Repeating a miracle: Cure for HIV/AIDS

By Bryan Le

Since the start of the epidemic, over 70 million people have been afflicted with HIV, and 35 million people have died from AIDS-related complications. Even today, almost 37 million people are living with HIV. Those are big numbers that are hard to fully comprehend—unlike the number two. Why do I bring up the number two? Because that is the total number of HIV-infected individuals who have been cured. There are more cartoon characters on a box of Rice Krispies than people who have been cured of HIV, which continues to impact millions of people world-wide.

The life cycle of the HIV virus is very well known [1]. **The virus attaches to white blood cells by binding to either the CCR5 protein or the CXCR4 protein**. These proteins can be thought of as doors that allow the virus to get into the cells. Once HIV is inside, the virus takes control of the cell to make more of itself. The newly created viruses then get released outside the infected cell where they can infect other cells. As the virus is creating more copies of itself, it inadvertently produces signals that tell the cell to die. This cycle keeps on repeating, and eventually the number of disease-fighting white blood cells is dramatically reduced. As a result, the body cannot fight off different diseases, such as bacterial infections and cancer. Currently, treatment for HIV/AIDS often includes antiretroviral drugs that target the HIV virus. Unfortunately, this form of treatment only suppresses HIV and is not a cure. Patients who stop using antiretroviral drugs often have the virus come back.

In 2006, there was profound excitement when news about the first human cured of HIV was reported. Otherwise known as the "Berlin patient," Timothy Ray Brown had previously lived with HIV for 11 years before developing acute myeloid leukemia [2]. Brown had a version of HIV that can only attach to the CCR5 protein. In an attempt to treat the cancer and increase resistance to HIV, his doctor elected to do a bone marrow transplant with white blood cells carrying a truncated CCR5 protein known as CCR5Δ32. The truncated protein prevents the virus from using the CCR5 protein to get inside the cell and thereby prevents the virus from completing its life cycle. Prior to the transplant, Brown's doctor destroyed the cells in his immune system with chemotherapy and irradiation [3]. One day before the transplant was performed, he discontinued his antiretroviral drugs. Upon transplantation, Brown experienced Graft versus Host disease (GvHD), in which the transplant recognized the patient's body as foreign and induced an inflammatory response. GvHD was alleviated with immunosuppressants. The transplanted bone marrow contained stem cells that multiplied and repopulated Brown's immune system with cells containing the CCR5Δ32 protein. At day 61, DNA analysis did not detect traces of his original CCR5 gene in the peripheral-blood monocytes, a type of white blood cell. It appeared he now only had white blood cells with CCR5Δ32. **Since the transplant, Brown has not had detectable traces of HIV** [4].

Unfortunately, other attempts to replicate the success of the Berlin patient have failed [5, 6]. As an example, the "Essen patient" received a stem cell transplant with CCR5Δ32, but the virus came back. It is currently unclear why the virus came back, but it is believed that the version of HIV in the Essen patient may have attributed to the resurgence. Unlike the Berlin patient, the Essen patient

had a version of HIV that can attach to the CXCR4 protein. Therefore, even though the lock on the front door was changed, the virus simply entered through the back door. Due to a lack of success, some began to wonder if the Berlin patient was just an anomaly.

In 2019, reports of the "London patient" circulated. **For the first time in almost 12 years, another person has been reportedly cured of HIV**. The London patient lived with HIV for 9 years before being diagnosed with Hodgkin's Lymphoma. Similar to the Berlin patient, the London patient also had a version of HIV that only attaches to the CCR5 protein. In response, the patient's doctor performed a stem cell transplant with CCR5Δ32. Interestingly, the London patient also experienced GvHD but not until 77 days post transplant. Over the course of 18 months after the surgery, multiple tests did not detect traces of HIV. This is particularly significant since, unlike the Berlin patient, the London patient did not receive irradiation and did not discontinue antiretroviral drugs until 16 months after transplantation. Since irradiation was not required, this means that stem cell transplants will be more accessible and safer to patients. It is still not clear whether chemotherapy and GvHD played a role in the removal of the virus.

While both the Berlin patient and the London patient were lucky enough to have a donor with the CCR5Δ32 protein, other patients are not. To translate the research to the general public, several researchers are looking to develop a viral delivery system that can delete the gene for the CCR5 protein. This would prevent the patient from making the CCR5 protein and prevent HIV from entering the cell. It is also possible to use the same delivery system to modify the donated stem cells to create CCR5Δ32. With enough advancement in research and technology, hopefully we can have more people cured of HIV than there are cartoon characters on a cereal box.

References

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