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Evolutionary Dynamics of HTLV-I

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Abstract. Using mathematical models to describe the in vivo dynamics of HTLV-I infection, an explanation is offered for the slow rate of evolution of HTLV-I relative to HIV-1. In agreement with experimental findings, it is assumed that cell activation is required for successful replication in T helper cells and that HTLV-I induces a significant degree of bystander activation. It is found that the rate of evolution of HTLV-I is limited by the restricted availability of activated uninfected T cells, both at high and low proviral loads. This limits the within-host sequence diversity of HTLV-I and may therefore account for the slow rate of evolution of the virus in the population. Specific differences in the in vivo dynamics of HTLV-I and HIV-1 are identified which may account for the discrepancy in the rate of evolution of these two retroviruses.

Key words: HTLV-I — HIV — Infectious transmission — Mitotic transmission — Mathematical model

Introduction

In HTLV-I infection, as in other persistent virus infections such as HIV-1 and hepatitis B, the virus load is strongly correlated with the risk of consequent disease. HTLV-I is associated with two types of disease: (i) adult T-cell leukemia (ATLL) and (ii) a range of subacute or chronic inflammatory diseases that affect chiefly the eye, skeletal muscle, or central nervous system. The most commonly recognized of the inflammatory conditions is HTLV-I-associated myelopathy/tropical spastic paraparesis (HAM/TSP), a chronic inflammation of the central nervous system that results in weakness or paralysis of the legs (Gessain et al. 1985; Osame et al. 1986). The risk of HAM/TSP rises sharply with the proviral load of HTLV-I (Nagai et al. 1998). The risk of the other inflammatory diseases associated with HTLV-I probably also depends on the provirus load; the factors associated with development of ATLL are not known and are not considered further here.

The concentration of cell-free HTLV-I in the plasma is negligible, so the proviral load [number of proviral copies per 100 peripheral blood mononuclear cells (PBMC)] is the appropriate measure of HTLV-I burden. The proviral load of HTLV-I can reach very high levels. A typical HAM/TSP patient carries about 10 provirus copies per 100 PBMC; since most infected cells carry a single proviral copy, this will be approximated to 10% PBMC. The host cells infected by HTLV-I are mainly CD4+CD45RO+ T cells, which constitute some 20–30% of the PBMC; therefore, a proviral load of 10% PBMC represents infection of approximately 30–50% of the available host cells.

Replication-competent retroviruses can spread within the host either by virion replication ("infectious spread") or by division of a provirus-carrying cell ("mitotic spread"). Infectious spread is associated with a much higher mutation rate, as it is mediated by the relatively error-prone reverse transcriptase. Because HTLV-I varies little in sequence compared with HIV-1, it has been widely accepted that the very high provirus load in HTLV-I infection is maintained by proliferation of in-

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fected T cells, induced by the Tax protein of HTLV-I. However, as we have recently argued elsewhere (Wodarz et al. 1999b), there are several indications that HTLV-I replicates persistently. The strongest lines of evidence for this are (i) the high ratio of nonsynonymous-to-synonymous nucleotide substitutions observed in the HTLV-I *tax* gene, which encodes the dominant target antigen recognized by anti-HTLV-I cytotoxic T lymphocytes (CTL), and (ii) the 100-fold fall in proviral load observed on treatment of patients with an inhibitor of reverse transcriptase (Taylor et al. 1999).

In a population genetic study in Japan we have found that possession of the HLA-A2 gene is associated with a twofold reduction in the risk of HAM/TSP (Jeffery et al. 1999). This observation is consistent with the interpretation that class I HLA-restricted CTL exert selection pressure on the *tax* gene (Bangham et al. 1999; Niewiesk and Bangham 1996; Niewiesk et al. 1994); this selection will be evident in the proviral sequences of HTLV-I only if the virus has replicated.

We recently showed (Wodarz et al. 1999b) that the relative sequence constancy of HTLV-I can be reconciled with persistent replication of the virus. At the high proviral loads that are typically seen in HAM/TSP patients, even in the presence of persistent HTLV-I replication most new HTLV-I-carrying cells arise by mitotic division of infected cells, because the supply of uninfected host cells becomes limiting. We concluded that one cannot infer a lack of persistent replication from the observed sequence constancy of the virus.

However, this explanation holds true only when the proviral load is high; it does not explain why the virus also accumulates few mutations in individuals with a lower proviral load. In this paper we introduce one further feature into the model that is well attested by experiment: HTLV-I-infected T cells induce activation and proliferation in neighboring T cells (Lal et al. 1996; Martin and Southern 1996; Wucherpfennig et al. 1992). Because HTLV-I can efficiently infect only activated, proliferating cells, this bystander T-cell activation has a profound effect on the efficiency of HTLV-I propagation in the host. We conclude that in HTLV-I infection, infectious spread of the virus in the host is limited by the restricted availability of activated uninfected CD4+CD45RO+ T cells, at both low and high proviral loads. The consequently limited within-host sequence diversity of HTLV-I could be a factor in the slow rate of evolution of the virus in the population (Ina and Gojobori 1990).

Basic Model of Virus Replication in T Cells

HTLV-I, like most exogenous retroviruses, can complete its replication cycle only in host cells that are activated and/or dividing. Breakdown of the nuclear envelope is required because active transport of the viral preintegration complex into the nucleus of the cell is inefficient. As discussed in Wodarz et al. (1999a), these assumptions complicate the basic virus infection dynamics. Here we demonstrate this with a simple model which takes into account activated proliferating T helper cells (x), infected T helper cells (y), and a CTL response (z). It is given by the following set of ordinary differential equations:

$$\begin{aligned} \dot{x} &= (\eta + rxy)\left(1 - \frac{x+y}{k}\right) - dx - \beta xy \\ \dot{y} &= \beta xy - ay - pyz \\ \dot{z} &= cy - bz \end{aligned} \qquad (1)$$

T helper-cell activation and proliferation are density dependent, i.e., the rate of activation and cell division declines as the total number of T helper cells reaches a certain carrying capacity (k). The majority of activated T cells will have been activated in response to the viral infection. We assume that this occurs at the density-dependent rate $rxy[1 - (x + y)/k]$. In addition, we assume that T cells become activated and proliferate independently of the infection in question (i.e., by other antigens) at a density-dependent rate $\eta[1 - (x + y)/k]$. This may be due to the presence of other pathogens in the host. The host cells die at a rate dx and become infected by the virus at a rate βxy. Infected cells die at a rate ay. The CTL population grows in response to antigen at a rate cy, declines at a rate bz, and kills infected cells at a rate pyz.

An important measure is the basic reproductive ratio of the virus (R_0). This denotes the number of secondary infected cells produced by each infected cell at the beginning of the infection. $R_0 > 1$ ensures virus persistence in the host. For the above model, the basic reproductive ratio of the virus is given by $R_0 = \eta\beta k/[a(\eta + dk)]$. Therefore, an important host parameter determining the value of R_0 is the rate of background activation of T helper cells (η). If there are no other infectious agents present in the host, η is likely to be relatively low, thus pushing R_0 below unity. However, contrary to the basic virus infection model (Nowak and Bangham 1996), successful establishment of T-cell infection may still be possible even if $R_0 < 1$. This is demonstrated for the case $\eta = R_0 = 0$, i.e., when there are no activated susceptible cells in the host at the beginning of the infection. In this case, the trivial equilibrium describing virus extinction is given by E1, $x^{(1)} = 0$, $y^{(1)} = 0$, $z^{(1)} = 0$ and is always stable. On the other hand, virus persistence is described by equilibrium E2,

$$x^{(2)} = \frac{kpc[y^{(2)}(r - \beta) - d] + y^{(2)} abr}{y^{(2)} r(pc + b\beta)}, \qquad z^{(2)} = cy^{(2)}/b$$

$$y^{(2)} = \frac{A + \sqrt{A^2 - 4\beta bdk(r\beta b + pcr)}}{2(r\beta b + pcr)}$$

where $A = \beta bk(r - \beta) - abr$.
This equilibrium is stable if $y^{(2)} > d/[r(1 - (y^{(2)}/k)) - \beta]$.

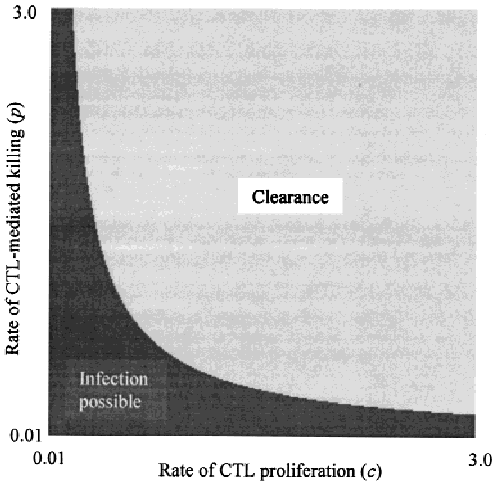

Fig. 1. Dependence of virus clearance versus persistence on the efficacy of the immune response in the basic model of T helper-cell infection (model 1). If the rate of CTL proliferation and/or the rate of CTL-mediated lysis lies above a threshold, the virus infection is cleared by the immune response. Parameters were chosen as follows: $k = 10$; $d = 0.1$; $a = 0.2$; $b = 0.1$; $\beta = 0.5$; $r = 2$.

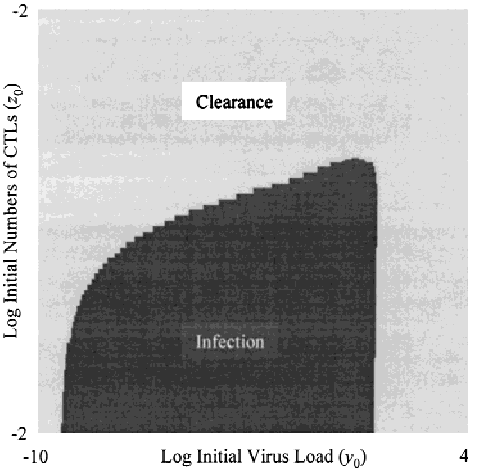

Fig. 2. Dependence of virus clearance versus persistence on initial conditions in the basic model of T helper cell infection (model 1). The initial virus load needs to lie above a threshold to activate a sufficient number of helper cells for infection to be possible. If the virus load lies above a threshold, the CTL response can grow very rapidly, suppressing the virus load to low levels not sufficient for the maintenance of a sufficient number of susceptible target cells. Hence the infection is cleared. If the initial number of CTL lies above a threshold, the virus cannot establish a persistent infection. Parameters were chosen as follows: $k = 10$; $d = 0.1$; $a = 0.2$; $c = 0.15$; $p = 1$; $b = 0.1$; $\beta = 0.5$; $r = 2$.

Therefore, mainly parameters influencing the virus load determine the stability of this equilibrium. Consequently, viral replication, the rate of activation/proliferation, and the life span of the cells need to be high enough for infection to be possible. But most importantly the efficacy of the CTL response needs to lie below a threshold for the virus persistence equilibrium to be stable (Fig. 1). That is, a high rate of CTL proliferation and CTL-mediated lysis may drive the virus extinct. This is because an efficient CTL response drives virus load to levels too low to maintain the population of activated host cells.

In the parameter region where both the virus extinction equilibrium (E1) and the virus persistence equilibrium (E2) are stable, initial conditions determine whether T-cell infection can successfully be established. As shown in Fig. 2, the initial virus load needs to be intermediate. It needs to lie above a threshold to activate a sufficient number of host cells for persistent replication to be possible. However, if the virus load lies above another threshold, the initial growth rate of the CTL response is too large. In theory it can therefore clear the infection. An increase in the initial number of CTL narrows the region of virus load initially required to establish an infection. If the initial number of CTL lies above a threshold, establishment of persistent infection becomes impossible (Fig. 2).

To summarize, unless the rate of background activation of T helper cells in the absence of the virus is high due to the presence of other pathogens in the host, successful establishment of T-cell infection depends on a complex balance between host and viral parameters as well as initial conditions and is relatively difficult to achieve. In HIV-1 infection, Wodarz et al. (1999a) demonstrated that infection of macrophages provides an important reservoir, elevating the basic reproductive ratio of the virus above unity and therefore enabling the rise of T-cell tropic variants. In contrast, HTLV-I can infect only CD4+ T cells. However, HTLV-I, like other retroviruses, may also spread within the host by division of provirus-containing cells, a process we refer to here as "mitotic transmission." In the following sections we examine how mitotic transmission alters the dynamics between HTLV-I and CD4+ T cells.

T-Cell Infection in HTLV-I: The Effect of Mitotic Transmission

Here we apply the basic model for virus replication in CD4+ T cells to HTLV-I by including mitotic transmission. Provirus-containing T cells are driven into proliferation by HTLV-I at a density-dependent rate $sy[1 - (x + y)/k]$. Based on models analyzed by Lipsitch et al. (1995) and Wodarz et al. (1999b), the equations describing these dynamics are

$$\begin{aligned} x &= (\eta + rxy)\left(1 - \frac{x+y}{k}\right) - dx - \beta xy \\ y &= \beta xy + sy\left(1 - \frac{x+y}{k}\right) - ay - pyz \\ z &= cy - bz \end{aligned} \qquad (2)$$

Infectious Versus Mitotic Transmission in R_0

For the above model, the basic reproductive ratio of the virus is given by $R_0 = (1/a)\{\beta[\eta k/(\eta + dk)] + s[dk/(\eta + dk)]\}$. Similar to the findings of Lipsitch et al. (1995) and

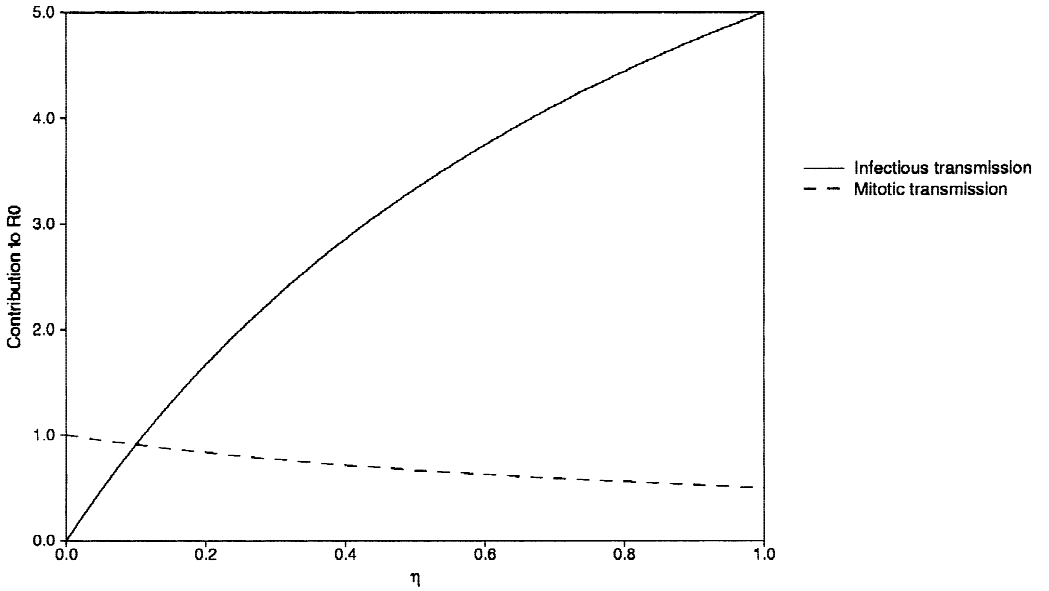

Fig. 3. The relative contribution of infectious versus mitotic transmission to the basic reproductive ratio of the virus (R_0) in the model for HTLV-I infection (model 2) depends on the rate of background activation of T helper cells (η). At a low rate of background activation of helper cells, mitotic transmission is essential for the establishment of an infection. As the rate of background activation of T helper cells is increased, the relative contribution of infectious transmission to the basic reproductive ratio of the virus increases. Parameters were chosen as follows: $k = 10$; $d = 0.1$.

Wodarz et al. (1999b), infectious and mitotic transmission contribute additively to R_0. However, in the present model, the relative contributions of these two routes of transmission to R_0 are determined by the level of background activation of T helper cells (η). The higher the rate of background activation of CD4+ T cells, the more important the contribution of infectious transmission and the lower the contribution of mitotic transmission to the basic reproductive ratio of the virus (Fig. 3). If the rate of background activation of T helper cells lies above a threshold, i.e., if $\eta > dk(s - a)/a$, persistent infection cannot be maintained by mitotic transmission alone. The reason is that the T helper cells stimulated independently of HTLV-I outcompete the proliferating infected CD4+ T cells. On the other hand, if the value of η lies below a threshold, i.e., if $\eta < adk/(\beta k - a)$, infectious transmission alone cannot maintain the virus population in the host. This is because, without background activation of T cells, there are no activated susceptible host cells at the beginning of the infection. To conclude, both infectious and mitotic transmissions are required to ensure persistent infection of HTLV-I. Without infectious transmission, HTLV may eventually be driven to extinction in the presence of other pathogens in the host. On the other hand, mitotic transmission in HTLV-I infection has the same effect on the dynamics as macrophage infection in HIV-1: if the level of activated host cells at the beginning of the infection is not high enough for R_0 due to infectious transmission to be greater than unity, mitotic transmission can elevate the basic reproductive ratio of the virus above unity. This ensures successful establishment of the infection and eliminates the complex and stringent conditions required for persistent replication in the absence of mitotic spread.

The Effect of Mitotic Transmission on the Rate of Mutation and Evolution

We concentrate on the parameter region where all T-cell activation is due to HTLV-I, i.e., $\eta = 0$. The contribution of infectious transmission to the basic reproductive ratio of the virus is zero, and $R_0 > 1$ requires the rate of mitotic transmission to be higher than the death rate of infected cells ($s > a$). It has been argued previously that a high rate of mitotic transmission, which is required for virus persistence in the present scenario, is responsible for the slow rate of evolution of HTLV-I since a high rate of mitotic transmission promotes a slow mutation rate due to the use of DNA polymerase rather than reverse transcriptase. Here we use the above-described model to determine the effect of mitotic transmission on the rate of mutation and evolution of HTLV-I.

Assuming that $\eta = 0$, the model is characterized by three equilibria. In the absence of an infection, the trivial equilibrium (E1) is attained. If $R_0 > 1$ and the virus establishes an infection, the system may move to one of two equilibria. The population of infected T helper cells controlled by the CTLs may persist without the presence of uninfected activated host cells. This is described by E3,

$$x^{(3)} = 0$$
$$y^{(3)} = \frac{bk(s-a)}{sb+pkc}$$
$$z^{(3)} = \frac{kc(s-a)}{sb+pkc}$$

Alternatively, the population of infected cells controlled by the CTLs may coexist with susceptible activated host cells. This is described by E4,

$$x^{(4)} = \frac{kcp[y^{(4)}(r-\beta)-d]+y^{(4)}b(ar-s\beta)-sbd}{y^{(4)}r(\beta b+cp)}$$

$$z^{(4)} = cy^{(4)}/b$$

$$y^{(4)} = \frac{B+\sqrt{B^2-4bd(\beta k-s)(\beta br+pcr)}}{2(\beta br+pcr)}$$

where $B = \beta bk(r-\beta)-b(ar-s\beta)$

Equilibrium E4 is stable and the population of uninfected activated CD4+ T cells will persist if $r > \{[k\beta b(s-a)+d(sb+pkc)](sb+pkc)\}/[bk(s-a)(pkc+ba)]$.

From the equilibrium expressions it is evident that the rate of mitotic transmission (s) and the efficacy of the immune response (c and p) are antagonistic determinants of virus load. Even in the presence of an immune response, a high rate of mitotic transmission can drive the virus load up to the carrying capacity if $s \gg cp$. Therefore, we can define an efficient immune response as keeping the virus load well below the carrying capacity; i.e., the CTL response is efficient if $cp \gg s$.

According to the above condition, three factors may decide whether uninfected activated host cells are present at equilibrium and thus whether the virus has a chance to spread by infectious transmission and to show a high mutation rate (Fig. 4).

1. An effective CTL response (high c and p) reduces the equilibrium virus load to very low values. Depending on the level of CD4+ T-cell proliferation (r), the virus load controlled by an efficient CTL response may be too low to induce sufficient activation/proliferation of the host cells. Therefore, if the CTL response is sufficiently strong, the virus loses its ability to spread by infectious transmission and requires mitotic transmission to persist in the host.
2. The rate of mitotic transmission can have two effects on the equilibrium levels of uninfected activated host cells, depending on the efficacy of the immune response. (a) If the rate of CTL proliferation and killing is high relative to the rate of mitotic transmission, i.e., if $s < (cpk+ba)[\sqrt{d(\beta k+d)}/b(\beta k+d)]+a$, an increase in the rate of mitotic transmission promotes the existence of uninfected activated host cells. It therefore increases the rate of infectious spread and thus the rate of mutation due to reverse transcriptase. The reason is that an efficient CTL response keeps the virus load at very low levels. Since mitotic transmission directly counters the CTL response, it can increase the virus load to levels sufficient for the activation of CD4+ T cells. (b) On the other hand, if the above condition is violated because the rate of CTL proliferation and killing is low relative to the rate of mitotic spread, an increase in the rate of mitotic transmission promotes the extinction of uninfected activated host cells. In this case, the reason is competition between uninfected and infected CD4+ T cells. Both proliferate but are limited by regulatory mechanisms such as growth factors so that the total number of activated CD4+ T cells cannot exceed a certain carrying capacity. If the efficacy of the CTL response is low and the rate of mitotic transmission becomes high, infected CD4+ T cells will be able to proliferate faster than uninfected host cells and therefore outcompete them. In this case, the virus load will reach levels near carrying capacity (k).
3. A fast rate of virus replication (high β) promotes the extinction of uninfected activated host cells, while a slow rate of replication promotes their persistence. This is analogous to an efficient predator leading to the extinction of the prey population.

These results have important implications for the number of mutations generated and for the rate of evolution of HTLV-I. A high number of mutations, as seen in HIV, results from the action of reverse transcriptase. In our model, the expected number of mutations occurring per unit time via this pathway will be proportional to the number of newly infected cells generated, and this is given by the expression βxy. If there are no activated susceptible host cells at equilibrium, the expected number of mutations per unit time will be very low because of the lack of reverse transcription. In the parameter region where the uninfected activated host cells coexist with infected cells, Fig. 5 shows how various factors influence the expected number of mutations generated. Increasing the efficacy of the immune system (c and p) reduces the expected number of mutations because an efficient CTL response decreases the virus load and thus the number of susceptible host cells. Increasing the rate of mitotic transmission (s) increases the expected number of mutations unless s is very high relative to the efficacy of the CTL response. The reason is that in the presence of a relatively strong immune response, an increase in the rate of mitotic transmission increases the virus load and consequently the activation of uninfected bystander cells. Increasing the rate of infectious transmission (β) increases the expected number of mutations for very low values of β. Higher rates of infectious transmission decrease the expected number of mutations because high values of β reduce the number of susceptible host cells toward extinction.

These trends suggest the following situation: if the immune system is relatively weak, mitotic transmission may drive the virus load near to the carrying capacity, reducing the number of susceptible host cells toward low values or even extinction. Thus, the expected number of mutations is low. On the other hand, an efficient CTL response may suppress the virus load to relatively low levels, not sufficient to maintain a significant number of

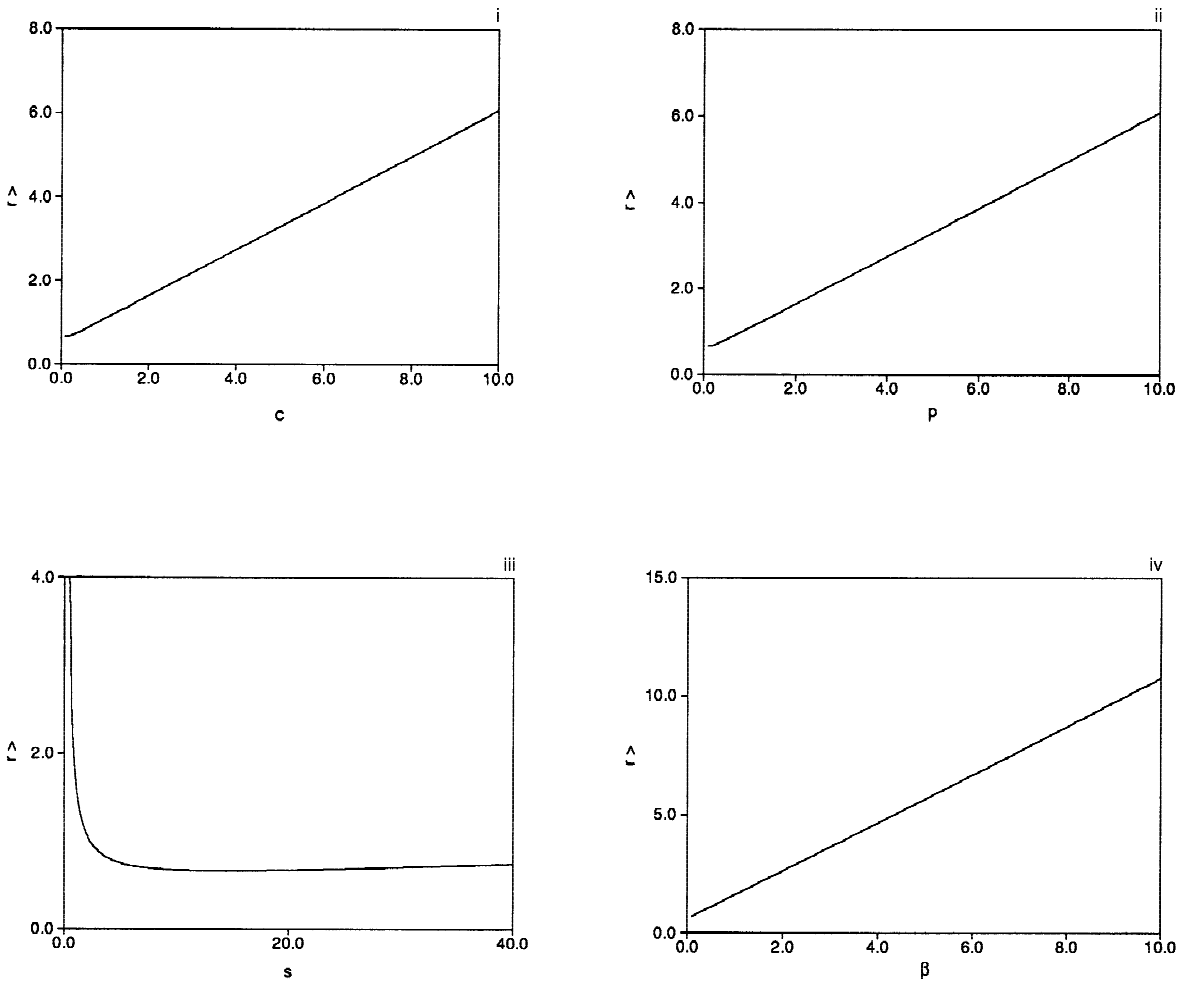

Fig. 4. The condition for extinction versus persistence of uninfected target cells in HTLV-I infection (model 2) depends on viral and immunological parameters. The graphs show the minimum rate of T cell activation (r) required for the persistence of uninfected susceptible target cells in dependence on the rate of CTL proliferation (c), the rate of CTL-mediated lysis (p), the rate of mitotic transmission (s), and the rate of infectious transmission (β). **(i)** An increase in the rate of CTL proliferation increases the chance of uninfected target cells becoming extinct because it reduces the virus load and thus the stimulus for helper-cell activation. **(ii)** The same is true for the effect of CTL-mediated lysis on the persistence of uninfected susceptible target cells. **(iii)** If the immune responsiveness of the host is strong relative to the rate of mitotic transmission, an increase in the rate of mitotic transmission promotes the persistence of uninfected susceptible target cells, since it increases the virus load and thus the stimulus for helper-cell activation. At relatively high rates of mitotic transmission, this effect is reversed: infected cells proliferate faster than uninfected cells and thus outcompete them. **(iv)** A high rate of infectious transmission drives the uninfected susceptible target cells extinct. Baseline parameters were chosen as follows: $k = 10$; $d = 0.1$; $a = 0.2$; $c = 1$; $p = 1$; $b = 0.1$; $\beta = 0.5$; $s = 14$.

susceptible activated host cells, therefore resulting again in a low expected number of mutations. The models have also made the counterintuitive suggestion that the number of mutations generated may be increased by a higher rate of mitotic transmission and decreased by a high rate of infectious transmission. Mitotic transmission has the effect of increasing the number of mutations by increasing the number of susceptible host cells, which would otherwise be relatively low or extinct, because of either a strong CTL response or a high rate of infectious transmission.

The term βxy describes the number of newly infected cells generated during a unit time interval, and the expected number of mutations will be proportional to this measure. However, it is more complicated to extrapolate from this to the rate of viral evolution. While the rate of successive substitutions of advantageous mutations is proportional to βxy, the rate of neutral evolution is proportional to the per capita rate of virus increase, given by βx. Whereas this measure is different and not directly proportional to the virus population size, it is indirectly proportional to the virus population size in our model. This is because the model assumes that target cells are CD4+ T cells and that CD4+ T cells are produced in response to antigen. Hence, the rate of neutral evolution will also be limited by target cell availability at both high and low virus loads. At high loads, the virus population is near carrying capacity, minimizing the number of sus-

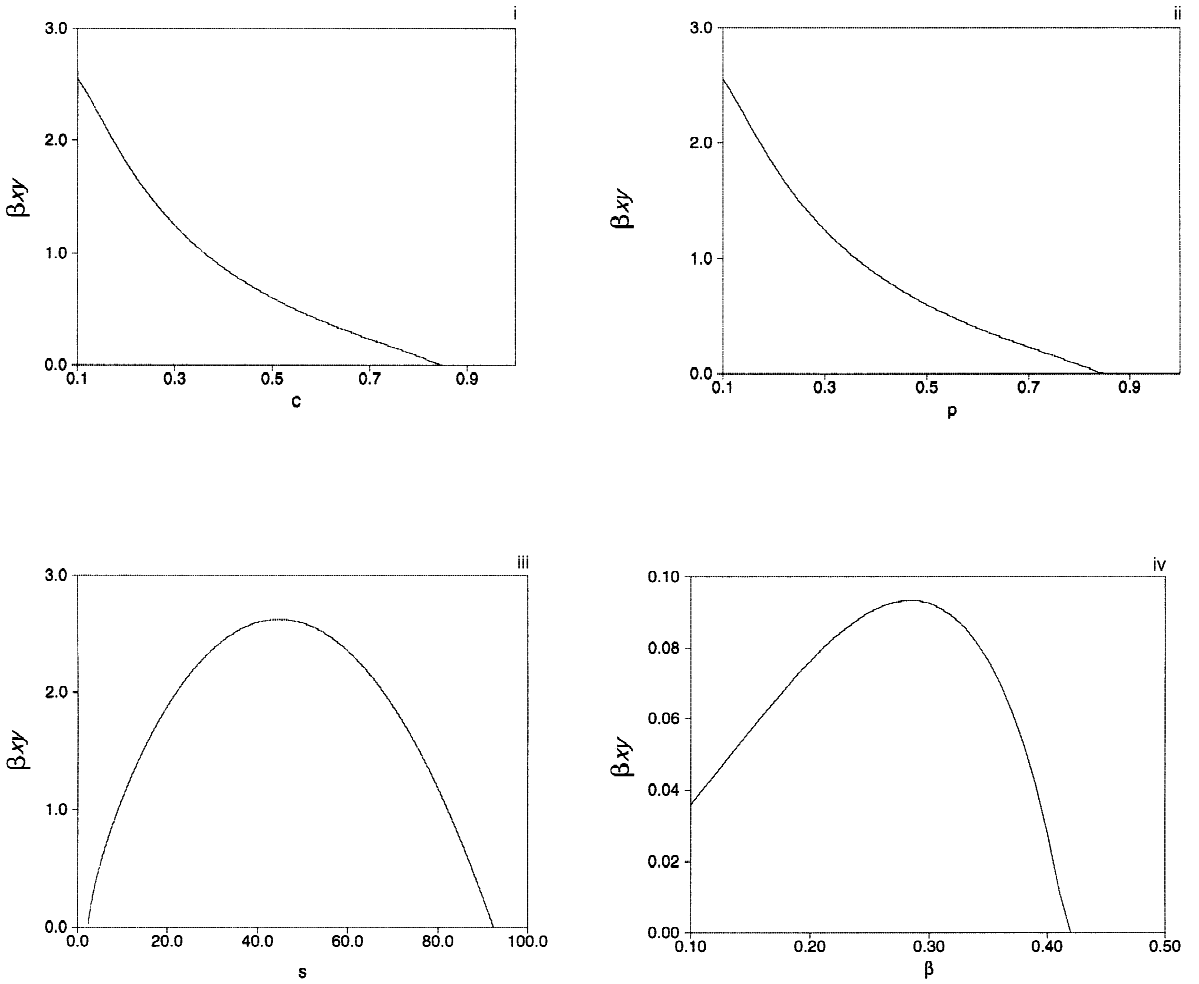

Fig. 5. Dependence of the number of mutations generated per unit time on viral and immune parameters in HTLV-I infection (model 2). We consider the parameter range where uninfected susceptible target cells persist. **(i)** A high rate of CTL proliferation (c) lowers the virus load and thus the availability of susceptible target cells. It therefore reduces the number of mutations generated. **(ii)** The same is true for a high rate of CTL-mediated lysis (p). **(iii)** If the rate of mitotic transmission (s) is low relative to the immune responsiveness of the host, an increase in s increases the virus load and the number of activated target cells and, therefore, increases the number of mutations generated. If the rate of mitotic transmission is relatively high, infected cells compete against uninfected cells, driving the virus load near the carrying capacity, diminishing the availability of susceptible uninfected target cells, and thus reducing the number of mutations generated. **(iv)** A high rate of infectious transmission (β) decreases the number of mutations generated because it reduces the number of activated susceptible target cells, except for very low values of β. Baseline parameters were chosen as follows: $k = 10$; $d = 0.1$; $a = 0.2$; $c = 1$; $p = 1$; $b = 0.1$; $\beta = 0.5$; $s = 2$; $r = 2$.

ceptible target cells. At low loads there is insufficient antigen to produce significant levels of activated, susceptible CD4+ T cells.

Conclusion

The rate of infectious spread of HTLV-I in vivo may be constrained by the lack of susceptible host cells. High immune responders have few activated cells because the viral load is low, while in low immune responders the majority of activated T cells is already infected. As a result, the virus evolves slowly, both in individuals and in the population.

Recent data on HLA gene frequencies in the host (Jeffery et al. 1999) support the idea that CTL surveillance plays an important part in limiting the provirus load of HTLV-I and are consistent with the previous finding that the dominant CTL target antigen of HTLV-I (Tax) is subject to positive selection in healthy carriers (the putative high CTL responders) of the virus (Bangham et al. 1999; Niewiesk and Bangham 1996; Niewiesk et al. 1994).

In contrast to HTLV-I, HIV evolves at a faster rate and attains significantly higher sequence diversity. Similarly to HTLV-I, HIV also infects T helper cells and requires activation and/or proliferation to complete its replication cycle in this cell type. It therefore faces the same difficulties in establishing a persistent infection as HTLV-I. However, while HTLV-I has solved this prob-

lem by strong mitotic spread, HIV has found a different solution. Wodarz et al. (1999a) have shown that the ability to infect antigen-presenting cells, especially macrophages, may raise the basic reproductive ratio of the virus above unity, thus allowing the establishment of a persistent infection. This is because cell activation or proliferation is not required for successful infection of macrophages, since the HIV preintegration complex can enter the nucleus of macrophages by active transport (Bukrinsky et al. 1991, 1992; Heinzinger et al. 1994; Stevenson 1994; Stevenson et al. 1995; Stevenson and Gendelman 1994). These infection dynamics can be analyzed by the basic model of virus infection (Nowak and Bangham 1996). In such a scenario, a strong CTL response reduces the virus load to low levels while increasing the number of uninfected host cells to high levels (Nowak and Bangham 1996). Therefore, in the presence of a strong CTL response, there is strong selection pressure on the virus and the availability of a sufficient number of susceptible host cells allows a high rate of reverse transcription. Consequently the rate of evolution of HIV is high (Nowak et al. 1991, 1995; Nowak and Bangham 1996; Regoes et al. 1998).

To conclude, our models suggest that the difference in the rate of evolution in HTLV-I and HIV-1 is due to the way in which these two retroviruses have overcome the problem of T helper-cell infection: HTLV-I may spread mitotically, resulting in a lack of susceptible host cells and thus in a slow rate of accumulation of sequence changes. In contrast, HIV infects macrophages. Consequently, the number of susceptible host cells is large in the presence of a strong CTL response, and the sequence changes can accumulate rapidly in the virus population.

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