Could Dual CRISPR Gene Editing Cure HIV?

Gene therapy that alters CCR5 receptors and excises HIV from infected cells eliminated the virus in mice.

May 15, 2023 By Liz Highleyman

Researchers have developed a combination approach that aims to eliminate HIV using two types of CRISPR gene editing, according to a report in Proceedings of the National Academy of Sciences. One CRISPR tool cuts out genes for the CCR5 receptor, which HIV uses to enter T cells, while another snips HIV genes out of cells that are already infected. So far, this approach has only been tested in mice, but the research could lay the groundwork for human cure studies.

“The idea to bring together the excision of HIV-1 DNA with inactivation of CCR5 using gene-editing technology builds on observations from reported cures in human HIV patients,” Kamel Khalili, PhD, of the Center for Neurovirology and Gene Editing at Temple University’s Lewis Katz School of Medicine, said in a university press release.

Antiretroviral therapy can keep HIV replication suppressed as long as treatment continues. But the virus inserts its genetic blueprints into the DNA of human cells and establishes a long-lasting reservoir that is unreachable by antiretrovirals. These so-called HIV proviruses can lie dormant in resting T cells indefinitely during treatment, but they start churning out new virus when the drugs are stopped. This latent virus has made curing HIV nearly impossible, save for a handful of people who received stem cell transplants for cancer treatment using donor cells with a rare mutation, known as CCR5-delta32, that prevents most strains of HIV from entering cells—a procedure far too risky and expensive for widespread use.

Khalili, Howard Gendelman, MD, of the University of Nebraska Medical Center, and colleagues tested a dual CRISPR-Cas9 approach in humanized mice engineered to have human-like immune cells. CRISPR is a gene-editing technique that cuts out selected segments of DNA. It consists of guide RNAs that pinpoint the desired genome location and Cas9 nuclease enzymes, which act as molecular scissors to make the cut. In this research, the guide RNAs and enzymes are delivered via an adeno-associated virus (AAV) vector.

The latest study builds on a decade of research on gene therapy to cure HIV, combining two approaches that are further along in development: a CRISPR technique that targets genes for the CCR5 receptor—in effect mimicking the CCR5-delta32 mutation—and a second CRISPR tool that

targets HIV DNA integrated into the human genome.

Several research teams and companies have explored various techniques for editing CCR5 receptors to make CD4 T cells resistant to HIV. Sangamo Therapeutics used zinc finger nuclease enzymes to cut out genes for the receptors. Some study participants saw a reduction in their viral reservoir and long-term CD4 count increases, and a few had a prolonged delay of viral rebound. American Gene Technologies is using a lentivirus vector to disable CCR5 receptors on HIV-specific CD4 cells. Most infamously, in 2018, Chinese researcher He Jiankui used CRISPR to disable the CCR5 gene in human embryos, resulting in the birth of twin girls.

Turning to HIV excision, in 2014, Khalili and colleagues published a groundbreaking study showing that a CRISPR tool could delete a segment of integrated proviral DNA that includes the gene for HIV's Gag protein, which is necessary for viral replication. A study published in 2019 showed that CRISPR could cut out integrated HIV genes and clear latent viral reservoirs in humanized mice treated with slow-release antiretroviral therapy dubbed LASER ART. The next year, a study of monkeys showed that the CRISPR tool excised segments of integrated SIV (an HIV-like simian virus) from blood cells and viral reservoir tissues; monkey studies also demonstrated long-term safety.

This work led to the development of EBT-101, a CRISPR-Cas9 therapy that uses dual guide RNAs to target three sites on the integrated HIV genome. Excision BioTherapeutics (a company cofounded by Khalili) announced that the first participant received the gene therapy in a Phase I/II clinical trial last July. If the study goes as planned, the patient is expected to interrupt antiretroviral therapy to see whether viral rebound occurs.

In the latest research, Khalili's team first infected humanized mice with HIV. Two weeks later, the mice were divided into six groups and treated with various combinations of LASER ART (cabotegravir, rilpivirine, lamivudine and abacavir), CRISPR that targets CCR5 receptors and CRISPR that cuts out integrated proviral HIV. One group got no treatment, one received both CRISPR tools without LASER ART, one received ART alone, one received ART plus the proviral HIV CRISPR, one received ART plus the CCR5 CRISPR and the final group received all three therapies.

All groups treated with LASER ART experienced viral suppression and CD4 cell restoration, with the highest counts seen in the group that received all three therapies. Replication-competent virus was eliminated in a majority of mice (58%) in the triple-therapy group. Using highly sensitive tests, the researchers could not detect intact HIV in the blood, spleen, lungs, kidneys, liver, gut, bone marrow or brain. In contrast, residual HIV was easily detected in untreated mice and those that experienced viral rebound. No off-target CRISPR toxicities were observed in any of the treated mice.

"CRISPR gene editing by targeting host CCR5 and HIV-1 LTR-Gag while controlling viral replication by antiretroviral drugs can lead to HIV-1 elimination in tissue reservoirs of infected animals," the study authors wrote. "Evidence was provided by the absence of viral rebound after 11 weeks following ART cessation." Mice treated with LASER ART plus only one type of CRISPR experienced

viral rebound but at lower levels, suggesting a reduction in the size of the viral reservoir.

“[T]he dual CRISPR therapy demonstrated statistically significant improvements in HIV-1 cure percentages compared to single treatments,” they concluded. “Taken together, these observations underscore a pivotal role of combinatorial CRISPR gene editing in achieving the elimination of HIV-1 infection.”

The researchers next plan to test the dual CRISPR approach in monkeys before moving on to human trials if the approach continues to show promise. Compared with stem cell transplantation from donors with the CCR5-delta32 mutation, CRISPR gene editing is “a simple and relatively inexpensive approach,” Khalili said, noting that the transplant procedure is risky and would not be applicable in resource-limited regions where HIV tends to be most common.

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