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T-cell induced pathogenesis in HIV: bystander effects and latent infection

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The progress of HIV is accompanied by the infection and decline of the population of CD4+ cells. This reduction in cells results from both cytolytic influences of the virus and virus-specific cytotoxic T-cell (CTL) responses. We seek to characterize the extent of CD4+ reduction caused by HIV-specific CTLs at equilibrium. Here we show that intermediate levels of cytotoxic killing of infected cells can be inferior to both strong and weak or absent immune responses. We further show that the deleterious effects of the CTL response are made worse by a slow immune response. Bystander effects in which uninfected cells are thought to be eliminated by non-specific CTL activation lead to small or negligible reductions in uninfected CD4+ cells. Latently infected cells containing pro-viral DNA and which become activated at a constant rate ensure that the immune response is more effective for a larger range of CTL activities and reduces T-cell associated pathology.

Keywords: apoptosis; HIV; virus evolution; immunopathology; cytopathic virus; mathematical model

1. PATHOGENESIS OF HIV INFECTION

The human immunodeficiency virus (HIV) is now credited as the principal cause of AIDS. The mechanisms by which HIV infection produces cellular pathogenesis remain unresolved but can be understood as either a cytolytic effect of the virus, some form of HIV-induced autoimmunity, T-cell apoptosis following non-specific stimulation ('bystander effects'), HIV-induced dysregulation of cytokines or an immunopathological consequence of cytotoxic T lymphocytes (CTLs). None of these mechanisms can on their own explain AIDS, but form the essential background to more inclusive theories of pathogenesis.

The CD8+ cytotoxic T cells play an important role in the clearance of virus infections (Zinkernagel 1996). CTLs are able to clear virus through a variety of mechanisms including direct lysis of infected cells displaying virus antigen using the perforin–granzyme system, the expression of Fas ligand and its interaction with Fas antigen on infected cells, and through the production of antiviral cytokines (Clark *et al*. 1996). The activation of perforin, mediated by major histocompatibility complex (MHC) class I glycoproteins is thought to be the most significant mechanism *in vivo*.

There is, however, a cost associated with CTL activity, in particular when targeted against non-cytopathic viruses which replicate efficiently in a broad range of cell types. This is because CTLs can induce immunopathology in those tissues and organs susceptible to active infection (Zinkernagel & Hengartner 1994). Two classic examples are infection of mice with lymphocytic choriomeningitis virus (LCMV) and infection of the liver with hepatitis B virus (HBV) (Moskophidis & Zinkernagel 1996).

In LCMV infection an MHC class I-restricted CTL activity causes both elimination of the virus and immunological disease. Exposure of neonates to LCMV leads to the elimination of the LCMV specific CD8+ T cells, allowing the virus to persist throughout life with few deleterious consequences. In the absence of immunological tolerance, LCMV infection can be fatal. For example, when the virus infects nervous tissue this leads to the undesired destruction of infected cells by CD8+ cells in the the choroid plexus and meninges.

Infection with HBV results in a variety of disease states according to time and dose of infection. Most pertinent in relation to this study is that when T cells are absent, virus is not eliminated and there is no destruction of infected cells, allowing the virus to be carried with few adverse consequences. When T-cell response is slow, a chronic, sub-acute or aggressive disease ensues following the destruction of hepatocytes by CD8+ cells (Gaman 1984).

Individuals infected with HIV-1 show a characteristic infection and reduction of CD4+ T cells leading to a generalized immunosuppression correlated with clinical progression to AIDS. As cytopathogenicity is not a characteristic feature of retrovirus infection, some have suggested that CD4+ decline is not produced by the lytic activity of the virus but is an indirect effect of CD8+ cell cytotoxicity as in LCMV and HBV (Zinkernagel & Hengartner 1994). If this is the case, the rate of spread of the virus and the responsiveness of the immune system become the most important determinants of disease pathology.

For the CTL response to significantly reduce the population of CD4+ cells, as is observed in AIDS patients, a large proportion of these cells must be infected with virus. Early estimates ranged from a ratio of productively infected to uninfecteds of 1 in 10^5 in the blood and up to 1 in 10^2 in the lymph system (Embretson *et al*. 1993). More recent studies estimate ratios of 5 in 10^6 in lymph and 7 in 10^7 in blood (Chun *et al*. 1997). These studies do not

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consider the possibility that only a fraction of the CD4+ cells are capable of sustaining active infection, and hence the ratio may be an overestimate of the effective susceptible population size. An alternative possibility is that this estimate conceals spatial variation in infection. Depletion of susceptible cells locally might reduce the population size of uninfected cells to below the population of infected cells. Such local effects might explain why disease ensues while the greater number of cells remain uninfected on average. A third mechanism explored in this study is that of bystander effects. Infected cells undergoing apoptosis release viral gp120 which may bind to uninfected cells. These cells are then treated as infected by the immune system, but lack replicating virus. This can lead to the non-specific activation of CTL and a reduction in uninfected cells.

Here we explore how the immunopathology of CTL response acting on infected cells can lead to a decline in CD4+ cells. The idea is that infected cells are removed by CTL killing where no response would often have been preferable. The effects of this response are worse when at intermediate values and best when absent or very strong. If the virus enters into latent infection, this has the effect of reducing the immunopathology associated with T-cell cytotoxicity. In contrast to cytolytic theories of infection, if immunopathology accounts for disease, then escape mutants could be associated with reduced pathology and an increase in disease latency.

2. VIRUS AND CTL DYNAMICS

In the simplest model we assume a self-regulating CTL response. Here the immune system is activated by foreign antigen and then reaches a constant level independent of both the density of virions and the number of infected cells. We identify four variables: the free virus particles v, uninfected CD4+ cells x, infected CD4+ cells y and CD8+ cells z. We assume that the uninfected cells are produced at a rate λ and die at a rate dx. The equations can be read as: free virus interacts with the uninfected cells to produce infected cells at a rate βxv. Infected cells die at a rate ay, and are killed by CTL at a rate pyz. Free virus buds from the infected cells at a rate ky and enters uninfected cells at a rate βxv. Virus dies at a rate uv. CTLs are produced by precursor cells at a constant rate c and die at a rate bz. We assume that c is positive if $y > 0$, that is if infection is present; otherwise $c = 0$. The model can be written using the following system of ordinary differential equations:

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

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

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

$$\dot{z} = c - bz. \tag{4}$$

The basic reproductive ratio of the virus in the absence of the CTL response is given by

$$R_0 = \frac{\beta\lambda k}{adu}. \tag{5}$$

If $R_0 > 1$ an infection can take place and the immune response will become activated. The ability of the virus to establish a persistent infection depends on its basic reproductive ratio in the presence of the CTL response. This is given by

$$R_\mathrm{I} = \frac{\beta\lambda k}{(a + a')du}, \tag{6}$$

where $a' = cp/b$ is the rate at which infected cells are eliminated by the CTL response at its equilibrium level.

If $R_\mathrm{I} < 1$ the infection can be cleared. In this case the virus will spread into the population initially, but once the immune system is activated each infected cell will, on average, give rise to less than one newly infected cell. This causes the virus population to die out.

If $R_\mathrm{I} > 1$ the infection persists and the equilibrium abundances of cells, virions and CTL are given by an immune-controlled equilibrium,

$$x^* = \frac{(a + a')u}{\beta k}, \tag{7}$$

$$y^* = \frac{\lambda}{a + a'} - \frac{du}{\beta k}, \tag{8}$$

$$v^* = \frac{\lambda k}{(a + a')u} - \frac{d}{\beta}, \tag{9}$$

$$z^* = c/b. \tag{10}$$

In the absence of a CTL response, the system converges to a target-cell controlled equilibrium identical to that above but with $z^* = 0$ and $a' = 0$.

The effects of the CTL response are to (i) reduce the equilibrium abundance of infected cells, (ii) reduce the equilibrium abundance of free virions, and (iii) increase the equilibrium abundance of uninfected cells.

The total number of cells (infected plus uninfected), however, may be increased or reduced by the CTL response. We have

$$x^* + y^* = \frac{au}{\beta k} + \frac{\lambda}{a} - \frac{du}{\beta k}. \tag{11}$$

We can consider the situation where the virus is assumed not to be cytopathic, in which $a = d$, and infected and uninfected cells have the same death rates. Here we find that $x^* + y^* = \lambda/d$. By adding a CTL response we necessarily reduce the total number of infected cells. If we take the case where the virus has the maximum possible cytopathicity, for which $R_0 = 1$, $a = \lambda\beta k/(ud)$, then again $x^* + y^* = \lambda/d$. If the virus has a higher level of cytopathicity, then it is unable to sustain infection. Between these two extremes of cytopathicity, the total number of cells is less than λ/d and a minimum number of cells $(x^* + y^*)$ is obtained at $a = \sqrt{(\lambda\beta k/u)}$.

Thus, if $a > \sqrt{(\lambda\beta k/u)}$ a CTL response will always increase the total number of cells. If, on the other hand, $a < \sqrt{(\lambda\beta k/u)}$ a weak CTL reponse could reduce the total number of cells, while a sufficiently strong immune reponse could increase it. We can express this result more precisely in terms of the strength of the immune response

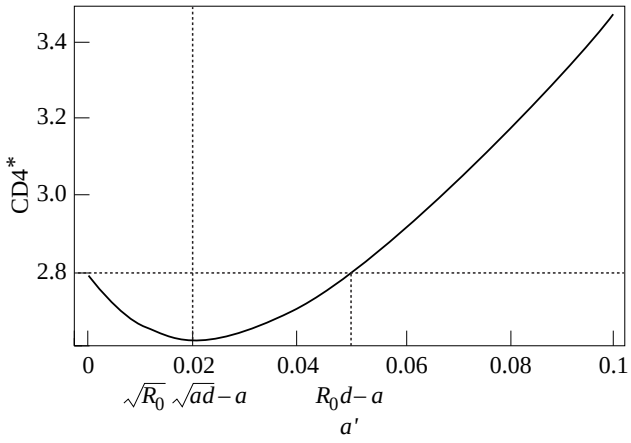

Figure 1. The reduction of CD4+ cells at equilibrium for different rates of CTL killing (a'). There is a minimum in the total number of CD4+ cells for increasing a'. Counterintuitively, it can be better to have no HIV-specific CTL response during infection. The parameter values used to generate this plot are $\lambda = 0.1$, $d = 0.001$, $\beta = 0.05$, $a = 0.05$, $k = 0.01$, $u = 0.01$.

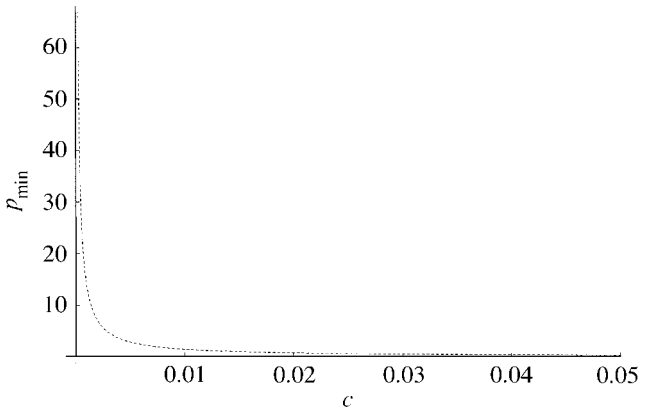

Figure 2. The minimum in total CD4+ cells (p_{min}) as a function of immune responsiveness c. When the immune system is highly reponsive, the minimum falls close to zero which implies that even weak or intermediate strengths of immune response can be worthwhile. The parameter values used to generate this plot are $\lambda = 0.1$, $d = 0.001$, $\beta = 0.05$, $a = 0.05$, $k = 0.01$, $b = 0.1$, $u = 0.01$.

a' (figure 1). The total number of cells is minimized at an intermediate immune activity given by

$$a' = \sqrt{R_0}\sqrt{(ad)} - a. \tag{12}$$

An alternative way of thinking about this result is to compare the total number of cells during infection in the absence of an immune response with the total number assuming an active immune response. One finds that when

$$a' < R_0 d - a, \tag{13}$$

it is better to be without an immune response altogether. Bear in mind that $R_0 d - a$ can be significantly larger than $\sqrt{R_0}\sqrt{(ad)} - a$ (figure 1). This difference is understood as the reduction in infected cells by the immune system from a previously target-cell controlled equilibrium. As this difference becomes larger, the immune system becomes deleterious for a greater range of immune activities.

These results are not merely a consequence of assuming that the CTL response is self-limiting. Let us consider a slightly more complex immune response in which

$$\dot{z} = cy - bz. \tag{14}$$

We assume that CTL is produced at a constant rate and is proportional to the number of infected cells. If we concentrate on the parameter p, which controls the rate of CTL-induced killing, we find that increasing the value of p reduces the total number of cells whenever $p < p_{min}$, where

$$p_{min} = \frac{abdu + 2bk\beta\lambda - ab\sqrt{u}\sqrt{(d^2u + 4k\beta\lambda)}}{2cu\lambda}. \tag{15}$$

The value of p_{min} decreases with increasing values of a. As before, this implies that the range of values over which the immune system is deleterious is reduced as the virus becomes more cytopathic. While this expression is rather complex, we again find an intermediate immune activity leading to the largest reduction in CD4+ cells.

(a) *CTL and immune responsiveness*

The rate at which the host generates a CTL response will be very important in an immunopathological infection, because a fast response will enable the virus to be removed with a minimal loss of cells. Using the more complex immune response term, we plot in figure 2 the relationship between p_{min} and CTL responsiveness c. As the rate of responsiveness increases, the threshold drops. This implies that CTL killing becomes more and more effective as the rate of responsiveness increases. Thus slow responders must mount a more aggressive CTL response against infected cells than fast responders in order to preserve the same equilibrium number of CD4+ cells.

These results can be understood intuitively. A very strong CTL response to infection will eliminate a large proportion of the virus before it invades new cells, while a very weak CTL response will allow previously infected cells to continue living. A low to intermediate response is not sufficiently strong to prevent the virus from spreading, but is strong enough to deplete the population of infected cells. If the immune response is swift, a lower level of CTL activity can be sufficient to preserve a large fraction of CD4+ cells from infection and thereby reduce the total amount of cell death.

In summary, these models tell us that: (i) an HIV-specific CTL response can reduce the total number of CD4+ cells at equilibrium; (ii) there is an intermediate value of cell death activity at which the number of CD4+ cells is minimized; and (iii) a faster rate of response to infection can substantially reduce the amount of cell death required to clear infection.

(b) *Apoptosis data*

There is now abundant evidence that CD4+ cells are killed by apoptosis during HIV infection (Clark *et al.* 1996; Wang *et al.* 1998). In particular, many CD4+ cells die through apoptosis during primary infection and this is associated with an increase in the number of CD8+ cells (Meyaard *et al.* 1992). The level of apoptosis is positively correlated with levels of viral RNA. This means that more cells are recorded as having undergone

apoptosis when viral load is high (Samuelson *et al*. 1997). In general, high numbers of CD8+ cells are associated with low virus titres at equilibrium (Hoffenbach *et al*. 1989) and the removal of CD8+ cells results in an increase in virus load (Brinchmann *et al*. 1990). Evidence also comes from SIV infection. CD4+ cells from SIV-infected African green monkeys do not undergo apoptosis and generally this species does not develop disease. In contrast, apoptosis is observed in CD4+ cells from SIV-infected macaques that do advance to AIDS (Gougeon *et al*. 1993). Patients with very vigorous immune responses tend to have low viral burdens and show a slow disease progression (Feinberg & McLean 1997). At the other extreme, HIV-infected transplant patients immuno-suppressed to reduce the chances of rejection, also progress very slowly towards disease (Schwarz *et al*. 1993). This last result could also reflect a reduced target cell availability (DeBoer & Perelson 1998). Thus it would seem that intermediate strength immune reponses are associated with the worst clinical outcomes as illustrated by the model.

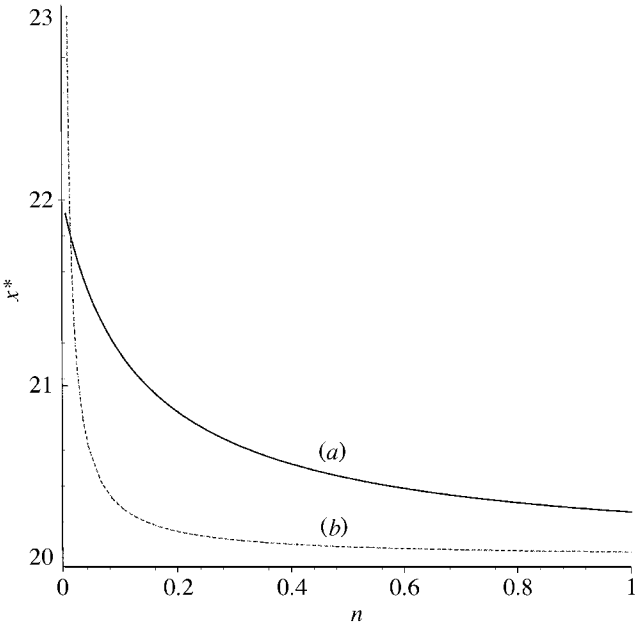

Figure 3. The influence of bystander effects (n) on the steady-state number of uninfected (x) CD4+ cells. The two curves represent two nonlinear immune functional responses: (a) the function $\dot{z} = cy/(k+y) - bz$ includes proliferation and a density dependent rate of replication, while (b) only includes immune proliferation, $\dot{z} = cy - bz$. The parameter values used to generate this plot are $\lambda = 0.5$, $d = 0.01$, $\beta = 0.001$, $a' = 0.1$, $a = 0.005$, $k = 0.05$, $p = 0.1$, $u = 0.01$, $b = 0.01$, $c = 0.001$.

3. BYSTANDER EFFECTS AND THE PARADOX OF CD4+ DEPLETION

In § 1 and § 2 of this paper we introduced the idea that a net reduction in CD4+ requires a large proportion of the total number of CD4+ cells to remain infected at equilibrium. Attempts to assay this proportion tend to produce ratios of $1{:}10^2$–$1{:}10^5$. One explanation provided for how CD4+ cells are destroyed without becoming infected is that they acquire toxic viral proteins from infected cells (Banda *et al*. 1992). If apoptosis occurs primarily in uninfected cells (Gougeon *et al*. 1993), the population of uninfected cells will be observed to decline even though the number of uninfected cells remains larger than the population of infected cells. To address this possibility we have extended the first model to allow uninfected cells to undergo cell death in proportion to the rate of death of infected cells. Thus,

$$\dot{x} = \lambda - dx - \beta vx - na'yx, \tag{16}$$

$$\dot{y} = \beta xv - (a + a')y, \tag{17}$$

$$\dot{v} = ky - uv. \tag{18}$$

If $R_I > 1$ the infection persists and the equilibrium abundances of cells, virions and CTL are given by

$$x^* = \frac{(a + a')u}{\beta k}, \tag{19}$$

$$y^* = \frac{\beta k\lambda - (a + a')du}{(a + a')\beta k + nua'(a + a')}, \tag{20}$$

$$v^* = \frac{k(\beta k\lambda - (a + a')du)}{((a + a')\beta k + nua'(a + a'))u}. \tag{21}$$

The term $na'yx$ describes the rate of destruction of uninfected cells acting via the CTL response on infected cells. This might reflect the influence of toxic viral proteins, such as liberated gp120. Again we find a minimum in the total number of CD4+ cells at equilibrium with respect to a'. Somewhat paradoxically with this choice of constant immune response, we find that bystander effects have no influence on the equilibrium number of uninfected cells. This is because the reduction in uninfected cells is accompanied by a concomitant reduction in the rate of infection. Frost & Michie (1996) have modelled the effect of apoptosis acting only on uninfected CD4+ cells and also find that this need not lead to a reduction in the population of uninfected cells at equilibrium.

In summary, at equilibrium for $R_I > 1$, (i) varying the value of n has no effect on the value of x^*, (ii) increasing n reduces the value of y^*, and (iii) increasing n reduces the viral load v^*.

We should not conclude that bystander effects will always have no effect on the equilibrium population of uninfected CD4+ cells. The results of our simple models can be function dependent—especially in our choice of immune functional response. In the previous model we assumed that the immune response was at steady state and unable to proliferate further CTLs in the presence of infected cells. The choice of alternative functional responses for the CTL which include this capacity, such as $\dot{z} = cy - bz$, or to include some form of density dependence, $\dot{z} = cy/(k+y) - bz$, can however lead to a reduction in the population of uninfected CD4+ cells for increasing values of n, assuming the population of uninfected cells is described by the differential equation $\dot{x} = \lambda - dx - \beta vx - nzyx$.

In figure 3 we plot the steady-state abundance of x^* for these two virus-dependent functional responses. Increasing the value of n reduces the equilibrium value of x^* (while

increasing the amplitude of damped oscillations approaching the equilibrium). While bystander effects can reduce the number of uninfected cells they do not do so by very much and certainly do not produce a reduction approaching an order of magnitude. Significantly from the perspective of biological realism, the reduction in uninfected CD4+ cells is less, all else being equal, assuming a logistic growth in CD8+ cells, than when one allows the population to grow exponentially.

4. THE IMPACT OF LATENTLY INFECTED CELLS

Once in the cell not all virus initiates active virion production. A large proportion of CD4+ cells are latently infected following the integration of pro-viral DNA into the host cell genome. Much of this DNA is not replication competent (Chun *et al*. 1997). Some of this material can remain quiescent for long periods of time before becoming activated (Bagasra & Pomerantz 1993; Embretson *et al*. 1993). Because the expression of viral proteins in these cells is low or absent, we can assume that from the perspective of the CTL response these cells are not infected and by and large evade immune surveillance. What effects are latently infected cells expected to have on T-cell mediated pathology?

We can write down a simple system to allow for the possibility of latent infection. We add a further state variable w which represents the population of latently infected cells. Free virus interacts with the uninfected cells to produce actively infected cells at a rate $f\beta xv$ and latently infected cells at a rate $(1-f)\beta xv$. Latently infected cells die at a rate ew and become actively infected cells at a rate αw.

As with the first model, we assume that the CTL response, once activated, reaches a constant level of productivity at b/c and we let $a' = cp/b$: the rate at which infected cells are eliminated by the CTL response at its equilibrium level. The parameter f is the probabilitiy that upon infection a cell enters directly into productive infection.

$$\dot{x} = \lambda - dx - \beta vx, \tag{22}$$

$$\dot{y} = f\beta xv - ay - pyz + \alpha w, \tag{23}$$

$$\dot{w} = (1-f)\beta xv - ew - \alpha w, \tag{24}$$

$$\dot{v} = ky - uv, \tag{25}$$

$$\dot{z} = c - bz. \tag{26}$$

The equilibrium of this system is given by

$$x^* = \frac{(a+a')u(e+\alpha)}{k(ef+\alpha)\beta}, \tag{27}$$

$$y^* = \frac{\lambda(ef+\alpha)}{(a+a')(e+\alpha)} - \frac{du}{k\beta}, \tag{28}$$

$$w^* = \left(\frac{du(a+a')}{k(ef+\alpha)\beta} - \frac{\lambda}{e+\alpha}\right)(f-1), \tag{29}$$

$$v^* = \frac{\lambda k(ef+\alpha)}{(a+a')(e+\alpha)u} - \frac{d}{\beta}. \tag{30}$$

The basic reproductive ratio of the virus with latent infection is given by

$$R_1^l = \frac{\beta\lambda k}{(a+a')du}\left(f + (1-f)\frac{\alpha}{\alpha+e}\right). \tag{31}$$

Because latently infected cells are not killed by CTLs, they act as a means of facilitating the spread of infection throughout the population of CD4+ cells. Reducing the value of f increases the number of uninfected cells (x^*) and reduces both the number of productively infected cells (y^*) and the virus load (v^*). The effects on the latent cells are more complex because these only increase for decreasing values of f when

$$R_1 > \frac{(e+\alpha)^2}{(ef+\alpha)^2}. \tag{32}$$

Thus the greater the proportion of virus entering into latent infection, the greater the reproductive rate must be to increase the proportion of latently infected cells. How do latently infected cells affect immunopathogenesis? Increasing the CTL killing rate (a') increases the number of uninfected cells (x^*), reduces the number of productively infected cells (y^*), and reduces the virus load (v^*).

As with the previous models, there is an intermediate value of a' at which the total number of cells $(x^* + y^* + w^*)$ is minimized. Considering the extreme cases, when $f = 1$ and $\alpha = 0$ the minimum occurs at

$$a' = \sqrt{R_0}\sqrt{(ad)} - a, \tag{33}$$

which is equivalent to the model with no latently infected cells. When $f = 0$ the minimum occurs when

$$a' = \sqrt{R_0}\sqrt{(ad)}\left(\frac{\alpha}{\alpha+e-d}\right) - a. \tag{34}$$

The value of the minimum is reduced as the virus becomes more cytopathic (increasing the value of a). Furthermore, investing in latently infected cells increases the range of values of a' over which the immune system remains effective. This can be seen from the expressions above by noting that $\alpha/(\alpha+e-d) \leqslant 1$ as $d \leqslant e$. This implies that the minimum is smaller when cells are latently infected.

As with the previous models, we can ask over what range of values of a' the total number of cells in the presense of an immune response remains below that in the absence of an immune response.

For the model with latency, this is given by

$$a' < R_0 d\gamma - a, \tag{35}$$

where

$$\gamma = \frac{(f+\alpha)^2}{(e+\alpha)(e+d(f-1)\alpha)}. \tag{36}$$

Let us consider the extreme cases. When $f = 1$ and $\alpha = 0$ then $\gamma = 1$, this being equivalent to the model with no latently infected cells.

When $f = 0$ which means that all virus starts in latent infection, then $\gamma \leqslant 1$ as $d \leqslant e$. All intermediate values of $0 < f < 1$ lie between the minimimum given by $f = 0$ and the maximum at $\gamma = 1$. Thus the range of activities over which infection with an immune system is worse than no immune system is lower with latently infected cells. Latent infection reduces both the extent of T-cell pathology and reduces the virus load.

We have assumed that all latently infected cells are capable of becoming activated and therefore are able eventually to produce virus. Most latently infected cells harbour defective pro-virus which is never fully expressed (Chun *et al*. 1997). This will ensure that latent infection makes matters even worse for the virus and better for the host. We have only explored that case in which virus remains replication competent.

(a) *Latent infection data*

Attempts to quantify the numbers of latently infected cells tend to produce variable results. Early studies suggested that infected, resting cells account for a significant fraction of the total pool of CD4+ cells (Bagasra & Pomerantz 1993; Embretson *et al*. 1993). More recent studies suggest that the fraction of replication-competent resting pro-virus is around 5 in 10^6 cells in lymph and 7 in 10^7 in blood. This compares with around 224 in 10^6 activated cells (Chun *et al*. 1997). It remains unclear from the data whether latently infected cells were once productive, or whether latent infection reflects acute infection before a productive phase. Some studies show that virus production seems to shut down during the course of infection increasing the number of latently infected cells (Li *et al*. 1996). The mechanisms by which virus enters into the latent state remain uncertain. There is some evidence that this is a consequence of changes in the pattern of pre-mRNA splicing reducing the quantity of polyprotein (Li *et al*. 1996). Alternative hypotheses are that the site of integration is important in determining subsequent expression or that transcription is terminated prematurely (Winslow *et al*. 1993).

5. SUMMARY AND THE IMMUNOPATHOLOGY OF PROGRESSION

Throughout this paper we have considered only the approach to steady-state solutions. With this analysis we found that (i) there is an intermediate CTL activity associated with the largest reduction in CD4+ cells, (ii) reduced responsiveness increases the equilibrium number of infected cells, (iii) bystander effects with a constant immune response cannot explain the discrepancy between the reduction in CD4+ cells and the small numbers of cells actively infected, while bystander effects combined with a nonlinear immune reponse can reduce the uninfected CD4+ cells but not by very much, and (iv) latent infection tends to reduce T-cell mediated immunopathology and virus load assuming no co-infection.

The model is unable to explain disease progression. Progression in chronic infection involves a slow and systematic decline in CD4+ cells and an increase in virus. This is equivalent to a temporal series of shifted steady-state values. Progression has been accounted for in terms of antigenic diversity (Nowak *et al*. 1991), increasing virulence (DeBoer & Boerlijst 1994), and immune exhaustion (Zinkernagel & Hengartner 1994). Most of these theories assume that virus is the direct cause of disease and that error-prone replication of the virus is able to produce large amounts of antigenic diversity and escape mutants. If the virus is not cytopathic, the activity of the immune system becomes the dominant factor in progression. This has two counterintuitive effects: the organism can remain healthier without an HIV-specific immune response and escape mutants can reduce CD4+ pathology by evading the CTL response.

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