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Double Trouble: HIV Latency and CTL Escape

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Abstract

HIV can enter a state of latency that allows it to persist for decades in antiretroviral drug-treated patients. In a recent *Nature* paper, Deng et al. (2015) show that this latent reservoir also contains a large number of cytotoxic T lymphocyte escape mutants, presenting another challenge to HIV cure efforts.

Two prominent features of HIV infection are its capacity to generate latent virus and its ability evade the immune system by rapidly mutating. A recent study by Deng and coworkers has demonstrated that these two characteristics are inter-connected and that the latent reservoir is heavily populated by viral genomes encoding cytotoxic T lymphocyte (CTL) escape mutations (Deng et al., 2015). Here, we discuss this important study and its implications for efforts to eradicate HIV from infected individuals.

HIV infects CD4+ T cells, and the continuous destruction of these cells over years leads to a weakened immune system and to the development of AIDS. High levels of HIV replication occur throughout infection, generating billions of new infected cells and free virions each day, which are cleared by a fierce immune response that includes HIV-specific CD8+ CTLs. This intense selection pressure against the virus leads to the selected outgrowth of viral CTL escape variants, which are mutated in commonly targeted CTL epitopes (Borrow et al., 1997).

Antiretroviral therapy (ART) inhibits HIV replication and prevents disease progression, but does not eliminate the virus completely from infected patients, primarily because of the presence of latently infected resting CD4+ T cells (Chun et al., 1997; Finzi et al., 1999). Latently infected cells harbor HIV DNA within their chromosomes but express little or no viral RNA and no viral proteins, rendering them beyond the reach of ART and essentially invisible to the immune system. However, these cells can produce infectious virus if they become stimulated; thus, they can rekindle virus replication if a patient discontinues ART. Different methods for depleting the latent reservoir have been proposed (reviewed in Marsden and Zack, 2013), but one strategy that is being vigorously investigated is an

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activation-elimination approach in which the host cell is induced to express viral proteins, allowing it to ideally be killed by viral cytopathic effects or by the host immune response. Various exogenous stimuli are currently being tested in efforts to safely and effectively activate latent HIV, but some of these induce only low levels of virus expression, which might not be sufficient to kill the host cell without a robust and effective immune response or other therapeutic intervention (Marsden and Zack, 2013; Shan et al., 2012).

In the study by Deng et al. (2015), the authors compared HIV sequences from resting CD4+ T cells in patients that were treated with ART during the acute phase of infection (within 3 months of HIV infection) with those obtained from patients who initiated therapy later during the chronic phase of infection. This analysis revealed that known CTL escape variants are rare in acute phase-treated patients, but in contrast, nearly 100% of the sequences from patients treated during the chronic phase harbored CTL escape mutations (Figure 1). Defective HIV genomes tend to accumulate in CD4+ cells over the course of infection, meaning that most HIV DNA present in resting CD4+ T cells is defective rather than latent (Ho et al., 2013). Interestingly, the authors also demonstrated that in contrast to what is seen in individuals treated early in infection, replication-competent HIV induced from latently infected cells from patients treated in the chronic phase also bear a large number of CTL resistance mutations. These data suggest that unless ART is initiated very early in the course of infection, the latent reservoir becomes populated almost exclusively with variants resistant to dominant CTL responses.

The presence of immunodominant CTL escape mutations in some HIV epitopes does not mean that other CTLs within the patients that are specific for alternative epitopes are incapable of effectively clearing virally infected cells. Therefore, the authors investigated whether broad peptide stimulation of CTLs from patients treated in the chronic phase of infection would allow the CTLs to kill cells infected with autologous HIV derived from the latent reservoir. Stimulation of the CTLs with any one of several mixtures of peptides corresponding to individual HIV proteins resulted in improved killing of HIV-infected cells. This was further investigated to show that only the CTLs targeting different unmutated (wild-type) epitopes, rather than CTL-escaped epitopes, efficiently eliminate autologous infected CD4+ T cells. Hence, these patients retain CTL clones that can effectively target unmutated HIV CTL epitopes if the CTLs are stimulated with the appropriate peptide (Figure 1).

To validate that CTLs targeting unmutated HIV epitopes can kill HIV-infected cells in vivo, the authors utilized a humanized mouse model. In this model, a newly generated immunodeficient mouse strain termed MIS$^{(KI)}$TRG was used as a recipient for patient-derived hematopoietic stem cells, which differentiated and expanded to form a human immune system within the mice. Autologous virus from the latent reservoir of the same patient was then injected into the mice. After the infection was established, autologous CTLs that had been stimulated with specific antigens were adoptively transferred into the mice. In mice that received control CTLs or CTLs stimulated with a peptide corresponding to an escaped epitope, the viral loads continued to increase; however, in mice receiving CTL pre-stimulated with peptides corresponding to other non-mutated, wild-type epitopes, viral loads

were substantially reduced. Thus, CTL clones targeting these unmutated epitopes were also effective at suppressing virus replication in vivo.

This study has several important implications for our understanding of latent HIV and efforts to eliminate the latent reservoir. The fact that early initiation of ART prevents the accumulation of CTL escape mutant viruses in the latent HIV reservoir provides another justification for starting ART early to treat HIV infection. This is in addition to the already understood benefits of early treatment, which include reducing the latent reservoir size and minimizing HIV-induced immune system damage (Ananworanich et al., 2012). This study also suggests that efforts directed toward stimulating a broader CTL response might be necessary to kill cells induced to express latent virus. The use of therapeutic vaccination strategies, genetically engineered CTLs that are pre-programmed with T cell receptors specific for these alternative HIV epitopes, anti-HIV envelope immunotoxins (Brooks et al., 2003), or broadly neutralizing antibodies (Halper-Stromberg et al., 2014) might also prove useful in this regard.

Finally, the fact that the new CTL-resistant viruses largely replaced the wild-type virus in the latent reservoir is of great interest and indicates that the latent reservoir is more malleable than previously appreciated, at least in the early stages of infection. This suggests that the reservoir could be substantially depleted if the natural rate of elimination of latently infected cells in untreated infection could be maintained while preventing new formation of latency with ART. This is essentially the goal of activation-elimination approaches and the focus of much current research.

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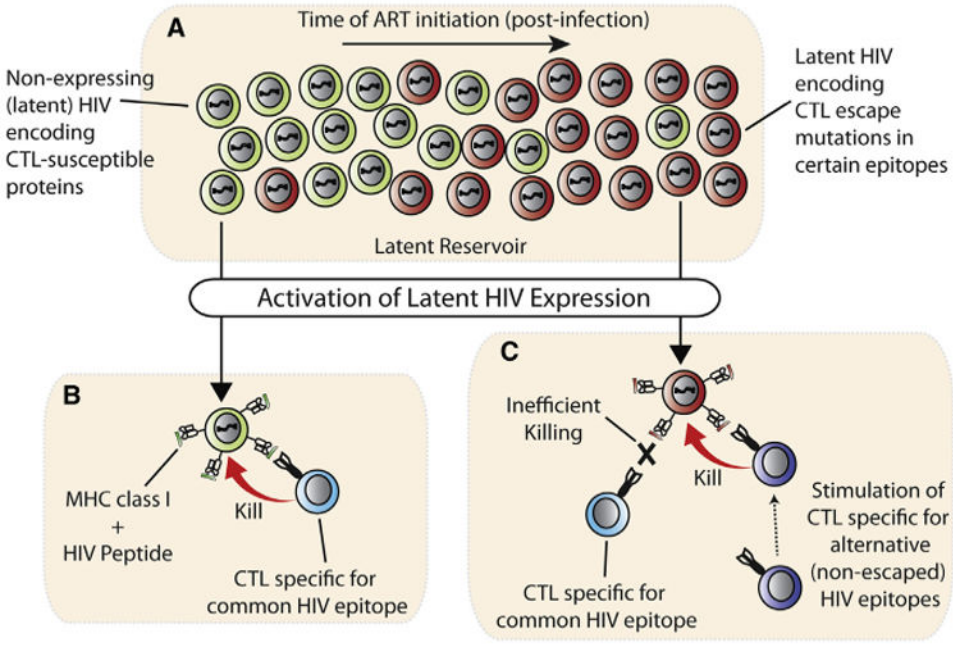

Figure 1. CTL Escape Mutant Viruses in the Latent HIV Reservoir

(A) Soon after HIV transmission, latently infected CD4+ T cells contain HIV genomes encoding primarily CTL-susceptible epitopes (green cells). However, these are replaced over time with viruses encoding CTL escape mutations (red cells). Early initiation of antiretroviral therapy (ART) can prevent this accumulation of resistant viruses.

(B) Upon expression of latent HIV, cells from patients that initiated ART early are susceptible to killing by CTL specific for wild-type immunodominant HIV epitopes.

(C) HIV variants isolated from individuals treated later in infection (>3 months post-infection) are resistant to killing by many CTLs that target common epitopes. Yet, these cells can still be killed by appropriately stimulated CTLs specific for other non-mutated epitopes. Hence, elimination of the latent reservoir may require both activation of latent virus expression and the stimulation of a broad CTL response.