amount of IL-2 administered.

If it is assumed that a cancer patient has about 10^7 cancer cells present at the time of diagnosis (t = 0), the rapid growth in tumor size without treatment is compared with that of this prescribed immunotherapy in Fig. 3a. Here, the goal of cancer immunotherapy would be to reduce this number to 0.98 x 10^7 cancer cells within two days. In this case, the final run involves 10,000 integration steps in a fourth-order Runge-Kutta integration of the differential equations since the system is stiff. The corresponding optimal control input (IL-2) given in Fig. 3b.

The optimal IL-2 dose is initially set at the maximum, and then decreased until the end of treatment. During treatment, the number of tumor cells is increased due to the initial lack of effector cells. Subsequently, the number of tumor cells is regressed by the immune system. Obviously, this is only a cursory introduction to the complex problem of adoptive immunotherapy for tumor regulation. After the tumor is restored to an acceptable size, a reduced IL-2 therapy may be applied to maintain that size or to further attenuate its size. Ideally, such therapy may be derived from the model and a desired performance index such as (2). It must be noted that such models and the prescribed therapy; to be successful, should be tuned according to each individual patient. That is, a model must be identified according to the individual's particular response characteristics and the prescribed therapy adjusted accordingly.

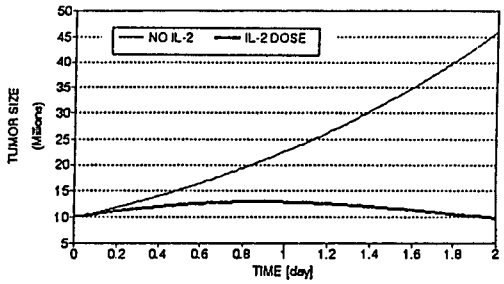

Fig. 3a Output response.

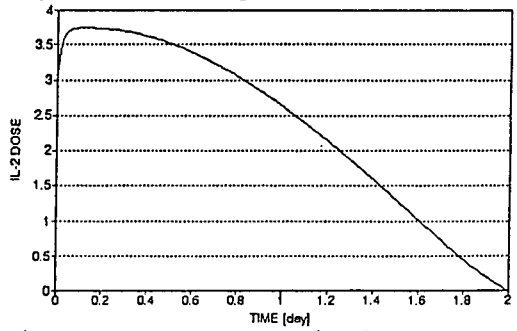

Fig. 3b Optimal control input.

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