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HIV

Seeking ultimate victory

HIV variants that have mutated to escape T-cell immune responses dominate the latent viral reservoir in most patients on antiretroviral therapy. This finding will need to guide therapeutic approaches targeting reactivated virus.

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In the ancient treatise *The Art of War*[1], Sun Tzu advises would-be victorious generals to "know thy enemy". Perhaps nowhere in medicine is this admonition more apt than in the effort to cure HIV infection. Although both physicians and patients would enthusiastically welcome a simple, virus-directed therapy that could safely and efficiently purge HIV from the body, the biological obstacles to HIV cure — either viral eradication or complete, sustained, off-treatment remission — are too many and too complex to permit such a straightforward approach[2,3]. A paper by Deng *et al.*[4] published on *Nature*'s website today contributes to the effort to defeat HIV by rigorously documenting one of these obstacles to cure, while at the same time pointing to a possible strategy to overcome this particular enemy strength.

Although combination antiretroviral therapy (cART) is highly effective at suppressing active HIV replication, these drugs do not target the reservoirs of latent (non-replicating) HIV that are established in infected CD4$^+$ memory T cells (a type of immune cell) early in infection and maintained over the lifetime of an individual[2,3]. These latently infected cells, which do not express viral proteins and are thus invisible to surveillance by the host's immune system, remain a source of virus that can reignite progressive infection when cART is stopped.

Drugs have been identified that can induce viral expression from latently infected cells *in vitro*, and possibly *in vivo*, and although overcoming latency remains a challenge, it looks increasingly likely that such agents will be improved to the point at which viral reactivation can be substantially accelerated[5,6]. However, contrary to initial hopes, cells with reactivated virus do not invariably die as a result of cell-lytic viral replication, but instead may survive and possibly even proliferate[7], indicating that eliminating such cells is an important therapeutic goal. The obvious solution to this problem is to co-opt the host immune system, particularly the ability of CD8$^+$ T cells (also called cytotoxic T lymphocytes, or CTLs) to recognize and kill infected cells that exhibit any HIV-gene expression. But even here, perhaps not surprisingly, the virus seems to retain the upper hand, by using its capacity for extensive genetic variation and rapid evolution to evade CTLs, through a process known as mutational escape[8].

Deng and colleagues addressed the key question of whether reactivated latent virus is recognized by an infected individual's HIV-specific T cells. The answer, at least in individuals started on cART more than three months after infection (chronic-phase cART), was daunting: more than 98% of HIV integrated into the patients' latently infected CD4$^+$ T cells contained sequence changes in regions (epitopes) of the viral Gag protein (the primary target of effective CTL responses) corresponding to previously characterized CTL-escape mutants (Fig. 1a). The researchers confirmed that these Gag mutations conferred functional immune escape by demonstrating that CD8$^+$ T cells from some of the patients given chronic-phase cART recognized the wild type, but not the mutant, forms of the relevant Gag epitopes. They also verified that the mutant sequences were present in replication-competent virus derived from the chronic-phase cART patients' latently infected CD4$^+$ T cells, indicating that mutant virus could contribute to viral re-emergence if cART were stopped.

By contrast, the authors observed that, in

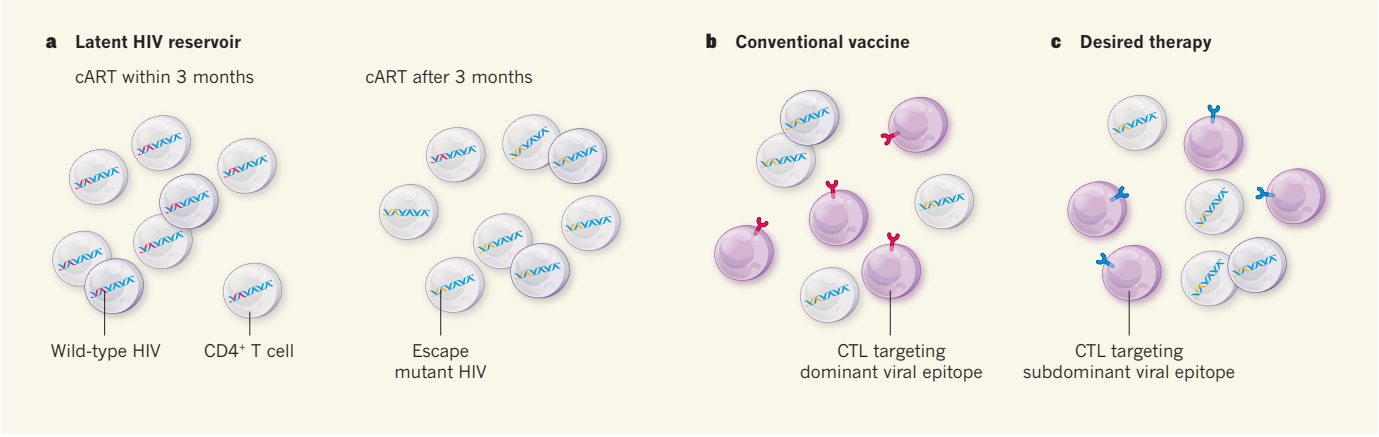

Figure 1 | Immune escape complicates targeting of the HIV reservoir. **a**, A reservoir of CD4$^+$ T cells containing latent (non-replicating) viruses is established soon after infection with HIV. Deng *et al.*[4] show that, in patients who have commenced combined antiretroviral therapy (cART) within three months of infection, most of these latent viruses have wild-type sequences at the regions encoding the viral structures towards which the CD8$^+$ cytotoxic T cells (CTLs) of the host immune system are predominantly directed (dominant viral epitopes; red). However, in patients starting cART later than this, more than 98% of the viruses have already mutated these sequences to 'escape' the immune response (dominant-epitope escape mutants; orange). Viral sequences encoding structures towards which little CTL activity is directed (subdominant viral epitopes) are shown in blue. **b**, The findings suggest that, in patients who start cART after three months, conventional vaccines will be ineffective in combating viruses reactivated from this reservoir, because such vaccines primarily mobilize CTLs that target the wild-type dominant viral epitopes. **c**, Instead, vaccines will need to be designed that mobilize CTLs targeting subdominant (non-mutated) viral epitopes and that may thus be able to kill cells harbouring reactivated latent virus.

patients who began cART within the first three months after HIV infection, the latent virus was of predominantly wild-type sequence (Fig. 1a). Intriguingly, these findings suggest that the latent HIV reservoir in untreated subjects is more dynamic than was previously thought. Of greater clinical importance is the implication that the conventional CTL responses against dominant HIV epitopes (which arise during the early phase of HIV infection and help to determine the level of viral replication during the chronic phase) will almost certainly not contribute to destroying reactivated latently infected cells (Fig. 1b). As such, these conventional CTL responses cannot be expected to supply the cell killing required for effective cure, even if the response is boosted by therapeutic vaccination using conventional vaccines — at least for the vast majority of HIV-infected individuals who are started on cART during chronic infection.

But the news from Deng and colleagues is not all bad. The investigators also found that chronically infected patients on cART retain $CD8^+$ T cells that are specific for subdominant, non-mutated Gag epitopes, and show that these cells can recognize and even kill cells infected with mutated virus *in vitro* and *in vivo* (in a humanized mouse model). The 'rub' with these data is that the efficiency of this cell killing seems to depend on *in vitro* preactivation of the $CD8^+$ T cells, and Deng *et al.* provide no evidence that these broadly targeted $CD8^+$ T cells can be directly recruited *in vivo* to clear cells harbouring reactivating virus in cART-suppressed infections.

However, the data are important for their clear indication that exploiting CTL responses in attempts to cure infection will require approaches that induce $CD8^+$ T-cell responses to subdominant epitopes (Fig. 1c) or to epitopes that are not naturally targeted at all during the course of HIV infection, as has been described for SIV infections in rhesus macaques[9]. Even these approaches will need to surmount yet more hurdles, including the presence of residual virus in immune-privileged 'sanctuary' sites, such as B-cell follicles[10].

Sun Tzu also advises generals to "avoid what is strong, and strike at what is weak". For curing HIV infections, this advice would translate to the identification and therapeutic targeting of HIV's weaknesses, and suggests that understanding barriers to cure and defining the biology underlying these barriers are the first steps towards overcoming this viral enemy. HIV cure will almost certainly require a multimodal therapeutic approach incorporating both pharmacological activation of latent reservoirs and immune-mediated clearance mechanisms, with each component designed to exploit one of this formidable enemy's few weaknesses. ■

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