Krajowa Konferencja Zastosowań Matematyki w Biologii i Medycynie

Jastrzębia Góra, 16th–20th September 2013

A SIMPLE MODEL FOR HSC–BASED THERAPY OF SINGLE–STRAIN IMMUNOSUPPRESSIVE VIRAL INFECTION

Adam Korpusik[1] **and Mikhail Kolev**[2]

[1]Faculty of Technical Sciences, University of Warmia and Mazury,
ul. M. Oczapowskiego 11, 10-719 Olsztyn, Poland
[2]Faculty of Mathematics and Computer Science, University of Warmia and Mazury,
ul. Słoneczna 54, 10-710 Olsztyn, Poland
[1] adam.korpusik@uwm.edu.pl, [2] kolev@matman.uwm.edu.pl

ABSTRACT

We propose a simple mathematical model describing the mechanism of HSC–based therapy in the case of immunosuppressive viral infection. Only one virus strain is considered. Our theoretical results are illustrated by numerical simulations.

INTRODUCTION

Adaptive immune response to viral infection is carried out by lymphocytes [1, 2]. These cells are virus–specific. They recognize the physical structure of the antigen and react specifically to given virus strain. B lymphocytes carry out the humoral response—effector B cells (plasma cells) secrete antibodies that neutralize virus particles in the system.

Cell–mediated (cellular) response is carried out by T lymphocytes [3]—cytotoxic T lymphocytes (CTL, CD8+) and T helper cells (Th, CD4+). Cellular response is directed against infected cells—CTL proliferate and differentiate into effector CTL that kill infected cells. Th cells are, on the other hand, responsible for expansion of memory cells [4]—they play a regulatory role in both humoral and cellular responses.

The ability to establish immunological memory is one of the most important features of the adaptive immune response. Numbers of virus–specific lymphocytes remain increased even after the infection is cleared from the system. This results in better responses in following encounters with the same antigen. Immunological memory is also one of the key factors for viral clearance in primary infection [3].

Some of viral infections (*e.g.* HIV, LCMV) impair immune responses by infecting Th lymphocytes. This way expansion of memory cells is limited and adaptive immune responses cannot fully develop. The immune system is reduced to innate and helper–independent responses and can not achieve viral clearance in this kind of infection.

One of the recent approaches in the search for effective treatment of immunosuppressive viral infection is to genetically modify human hematopoietic stem cells (HSCs) to create virus–specific CTL. The idea of HSC–based therapy [5, 6] is to obtain patient's HSCs, modify them to bear a concrete T cell receptor and introduce these cells into patient's thymus. This should create CTL

specific to given virus strain. Since the creation of these cells is independent of virus stimulation, the effects of immunosuppression are limited. Moreover, these newly produced CTL have to pass the selection process in the thymus—autoimmunity is avoided and the therapy should be safe for the patient.

The HSC–based therapy gives promising experimental results. CTL created from modified HSCs were capable of *ex vivo* and *in vivo* suppression of virus population in humanized laboratory mice [7, 8]. In the latter experiment, a much stronger adaptive response was observed compared to control. The depletion of Th cells and spread of infection were significantly reduced.

In this paper, we propose a simple mathematical model for HSC–based therapy of immunosuppressive viral infection. We consider the cellular immune response for a single–strain infection. Next, we examine the influence of therapy on interacting populations. Our result are then illustrated by numerical simulations.

MATHEMATICAL MODEL

We use the basic model for virus–induced impairment of help [3] with additional equation for virus dynamics (as in [9]) and additional source term γ describing possible influx of precursors in Eq. (4). We consider the concentrations of the following populations

- x—uninfected Th lymphocytes,
- y—infected Th lymphocytes,
- v—virus particles,
- w—precursor cytotoxic T lymphocytes,
- z—effector cytotoxic T lymphocytes.

Our model is given by the following system of differential equations

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

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

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

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

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

Initial conditions of the model are assumed to be nonnegative. Parameters (positive) denote the rates of: production (λ) and natural death (d) of uninfected Th cells, virus infectivity (β), natural death (a) and effector CTL–mediated destruction (p) of infected cells, production of virus particles by infected cells (k), natural death of virus particles (u), antigen–dependent proliferation of precursor CTL (c), differentiation into effector CTL (q), natural death of precursor (b_1) and effector (b_2) CTL.

Additional parameter γ denotes the rate of antigen–independent production of virus–specific precursor CTL in the patient's thymus. The idea of therapy is to increase this rate of production by the use of genetically engineered hematopoietic stem cells.

The right–hand sides of Eqs. (1)–(5) are polynomial functions. Therefore, for given initial conditions, there exist a unique solution of the system [10].

If the basic reproductive ratio of the virus R_0 (the average number of newly infected cells produced by a single infected cell) is less than 1, virus particles fail to establish a persistent infection and our system converges to the following "virus free" equilibrium

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

However, if viral replication is strong enough ($R_0 > 1$), persistent infection is established. "Virus persistence" equilibrium expressions are as follows

$$y = \frac{u}{k} v, \tag{7}$$

$$v = \frac{\lambda - dx}{\beta x}, \tag{8}$$

$$w = \frac{b_2 z}{qy}, \tag{9}$$

$$z = \frac{\beta k x - au}{pu}, \tag{10}$$

and x is a root of a third degree polynomial in the following form

$$f(x) = Ax^3 + Bx^2 + (C - qpd\gamma)x + (D + qp\lambda\gamma), \quad A < 0. \tag{11}$$

It can be shown that our model has at least one stable "virus persistence" equilibrium [11]

Theorem 1. *There exists at least one $x_0 \in (0, \lambda/d)$ such that $f(x_0) = 0$ and $\lim_{x\to x_0^-} f(x) > 0 > \lim_{x\to x_0^+} f(x)$.*

Proof. Limits at the ends of the interval $(0, \lambda/d)$ are equal to

$$\lim_{x\to 0^+} f(x) = \lambda q(p\gamma + b_2 a), \quad \lim_{x\to(\frac{\lambda}{d})^-} f(x) = -b_1 b_2 \frac{\beta k\lambda}{ud}(\frac{\beta k\lambda}{ud} - a).$$

All of the parameters of the model are positive. Moreover

$$\frac{\beta k\lambda}{uda} = R_0^* \geq R_0 > 1,$$

where R_0^* is the basic reproductive ratio of the virus in the absence of immune response [9]. Hence

$$\lim_{x\to 0^+} f(x) > 0, \quad \lim_{x\to(\frac{\lambda}{d})^-} f(x) < 0.$$

From the intermediate value theorem and the form of the function $f(x)$, we obtain the desired result. □

The proposed model has only two equilibria ("virus free" and "virus persistence"). However, the original (non–modified) model for virus–induced impairment of help [3] has an additional "CTL extinction" equilibrium (for very high rates of viral replication). This equilibrium is not present in our model, as a consequence of introducing the parameter γ in Eq. (4).

RESULTS OF THERAPY

We will now examine how HSC–based therapy (increase in parameter γ) influences the interacting populations. In the absence of infection (Eqs. (6)), therapy will only affect the numbers of virus–specific precursor CTL. Increased precursor CTL count will in turn result in much stronger initial response to antigen stimulation.

In the case of persistent infection, we get the following results

Theorem 2. *For a stable "virus persistence" equilibrium, the increase of γ results in higher equilibrium values of x, w and z, and lower values of y and v.*

Proof. The equilibrium value of x is given by $f(x) = 0$ (Eq. (11)). Since $x \in (0, \lambda/d)$ (Eqs. (6))

$$\frac{df}{d\gamma} = qp(\lambda - dx) > 0.$$

Thus, for every stable equilibrium ($x_0 \in (0, \lambda/d)$ such that $f(x_0) = 0$ and $\lim_{x\to x_0^-} f(x) > 0 > \lim_{x\to x_0^+} f(x)$)

$$\frac{dx_0}{d\gamma} > 0. \tag{12}$$

We have shown that a small increase in γ results in higher equilibrium value of x. This is also true for bigger changes in γ (since the function $f(x)$ is a third polynomial with $A < 0$ and at least one stable equilibrium in $x \in (0, \lambda/d)$). Now, let's see how the change in γ affects the equilibrium values of other populations. From Eq. (12) and Eqs. (7)–(10), we get

$$\frac{dv}{d\gamma} = \frac{dv}{dx}\frac{dx}{d\gamma} = \frac{-\lambda}{\beta x^2}\frac{dx}{d\gamma} < 0, \quad \frac{dy}{d\gamma} = \frac{dy}{dv}\frac{dv}{d\gamma} = \frac{u}{k}\frac{dv}{d\gamma} < 0,$$

$$\frac{dz}{d\gamma} = \frac{dz}{dx}\frac{dx}{d\gamma} = \frac{\beta k}{pu}\frac{dx}{d\gamma} > 0, \quad \frac{dw}{d\gamma} = \frac{b_2}{qy^2}(y\frac{dz}{d\gamma} - z\frac{dy}{d\gamma}) > 0.$$

□

As it turns out, therapy is beneficial for the patient even after the immune impairing infection is established (see Table 1). Increased virus–independent CTL production results in restoration of both CTL populations, reduced Th cell depletion, suppression of viral replication and plasma viremia. Our theoretical results match those obtained in relevant *in vivo* experiment [8].

Table 1. Influence of γ on interacting populations in stable "virus persistence" equilibrium

CTL production in thymus (γ)	uninfected Th cells (x)	infected Th cells (y)	free virus particles (v)	precursor CTL (w)	effector CTL (z)
↗	↗	↘	↘	↗	↗

NUMERICAL SIMULATIONS

In order to illustrate our theoretical results, we set the initial conditions and parameters of the model to simulate a viral infection with impaired cellular response

$$x_0 = 1, \quad y_0 = 0, \quad v_0 = 0.1, \quad w_0 = 1, \quad z_0 = 0,$$

$$\lambda = 1, \ \ d = 1, \ \ \beta = 2, \ \ a = 3, \ \ p = 5, \ \ k = 8,$$

$$u = 1, \ \ \gamma = 0.1, \ \ c = 1, \ \ q = 0.2, \ \ b_1 = 0.1, \ \ b_2 = 1.$$

Then, at a certain point in time ($t = 15$), therapy is introduced ($\gamma = 1$).

The following effects of therapy are illustrated: reduction of Th cell depletion (Fig. (1)), suppression of viral replication (Fig. (2)) and restoration of cellular response (Fig. (3)).

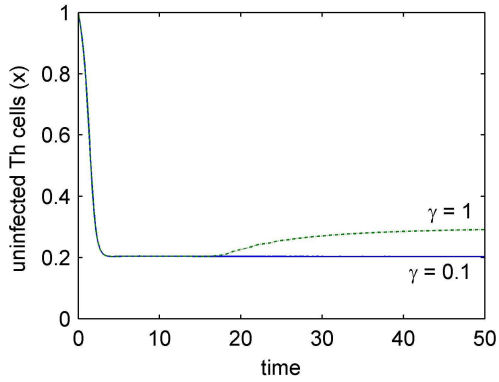

Figure 1. Reduced Th cell depletion—dynamics of uninfected Th cells.

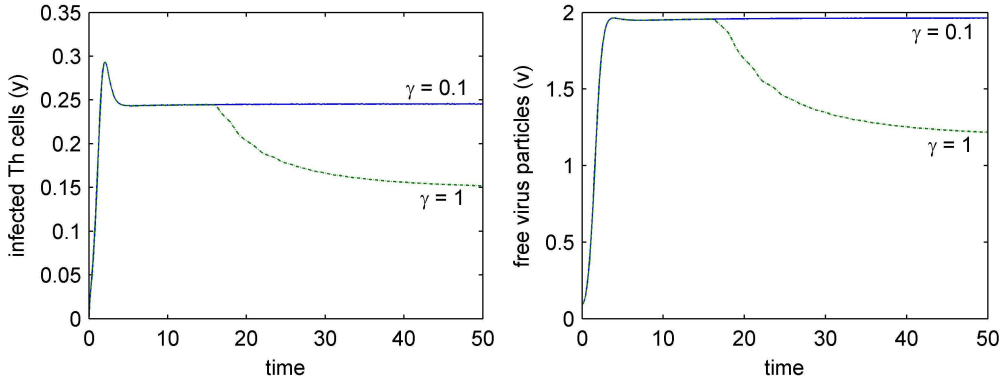

Figure 2. Suppression of viral replication—dynamics of (i) infected Th cells (ii) virus particles.

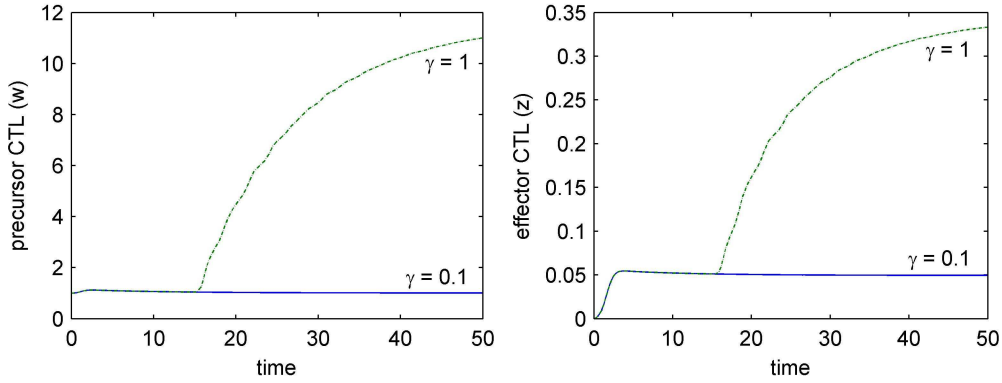

Figure 3. Restoration of cellular response—dynamics of (i) precursor and (ii) effector CTL.

CONCLUSIONS

Hematopoietic stem cell based therapy gives hope for new effective kind of treatment of immunosuppressive infections. There are two major advantages of this approach

(1) Production of virus–specific CTLs is independent of antigen stimulation—the effects of immunosuppression are limited.

(2) Newly produced cells have to pass the selection process in the thymus—autoimmunity is avoided.

In this paper we have proposed a mathematical model able to describe important features of the therapy based on the use of genetically modified HSCs. The results of our analyzes match the outcome of relevant *in vivo* experiment [8] and confirm the efficacy of the therapy. External, antigen–independent production of CTL should reduce the severity of infection and lead to restoration of immune responses.

However, our mathematical model only describes a single–strain infection (this is because no mutation was observed in the relevant experiment [8])—viral evolution may be sufficient to escape the engineered virus–specific CTL response. Therefore, our future research will address the development of the model describing the therapy of multiple–strain infections.

REFERENCES

[1] A. Abbas and A. Lichtman: *Basic Immunology: Functions and Disorders of the Immune System*, Elsevier, Philadelphia, 2004.

[2] G. Pinchuk: *Schaum's Outline of Theory and Problems of Immunology*, McGraw–Hill Companies, New York, 2002.

[3] D. Wodarz: *Killer Cell Dynamics: Mathematical and Computational Approaches to Immunology*, Springer, New York, 2007.

[4] E.M. Janssen, E.E. Lemmens, T. Wolfe, U. Christen, M.G. von Herrath, and S.P. Schoenberger: *CD4+ T cells are required for secondary expansion and memory in CD8+ T lymphocytes*, Nature **421** (2003), 852–856.

[5] H.P. Kiem, K.R. Jerome, S.G. Deeks, and J.M. McCune: *Hematopoietic–Stem–Cell–Based Gene Therapy for HIV Disease*, Cell Stem Cell **10** (2012), 137–147.

[6] S.G. Kitchen, S. Shimizu, and D.S. An: *Stem cell–based anti–HIV gene therapy*, Virology **411** (2011), 260–272.

[7] S.G. Kitchen, M. Bennett, Z. Galić, J. Kim, Q. Xu, A. Young, A. Liberman, A. Joseph, H. Goldstein, H. Ng, O. Yang, and J.A. Zack: *Engineering Antigen–Specific T Cells from Genetically Modified Human Hematopoietic Stem Cells in Immunodeficient Mice*, PLoS One **4** (2009), e8208-1–e8208-9.

[8] S.G. Kitchen, B.R. Levin, G. Bristol, V. Rezek, S. Kim, C. Aguilera-Sandoval, A. Balamurugan, O.O. Yang, and J.A. Zack: *In Vivo Suppression of HIV by Antigen Specific T Cells Derived from Engineered Hematopoietic Stem Cells*, PLoS Pathogens **8** (2012), e1002649-1–e1002649-13.

[9] R.M. Anderson and R.M. May: *Infectious Diseases of Humans: Dynamics and Control*, Oxford University Press, Oxford, 1991.

[10] U. Foryś: *Matematyka w Biologii*, WNT, Warszawa, 2005.

[11] J.D. Murray: *Mathematical Biology I: An Introduction*, Springer, New York, 2002.