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A Mathematical Model for the Proliferation and Death of T Cells

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We proposed a mathematical model to represent the kinetics of the proliferation and death of T cells. The model was described by introducing several values; i.e. the concentration of dose of the antigen and IL-2, the amount of T cell receptor and death factor, as well as the amount of T cells. We assumed that the switching between the proliferation and the death of T cells was ascribed to the relative value of the concentration of IL-2 and the death factor. The results by the numerical analysis was consistent with the experimental observation of the proliferation and death process of T cells.

Key Words
Mathematical model,
T cell,
IL-2,
Death factor.

INTRODUCTION

While B cells are derived from the bone marrow precursor cells, the precursor cells passed through thymus are differentiated into T cells. T cells are then distributed to the peripheral lymphoid organs such as the spleen or lymph nodes. They are activated by encountering with an antigen presented on antigen-presenting dendritic cells in an antigen-specific fashion. Activated T cells proliferate and release cytokines to promote subsequent immune responses: T cells support the maturation and the differentiation of B cells antibody-secreting plasma cells. They also support the maturation of cytotoxic T cells from their precursor state, and in this way T cells inintiate fully competent humoral and cellular immune responses against invading antigens. Activated T cells, on the other hand, succumb to activation-induced cell death. This is a process of programmed cell death which is biologically characterized by apoptosis[1]. Both proliferation and death are required for the normal function of T lymphocytes as well as for the normal immune response.

Immune response is unique in that it is strictly antigen-specific, and thus numerous lymphocytes harboring different antigenic specificity are required. T cells should proliferate when necessary and they must die when they are no longer necessary. Thus, immune response is very unique in that its response is dynamically regulated. The purpose of this study is to clarify the dynamical characteristics among T cell responses.

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MATERIALS AND METHODS

When an antigen comes from the circulation, it is first trapped by antigen-presenting cells (APC) in lymphoid organs. The antigen is then degraded into small peptides containing 10-20 amino acids within the APC. The peptides are incorporated in the cleft of human leukocyte antigen (HLA), and presented to T cells. T cells are then activated upon recognition of particular antigen peptides in the context of HLA. T cells become activated when the second signal, i.e. accessory signal, is transmitted in conjunction with the antigen peptide and HLA[2].

T cells, stimulated with the antigen peptide and HLA, strongly proliferate and release cytokines such as interleukin-2 (IL-2). Due to the strong proliferation, however, most of the T cells die with the mechanism of apoptosis and the only minor fraction of T cells goes into the memory state: This process is called activation-induced cell death. Recent findings suggest that this process is an active process requiring the participation of death-inducing factors.

We present here a mathematical model describing a dynamical state of the proliferation and death of T cells. Since incoming antigen is first degraded into peptides within APC, we assume that the amount of antigenic peptide is proportional to the concentration of antigen. We also assume that the rate of the digestion into peptides within APC is constant. Consequently the following reaction takes place in which Ag (equivalent to the peptide-HLA complex) is recognized by the T cell receptor (TCR) directly.

$$[Ag]/[T]+[TCR] \xrightarrow{k_1} [TCR\cdot Ag] \qquad (1)$$

where [Ag]/[T] means the concentration of Ag for one T cell. [TCR] and [TCR·Ag] represent the amount of TCR and the TCR occupied by antigen peptides, respectively. The brackets [* *] mean the concentration or number of the argument * *, hereafter.

We assumed that IL-2 is produced in proportion to the [TCR·Ag] and the TCR will become free from TCR·Ag again. The following equation is constructed.

$$[TCR\cdot Ag] \xrightarrow{k_2} [IL\text{-}2]+[TCR] \qquad (2)$$

Because the TCR will regain the ability to make complex with the Ag, it is incorporated in the term [TCR] in equation (1).

T cells proliferate in proportion to the concentration of IL-2 in the cell. On the other hand, T cells die due to activation-induced cell death. As to the mechanism of activation-induced cell death, in addition to the production of IL-2, activation of T cells also leads to the synthesis of Fas and Fas ligand on T cells thereby facilitating mutual killing of T cells through Fas and Fas ligand interaction. Upon T cell activation, therefore, two kinds of signals are triggered simultaneously: One is synthesis of IL-2 which supports proliferation and growth of T cells and the other is the induction of death signal which facilitates death of T cells. Therefore, the proliferation and death of T cells are governed by introducing a death factor x as follows:

$$\begin{cases} \text{if } [\text{IL-2}]>[x] \text{ then} \\ \text{T cells proliferate with the rate } k_5 \\ \\ \text{if } [\text{IL-2}]<[x] \text{ then} \\ \text{T cells die with the rate } k_6 \end{cases} \quad (3)$$

The death factor x in equation (3) can be regarded as a threshold for switching the proliferation and/or death process.

According to the above suppositions, we obtained the following equations:

$$\frac{d[\text{TCR}\cdot\text{Ag}]}{dt} = k_1\frac{[\text{Ag}]}{[\text{T}]}[\text{TCR}]-k_2[\text{TCR}\cdot\text{Ag}] \quad (4)$$

$$\frac{d}{dt}\left(\frac{[\text{Ag}]}{[\text{T}]}\right) = -k_1\frac{[\text{Ag}]}{[\text{T}]}[\text{TCR}] \quad (5)$$

$$\frac{d[\text{TCR}]}{dt} = -k_1\frac{[\text{Ag}]}{[\text{T}]}[\text{TCR}]+k_2[\text{TCR}\cdot\text{Ag}] \quad (6)$$

$$\frac{d[\text{IL}-2]}{dt} = k_2[\text{TCR}\cdot\text{Ag}] \quad (7)$$

$$\frac{d[x]}{dt} = k_3[\text{IL}-2]+k_4[\text{TCR}\cdot\text{Ag}] \quad (8)$$

$$\frac{d[\text{T}]}{dt} = \begin{cases} k_5([\text{IL-2}]-[x])[\text{T}] & \text{if } [\text{IL}-2]>[x] \\ k_6([\text{IL-2}]-[x])[\text{T}] & \text{if } [\text{IL}-2]<[x] \end{cases} \quad (9)$$

These etuations are solved with initial conditions for each variable.

RESULTS AND DISCUSSIONS

The set of governing equations from (4) to (9) can be regarded as follows: The equation (4) governs the generation of [TCR·Ag]. The first term of the right hand side of the equation (4) means the generation of [TCR·Ag], while the second term corresponds to the resolution of [TCR·Ag] as derived from the equation (2). Similarly, the equation (5) represents the rate of decrease of Ag and the equation (6) is the rate of increase and/or decrease of TCR derived from the kinetics of chemical reaction. For the sake of simplicity, we did not include the effect of accessory signals here. Equations (7) and (8) are the rate of yields of IL-2 and death factor x, respectively; while the equation (9) represents the proliferation and/or death of T cells, which depends on the sign as well as the magnitude of [IL-2]−[x].

We obtain the dynamical responses of each variables when the equations from (4) to (9) are solved under the initial conditions. As initial conditions, the number of T cells and the concentration of TCR are represented by $[\text{T}]_0$ and $[\text{TCR}]_0$, respectively. The initial amounts of antigen and IL-2 are specified by $[\text{Ag}]_0$ and $[\text{IL-2}]_0$, respectively. We also assume here that TCR is not occupied by antigen at the outset. Since the recognition of antigen in the context of HLA by T cells was considered to be an instan-

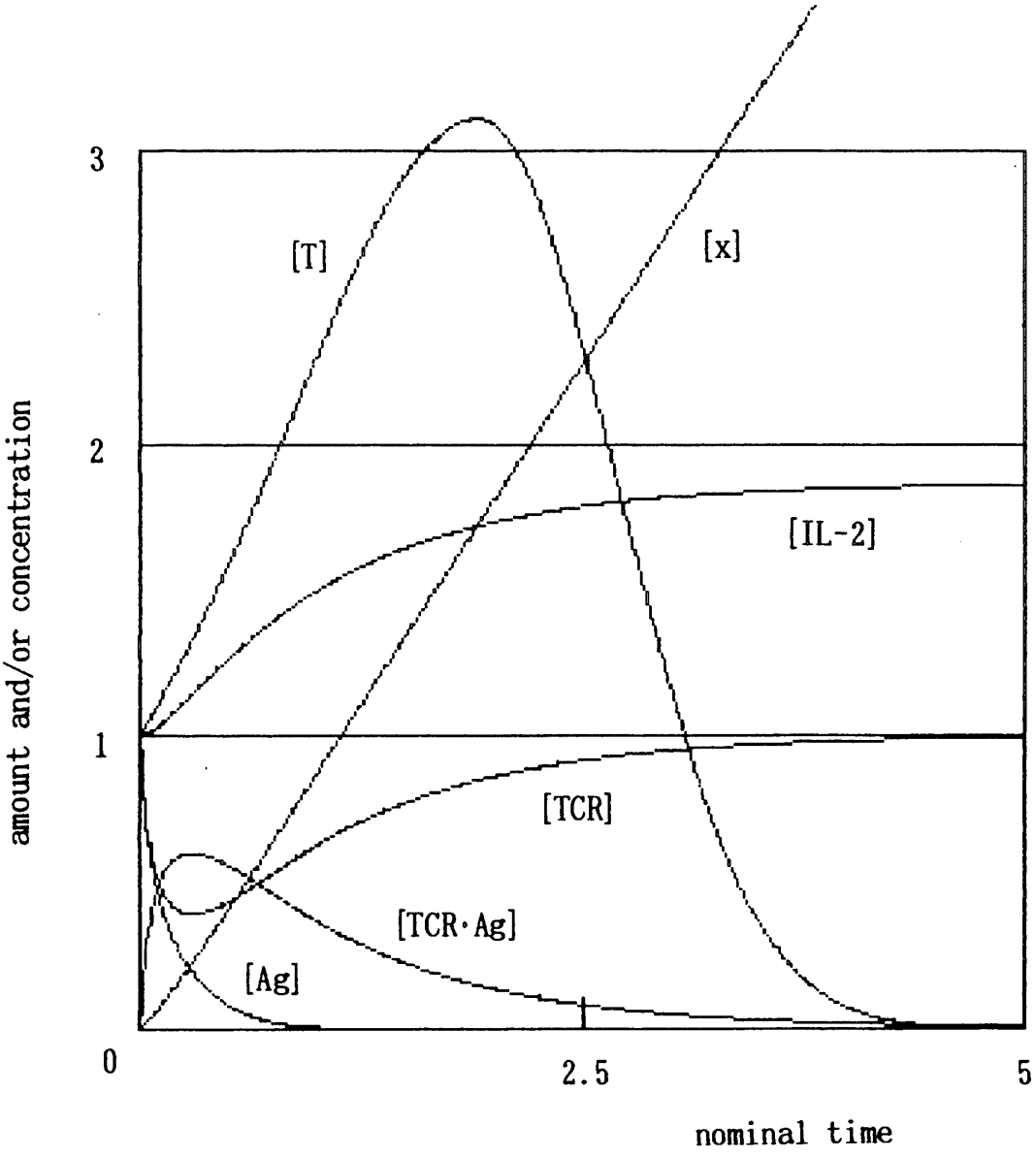
Table 1. Velocity constants of reaction and initial conditions

Velocity Constant of Reaction	Initial Condition
$k_1 = 10$	$[\text{T}]_0 = 1$
$k_2 = 1$	$[\text{Ag}]_0 = 1$
$k_3 = 1/2$	$[\text{IL-2}]_0 = 1$
$k_4 = 1/2$	$[\text{TCR}]_0 = 1$
$k_5 = 1$	$[\text{TCR}\cdot\text{Ag}]_0 = 0$
$k_6 = 2$	

taneous process as compared with the duration required for the release of IL-2 and proliferation of T cells, we may assume that [T] in the equation (5) is constant, and the reaction velocity constants were set as $k_1 = 10$ and $k_2 = 1$ for the same reason.

For the first example of this simulation, the reaction velocities and initial conditions are assigned as in Table 1. The results are shown in Figure 1; [Ag] and [TCR] decrease rapidly when Ag is trapped by TCR while [TCR-Ag] is increased. Since [IL-2] increases in response to the rapid increase of [TCR-Ag], T cells proliferate rapidly in response to the difference between [IL-2] and [x].

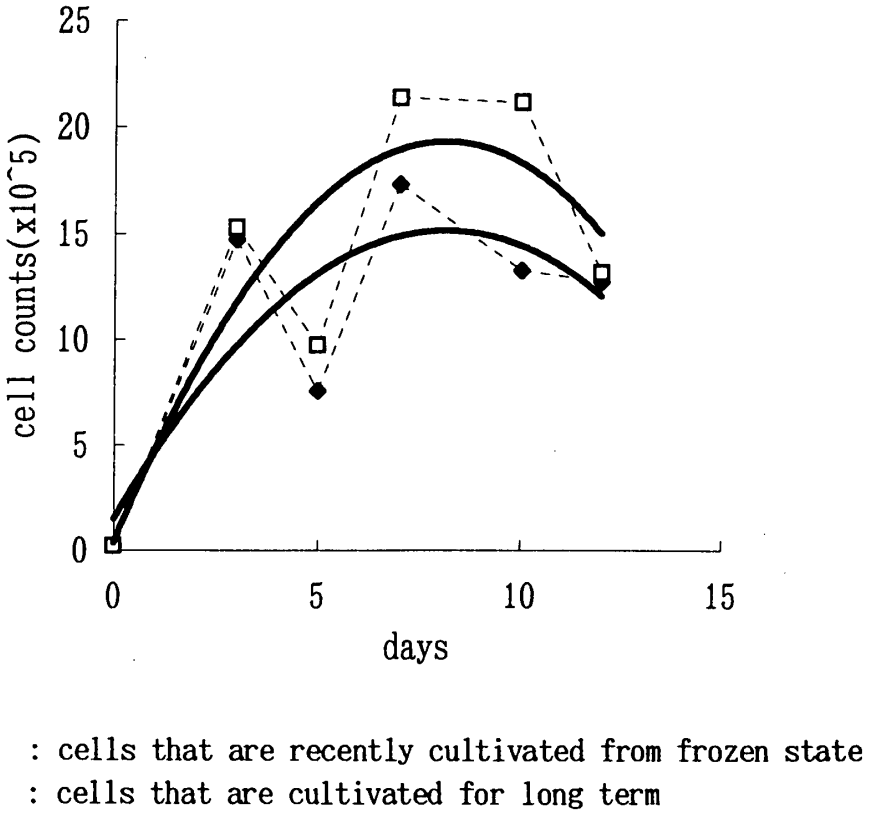
However, in the condition where [IL-2] does not decrease, the situation such as in the test tube or in the lymphoid organs in the body where lym-



Fgiure 1. A simulation of proliferation and death of T cell (Model I)

phocytes are clustered altogether within a restricted small space and therefore IL-2 once produced does not disperse significantly, the death factor x is increased in response to increased amounts of [IL-2]. T cells begin to decrease or die when [x] surpassed [IL-2]. However, in the peripheral tissues other than lymphoid organs in the body, IL-2 can be dispersed freely and therefore [IL-2] decreases rapidly. As long as [IL-2] is greater than the threshold [x], T cells continuously increase according to the upper condition of the equation (9), whereas T cells diminish by the lower condition of the equation (9) when the concentration of IL-2 becomes lower than that of the factor x.

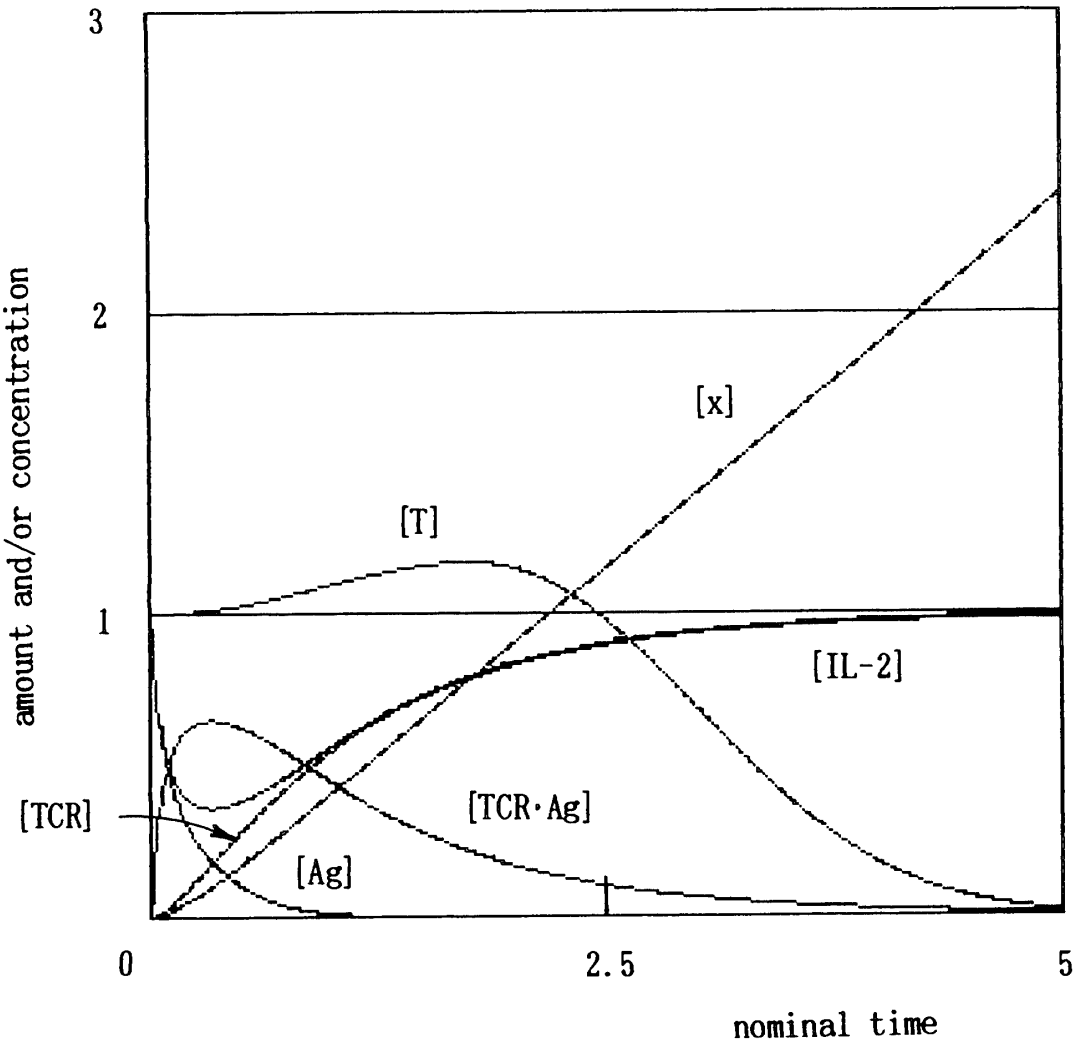
We also made an experimental observation through the cultivation to support the proposed model. One of the experimental results was shown in Figure 2. T cells cultivated in this case were composed of two groups; one is cultivated recently from frozen state and the other is cultivated for long term. Each group of T cells was maintained in RPMI medium consisting of 10% fetal bovine serum, 5% concanavalin A suppriments, 50 μM 2-mercaptoethanol, 50 U/ml penicillin and 50 μg/ml streptomycin. For the initial condition to stimulate T cells



Fgiure 2. An experimental result under the cultivation of T cells

by an antigen, 30 μg/ml keyhole limpet hemocyanin (KLH) was applied to the T cell medium. The cells were stained with Trypan blue, and then non-stained cells were counted for twelve days. Figure 2 showed that at the initial stimulation the T cells began to proliferate rapidly, while they finally fell into cell-death. The results obtained by both groups stands for the numerical outcomes in Figure 1.

Since proliferation of T cells is highly dependent on the concentration of IL-2, we tried the second example by using the same initial conditions as in the Table 1 except for $[IL\text{-}2]_0 = 0$. This corresponds to the in vitro cell culture condition where T cells are stimulated without prior addition of IL-2. The result shown in Figure 3 indicates that the production of IL-2 and subsequent proliferation of T cells in response to antigen stimulation are hoth minute, where [IL-2] begins to increase slightly, but because



Fgiure 3. A simulation of proliferation and death of T cell (Model II)

the concentration of the IL-2 does not exceed the threshold, the amount of T cells decrease. This result shows that the T cells do not proliferate markedly without the initial does of IL-2, which is consistent with the result of the cultivation of the T cells. We regard that the proposed model can be applied to the experimental data by adapting the proliferation rate k_5, death rate k_6 together with the other velocity constants of reaction.

With regard to T cell activation a recent hypothesis proposes that T cells are not activated but rather become anergic when stimulated only with antigen in the context of HLA. Although this hypothesis is commonly accepted, further critical examinations should be made.

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