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Gene editing technology helps excise segment of HIV-1 DNA from genomes of living animals

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Using gene editing technology, researchers at the Lewis Katz School of Medicine at Temple University have, for the first time, successfully excised a segment of HIV-1 DNA - the virus responsible for AIDS - from the genomes of living animals. The breakthrough, described online this month in the journal *Gene Therapy*, is a critical step in the development of a potentially curative strategy for HIV infection.

"In a proof-of-concept study, we show that our gene editing technology can be effectively delivered to many organs of two small animal models and excise large fragments of viral DNA from the host cell genome," explained lead investigator on the study, Kamel Khalili, PhD, Laura H. Carnell Professor and Chair of the Department of Neuroscience, Director of the Center for Neurovirology, and Director of the Comprehensive NeuroAIDS Center at the Lewis Katz School of Medicine at Temple University (LKSOM).

Current treatment for HIV infection is centered on the use of a combination of antiretroviral drugs. While antiretroviral drug therapy can effectively suppress HIV replication, it has no ability to eliminate HIV-1 from infected cells. Moreover, when antiretroviral therapy is interrupted, HIV replication rebounds, placing patients at risk for developing acquired immune deficiency syndrome, or AIDS. Such latent infections develop because HIV DNA is able to persist in the genomes of CD4+ memory T-cells and perhaps in other cellular reservoirs where the virus remains silent and is unaffected by current therapy.

In earlier research, Dr. Khalili and colleagues were able to show that their novel gene editing system, which is based on CRISPR/Cas9 technology, has the extraordinary ability to eliminate HIV-1 from infected cells in vitro with no adverse effect on the host cells. In ex vivo experiments using clinical specimens, including T-cells from patients infected with HIV that were expanded in culture, they showed that viral replication was significantly reduced following treatment with the gene editing system.

The latest study was designed specifically to test whether the gene editing technology could also eliminate HIV-1 in transgenic rats and mice, in which HIV DNA is incorporated into the genome of every cell and organ of the experimental animals. In order to deliver the technology to cells in living animals, Dr. Khalili and colleagues employed a recombinant adeno-associated viral (rAAV) vector delivery system. They also engineered the gene editing apparatus to cleave the integrated HIV-1 DNA in the host cell genome, leading to excision of the viral DNA fragment from the host genome.

Two weeks after delivery of the rAAV CRISPR/Cas-9 molecules into the bloodstream, the researchers analyzed the DNA of tissues collected from the animals. The results showed that the targeted segment of HIV-1 DNA had been excised from the viral genome in every tissue, including the brain, heart, kidney, liver, lungs, spleen, and blood cells. Analyses of viral RNA in the rat model showed that the strategy significantly reduced levels of HIV-1 RNA in circulating lymphocytes, as well as in lymph nodes, indicating that viral genome excision had significantly impacted HIV-1 gene expression in cells carrying integrated viral DNA.

"The ability of the rAAV delivery system to enter many organs containing the HIV-1 genome and edit the viral DNA is an important indication that this strategy can also overcome viral reactivation from latently infected cells and potentially serve as a curative approach for patients with HIV," said Dr. Khalili. The excision strategy used in this study, which led to the removal of a large fragment of HIV-1 DNA, eliminates any chance for the development of replication-competent virus or escape events.

The clinical implications of the new study are far-reaching. The gene editing platform by itself may be able to eradicate HIV-1 DNA from patients, but it is also highly flexible and potentially could be used in combination with existing antiretroviral drugs to further suppress viral RNA. It also could be adapted to target mutated strains of HIV-1.

Dr. Khalili noted that a clinical trial could happen within the next several years. In the meantime, the next step is to conduct a follow-up study in a larger group of animals, in which the researchers plan to monitor for effects of the treatment, its safety, and other important indices.

Source:
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