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Dynamics of T-cell antagonism: enhanced viral diversity and survival

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In rapidly evolving viruses the detection of virally infected cells can possibly be subverted by the production of altered peptides. These are peptides with single amino acid changes that can dramatically change T-cell responses, e.g. a loss of cytotoxic activity. They are still recognized by the T cell, but the signals required for effector function are only partially delivered. Thus, altered peptide presenting cells can act as decoy targets for specific immune responses. The existence of altered peptides *in vivo* has been demonstrated in hepatitis B and HIV. Using a mathematical model we address the question of how these altered peptides can affect the virus–immune system dynamics, and demonstrate that virus survival is enhanced. If the mutation rate of the virus is sufficient, one observes complex dynamics in which the antagonism acts so as to maintain the viral diversity, possibly leading to the development of a mutually antagonistic network or a continual turnover of escape mutants. In either case the pathogen is able to outrun the immune system. Indeed, sometimes the enhancement is so great that a virus that would normally be cleared by the immune system is able to outrun it.

Keywords: altered peptides; antagonism; decoy targets; virus dynamics; diversity threshold; mathematical modelling

1. INTRODUCTION

The detection of virus infected cells by the presentation of viral peptides on their surface in major histocompatability complex (MHC) class I molecules can be subverted through direct intervention of the virus in the presentation processes (Spriggs 1996). However, the observation that single mutations in the amino acid sequence of presented peptides can dramatically alter the response of cytotoxic T cells suggests that viruses with high mutation rates can evade the immune response by expressing a diverse population of peptides. These so called altered peptides can antagonize T-cell responses *in vitro*, i.e. the presence of the altered peptide reduces the T-cell response to the original peptide (Sette *et al.* 1994). Experiments have shown that this antagonism is not a result of competition for presentation. Altered peptides can also cause partial responses such as cytokine secretion but not proliferation. Such peptides are called partial agonists. The demonstration of altered peptides in hepatitis B and HIV patients (Bertoletti *et al.* 1994; Klenerman *et al.* 1994), and the inhibition of the onset of a model autoimmune disease by altered peptides (Franco *et al.* 1994), support the hypothesis that altered peptides are important in T-cell recognition *in vivo*. To verify that altered peptides can reduce immune system efficiency against a viral pathogen requires an understanding of the way antagonism modifies viral dynamics, and the identification of a distinctive experimental signature. Our study suggests that such an identifying signature is provided by high viral diversity.

The molecular basis of antagonism is understood as an interruption of the sequence of events that occurs on T-cell contact with the target. After initial recognition between the T-cell receptor (TCR) and the MHC-peptide complex, the first step in the interaction is an upregulation of adhesion molecules (Berke 1994). This results in the formation of a conjugate; a pairing between the target cell and the T cell. Serial triggering of TCRs then occurs in which a small number of MHC-peptide molecules switch multiple TCRs (Valitutti *et al.* 1995). The level of TCR occupancy determines the T-cell response, specific cytotoxicity is detected at very low MHC-peptide densities, while increasing levels of occupancy are required for cytokine secretion, calcium fluxes and proliferation (Valitutti *et al.* 1996). The half-life of the MHC-peptide–TCR complex appears to determine whether the peptide acts as an agonist, antagonist or partial agonist. Agonist peptides tend to have half-lives of 1–10 s, while partial agonists and antagonists have shorter half-lives (Valitutti & Lanzavecchia 1997). Models of T-cell selectivity based on kinetic proof reading have been suggested (McKeithan 1995), where the time of TCR–MHC-peptide interaction determines the length of the signalling cascade induced, and thus, peptides with shorter half-lives deliver only partial signals. There is direct experimental evidence of a difference in signals in the case of partial agonists (Sloan-Lancaster & Allen 1996). In contrast, conjugate formation is unaffected by the presence of antagonists (Rüppert *et al.* 1993), which is possibly explained by the observation that the signals determining conjugate formation and those related to cytotoxicity, cytokine secretion and proliferation have distinct molecular pathways (O'Rourke & Mescher 1992). A recent examination of an HIV antagonist peptide demonstrated that the interaction of T cells with the altered peptide had no 'memory', i.e. the T cells

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retained an unimpaired capacity to lyse targets bearing the wild-type peptide after exposure to the antagonist peptide (Sewell *et al*. 1997). This contrasts to partial agonists which can induce a state similar to anergy (Jameson & Bevan 1995).

Extrapolating these ideas to the *in vivo* cytotoxic immune response there are two obvious ways in which antagonism might function. First, protection at a population level could be achieved by different target populations presenting the agonist and antagonist. Conjugate formation of T cells with antagonist presenting cells would explain the observed *in vitro* data (Jameson *et al*. 1993; Klenerman *et al*. 1994), a possibility that is plausible given the different signalling pathways for conjugate formation and effector function (O'Rourke & Mescher 1992). The fact that T cells are less efficient against their specific target population in the presence of antagonist presenting cells can then be explained, because they spend less time in lysing their targets. A similar effect has been observed in the competition of anergized T cells for time with antigen presenting cells (Lombardi *et al*. 1994). Second, individual target cells could be protected from detection by presenting the agonist and antagonist concurrently. This requires proteins containing the agonist and antagonist peptides to originate endogenously in the cytoplasm for presentation on MHC class I molecules (Brodsky & Guagliardi 1991), and thus would require multiple infections or some similar mechanism. We expect the former mechanism based on population heterogeneity to afford stronger protection against the immune system because it acts at a population level and does not rely on rare events such as multiple infections. We model this form of antagonism for the case of cytotoxic T cells and consider whether it can be an efficient evasive strategy against the immune system.

Our approach is to consider the effects of competition between infected cell populations presenting the agonist and those presenting the antagonist. The antagonist presenting targets are decoy targets, a decoy activity analogous to the decoy ligands of molecular biology. The ability to distinguish similar peptides requires more time than dissimilar peptides, e.g. kinetic proof reading (McKeithan 1995), and thus partial agonist and antagonist presenting cells will be effective competitors. Ecological competition is a familiar mechanism and generally leads to competitive exclusion. For instance, competition between viral strains and epitopes leads to dominance by the fittest viral strain (Nowak & May 1992; Nowak *et al*. 1995) and the epitope with the strongest feedback on the immune system, i.e. immunodominance (De Boer & Perelson 1994). Even though these systems can have complex dynamics such as epitope switching (Nowak *et al*. 1995), competitive exclusion holds in some form. By contrast, for antagonism by decoy targets the situation is completely different and competitive exclusion does not operate. Instead, antagonism causes the immune system to efficiently attack numerically dominant strains and select for viral diversity.

2. THE MATHEMATICAL MODEL AND PARAMETER ESTIMATES

We denote the population size of cells infected by viral strain i by C_i, with a specific CD8 immune response involving T cells, $\mathcal{T}_i$. We assume no cross reactivity between strains, effectively defining a strain as a mutant that requires a new CD8 response. We model the T-cell target cell interaction by reactions of the form,

$$\mathcal{T}_i + C_j \underset{\beta_{ij}}{\overset{\alpha_{ij}}{\rightleftharpoons}} D_{ij} \xrightarrow{k\delta_{ij}} (1+\rho)\mathcal{T}_i.$$

A T-cell $\mathcal{T}_i$ (specificity i) forms a conjugate D_{ij} with a cell presenting (and infected by) viral strain j. The rate of formation of conjugates D_{ij} is proportional to the size of both populations,with a rate constant α_{ij} dependent on the T-cell specificity i and viral strain j. In the case of a correct pairing, D_{ii}, the target is destroyed at a rate k releasing the T cell ($\delta_{ij} = 1$ if $i = j$, zero otherwise). In the case of a T cell adhered to a target presenting the antagonist, we assume that the T cell and target separate after failure of effector signal transduction, releasing the T cell to find a new target (here $\beta_{ij} = \beta$ if $i \neq j$, i.e. independent of i and j, and $\beta_{ii} = \gamma \ll \beta$). Registering the failure of this signal and the subsequent separation is not an instantaneous process. As a system of ordinary differential equations we have,

$$\begin{aligned}
\dot{\mathcal{T}}_i &= (k(1+\rho) + \gamma - \beta)D_{ii} + \sum_j [\beta D_{ij} - \alpha_{ij}\mathcal{T}_i C_j],\\
\dot{C}_j &= rC_j + (\gamma - \beta)D_{jj} + \sum_i [(\beta + r)D_{ij} - \alpha_{ij}\mathcal{T}_i C_j],\\
\dot{D}_{ij} &= \alpha_{ij}\mathcal{T}_i C_j - \beta D_{ij} - (k - \beta + \gamma)D_{ii}\delta_{ij}. \qquad (1)
\end{aligned}$$

The biological processes included in our model are discussed in turn below, with emphasis on justification and estimation of parameter values.

(a) *T-cell proliferation*

The rate of division of the T-cell population and the rate of T-cell effector function, i.e. the destruction of targets, are both dependent on the presence of antigen(Cohen *et al*. 1992). These processes can be separated at a molecular level and the signalling is hierarchical, i.e. the proliferation of T cells requires high levels of TCR occupancy (Valitutti *et al*. 1996), while CD8 cells can destroy targets that are presenting only a few MHC-peptide molecules. Proliferation is also regulated by cytokine and CD4 help. However, these fine details do not need to be included since the behaviour of the population as a whole governs the immune response. We assume that T-cell responses to specific targets are all similar and neither cytotoxic or proliferative signals are delivered with an antagonist presenting target. Therefore, at a population level, T-cell proliferation and cytotoxicity are correlated, an assumption that is supported experimentally by the observation that the phenotype of the effector and precursor cells (cells able to proliferate)are both circulating (low L-selectin expression), and (as yet) indistinguishable during the acute infection phase (Razvi *et al*. 1995). Replication is parameterized by the parameter ρ, set to $1/24$ in the simulations, where T-cell replication requires ρ^{-1} targets to be destroyed on average, i.e. most conjugates formed by a particular T cell are with targets that express insufficient MHC-peptide to stimulate replication, but for one in every ρ^{-1} interactions there is sufficient expression of TCR and MHC-peptide to deliver the proliferation

signal. The maximum growth of the T-cell population is achieved if agonist presenting targets are in excess when the doubling time approaches $\ln 2(k\rho)^{-1}$, set to 8 h in the simulations.

(b) *Viral growth*

Virally infected cells are assumed to give rise to new infected cells at an average rate r, which may depend on the strain. This models the complex process of releasing virions which must then survive antibody and complement clearance, attach to a host cell of the correct trophism through the molecular receptor, and take over the host synthesis machinery for replication of the viral genome. We are able to simplify this process because it is not directly involved in the antagonism mechanism under study. In the absence of antagonism, the immune response against a given viral strain eventually controls and eliminates that strain provided $k\rho > r$, i.e. the immune system replication rate exceeds the reinfection rate of the virus. This suggests co-operation between the humoral and cellular immune responses, the former reducing the reinfection rate sufficiently that the cytotoxic response can be effective. We exploit this to create a relatively high viral load in the start-up phase of the simulation (first peak in figure 1), after which the viral growth rate is $0.4\,\mathrm{d}^{-1}$, a typical value for HBV turnover of infected cells (Nowak *et al*. 1996).

(c) *Break-up kinetics of conjugates formed with antagonist targets*

For antagonism to be effective as a defence against the immune system, the targets presenting the antagonist must be effective competitors for T cells. In particular, the rate at which T cells return to the circulating pool after conjugating to a target presenting the antagonist must be of the same order as that for an agonist T-cell coupling. Unfortunately, an estimate for this rate is unavailable at present, although the *in vitro* experiments of Jameson *et al*. (1993) suggest that the half-life of the agonist conjugate is less than 20 times that of the antagonist conjugate, while the absence of observable stable conjugates with antagonist presenting cells indicates that these conjugates break up faster than their agonist analogues (Rüppert *et al*. 1993). For CD8 cells, the lysis/apoptosis of the target is performed on a time-scale of 30 min (Yannelli *et al*. 1986). We assume that decoupling from a target presenting the antagonist takes, on average, 5 min i.e. six times faster than destroying and decoupling from an agonist. Our value for this rate comes from the observation that conjugate formation with an agonist presenting target leads to a rearrangement of the Golgi apparatus and microtubule-organizing centre (MTOC) (Podack & Kupfer 1991; Yannelli *et al*. 1986), a process that is complete in about 5 min. Thus the absence of the signals for this rearrangement could clearly be registered within this time-scale. As the release rate from an antagonist presenting cell is increased the effect of antagonism is reduced.

In a high density mixture of targets presenting the agonist or antagonist peptides, actual surface areas of contact should be modelled since conjugates consisting of multiple targets and T cells would form. Thus, our assumptions are expected to be realistic provided that the number of infected cells is much smaller than the carrying capacity of the infected tissue. We assume this is the case, which also avoids any complications due to saturation. For instance, in hepatitis, the infected cells C_i are located in the liver where there are approximately 10^{11} hepatocytes, the carrying capacity of the tissue. Under these assumptions the infection is expected to increase exponentially.

(d) *Frequency of antagonist peptides*

It remains to specify the dependence of the rate constant α_{ij} on the specificity i and viral strain j. We assume that two randomly selected strains are an agonist/antagonist pair with probability p. Estimates for p come from altered peptide studies (Jameson *et al*. 1993), where 40% of altered peptides at the TCR contact sites were observed to display antagonism, although a proportion also acted as partial agonists. We assume a value of $p = 0.2$ to allow for possible effects of mutations at other sites, such as changes in MHC binding and processing. Further, we assume that the rate of conjugate formation with a target is independent of whether the target is presenting the agonist or the antagonist. Thus the rate of coupling $\alpha_{ii} = \alpha$, $\alpha_{ij} = \alpha A_{ij}$, $i \neq j$, where $A_{ij} = 1$, $(i \neq j)$ with probability p and zero otherwise. We call the matrix A the antagonism matrix. More general forms of A are expected to give similar results, since the essential property is that the viral population separates, for a given strain, into a population of strong antagonists and a population of weak/non antagonists.

(e) *Generation of mutants*

In our model the infection persists through production of escape mutants. Mutations are treated stochastically, i.e. each infected cell gives rise to an infected cell, infected by a mutant, with probability μr per unit time. For a viral strain i, the expected number of mutants produced throughout its lifetime is $\nu_i = \mu \int_{t_0}^{\infty} dt C_i(t)$, where t_0 is the time when i appeared. The integral is finite since each strain has a finite lifetime, the specific immune response eventually controlling each strain (provided $k\rho > r$ and viral runaway has not occurred, see below). The number of mutants produced by strain i is Poisson distributed with mean ν_i. Figure 2*b* plots the variation of ν with the (maximum) immune system replication rate $k\rho$. As the immune system replication rate decreases the virus attains a higher load, which increases the number of mutants produced. In the absence of antagonism all values of ν_i are equal with a value of 0.44 in the simulations ($k\rho = 2\,\mathrm{d}^{-1}$). For $\nu < 1$ the virus eventually dies out with a probability of 1. We consider the effects of antagonism on a virus that would normally be cleared and ask whether antagonism can cause viral persistence. In this case the infection persists if the virus population develops sufficient antagonism so that each strain produces (on average) more than one escape mutant. This can then lead to uncontrolled exponential growth of certain viral strains.

3. RESULTS

A typical trajectory is shown in figure 1. The pattern of the time series contains some characteristic features. In particular, alternating periods of exponential growth and decay of the viral load occur. The periods of decay are terminated by the exponential growth of new escape

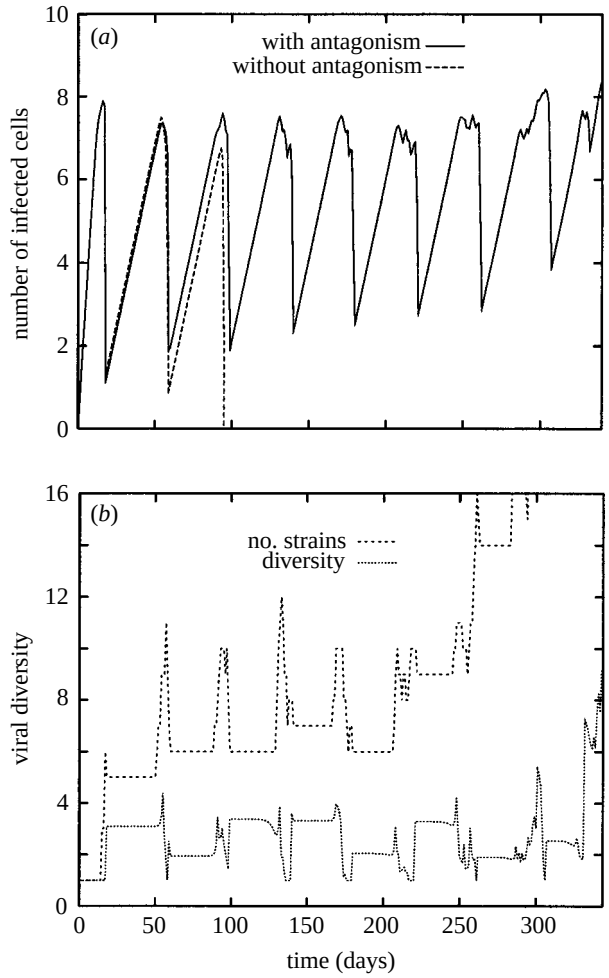

Figure 1. (*a*) Typical trajectories with and without antagonism (logs). (*b*) A plot of the number of active strains and the viral diversity $D_{\max}$ for the trajectory with antagonism. Rapid changes in these quantities correspond to the times of numerical dominance of a strain, and its subsequent removal by the immune system. Our simulations use $p = 0.2$, $r = 0.4$ d^{-1}, $k = 48$ d^{-1}, $\alpha = 5 \times 10^{-5}$ d^{-1} cell^{-1}, $k\rho = 2$ d^{-1}, $\beta_{ij} = 300$ d^{-1} cell^{-1}, $i \neq j$, $\beta_{ii} = 4$ d^{-1} cell^{-1}, and $\mu = 2 \times 10^{-8}$.

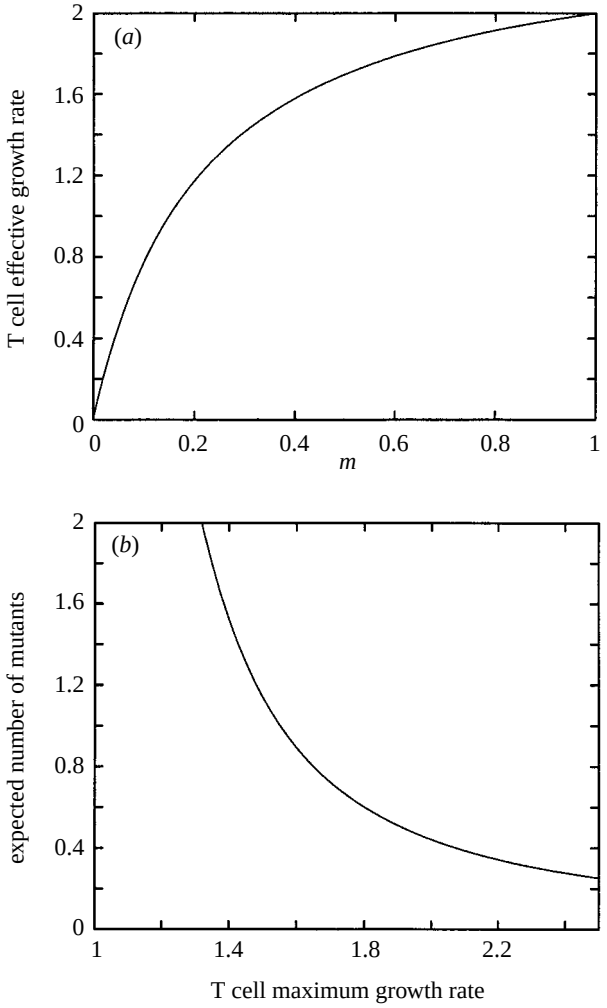

Figure 2. (*a*) The approximate growth rate $e_{ff}(m)k\rho$ of a specific T-cell strain, as a function of the detectability m_i of the corresponding viral strain. (*b*) The expected number of mutants, ν, versus the T-cell growth rate for a given strain, in the absence of antagonism. The figure plots the variation of ν with the maximum immune system replication rate, $k\rho$. Other parameters are identical to those in figure 1. The corresponding behaviour for specific responses in the simulation of figure 1 will be similar as a function of the T-cell effective growth rate.

mutants. The approximate periodicity is due to mutants appearing in (short) time intervals around each peak when the number of infected cells is highest. The periodicity decays over time due to the loss of coherence by stochastic effects. In our treatment mutations and antagonistic interactions (through the matrix A_{ij}) are treated stochastically. A complete stochastic simulation (including small number effects) is not expected to differ significantly from this model.

Antagonism reduces the efficiency of specific immune responses in two ways, first through reducing cytotoxic responses and second by reducing replication signals received by the T cells. The degree of antagonism is measured by the detectability m_i of the viral strain to which it is specific, defined as the ratio

$$m_i = \frac{C_i}{C_i + \sum_j A_{ij} C_j}. \qquad (2)$$

This is the probability that on formation of a conjugate the specific T cell has adhered to a target presenting the agonist. Under conditions of excess antigen presenting cells, the cytotoxic efficiency and replication rate of T cells, $\mathcal{T}_i$, are reduced in our model by the same factor since an assumed proportion, ρ, of conjugations that destroy targets give rise to replication. The efficiency of these processes is given by (see figure 2*a*),

$$e_{ff}(m_i) \sim \frac{m_i \beta}{k + m_i(\beta - k)} \leqslant 1. \qquad (3)$$

This formula can be understood by considering the time delay (β^{-1}) caused by pairing with an antagonist presenting cell. There is a probability $1 - m_i$ per conjugation of pairing to an antagonist target and incurring this delay. The average time to destroy a target increases from k^{-1} to $k^{-1} + \sum_r r\beta^{-1} m_i (1 - m_i)^r = k^{-1} + (1 - m_i) m_i^{-1} \beta^{-1}$, where the summation is over the number of possible incorrect pairings prior to conjugate formation to a correct

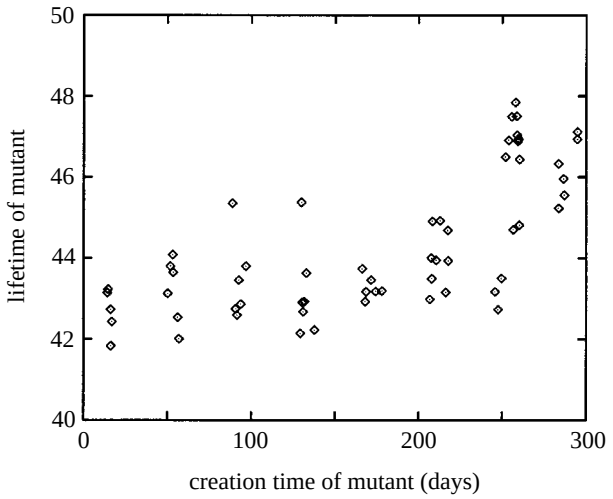

Figure 3. The lifetime of the viral strains in the simulation of figure 1, plotted against their time of appearance. All escape mutants created after 296 days have lifetimes in excess of 48 days, surviving until the end of the simulation. In the absence of antagonism the lifetime is 39 days. Antagonism increases the length of both the growth and elimination phases of the viral strains through reducing the immune system efficiency. Antagonism also makes it difficult to eliminate a strain even through the immune system has it under control. These strains may later expand again if sufficiently antagonized.

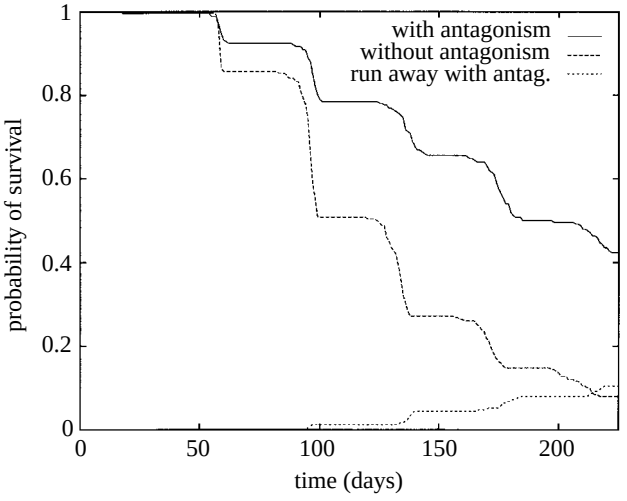

Figure 4. Comparison of survival probabilities over time for a virus with and without antagonism, based on a Monte-Carlo calculation of 250 simulations. The probability of attaining a load of 10^8 cells is also shown, a load where the rate of new escape mutants appearing is sufficient that clearance is improbable. These infections continue to turnover an increasing number of escape mutants until an antagonistic network is produced that allows viral runaway. After 220 days, in the absence of antagonism, over 90% of patients have cleared the virus, and the remaining infected patients will eventually clear the virus. In the presence of antagonism, 40% of patients have not cleared the virus, and over 10% have a viral load that is impossible to clear.

target. The formula now follows. For a 50% reduction in replication and cytotoxicity the detectability must fall to $m_i = k/(k+\beta)$. Comparing to the *in vitro* data, a 20 : 1 ratio of decoys to targets produces a 50%reduction in specific lysis (Jameson & Bevan 1995). This suggests $\beta/k < 20$ since in these experiments the time to locate targets is not insignificant relative to the time to destroy a target as assumed by the above formula (targets in excess).

The increase in the lifetime of the viral strains over the course of the simulation demonstrates the gradual loss of immune system efficiency, figure 3. The number of mutants per strain is also increased over time, a decrease in immune efficiency producing a pronounced increase in the probability of producing escape mutants, figure 2*b*. For persistence, antagonism must achieve a 25% reduction in immune system efficiency, i.e. m is approximately 0.3, so that each strain produces one escape mutant on average, figure 2*b*. The number of strains required to achieve this value is about ten for the simulations of figure 1 (using m approximately $1/1+(N-1)p$, for N strains of equal load). The simulation in figure 1 displays a change in behaviour when the number of strains approaches this value, the viral load and the number of strains increasing more rapidly after this time. Thus, antagonism can increase the expected number of escape mutants per strain in excess of 1, leading to persistence through a continual turnover of strains. Trajectories that do not obtain sufficient antagonism in their viral population are cleared. The probability of the viral infection surviving for a given length of time is shown in figure 4.

Viral strains that numerically dominate are not protected by antagonism and the immune system is more effective against these strains than other antagonistically protected strains. Therefore antagonism selects for high diversity and the fastest growing strains only dominate for a limited period. This diversity-induced protection can result in the production of a mutually antagonistic network of viral strains, where the immune system is antagonized to such a degree against each strain of the network that it can no longer contain the virus which grows without bound. The strains in the network multiply exponentially, and the diversity remains high. This is in contrast to the HIV models of Nowak & May (1992) where the system is eventually dominated by the single fastest growing strain. Thus antagonism prevents competitive exclusion operating. Even if the strains have different rates of infecting susceptible cells (r_i depends on i), the selection against numerically dominant viral strains maintains diversity and mutually antagonistic networks still develop. However, these networks cannot retain coherence indefinitely, i.e. the fact that the viral strains of the network have different replication rates ultimately destabilizes the network, and there is a slow turnover of runaway strains in the antagonistic network.

The existence of the mutually antagonistic network can be understood as follows. For a mixture of N strains there are $N-1$ independent detectabilities m_i, i.e. by varying the viral populations' C_i we are unable to reduce the immune response against all of the strains concurrently. However there is a minimum value m^* (dependent on the antagonism matrix A_{ij}) such that for specified frequency ratios all strains are equally protected, i.e. the detectabilities are all equal $m_i = m^*$. The minimum, m^*, decreases as the antagonism matrix acquires more internal links, i.e. each strain protects an increasing number of other strains. This becomes more probable as the number of strains, N, increases. In analogy to the single strain case

the virus network is controlled if the T-cell effective growth rate is greater than the infection rate of the virus, i.e. $e_{ff}(m^*)k\rho > r$. Thus, high levels of antagonism can lead to a failure in meeting this condition and the network exhibits runaway with the viral strains increasing exponentially, without bound, at rate r. Under conditions of random generation of mutants, viral runaway requires a sufficient number of strains to be present such that the probability of producing a network capable of runaway is sufficiently high. Thus, as the number of strains increases through continual turnover of escape mutants, a network will eventually be established that can outrun the immune system. This growth will be limited by effects not included in this model, e.g. liver capacity, death of host, etc. A threshold criteria can be derived based on the following diversity index,

$$D_{\max} = (\max_i f_i)^{-1}, \tag{4}$$

where f_i are the partial fractions of each strain, $f_i = C_i/C_{\text{tot}} \times D_{\max}$ is the effective number of strains if each had a density equal to the most common. Viral runaway is possible only if the diversity satisfies the following threshold condition,

$$D_{\max} > \frac{1}{m_c}, \text{ where } m_c \text{ is determined by } e_{ff}(m_c)k\rho = r. \tag{5}$$

(This condition is valid for general antagonistic matrices satisfying $A_{ij} \leqslant 1$.) This is a necessary condition, but is not sufficient, i.e. satisfying this condition does not guarantee that the virus outruns the immune system.

The previous analysis focuses on the reduction of the proliferation rate of the T cells, which can lead to a set of viral strains outrunning the immune system. However, conjugation of T cells with decoy targets has two effects, a reduction in the time spent by specific T cells in destroying their targets (and also reducing proliferative signals), and the removal of targets from surveillance by forming conjugates with T cells that cannot destroy those cells. These effects are important in delaying the detection of new strains. The relative importance of this delay and the ability to outrun the immune response are dependent on the T-cell replicative dynamics. Simulations (not shown) with models incorporating dedicated precursor and effector subsets indicate that decoy activity can be as effective in these models, although runaway of an antagonistic network requires higher viral diversity, an effect balanced by an increased susceptibility to delay in mounting an immune response. This type of structure is relevant to an initial naïve cell activation and proliferation phase. The ability to elicit different responses from T cells (homogeneously as a population) by varying the TCR occupancy (Valitutti *et al*. 1996), suggests that a dedicated proliferative subset is transient. However, as we have indicated, such variations in the exact nature of the T-cell dynamics cannot remove the detrimental effects of decoy activity.

Separation of the effects of antagonism on cytotoxicity and T-cell proliferation is also relevant in extending this work to partial agonists. In HIV antagonist peptides can act as partial agonists and stimulate replication of wild-type T cells, although not as efficiently as the wild-type peptide (Klenerman *et al*. 1995). These peptide antagonists still decoy the T cells from lysing their specific targets, but the replication rate of the T cells is not reduced as effectively as assumed here. However, such a viral strain would enhance the growth of a protective set of T cells concomitantly with the specific T cells. This reduces the efficiency of the immune system even against numerically dominant strains. Thus, partial agonists will not exhibit such strong selective pressure for viral diversity as pure antagonists, although diversity will still enhance their survival.

4. DISCUSSION

The antagonist activity exhibited by altered peptides can be separated into antagonism of signals at an individual cell level, and antagonism of population responses through decoy activity. The former is characterized as an antagonism of cellular signals under the coincident presentation of agonist and antagonist peptides on the same target cell. The latter is a result of the competition for T-cell time between the true targets presenting the agonist and decoy non-lysable targets presenting the antagonist peptide. The resulting loss in efficiency of the T-cell response through this decoy activity will be common to all altered peptides, i.e. even partial agonists will reduce T-cell efficiency by reducing the time spent in forming conjugates with agonist presenting cells where optimal proliferative and cytotoxic signals are delivered. The immune response to a rapidly evolving virus could involve both forms of antagonism, in addition to complexities such as cross reactivities, multiple epitopes and other viral defence mechanisms (Spriggs 1996). However, we have demonstrated that provided the kinetics of breakup of conjugates with antagonists is on the scale of minutes, then population antagonism by decoy activity can be significant, and will form a background on which these other effects operate. In particular there is

(i) Enhanced viral survival.

(ii) Progressive loss of immune system efficiency.

(iii) Selection for viral diversity.

(iv) No competitive exclusion.

As the viral diversity increases, the protection afforded the virus by decoy activity is increased which suggests viral diversity as a signature for systems where this decoy activity is important.

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