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Hematopoietic stem cell based therapy of immunosuppressive viral infection—Numerical simulations

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ABSTRACT

In the light of recent advantages in stem cell research and gene based therapies of viral infections, we present a numerical experiment referring to hematopoietic stem cell based therapy of immunosuppressive viral infection. We use a variation of basic mathematical model for impairment of help to simulate immune impairing infection. Next, we increase virus-specific CTL production (as in therapy) in different stages of infection. Obtained results are analyzed and compared with results from recent *in vivo* experiment.

1. Introduction

The immune system of higher organisms utilizes innate and adaptive (acquired) immune responses to fight viral infections [1,2]. Innate immunity is not virus-specific and consists of many diverse mechanisms (*e.g.* stomach acid, inflammation, and macrophages). Adaptive immune mechanisms are virus-specific, *i.e.* they react specifically to given virus strain (lymphocytes can recognize the physical structure of virus particles). Moreover, adaptive mechanisms can establish immunological memory for better responses in following encounters with the same antigen.

There are two branches of adaptive immunity [3]. Humoral immune responses are carried out by B lymphocytes and antibodies. They are directed against free virus particles in the system. Cell-mediated (cellular) immunity is, on the other hand, directed against infected cells that produce new virus particles. It is carried out by cytotoxic T lymphocytes (CTL, CD8+) and T helper lymphocytes (Th cells, CD4+) [4]. In response to antigen stimulation, the population of precursor CTL proliferates and differentiates into effector CTL that recognize and kill infected cells [5]. Th cells play a regulatory role in both humoral and cellular responses.

Some of viral infections are immunosuppressive, *i.e.* they can impair immune responses (*e.g.* HIV and LCMV [6]). One way

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to achieve this is to infect Th lymphocytes. Since functional Th cells are needed for expansion of memory cells [7], successful infection will reduce adaptive immunity to weak helper-independent responses only.

There are many approaches to develop a successful treatment of immunosuppressive infection. Among others, we can distinguish gene based therapies. Until now, they have focused on redirecting mature CTL towards selected antigen (see *e.g.* [8]). However, recent advantages in stem cell research (*e.g.* blood cells can now be reversed to stem cell state [9]) make it possible to develop new strategies. One such strategy is to genetically modify human hematopoietic stem cells (HSC) to create functional virus-specific CTL, capable of suppression of virus spread.

Hematopoietic stem cells are present in the bone marrow. These cells give rise to T cell precursors that are translocated to the thymus. Within the thymus, they mature into CD8+ lymphocytes specific for a vast repertoire of antigenic epitopes. After the selection process, these cells translocate to lymph nodes, where they may be activated to CTL.

The idea underlying the HSC-based therapy (see *e.g.* [10,11]) is to obtain HSCs of the patient and genetically modify them to bear a concrete T cell receptor. These modified cells are then introduced into thymus. This should result in production of CTL specific to given virus strain. The main advantage of this approach is the fact that these newly produced cells have to pass the selection process in the thymus (autoimmunity is avoided). Moreover, this production of CTL is independent of antigen stimulation, so the effects of immune impairment are limited.

Recent experiments related to HSC based therapy have shown that CTL derived from genetically modified HSCs were capable of *ex vivo* and *in vivo* suppression of virus population [12,13]. In the latter experiment, the following results were reported: multilineage human hematopoiesis, creation of effector CTL, reduced Th cell depletion, suppression of HIV replication and plasma viremia.

Interestingly, antigenic escape was not observed in the mentioned *in vivo* experiment. This gives us a clear view on virus-immune system dynamics, but it makes it hard to evaluate the obtained results. For more details on limitations of this approach see Section 4.

2. Materials and methods

2.1. Mathematical model

In order to best address the results of experiment described in [13], we propose a modified version of the basic model for virus-induced impairment of help presented in [4]. We introduce two alterations of the basic model: (i) an additional equation is used to describe the virus dynamics (as in the model of virus dynamics in [14]) and (ii) an additional term γ is introduced to describe the effects of therapy.

The model consists of five ordinary differential equations. Initial conditions, as well as all the parameters of the model, are assumed to be nonnegative. The following equations describe the dynamics of uninfected Th cells (x), infected Th cells (y), free virus (v), precursor (w) and effector (z) CTL:

$$\dot{x} = \lambda - dx - \beta xv, \tag{1}$$

$$\dot{y} = \beta xv - ay - pyz, \tag{2}$$

$$\dot{v} = ky - uv, \tag{3}$$

$$\dot{w} = \gamma + cwxy - qwy - b_1 w, \tag{4}$$

$$\dot{z} = qwy - b_2 z. \tag{5}$$

Note that the expansion of precursor CTL population (see Eq. (4)) is proportional not only to numbers of precursor CTL (w) and infected cells (y), but also to numbers of uninfected Th cells (x). This is because the lack of functional Th cells results in limited expansion of memory CTL and may lead to impairment of immune responses.

Parameter λ in Eq. (1) denotes the rate of production of T helper cells, while d denotes the rate constant of their natural death. Th cells are infected by virus particles with a rate constant β. Infected cells' (Eq. (2)) natural death rate constant is denoted by a. Parameter p denotes the rate constant of effector CTL-mediated killing of infected cells. Virus particles (Eq. (3)) are produced with a rate constant k and die with a rate constant u.

In response to antigen stimulation, virus-specific precursor CTL start to proliferate and differentiate into effector cells. This is described by parameters c and q, respectively. Parameters b_1 and b_2 denote natural death rate constants of precursor and effector CTL.

Precursor CTL are produced in the thymus with a rate γ, regardless of antigen stimulation. Since effective CTL response is impaired (due to depletion of healthy Th cells), the idea of therapy is to increase this rate of virus-specific CTL production (γ) with the use of engineered hematopoietic stem cells.

According to [4], the outcome of infection depends on the relation between the rate of viral replication and strength of immune response. It can be shown that if immune response is strong enough to achieve virus clearance, our system converges to the following "virus-free" equilibrium:

$$x = \frac{\lambda}{d}, \quad y = 0, \quad v = 0, \quad w = \frac{\gamma}{b_1}, \quad z = 0. \tag{6}$$

Note that in the absence of infection the number of virus-specific CTL is proportional to parameter γ. This implies that applying treatment prior to infection should result in higher initial CTL count (thus in a stronger initial response).

In the case of persistent infection (when virus particles are not cleared from the system), the equilibrium expressions are given by a third degree polynomial. Therefore, we will obtain the results by numerical simulations. More details on the "virus persistence" equilibrium can be found in [15].

Originally, the (non-modified) basic model for virus-induced impairment of help [4] has an additional "CTL extinction" equilibrium. It occurs when viral replication is very high and too many Th cells are infected. Low numbers of functional Th cells impair CTL responses, and virus can