MedicalXpress

Towards elimination of HIV reservoirs

November 5 2015

Current antiretroviral therapy can keep HIV in check and prevent AIDS in the vast majority of treated patients. However, as it is unable to eliminate viral reservoirs and cure the infection, patients need to stay on the life-long treatment, and deal with the potential side effects of drugs and chronic inflammation due to low-level viral infection. A study published on November 5th in *PLOS Pathogens* reports that engineered molecules that target both killer T cells and HIV-infected cells that contain viral envelope protein (Env) can induce killing of the HIV-infected cells and further reduce the levels of detectable HIV expression in blood cells taken from HIV-positive patients on antiretroviral therapy.

The proposed "kick and kill" strategy to eliminate HIV combines pharmacologic activation of latent HIV expression to make infected cells visible to the immune system with subsequent immune-mediated killing. Working on the "kill" step, a team of researchers led by Scott Koenig from MacroGenics in Rockville, USA, and Tomas Cihlar from Gilead Sciences in Foster City, USA, designed and evaluated so-called Dual-Affinity Re-Targeting (DART) bispecific molecules. The molecules have two arms: the first binds specifically to the HIV Env protein, and the second one to CD3, a molecule found on cytotoxic (or killer) T cells. In contrast to using a kill-strategy that is based on HIV-specific killer T cells, the DART CD3-binding arm can potentially recruit and activate any kind of killer T cell, thereby mounting a much broader attack on the Env-expressing target cells.

Based on six different anti-Env antibodies, the researchers generated a set of DART molecules and tested them in a mix of resting CD4 T cells

isolated from donors and infected with wild-type HIV isolates and unstimulated CD8 T cells from the same individuals. As opposed to dividing cell lines or mitogen-stimulated latency models, the researchers argue that these cells may better approximate the resting state and corresponding low levels of surface Env expressed on reservoir cells from HIV-infected individuals on antiretroviral therapy. They found that DART-mediated co-engagement of HIV-infected CD4 target and CD8 effector cells results in effector cell activation and target cell killing.

In addition, the researchers were able to show that the DART molecules were capable of reducing the level of HIV expression ex vivo in blood cells isolated from HIV-infected participants on suppressive antiretroviral therapy, suggesting that DART-mediated killing of reservoir cells takes place. "Ultimate proof of reservoir reduction would have to be obtained by in vivo testing of DART molecules", the researchers acknowledge, and suggest that their results "provide support to evaluate the bispecific T-cell redirecting molecules in an animal model of HIV latency to determine whether the HIV reservoir can be safely reduced in vivo."

More information: *PLOS Pathogens*, dx.plos.org/10.1371/journal.ppat.1005233

Provided by Public Library of Science