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ORIGINAL ARTICLE

Multistability in a Model for CTL Response to HTLV-I Infection and Its Implications to HAM/TSP Development and Prevention

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Abstract Human T-cell leukaemia/lymphoma virus type I (HTLV-I) is a retrovirus that has been identified as the causative agent of HTLV-I-associated myelopathy/tropic spastic paraparesis (HAM/TSP) and other illnesses. HTLV-I infects primarily $CD4^+$ T cells and the transmission occurs through direct cell-to-cell contact. HAM/TSP patients harbor higher proviral loads in peripheral blood lymphocytes than asymptomatic carriers. Also, HAM/TSP patients exhibit a remarkably high number of circulating HTLV-I-specific $CD8^+$ cytotoxic T lymphocytes (CTLs) in the peripheral blood. While CTLs have a protective role by killing the infected cells and lowering the proviral load, a high level of CTLs and their cytotoxicity are believed to be a main cause of the development of HAM/TSP. A mathematical model for HTLV-I infection of $CD4^+$ T cells that incorporates the $CD8^+$ cytotoxic T-cell (CTL) response is investigated. Our mathematical analysis reveals that the system can stabilize at a carrier steady-state with persistent viral infection but no CTL response, or at a HAM/TSP steady-state at which both the viral infection and CTL response are persistent. We also establish two threshold parameters R_0 and R_1, the basic reproduction numbers for viral persistence and for CTL response, respectively. We show that the parameter R_1 can be used to distinguish asymptomatic carriers from HAM/TSP patients, and as an important control parameter for preventing the development of HAM/TSP.

Keywords HTLV-I · HAM/TSP · CD4 T cells · CD8 T cells · Global dynamics · Lyapunov functions

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1. Introduction

Human T-cell leukaemia/lymphoma virus type I (HTLV-I) is a human retrovirus that can cause a slowly progressive neurologic disease HTLV-I-associated myelopathy/tropical spastic paraparesis (HAM/TSP) (Gessain et al., 1985; Osame et al., 1986). The number of HTLV-I-infected people is estimated between 15 to 25 million worldwide. The infection is endemic in the southern region of Japan, the Caribbean Islands, the equatorial regions of Africa, South America, the Middle East. and Melanesia (Kubota et al., 2000). The majority of HTLV-I-infected individuals remain as lifelong asymptomatic carriers (ACs), while approximately 0.25% to 3% develop HAM/TSP (Kaplan et al., 1990; Yamano et al., 2002). Unlike HIV viruses, which break free from host cells and infect other T cells, HTLV-I viruses are not very infectious and seldom found in plasma (Okochi et al., 1984). Direct cell-to-cell contact is required to transmit the viruses among $CD4^+$ T cells, which HTLV-I preferentially infects in vivo (Cann and Chen, 1996; Richardson et al., 1990; Shiraki et al., 2003). The exact mechanism for the cell-to-cell spread is a subject of current research. It is shown (Igakura et al., 2003) that cell contact rapidly induces polarization of the cytoskeleton of the infected $CD4^+$ T cell to the cell–cell junction. HTLV-I core (Gag protein) complexes and the HTLV-I genome accumulate at the cell–cell junction and are then transferred to the uninfected cell. In an infected cell, integrated viral DNAs are called *proviruses*.

HTLV-I-infected patients harbor remarkably high proviral loads in peripheral blood lymphocytes (PBLs), ranging from 2% to 20% among HAM/TSP patients, and from 0.04% to 8% among ACs (Kira et al., 1991; Kubota et al., 1993). Moreover, HAM/TSP patients show high levels of circulating HTLV-I-specific $CD8^+$ cytotoxic T lymphocytes (CTLs), which are specific for an immunodominant HLA-A2-restricted epitope, HTLV-I Tax 11–19. HTLV-I Tax 11–19-specific $CD8^+$ CTLs are estimated in the range of 1:75 to 1:320 $CD8^+$ lymphocytes in the PBL of HAM/TSP patients (Elovaara et al., 1993; Koenig et al., 1993). Activated $CD8^+$ CTLs are also found in the cerebrospinal fluid (Greten et al., 1998). Recent clinical evidence shows that peripheral $CD8^+$ T lymphocytes produce interleukin (IL) 2, γ-interferon (IFN-γ), and tumor necrosis factor α (TNF-α) in HAM/TSP patients (Greten et al., 1998). Collectively, these findings suggest that, on the one hand, the CTLs have a protective role to the host by lowering the proviral load (Asquit and Bangham, 2007; Mosley et al., 2005); and on the other, a high level of HTLV-I-specific $CD8^+$ T lymphocytes and their cytotoxic effects may be the cause for the inflammatory responses in HAM/TSP patients (Jacobson, 2002). Preventive measures that can regulate the HTLV-I-specific CTL response to a low level may effectively prevent the development of HAM/TSP.

CTL response to HTLV-I infection, especially the correlation between proviral load and responsiveness of CTLs, has been investigated using mathematical models in Nowak and Bangham (1996), Nowak and May (2000), Wodarz et al. (1999). In Wodarz et al. (1999), a mathematical model is investigated that incorporates HTLV-I infection of $CD4^+$ T cells, HTLV-I induced mitotic division in infected CD4s, and HTLV-I specific CTL response. While the focus in Nowak and May (2000), Wodarz et al. (1999) is to explain immunological phenomena using mathematical models, the goal of the present paper is to provide a complete mathematical analysis of the dynamics of CTL response to HTLV-I infection in a special case of the model considered in Wodarz et al. (1999), in which we ignore the mitosis of $CD4^+$ T cells. Our analysis reveals for the first time the existence of

two possible equilibria where the HTLV-I infection is persistent, and both equilibria can be stable in reasonable parameter regions.

To set up a mathematical model for the dynamics of CTL response to HTLV-I infection in vivo, the CD4$^+$ T-cell population is partitioned into uninfected and infected compartments, whose numbers at time t are denoted by $x(t)$, $y(t)$, respectively. Similarly, we consider a compartment of HTLV-I-specific CD8$^+$ T cells, and let $z(t)$ denote their numbers at time t. Since HTLV-I infection occurs by cell-to-cell contact between infected cells and uninfected ones, a bilinear incidence βxy is assumed (Nowak and May, 2000; Perelson and Nelson, 1999), where β is the transmission coefficient. Soon after the primary infection, HTLV-I-carrier cells confront a strong antibody response targeted mainly to Tax proteins (Bangham, 2000; Manns et al., 1991). Moreover, the low mutation rate observed during HTLV-I replication (Mansky, 2000; Mortreux et al., 2001) suggests that only a fraction $\sigma \in [0, 1]$ of cells newly infected by contact will survive the antibody immune response. CTL-driven elimination of infected CD4$^+$ cells due to the cytotoxic actions of CD8$^+$ T cells is assumed to be of the form γyz, where γ is the rate of CTL-mediated lysis. Anti-HTLV-I CTLs reduce the proviral load, but this reduction would imply less stimulation for CTL proliferation. Therefore, it is reasonable to consider that CD8$^+$ T-cell stimulation has a density-dependent form $\nu yz/(z + K)$, where ν denotes the cytotoxic responsiveness. The CTL responsiveness depends on the contact frequency and attachment effectivity between T-cell receptors and MHC-I molecules. The form of response function $z/(z + K)$ is more general than that in Nowak and Bangham (1996), Nowak and May (2000), Wodarz et al. (1999).

The maintenance of the CD4$^+$ T-cell pool may involve proliferation of mature cells in the periphery or maturation of hematopoietic stem cells (Clark et al., 1999). It is customary to assume CD4$^+$ T cells are produced at constant rate λ and all of them are susceptible (Nowak and May, 2000; Perelson and Nelson, 1999). The probability of lymphocyte elimination in function of time is unknown (Perelson and Nelson, 1999), thus constant per capita elimination rates are generally assumed: μ_1 and μ_2 represent the removal rates of uninfected and infected CD4$^+$ T cells, respectively, and μ_3 that of HTLV-I-specific CD8$^+$ T cells. All parameters are assumed to be positive. A transfer diagram is shown in Fig. 1.

The preceding assumptions and the transfer diagram lead to the following system of differential equations:

$$
\begin{aligned}
x' &= \lambda - \mu_1 x - \beta xy, \\
y' &= \sigma \beta xy - \mu_2 y - \gamma yz, \\
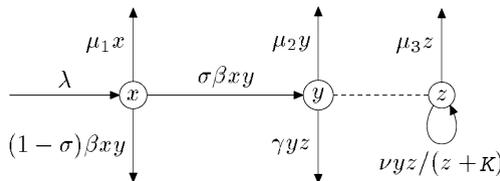z' &= \nu \frac{yz}{z + K} - \mu_3 z.
\end{aligned}
\tag{1}
$$

Fig. 1 Transfer diagram for the CTL response to HTLV-I infection.

From the first equation of (1), we obtain $x' \leq \lambda - \mu_1 x$, and thus $\limsup_{t\to\infty} x(t) \leq \frac{\lambda}{\mu_1}$. Adding the first two equations of (1), we get

$$\big(x(t) + y(t)\big)' = \lambda - \mu_1 x(t) - \mu_2 y(t) - (1 - \sigma)\beta x(t)y(t) - \gamma y(t)z(t)$$
$$\leq \lambda - \widetilde{\mu}\big(x(t) + y(t)\big),$$

where $\widetilde{\mu} = \min\{\mu_1, \mu_2\}$. Thus, $\limsup_{t\to\infty}(x(t) + y(t)) \leq \frac{\lambda}{\widetilde{\mu}}$. From this relation and (1), we conclude that, for a solution $(x(t), y(t), z(t))$ of (1) with $x(0) + y(0) \leq \lambda/\widetilde{\mu}$, the following differential inequality holds:

$$z'(t) \leq \nu y - \mu_3 z \leq \nu \frac{\lambda}{\widetilde{\mu}} - \mu_3 z,$$

and, therefore, $\limsup_{t\to\infty} z(t) \leq \frac{\nu\lambda}{\widetilde{\mu}\mu_3}$. Thus, the dynamics of system (1) can be analyzed in the following feasible region:

$$\Gamma = \left\{ (x, y, z) \in \mathbb{R}_+^3 : x \leq \frac{\lambda}{\mu_1}, x + y \leq \frac{\lambda}{\widetilde{\mu}}, z \leq \frac{\nu\lambda}{\widetilde{\mu}\mu_3} \right\}. \tag{2}$$

The region Γ is positively invariant and the model is well posed.

We will show that, in addition to the infection-free equilibrium $P_0 = (\lambda/\mu_1, 0, 0)$, system (1) can have two chronic-infection equilibria $P_1 = (\overline{x}, \overline{y}, 0)$ and $P_2 = (x^*, y^*, z^*)$ in Γ, where $\overline{x}, \overline{y}, x^*, y^*, z^*$ are all positive and will be given later. The equilibrium P_1 corresponds to the steady-state of asymptomatic carriers, namely, of chronic HTLV-I infection with no CTL response, while P_2 that of HAM/TSP patients, namely, of chronic HTLV-I infection with persistent CTL response. Which of the three steady-states the system eventually settles to is determined by a combination of two threshold parameter

$$R_0 = \frac{\sigma\beta\lambda}{\mu_1\mu_2} \quad \text{and} \quad R_1 = \frac{\sigma\beta\lambda\nu}{\mu_2(\mu_1\nu + \beta\mu_3 K)}. \tag{3}$$

We call R_0 and R_1 the basic reproduction numbers for viral infection and for CTL response, respectively. Note that $R_1 < R_0$ always holds. The following three outcomes are possible:

(a) If $R_0 \leq 1$, the infection-free equilibrium P_0 is globally stable in the feasible region Γ, and no chronic HTLV-I infection is possible.
(b) if $R_1 \leq 1 < R_0$, then P_0 is unstable, the carrier equilibrium P_1 is stable, and all solutions in the interior of Γ converge to P_1. In this case, HTLV-I infection always becomes chronic, but no CTL response can be established. The system behaves like that of an asymptomatic carrier.
(c) If $1 < R_1$, then both P_0 and P_1 are unstable. The HAM/TSP equilibrium P_2 in the interior of Γ is stable. System (1) is uniformly persistent and all persistent solutions converge to P_2. In this case, both a chronic HTLV-I infection and a long-term positive CTL response are established. The system mimics that of a HAM/TSP patient.

The parameter R_0 is the standard basic reproduction number in the literature of compartmental models. It measures the average number of secondary infections caused by a single infected CD4$^+$ T cell in a T-cell population at the infection-free equilibrium (Nelson et al., 2000; Nowak and May, 2000). Thus, R_0 is the threshold parameter that determines if a chronic HTLV-I infection can be established in the CD4$^+$ T-cell population. In the face of a chronic infection, namely when $R_0 > 1$, the parameter R_1 determines if a long-term HTLV-I specific CTL response can be established. The value of R_1 may help to explain why some people develop HAM/TSP while the majority of infected individuals remain as ACs. From a control viewpoint, making $R_0 < 1$ will achieve clearance of HTLV-I viruses, and hence the ultimate control and prevention of HTLV-I infection; while making $R_1 < 1$ will keep the level of CTL response low to reduce its cytotoxic effects, and prevent an AC from developing HAM/TSP. Considering that $R_1 < R_0$, and the fact that the majority of HTLV-I infected people are ACs, our results show that maintaining $R_1 < 1$ while allowing $R_0 > 1$ can be a practical and achievable control and prevention strategy for HAM/TSP.

The plan of the paper is as follows. In Sections 2 and 3, we describe the dynamics of system (1). In Section 4, we discuss the implications of our mathematical results and various roles of CTL-related parameters in the development of HAM/TSP. The conclusions are summarized in Section 5. The proof of our main result is given in the Appendix at the end of the paper.

2. Equilibria

The infection-free equilibrium $P_0 = (\lambda/\mu_1, 0, 0)$ always exists. A chronic-infection equilibrium $P_1 = (\overline{x}, \overline{y}, 0)$ with no CTL response exists when $R_0 > 1$, where R_0 is given in (3) and

$$\overline{x} = \frac{\mu_2}{\sigma\beta} = \frac{\lambda}{\mu_1 R_0}, \qquad \overline{y} = \frac{\mu_1(R_0 - 1)}{\beta}. \tag{4}$$

We call P_1 the *carrier equilibrium*. A chronic-infection equilibrium $P_2 = (x^*, y^*, z^*)$ with CTL response ($z^* > 0$) will be called a *HAM/TSP equilibrium*. The coordinates x^*, y^*, z^* must satisfy

$$0 = \lambda - \mu_1 x^* - \beta x^* y^*,$$
$$0 = \sigma\beta x^* y^* - \mu_2 y^* - \gamma y^* z^*, \tag{5}$$
$$0 = \nu \frac{y^* z^*}{z^* + K} - \mu_3 z^*.$$

From the second and third equations of (5), we obtain

$$x^* = \frac{\gamma z^* + \mu_2}{\sigma\beta} \geq \frac{\mu_2}{\sigma\beta} = \overline{x} \quad \text{and} \quad y^* = \frac{\mu_3(z^* + K)}{\nu}. \tag{6}$$
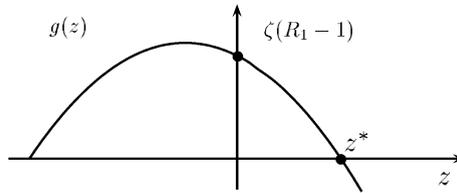
Fig. 2 Graphic illustration of the uniqueness of the chronic-infection equilibrium P_2 with CTL response.

Substitute (6) into the first equation of (5), we obtain that z^* is a positive root of the quadratic polynomial

$$g(z) = \zeta \left[R_1 - 1 - z \left(\frac{\gamma}{\mu_2} + \frac{\beta \mu_3}{\mu_1 \nu + \beta \mu_3 K} \right) - z^2 \left(\frac{\gamma \beta \mu_3}{\mu_2 (\mu_1 \nu + \beta \mu_3 K)} \right) \right], \qquad (7)$$

where

$$\zeta = \frac{\mu_2 (\mu_1 \nu + \beta \mu_3 K)}{\sigma \beta \nu}.$$

Observe that $g(0) = \zeta(R_1 - 1)$, $g'(0) < 0$, and the graph of g is concave down. These observations imply that g has a unique positive root if $R_1 > 1$; see Fig. 2. We thus have the following result.

Theorem 2.1. *If $R_0 \leq 1$, then $P_0 = (\lambda / \mu_1, 0, 0)$ is the only equilibrium in Γ. If $R_1 \leq 1 < R_0$, there is only the carrier equilibrium $P_1 = (\overline{x}, \overline{y}, 0)$ with $\overline{y} > 0$. If $R_1 > 1$, there are two chronic-infection equilibria: P_1 and the HAM/TSP equilibrium $P_2 = (x^*, y^*, z^*)$ with $x^*, y^*, z^* > 0$.*

3. Stability of equilibria and global dynamics

The global dynamics of system (1) is described in the following theorem. The proof is given in the Appendix.

Theorem 3.1.

(a) *If $R_0 \leq 1$, then the infection-free equilibrium P_0 is globally asymptotically stable in the closed region Γ.*

(b) *If $R_1 < 1 < R_0$, then P_0 is unstable, and the carrier equilibrium $P_1 = (\overline{x}, \overline{y}, 0)$ on the boundary of Γ is globally asymptotically stable in $\Gamma \setminus \{x\text{-}axis\}$.*

(c) *If $R_1 > 1$, then P_0 and P_1 are both unstable, and the HAM/TSP equilibrium is globally asymptotically stable in the interior of Γ.*

Theorem 3.1 completely determines the global dynamics of (1). It establishes R_0 and R_1 as two sharp threshold parameters. These threshold parameters together determine the outcomes of the HTLV-I infection:
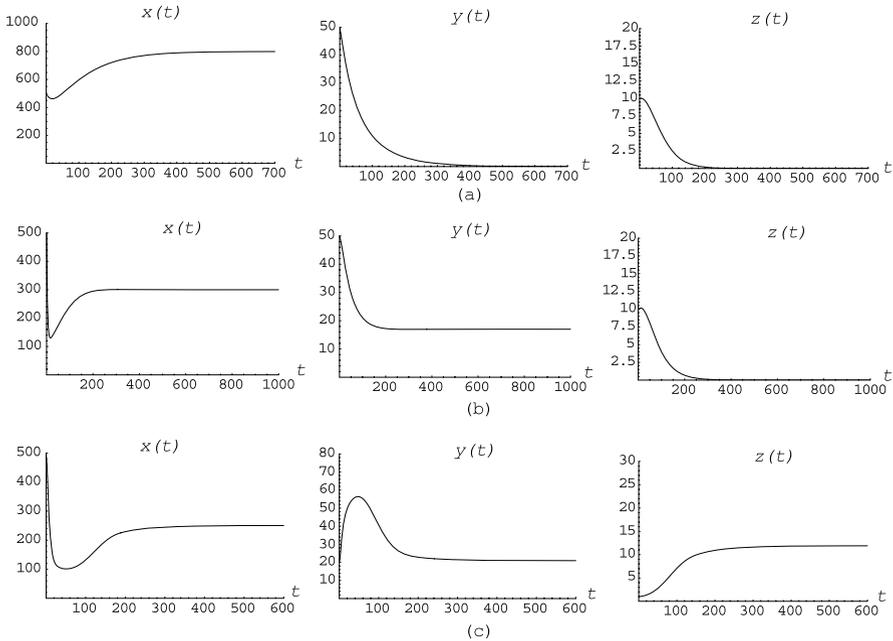
Fig. 3 Numerical simulations demonstrate three distinct outcomes of system (1). In (a), $R_0 \leq 1$, all solutions converge to the infection-free equilibrium $P_0 = (\lambda/\mu_1, 0, 0)$. In (b), $R_1 < 1 < R_0$, all interior solutions converge to the carrier equilibrium $P_1 = (\bar{x}, \bar{y}, 0)$. In (c), $R_1 > 1$, all interior solutions converge to the HAM/TSP equilibrium $P_2 = (x^*, y^*, z^*)$.

(1) If $R_0 \leq 1$, then the HTLV-I viruses are cleared.

(2) If $R_1 < 1 < R_0$, then HTLV-I infection becomes chronic but with a low level of proviral load, and causes no CTL response. The system can be characterized as that of an AC.

(3) If $1 < R_1$, then the HTLV-I infection is chronic with a high level of proviral load and causes a persistent CTL response. The system can be characterized as that of a HAM/TSP patient.

The results in Theorems 2.1 and 3.1 are illustrated by numerical simulations shown in Fig. 3. For our numerical simulations, the time scale is days. A production rate of CD4$^+$ T cells is $\lambda = 20$ cells/mm/day^3, which is of the same order of magnitude as the one proposed in Nelson et al. (2000). The removal rates of infected and uninfected CD4$^+$ T cells are chosen to be equal, i.e., $\mu_1 = \mu_2$, and the rates are selected in the range of 0.01–0.05 day^{-1}, which is within the range given in Nelson et al. (2000). The death rate for HTLV-I-specific CD8$^+$ cells is assumed to be equal to that of the CD4$^+$, i.e., $\mu_3 = \mu_1$. The average CD4$^+$ T-cell count in a healthy adult is approximately 1000 cells/mm^3. Using Perelson's scaling relation (Perelson, 1989), values of β in the range of 10^{-3} mm^3/cell/day are chosen. The range for σ is chosen as $(0.01, 0.05)$. The range for ν is $(0.001, 0.03)$, and that for γ $(0.002, 0.02)$. We set $K = 1$. Within these ranges of parameter values, the gap between R_0 and R_1 can be as big as one order of magnitude.

4. Biological implications

In this section, we discuss biological implications of our mathematical results in the previous two sections.

4.1. Asymptotic carriers and HAM/TSP patients

The majority of HTLV-I-infected individuals remain as lifelong asymptomatic carriers even though they harbor detectable proviral loads. The basic reproduction number in the presence of CTL response, R_1, determines whether a long-term anti-HTLV-I CTL response can be established. When $R_1 < 1$, CD8$^+$ T cells remain at a sufficiently low level that cytotoxicity in the peripheral blood remains low. Thus, it is likely that $R_1 < 1$ hold for ACs. In contrast, the high level of CD8$^+$ in HAM/TSP patients suggests that $R_1 > 1$ is likely for most of them. Therefore, the value of R_1 may be used to distinguish ACs from HAM/TSP patients.

4.2. Two different control strategies

The basic reproduction number in the absence of CTL response, R_0, determines whether a chronic HTLV-I-infection can be established. Thus, a *total control* strategy should achieve a reduction of R_0 to below 1, e.g., through a reduction in the ratio β/μ_2. It is shown in Macchi et al. (1997) that the reverse-transcriptase inhibitor zidovudine (AZT) inhibits transmission of HTLV-I to PBLs and reduces β/μ_2. Therefore, in principle, R_0 could be reduced with the help of reverse-transcriptase inhibitors.

In practice, it may be more realistic and even desirable to keep the infected individuals in the asymptomatic stage and prevent the development HAM/TSP. The basic reproduction number in the presence of CTL response, R_1, determines whether a persistent anti-HTLV-I CTL response can be established. When $R_1 < 1$, CD8$^+$ T cells remain at a sufficiently low level that cytotoxicity in the peripheral blood remains low. A more practical control strategy is to keep the values of R_0 and R_1 in the range of $R_1 < 1 < R_0$ to prevent the development of HAM/TSP. From (3), we have the relation

$$R_1 = R_0 \left(\frac{1}{1 + \frac{\beta}{\mu_1} \frac{K\mu_3}{\nu}} \right). \tag{8}$$

This relation shows that, given the same level of viral production in terms of R_0 and β/μ_1, individuals with lower ratio $\frac{K\mu_3}{\nu}$ will have smaller R_1, and hence a lower risk to develop HAM/TSP. In Section 4.5, we will see that this ratio can be regarded as a threshold value for the equilibrium proviral load $\bar{y}$ the immune system will tolerate without mounting a CTL response.

4.3. Positive correlation between proviral load and CD8 levels

Clinical experiments in the PBLs of HAM/TSP patients show that there exists a positive correlation between the proviral load and the CD8$^+$ T-cell level (Nagai et al., 2001). Note that, when $R_1 > 1$, the relation (6) can be rewritten as

$$y^* = \frac{1}{d}(z^* + K), \tag{9}$$

where $d = \frac{\nu}{\mu_3}$. This relation shows that, at equilibrium, the $CD8^+$ T-cell level is proportional to the proviral load, which is in accordance with the experiments.

4.4. The role of CTL-driven elimination rate γ

Note in (3) that the rate of CTL-driven elimination, γ, does not affect the values of R_1 nor R_0. Nevertheless, a larger γ leads to lower $CD8^+$ CTL levels as we show in the next result.

Theorem 4.1. *Assume that $R_1 > 1$. Then both y^* and z^* are decreasing functions of γ.*

Proof: Rewrite the function g in (7) as

$$g(z) = d - c(\gamma + b)z - a\gamma z^2,$$

where $a, b, c,$ and d are positive constants independent of γ. Let $z^* = z^*(\gamma)$ be the positive root of g. Then implicit differentiation leads to

$$\frac{dz^*}{d\gamma} = -\frac{cz^* + az^{*2}}{c(\gamma + b) + 2a\gamma z^*} < 0,$$

and thus z^* decreases as γ increases. From the linear relation (9) between y^* and z^*, we know that y^* also decreases as γ increases. $\qquad\square$

A larger γ means that CTLs eliminate infected CD4s more effectively, and by Theorem 4.1, the body then requires fewer CTLs to maintain the proviral load at equilibrium. A lower level of CTLs in turn lowers the cytotoxic effects of the CTL response. This agrees with the earlier observation that HAM/TSP patients may have less effective CTL functions than asymptomatic carriers (Nowak and Bangham, 1996; Wodarz et al., 1999).

4.5. CTL response: what constitutes a good responder?

Analysis in Sections 4.3 and 4.4 show that HTLV-I specific CTLs play a protective role in keeping the HTLV-I proviral load in check, and a more efficient CTL lysis will lead to lower levels of CTLs and proviral load. While this suggests ACs may have more efficient CTLs, it does not explain the observed inter-individual differences of proviral load and CTL levels, nor does it explain why many ACs have a higher proviral load than HAM/TSP patients (Asquit and Bangham, 2007; Bangham et al., 2009). Related to CTL efficacy, or CTL responsiveness in particular, questions remain as to what constitutes a good responder, and thus reduces risk of developing HAM/TSP.

In model (1), CTL responsiveness to HTLV-I is related to parameters ν, μ_3, and K. Which of these parameters is more important to determine responsiveness? Our criterion for ACs, $R_1 < 1$, can offer new insights into this question. From (3), we have

$$R_1 < 1 \quad \Longleftrightarrow \quad \bar{y} < \frac{K\mu_3}{\nu}. \tag{10}$$

In this relation, $\bar{y} = \frac{\mu_1}{\beta}(R_0 - 1)$ is the equilibrium level of proviral load in the absence of CTL response. The ratio $\frac{K\mu_3}{v}$ is only related to the CTL response. Relation (10) establishes $\frac{K\mu_3}{v}$ as the threshold level of proviral load the body will tolerate without mounting any CTL response. This can also be seen from the z equation in (1)

$$z' = \frac{v}{K}\left(\frac{y}{z/K + 1} - \frac{K\mu_3}{v}\right)z.$$

If the proviral load $y(t)$ is less than the threshold $K\mu_3/v$, we have

$$z' \leq \frac{v}{K}\left(y - \frac{K\mu_3}{v}\right)z \leq 0,$$

and $z(t)$ will decrease exponentially. If, on the other hand, $y(t) > K\mu_3/v$ and $z(t)$ is small, then we have

$$z' \approx \frac{v}{K}\left(y - \frac{K\mu_3}{v}\right)z,$$

and $z(t)$ will increase exponentially. Accordingly, whether an individual is a good responder depends on the relationship between the ability of viral production represented by $\bar{y} = \frac{\mu_1}{\beta}(R_0 - 1)$ and the capacity of the CTL response represented by $K\mu_3/v$.

The analysis above may explain a key difference between ACs and HAM/TSP patients, and offer a plausible mechanism for HAM/TSP development among HTLV-I infected people ($R_0 > 1$): if $R_1 > 1$, then $\bar{y} > K\mu_3/v$. The body will mount a persistent CTL response to HTLV-I, and a positive equilibrium (x^*, y^*, z^*) will be reached. If $R_1 < 1$, then $\bar{y} < K\mu_3/v$. The equilibrium level of proviral load is below the tolerated threshold. The body will not mount a CTL response. In this case, even if the proviral is transiently above the threshold $K\mu_3/v$, either due to new infection or stochastic fluctuations, the body can mount a short-term CTL response to bring the proviral load below the threshold and then shut down the CTL response. A key difference between ACs and HAM/TSP patients may be the intermittent or persistent presence of CTL cytotoxicity in the body. This difference will be further investigated in our future studies.

5. Summary

CD8$^+$ cytotoxic T lymphocytes eliminate infected cells by releasing pore-forming proteins and inflammatory cytokines such as IFN-γ and TNF-α. In HTLV-I infection, CD8$^+$ T cells target primarily the Tax proteins expressed on the surface of infected CD4$^+$ T cells (Parker et al., 1992; Yamano et al., 2002). It has been observed that HAM/TSP patients harbor abundant numbers of anti-Tax CTLs. Furthermore, HTLV-I-specific CD8$^+$ T cells have been found in the cerebrospinal fluid of HAM/TSP patients (Nagai et al., 2001). These observations suggest that the high level of CD8$^+$ T cells and their cytotoxic effects contribute to the pathogenesis of HAM/TSP.

A mathematical model for the CD8$^+$ T-cell response to HTLV-I infection is investigated. The model considers that HTLV-I-infected cells are eliminated at rate γ by CTLs.

Since infected $CD4^+$ T cells stimulate $CD8^+$ to proliferate, a density-dependent proliferation with ν as the average rate of proliferation (also called responsiveness) is considered (Nowak and Bangham, 1996). The number of equilibria and the global dynamics of system (1) depends on the basic reproduction number in the absence of CTL response, R_0, and the basic reproduction number in the presence of CTL response, R_1. The threshold parameter R_0 determines whether the HTLV-I infection is chronic among the $CD4^+$ T-cell pool. On the other hand, the parameter R_1 determines whether a long-term $CD8^+$ CTL response can be maintained.

Based on the high levels of $CD8^+$ CTL in HAM/TSP patients, it is likely that those patients have $R_1 > 1$, whereas asymptomatic carriers (ACs) are likely to have R_1 values below 1. Moreover, when $R_1 > 1$, there exists a positive correlation between the proviral load and the $CD8^+$ T-cell level at equilibrium. This correlation has been clinically verified in HAM/TSP patients (Nagai et al., 2001). Therefore, the parameter R_1 could be a useful threshold parameter to distinguish ACs from HAM/TSP patients, and a useful control parameter to prevent ACs from developing HAM/TSP.

The equilibrium proviral load is the result of a dynamic interaction of HTLV-I infection and HTLV-I specific CTL response. The threshold parameter R_1 captures this interaction: $R_1 < 1$ is equivalent to $\bar{y} < \frac{K\mu_3}{\nu}$. The ratio $\frac{K\mu_3}{\nu}$ describes the immune system's tolerance of proviral load level. Such a relation explains individual differences of HTLV-I proviral load and why some ACs have a higher proviral load than HAM/TSP patients. It also suggests that the proviral load level of an infected individual should be weighed in relation to the individual's CTL response capacity to determine the risk for HAM/TSP development. On the other hand, the efficiency parameter γ for CTL lysis does not change the values of R_1. If higher values of R_1 serves as a determinant for HAM/TSP development, the efficiency of CTL lysis will not separate ACs from HAM/TSP patients. More realistic models that incorporate HTLV-I induced mitosis as in Wodarz et al. (1999) and Gómez-Acevedo and Li (2005) need to be investigated to gain a better understanding of the dynamics interaction of HTLV-I infection and CTL response.

Acknowledgements

Appendix

This Appendix contains the proof of Theorem 3.1.

Proof of (a): We assume that $R_0 \leq 1$ and thus P_0 is the only equilibrium in the positively invariant region Γ. To show that P_0 is globally stable in Γ, consider a Lyapunov function

$L = y$. We have

$$L' = y' = \sigma\beta xy - \mu_2 y - \gamma yz \le y(\sigma\beta x - \mu_2) \le \mu_2 y\left(\frac{\sigma\beta x}{\mu_2} - 1\right) \le \mu_2 y(R_0 - 1) \le 0,$$

if $R_0 \le 1$. The maximal compact invariant set in $\{(x, y, z) \in \Gamma : L' = 0\}$ is the single-ton $\{P_0\}$. The global stability of P_0 follows from the LaSalle invariance principle (LaSalle, 1976). □

Proof of (b): We assume that $R_1 \le 1 < R_0$. In this case, P_0 is unstable, P_1 exists on the boundary of Γ, and P_2 does not exist in the feasible region. To show that $P_1 = (\overline{x}, \overline{y}, 0)$ is globally stable in Γ, we consider a Lyapunov function

$$V = V(x, y, z) = x - \overline{x}\ln x + \frac{1}{\sigma}(y - \overline{y}\ln y) + \frac{\gamma K z}{\sigma v}, \quad (x, y, z) \in \mathbb{R}_+^3,$$

where $\overline{x}$, $\overline{y}$ are given in (4). It can be verified that V has a global minimum at the equilibrium point P_1, and thus $V - V(P_1) \ge 0$ is positive definite with respect to P_1. From (1) and (4), we obtain

$$\frac{dV}{dt} = x'\left(1 - \frac{\overline{x}}{x}\right) + \frac{y'}{\sigma}\left(1 - \frac{\overline{y}}{y}\right) + \frac{\gamma K z'}{\sigma v}$$

$$= (\lambda - \mu_1 x - \beta xy) + \left(\beta xy - \frac{\mu_2}{\sigma}y - \frac{\gamma}{\sigma}yz\right) - \left(\lambda\frac{\overline{x}}{x} - \mu_1\overline{x} - \beta\overline{x}y\right)$$

$$- \left(\beta x\overline{y} - \frac{\mu_2}{\sigma}\overline{y} - \frac{\gamma}{\sigma}\overline{y}z\right) + \frac{\gamma K}{\sigma}\frac{yz}{z + K} - \frac{\gamma\mu_3 K}{\sigma v}z.$$

From (4), it follows that $\lambda = \mu_1\overline{x} + \beta\overline{x}\overline{y}$. Therefore,

$$\frac{dV}{dt} = (\mu_1\overline{x} + \beta\overline{x}\overline{y} - \mu_1 x) - \left(\frac{\mu_2}{\sigma}y + \frac{\gamma}{\sigma}yz\right) - \left(\mu_1\frac{\overline{x}^2}{x} + \frac{\beta\overline{x}^2\overline{y}}{x} - \mu_1\overline{x} - \beta\overline{x}y\right)$$

$$- \left(\beta x\overline{y} - \frac{\mu_2}{\sigma}\overline{y} - \frac{\gamma}{\sigma}\overline{y}z\right) + \frac{\gamma K}{\sigma}\frac{yz}{z + K} - \frac{\gamma\mu_3 K}{\sigma v}z$$

$$= \mu_1\overline{x}\left(2 - \frac{\overline{x}}{x} - \frac{x}{\overline{x}}\right) + \beta\overline{x}\overline{y} - \frac{\beta\overline{x}^2\overline{y}}{x} + \beta\overline{x}y - \beta x\overline{y} + \frac{\mu_2}{\sigma}(\overline{y} - y)$$

$$+ \frac{\gamma K}{\sigma}\frac{yz}{z + K} - \frac{\gamma}{\sigma}yz + \frac{\gamma}{\sigma}\overline{y}z - \frac{\gamma\mu_3 K}{\sigma v}z.$$

Since $\sigma\beta\overline{x} = \mu_2$, we have

$$\frac{dV}{dt} = (\mu_1\overline{x} + \beta\overline{x}\overline{y})\left(2 - \frac{\overline{x}}{x} - \frac{x}{\overline{x}}\right) + \frac{\gamma}{\sigma}z\left(\overline{y} - \frac{\mu_3 K}{v}\right) - \frac{\gamma yz^2}{\sigma(z + K)}.$$

Using (3) and (4), we obtain

$$\frac{dV}{dt} = (\mu_1\overline{x} + \beta\overline{x}\overline{y})\left(2 - \frac{\overline{x}}{x} - \frac{x}{\overline{x}}\right) + \frac{\gamma(\mu_1 v + \mu_3\beta K)}{\sigma\beta v}(R_1 - 1)z - \frac{\gamma yz^2}{\sigma(z + K)} \le 0.$$

For the last step, the inequality $\sqrt{ab} \leq (a+b)/2$, for $a, b \geq 0$, is used. This relation and the positive definiteness of $V - V(P_1)$ with respect to P_1 prove the stability of P_1 and its global attractivity in the interior of Γ when $R_1 \leq 1 < R_0$. $\qquad\square$

Proof of (c): In this case, we assume that $1 < R_1$. Both P_0 and P_1 are unstable, using the Lyapunov functions in the proof of previous two cases. $P_2 = (x^*, y^*, z^*)$ exists in the interior of Γ. We want to show that P_2 is globally stable in the interior of Γ. Consider a Lyapunov function

$$W(x, y, z) = (x - x^* \ln x) + \frac{1}{\sigma}(y - y^* \ln y) + \frac{\gamma(z^* + K)}{\sigma v}(z - z^* \ln z),$$

for $(x, y, z) \in \mathbb{R}_+^3$, where x^*, y^*, z^* are coordinates of the equilibrium P_2, and satisfy equations in (5). Note that W has a global minimum at P_2 and $W - W(P_2) \geq 0$ is positive definite with respect to P_2. Direct calculation and (1) lead to

$$\frac{dW}{dt} = x'\left(1 - \frac{x^*}{x}\right) + \frac{y'}{\sigma}\left(1 - \frac{y^*}{y}\right) + \frac{\gamma(z^* + K)}{\sigma v}z'\left(1 - \frac{z^*}{z}\right)$$

$$= (\lambda - \mu_1 x - \beta xy) + \left(\beta xy - \frac{\mu_2}{\sigma}y - \frac{\gamma}{\sigma}yz\right)$$

$$+ \left(\frac{\gamma(z^* + K)}{\sigma}\frac{yz}{z + K} - \frac{\gamma(z^* + K)\mu_3}{\sigma v}z\right) - \left(\lambda\frac{x^*}{x} - \mu_1 x^* - \beta x^* y\right)$$

$$- \left(\beta xy^* - \frac{\mu_2}{\sigma}y^* - \frac{\gamma}{\sigma}y^* z\right) - \left(\frac{\gamma(z^* + K)}{\sigma}\frac{yz^*}{z + K} - \frac{\gamma(z^* + K)\mu_3}{\sigma v}z^*\right).$$

Using $\lambda = \mu_1 x^* + \beta x^* y^*$ in (5), we obtain

$$\frac{dW}{dt} = (\beta x^* y^* + \mu_1 x^* - \mu_1 x) - \left(\frac{\mu_2}{\sigma}y + \frac{\gamma}{\sigma}yz\right)$$

$$+ \left(\frac{\gamma(z^* + K)}{\sigma}\frac{yz}{z + K} - \frac{\gamma(z^* + K)\mu_3}{\sigma v}z\right)$$

$$- \left(\beta\frac{x^{*2}y^*}{x} + \mu_1\frac{x^{*2}}{x} - \mu_1 x^* - \beta x^* y\right) - \left(\beta xy^* - \frac{\mu_2}{\sigma}y^* - \frac{\gamma}{\sigma}y^* z\right)$$

$$- \left(\frac{\gamma(z^* + K)}{\sigma}\frac{yz^*}{z + K} - \frac{\gamma(z^* + K)\mu_3}{\sigma v}z^*\right)$$

$$= \mu_1 x^*\left(2 - \frac{x^*}{x} - \frac{x}{x^*}\right) + \beta x^* y^* - \beta\frac{x^{*2}y^*}{x} + \beta x^* y - \beta xy^* + \frac{\mu_2}{\sigma}(y^* - y)$$

$$+ \frac{\gamma}{\sigma}(y^* z - yz) + \left(\frac{\gamma(z^* + K)}{\sigma}\frac{yz}{z + K} - \frac{\gamma(z^* + K)\mu_3}{\sigma v}z\right)$$

$$- \left(\frac{\gamma(z^* + K)}{\sigma}\frac{yz^*}{z + K} - \frac{\gamma(z^* + K)\mu_3}{\sigma v}z^*\right).$$

Using Eqs. (5) and (6), we have

$$
\begin{aligned}
\frac{dW}{dt} &= \mu_1 x^* \left(2 - \frac{x^*}{x} - \frac{x}{x^*} \right) + \beta x^* y^* - \beta \frac{x^{*2} y^*}{x} + \beta x^* y - \beta x y^* \\
&\quad + \left(\beta x^* - \frac{\gamma}{\sigma} z^* \right)(y^* - y) + \frac{\gamma}{\sigma}(y^* z - yz) \\
&\quad + \left(\frac{\gamma(z^* + K)}{\sigma} \frac{yz}{z + K} - \frac{\gamma}{\sigma} y^* z \right) \\
&\quad - \left(\frac{\gamma(z^* + K)}{\sigma} \frac{yz^*}{z + K} - \frac{\gamma}{\sigma} y^* z^* \right) \\
&= (\mu_1 x^* + \beta x^* y^*) \left(2 - \frac{x^*}{x} - \frac{x}{x^*} \right) + \frac{\gamma}{\sigma}(yz^* - yz) \left(1 - \frac{z^* + K}{z + K} \right) \\
&= (\mu_1 x^* + \beta x^* y^*) \left(2 - \frac{x^*}{x} - \frac{x}{x^*} \right) - \frac{\gamma}{\sigma} \frac{y}{z + K}(z - z^*)^2 \le 0,
\end{aligned}
$$

for all (x, y, z) in the interior of Γ. Furthermore, in the interior of Γ, $dW/dt = 0$ only occurs when $x = x^*$, $y = y^*$ and $z = z^*$. This, together with the positive definiteness of $W - W(P_2)$, proves the global stability of P_2 when $R_1 > 1$. $\qquad\qquad\square$

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