HIV escape: there and back again

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HIV mutates to avoid the pressure of the immune system. This process is balanced by the need of the virus to replicate efficiently. Two studies examine this dynamic as the virus infects new hosts (pages 275–281 and 282–289).

HIV is a moving target. The virus replicates rapidly and has a high mutation rate creating highly diverse 'quasispecies'. These quasispecies are fertile substrates for darwinian selective pressures favoring the best-adapted, most 'fit' genetic variants. Efforts to develop effective treatments and vaccines must overcome the complex evolutionary dynamics in HIV-infected individuals and within affected populations.

As HIV spreads from individual to individual, genetically diverse viruses confront the most highly polymorphic gene family in humans—that encoding the human leukocyte antigen (HLA) class I and II proteins. These proteins determine which specific peptide sequences (epitopes) are presented to and recognized by host $CD8^+$ and $CD4^+$ T cells, respectively. In the confrontation between genetically diverse HIV variants and genetically diverse human hosts, viral variants can be selected that harbor mutations in specific viral epitopes that escape recognition by host immune effector cells. This process, in which replicating HIV quasispecies adapt in response to selective pressures exerted by host virus-specific immune responses, has been best studied in the case of HIV-specific cytotoxic T lymphocytes (CTLs), which recognize and kill virus-infected cells.

In this issue, two reports examine the forces governing selection of CTL escape variants within individuals, and the ability of these variants to persist upon secondary transmission[1,2]. These reports provide informative examples of how relative viral fitness costs associated with different CTL escape mutations can influence which variants emerge in infected individuals, and which are transmitted to and persist within new hosts. The results frame fundamental questions that need to be resolved as the AIDS pandemic expands and as vaccine development efforts strive to stop it.

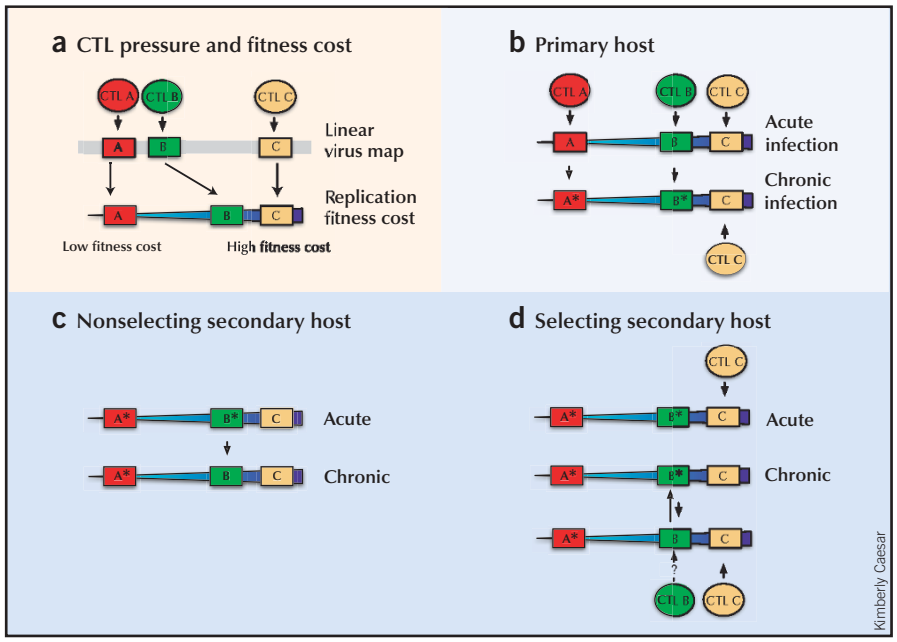

Figure 1 Balancing selection pressure against fitness cost. (**a**) Targeting of multiple epitopes by cytotoxic T lymphocytes (CTLs). In some cases, CTL responses may positively select for mutant viruses containing sequences within these epitopes that are no longer recognized by the CTL[9]. Each selected mutation will carry a potential replicative fitness cost. (**b**) A primary host capable of making CTL responses to epitopes A, B and C. The fitness landscape changes and mutants are positively selected, even at the cost of reduced viral fitness (though some mutations, as in epitope C, may be incompatible with replication). (**c**) The selected mutants are returned to a nonselecting environment, such as a host that does not share HLA alleles with the donor. Reversion will depend on where the mutation lies along the fitness continuum. (**d**) Transmission of selected mutants to a host that shares HLA alleles with the donor. Not only do the neutral mutations remain fixed (such as epitope A), but the mutations associated with a significant replicative fitness cost (such as epitope B) also fail to revert. This strongly suggests that 'selecting secondary hosts' mount an effective CTL response specific for the wild-type epitope B, although such responses have thus far eluded detection.

Given the difficulties in eliciting antibody responses that effectively neutralize HIV, efforts to develop an effective vaccine have focused on the induction of cellular immune responses (especially $CD8^+$ T cells) to HIV antigens[3]. Although vaccine-elicited CTL responses are unlikely to prevent infection outright, they will hopefully control HIV replication, slow the progression to AIDS and decrease secondary transmission.

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This hope has been tempered by recent studies that have suggested that, with time and successive transmission events, CTL escape mutations may become fixed in circulating HIV quasispecies in response to selective pressure from CTL responses restricted by the most prevalent HLA alleles[4,5]. If these inferences are correct, HIV populations may evolve to become increasingly 'invisible' to the CTL responses restricted by the HLA alleles that predominate in a given human population—making HIV vaccine immunogen selection an even more complicated process than currently appreciated[6]. For such population-level outcomes to occur, however, CTL escape variants would need to persist and be favored as the virus is transmitted from one person to another.

Escape from the epitope-specific CTL responses generated by an infected person is not universal. Indeed, many epitope-encoding sequences persist in replicating virus populations, even in the face of strong specific $CD8^+$ T-cell responses[7]. The reasons why some epitopes targeted by CTLs give rise to escape mutations, while others do not, are not completely understood. In some cases, structural constraints on key viral functions make certain potential escape mutations incompatible with virus replication. However, for these and other, less constrained, epitopes, CTLs may persist but be functionally impaired. The consequences of CTL escape and dysfunction help explain why there is no clear association between the level of HIV antigen–specific $CD8^+$ T cells and control of viremia[8].

Mutations at epitopes targeted by different CTL responses can arise with widely varying kinetics[9]. Rapidly emerging variants are likely to face a low 'genetic barrier' (requiring only one or a few nucleotide changes) and carry a low fitness cost. In contrast, mutations arising later are likely to carry a higher fitness cost and must overcome higher genetic barriers, requiring additional compensatory mutations, to enable appreciable viral replication (**Fig. 1a**).

Mutations with a relatively low fitness cost are expected to revert slowly or not at all upon transfer to a second host, even if the new host does not share the same restricting HLA allele as the original host (**Fig. 1b–d**). In this way, escape mutations can propagate throughout a population[4,5,10], as has also been observed for influenza A (ref. 11). The fate, upon transmission, of escape mutations with high fitness costs is more complicated, and reversion may not occur if the new host shares the relevant HLA class I allele (and CTL response to the parental epitope) with the virus donor.

Leslie *et al.*[1] focused on a specific CTL epitope in the HIV-1 Gag protein[1]. This epitope is restricted by two related HLA alleles, *HLA-B57* and *HLA-B*5801*, both of which are associated with delayed progression of HIV disease[12]. The authors found that the majority of *B57*-positive or *B*5801*-positive HIV-infected individuals select for CTL escape variants in this Gag epitope. Notably, the authors also observed that the *gag* mutation that enabled CTL escape reverted to wild type after transmission to individuals with HLA class I alleles other than *B57* and *B*5801*. In contrast, a second mutation within the same epitope did not revert after transmission to HLA-unrelated hosts.

These data indicate that relative fitness costs can influence the selection for and reversion of CTL escape variants in HIV-infected individuals. They also show that the ability of CTL escape variants to disseminate within human populations is complex, involving the magnitude of selection pressure exerted by specific CTLs, the fitness costs associated with CTL escape mutations, and the relative probability that the emergent escape variants will be transmitted to individuals who share the relevant restricting HLA class I alleles.

Friedrich *et al.*[2] explored CTL escape mutant fitness and persistence after transmission of SIV in experimentally infected rhesus macaques[2]. The authors focused on three well-characterized epitopes (one each in Gag, Tat and Nef) that are restricted by defined macaque MHC class I alleles. The kinetics of selection for CTL escape variants in these epitopes had been defined previously, with mutations arising in the Tat epitope early in infection, in the Nef epitope somewhat later, and in the Gag epitope less readily and only after prolonged infection.

Friedrich *et al.* found that an SIV variant engineered to include all three CTL escape mutations replicated less well than the wild-type virus in tissue culture. However, despite the significant fitness impairment observed *ex vivo*, the engineered virus remained stable after infecting macaques expressing restricting MHC class I alleles. In contrast, the Gag and Nef epitopes reverted to wild-type sequences within weeks after infection of MHC class I–mismatched macaques, whereas the Tat epitope did not revert. These data indicate that the Tat escape variants carry little, if any, fitness cost, whereas the specific Gag and Nef mutations do carry such a burden. In the absence of a relevant immune response, the revertants outcompete the sluggish escape variants.

Not surprisingly, both studies document similar phenomena, as evolutionary theory predicts that some CTL epitopes will revert and others will not, depending on relative fitness and the magnitude of selective pressure. The data are also in line with the dynamics of HIV evolution in response to antiretroviral drug treatment. We now appreciate how considerations of drug potency, genetic barriers and fitness costs influence the emergence of drug-resistant HIV variants. With these insights, the effectiveness of antiretroviral therapy has improved substantially[13]. HIV replication can now be durably controlled using rational combinations of drugs that individually do not appear very promising, but collectively can modulate the outgrowth of viral variants with reduced susceptibility to antiviral drugs.

Just as we have learned to juggle combinations of antiretroviral drugs, we must similarly learn to define the most effective array of immunogens in a vaccine. The ultimate goal is to produce HIV vaccines that elicit immune responses that contain virus replication as effectively as contemporary antiretroviral therapies. These new studies of CTL escape help illuminate the opportunities and challenges that lie ahead, as AIDS vaccine efforts strive to overcome the extraordinary diversity of HIV and its complex interactions with the human immune system.

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