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Neutralizing the HIV Reservoir

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Abstract

Halper-Stromberg et al. use a humanized mouse model to demonstrate that broadly neutralizing antibodies, when administered with a combination of HIV latency activators, can reduce persistent HIV reservoirs, as measured by plasma virus rebound. Their results support the use of broadly neutralizing antibodies in HIV-reservoir-purging strategies.

Human immunodeficiency virus (HIV) infection causes devastating damage to the host immune system, culminating in the development of acquired immunodeficiency syndrome (AIDS). Antiretroviral therapy (ART) can inhibit HIV replication, suppress HIV plasma viral loads to undetectable levels, and prevent disease progression. Yet ART alone is not curative. Instead, HIV persists in rare cellular reservoirs within treated individuals, allowing virus to rapidly re-emerge if therapy is stopped (Marsden and Zack, 2013). Several cellular reservoirs might contribute to the maintenance of HIV during ART, but the largest and best understood consists of latently infected memory CD4+ T cells (Chun et al., 1997;Finzi et al., 1999;Wong et al., 1997). These long-lived cells harbor integrated, nonexpressing HIV proviruses within their chromosomes, and in this latent state the virus is not susceptible to immune effector mechanisms or antiretroviral drugs. However, if the host cell becomes stimulated, the latent virus can be awakened to produce new infectious virions. Latently infected cells can persist for decades in infected individuals even during effective ART (Finzi et al., 1999). Therefore, if an HIV cure is to be achieved, methods will have to be developed to eliminate the latent reservoir. In this issue of *Cell*, Halper-Stromberg et al. provide a proof of concept that it is possible to target the HIV reservoir (Halper-Stromberg et al., 2014).

A key requirement for testing methods intended to eliminate persistent HIV reservoirs is the availability of relevant small animal models for HIV latency. Humanized mice have served as models for HIV infection and pathogenesis for more than 25 years (Namikawa et al., 1988). In these models, introduction of human cells into immunodeficient mice allows the

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generation of a human immune system, complete with CD4+ cells susceptible to infection with HIV (Figure 1). Humanized mouse models have continuously been refined to provide more comprehensive and authentic immune reconstitution. Using these advanced approaches, it is now possible to infect mice with HIV, treat them with antiretroviral drugs, and show that HIV latency is formed in multiple tissues, providing a tractable system for testing HIV reservoir purging strategies (Choudhary et al., 2012;Denton et al., 2012;Marsden et al., 2012).

Utilizing a humanized mouse model, Halper-Stromberg et al. show that broadly neutralizing anti-HIV antibodies (bNAbs) can be used to influence the formation and maintenance of persistent HIV reservoirs (Halper-Stromberg et al., 2014). These bNAbs bind to the viral envelope glycoprotein spikes present on the surface of the virus particle and infected cells and are capable of neutralizing a diverse range of HIV strains. The authors first demonstrate that bNAbs can be used for postexposure prophylaxis if administered soon after primary infection. They show that, when a mixture of three bNAbs is introduced in multiple doses beginning at day 4 post infection, the majority of recipient mice do not show a subsequent rebound in plasma viremia. This is important because HIV has likely already gone through several replication cycles by this time point, and treatment with ART at this stage is not usually sufficient to prevent the establishment of a persistent infection. The improved efficacy of bNAbs in this context is likely because antibodies function very differently from ART. Antibodies interact with the broader immune response in a variety of ways, including through antibody-dependent cell-mediated cytotoxicity, formation of immune complexes leading to improved clearance, and direct inhibition of virion infectivity/cell-cell virus transfer by neutralization. The authors further show that this effect is greatly reduced in mice receiving antibodies that are missing their Fc portions, suggesting that Fc receptors are involved in the process.

Nonetheless, when bNAbs were administered at 2–3 weeks post infection, after persistent reservoirs are already established, viral loads are suppressed to undetectable levels but eventually rebound as antibody concentrations wane, suggesting that underlying viral reservoirs remain. One potential strategy for purging latent HIV reservoirs is to induce virus expression, which might allow killing of the host cell by viral cytopathic effects or by the immune response against the virus. This is sometimes referred to as an “activation-elimination” or “kick and kill” approach to reservoir purging and would ideally be performed under continuous ART to prevent newly expressed virus from spreading to additional host cells. This approach could be augmented by the inclusion of agents that can recognize and specifically kill the newly expressing cells, such as anti-HIV Env immunotoxins or genetically engineered HIV-specific cytotoxic T lymphocytes (Marsden and Zack, 2013).

To try to flush out virus from persistent reservoirs, the authors then tested several latency-reversing agents (LRAs) individually along with the antibody therapy, including the histone deacetylase inhibitor vorinostat, the BET bromodomain protein inhibitor I-BET 151, and the immune modulatory anti-CTLA4 antibody. These individual LRAs do not significantly affect rebound. However, when all three LRAs are administered together in conjunction with the bNAbs, a significant reduction in the number of mice showing plasma virus

rebound is achieved. It therefore appears that the combination of latency-reversing agents is able to upregulate HIV expression in reservoir cells to a sufficient level for them to be eliminated by the bNAbs (Figure 1). The “reservoir cells” in this case may be truly latently infected cells expressing no viral proteins or persistently infected cells expressing viral proteins below the threshold needed for clearance by bNAbs. Therefore, in this system, the bNAbs appear to function in place of ART to suppress viral loads and inhibit virus spread from latently infected cells following activation, and also as agents that aid in the clearance of productively infected cells and free virions induced by efficient virus reactivation.

This study shows the potential for using bNAbs for HIV reservoir clearance. The observation that a reduction in plasma virus rebound only occurs when a combination of different LRAs is used reinforces a growing appreciation in the field that synergistic activation achieved by multiple activating agents that operate via different pathways is likely to provide more complete and robust virus activation in vivo than individual agents used in isolation. As better activators of latent virus are identified, the reservoir clearance achieved with this type of approach might be further improved. More generally, this study provides an important proof of concept that HIV reservoirs can be impacted in a relevant in vivo system using activation-elimination approaches, which can in turn produce the clinically relevant outcome of a delay in viral rebound. These data also strengthen the case for the inclusion of anti-HIV antibody approaches such as passive immunization, therapeutic vaccination to elicit B cell responses, or gene therapy using vectors encoding broadly neutralizing antibodies (Balazs et al., 2012) in future HIV cure strategies.

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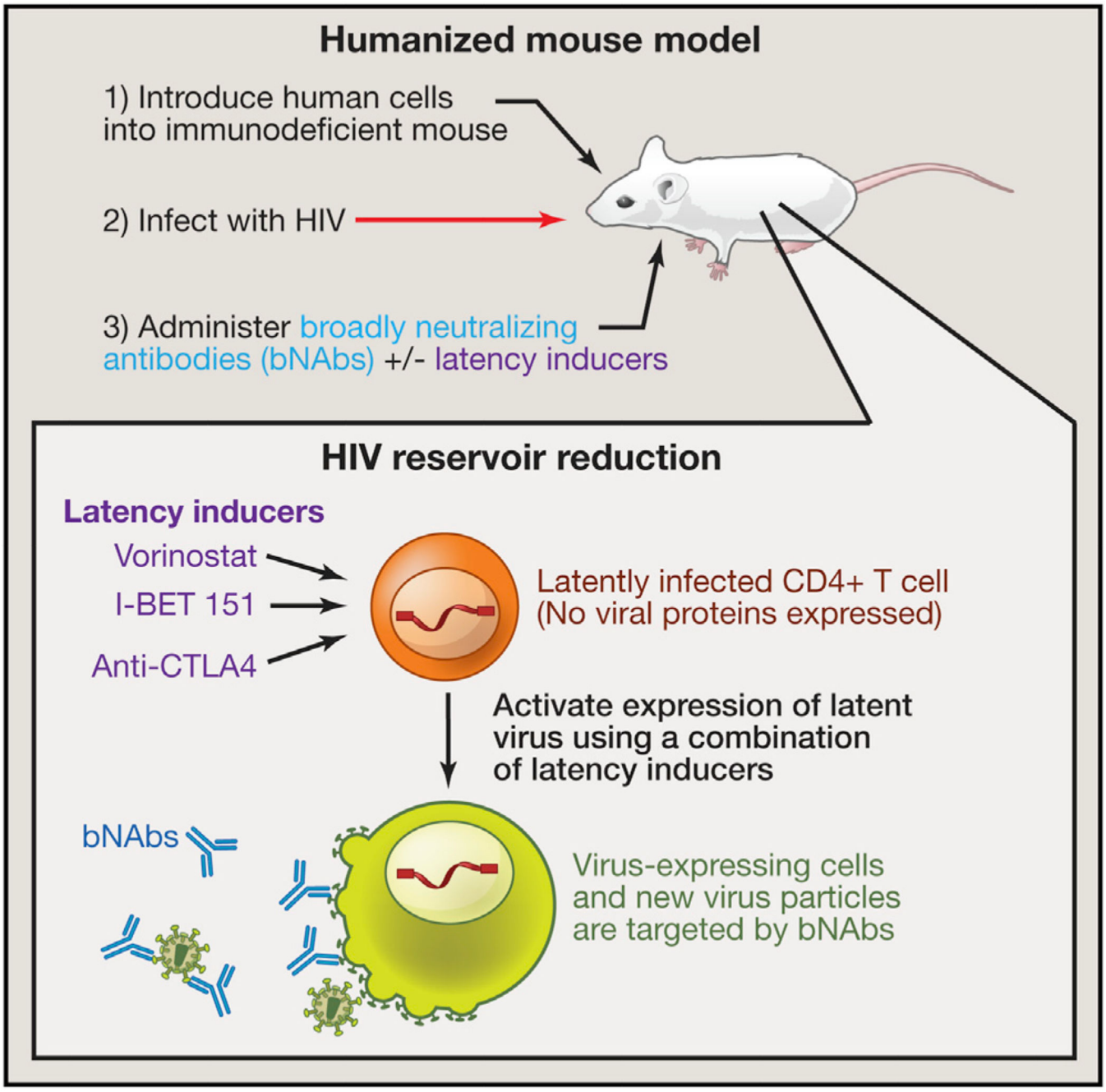

Figure 1.
HIV Reservoir Reduction in Humanized Mice Using Latency Activators and bNAbs