Gene-edited stem cells show promise against HIV in non-human primates

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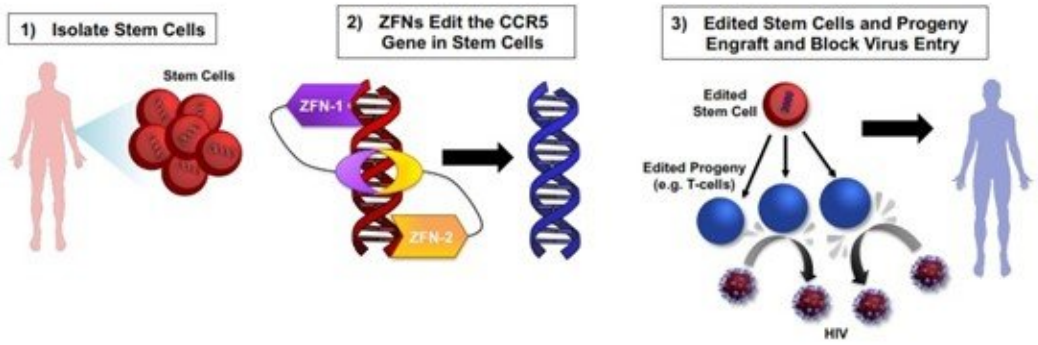

Most strains of HIV use the CCR5 gene to enter host cells. Our study shows that editing CCR5 leads to a reduction in the number of infected cells throughout the body. Credit: Grace Choi

Gene editing of bone marrow stem cells in pigtail macaques infected with simian/human immunodeficiency virus (SHIV) significantly reduces the size of dormant "viral reservoirs" that pose a risk of reactivation. Christopher Peterson of the Fred Hutchinson Cancer Research Center in Seattle, WA, and colleagues present these findings in *PLOS Pathogens*.

In 2007, HIV-positive Timothy Brown, also known as the Berlin Patient, received a bone marrow stem cell transplant to treat his leukemia. The procedure eliminated HIV from his system, likely facilitated by a

mutation in the gene CCR5 in the donor cells that made them resistant to HIV. However, it is rare to find matching donors with CCR5 mutations, and transplant is considered too dangerous for otherwise healthy HIV-positive patients, due to risk of donor cells attacking patients' cells.

To address this challenge, Peterson and colleagues are exploring the use of gene editing techniques to introduce the CCR5 mutation into a patient's own stem cells. In previous work, they demonstrated the ability to safely remove bone marrow stem cells from a healthy macaque, edit the CCR5 gene, and transplant the cells back into the macaque, where the CCR5-mutant cells successfully multiplied.

Now, the research team has performed the same technique in macaques infected with simian/human immunodeficiency virus (SHIV) and receiving antiretroviral therapy, making them analogous to HIV-infected people undergoing treatment to keep their HIV levels low. The scientists found that, after transplant, the CCR5 gene-edited cells were able to multiply in the macaques, giving rise to white blood cells that also had the mutation and were therefore resistant to SHIV.

Tissue analysis of the macaques detected edited cells in viral reservoirs—collections of infected cells that have been hijacked by SHIV to produce more copies of the virus, but are currently in a dormant state. The edited cells appeared to reduce the size of these reservoirs, which is notable because viral reservoirs may reactivate to produce more SHIV at any time, and antiretroviral therapies have no effect on them.

Over time, about 4 percent of each macaque's white blood cells consisted of cells with the CCR5 edit—too low a percentage to induce SHIV remission without also continuing antiretroviral therapy. The research team is now working to increase the efficiency of their gene-editing technique in order to raise this percentage. With better efficiency and in combination with other strategies, gene editing could one day help

fight HIV in people.

More information: Peterson CW, Wang J, Deleage C, Reddy S, Kaur J, Polacino P, et al. (2018) Differential impact of transplantation on peripheral and tissue-associated viral reservoirs: Implications for HIV gene therapy. *PLoS Pathog* 14(4): e1006956. doi.org/10.1371/journal.ppat.1006956

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