Disabling CCR5 Could Be Key to a Cure—but at What Cost?

Interfering with this receptor on immune cells could have harmful health consequences.

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Interfering with the function of the CCR5 receptor on immune cells could lead to detrimental health outcomes, including shorter survival, according to a recent study. This finding potentially could have implications for HIV treatments that block CCR5 and cure approaches that involve deleting or disabling the receptor.

Chemokine receptor type 5, better known as CCR5, is a protein on the surface of certain white blood cells that plays a role in regulating immune responses. In order to enter cells, HIV must attach to both the CD4 receptor on T cells and a second coreceptor, either CCR5 or CXCR4. Up to 90% of newly transmitted HIV uses CCR5.

A small proportion of people—around 10% of Europeans, but only a tiny percentage of Africans and Asians—carry a natural genetic mutation called CCR5-delta32. People with two copies of this mutation (known as being homozygous) produce nonfunctional CCR5 coreceptors, and their CD4 cells are not susceptible to infection by most strains of HIV.

The only person known to have been cured of HIV—Timothy Ray Brown, formerly known as “the Berlin Patient”—received bone marrow transplants to treat leukemia from a donor with a double CCR5-delta32 mutation. Although Brown stopped antiretroviral therapy at the time of his first transplant, his viral load did not rebound. Researchers have extensively tested his blood, gut, brain and other tissues, but over the course of 12 years, they have found no replication-competent HIV. Earlier this year, researchers announced that a second man (dubbed “the London Patient") who received a transplant of CCR5-delta32 stem cells to treat lymphoma is also in long-term remission after stopping antiretrovirals, with no detectable HIV for 18 months at the time of the report.

The oral antiretroviral drug Selzentry (maraviroc) works by blocking CCR5 and preventing HIV from using the coreceptor. The experimental monoclonal antibody leronlimab (PRO 140) likewise binds to and prevents HIV from using CCR5 to enter cells.

But HIV cure researchers are also trying to develop therapies that would permanently delete or disable CCR5. One gene therapy approach uses a zinc finger nuclease carried by a harmless virus

to cut the CCR5 gene out of CD4 cells. Using this method to delete or disable the CCR5 gene in stem cells—which give rise to CD4 cells and all other blood cells—could potentially result in lasting resistance to HIV infection.

Another gene-editing method called CRISPR-Cas9 might be used to accomplish the same goal. Chinese researcher He Jiankui generated headlines late last year when he announced that he had used CRISPR technology to edit the genes of human embryos to make children resistant to HIV. His experiment led to the birth of twin girls who have defective CCR5 genes but not the intended delta32 deletion.

A recent study, however, raises questions about the potential negative effects of deleting or disrupting CCR5. The CCR5-delta32 mutation is thought to have evolved to fend off certain diseases—possibly bubonic plague or smallpox—but it may also have some detrimental consequences.

Xinzhu "April" Wei, PhD, and Rasmus Nielsen, PhD, of the University of California, Berkeley, explored the fitness effects of the CCR5-delta32 mutation by analyzing genetic sequences and death registry data from 409,693 adults of British ancestry, ages 41 to 78, who provided samples to the U.K. Biobank.

As reported recently in Nature Medicine, the researchers found that the frequency of the mutation substantially decreased over time. They estimated that individuals with double or homozygous mutations had a 21% increase in all-cause mortality by age 76 compared with those with one or no copies of the mutation. Having a single or heterozygous mutation did not appear to raise the risk of death.

Although the researchers did not have adequate data about the causes of death, one possible reason could be that people with a double CCR5-delta32 mutation may be more likely to develop complications from and die of influenza. Previous research showed that missing CCR5 raises susceptibility to West Nile virus, though this is not common enough in the United Kingdom to have influenced mortality rates.

"It is perhaps not unexpected that homozygosity for a deletion in a functional gene is associated with reduced fitness," the study authors wrote. "It underscores the idea that introduction of new or derived mutations in humans using CRISPR technology, or other methods for genetic engineering, comes with considerable risk even if the mutations provide a perceived advantage. In this case, the cost of resistance to HIV may be increased susceptibility to other, and perhaps more common, diseases."

Some medical experts and advocates have expressed concerns about what these findings might mean for HIV treatment and cure approaches involving CCR5. Overall, most agree that current therapies that block intact CCR5 coreceptors seem to be safe. But permanently deleting or disabling CCR5 may be another story.

Paul Sax, MD, of Brigham and Women's Hospital in Boston, noted that people who are born with

and grow up with two CCR5-delta32 mutations may differ from those in whom CCR5 is altered during adulthood. “We simply don’t know whether people who acquire it late in life will be better or worse off than those born with the mutation,” he wrote in his New England Journal of Medicine Journal Watch blog.

Sax also raised a philosophical issue about HIV cure research:

> The reality is that there’s tremendous interest in HIV cure, especially among those with HIV, risks notwithstanding.
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> So great is this interest that many of us have even been asked by our patients whether they can have a bone marrow transplant.
>
> That these questions mostly come from people doing quite well on their HIV therapy signals a powerful patient-driven motivation for HIV cure—one that sadly seems more related to ongoing HIV stigma than to the medical issues of current HIV treatment.
>
> Which is why it’s not so clear that this latest research finding should dampen the pursuit of CCR5-driven cure strategies.
>
> Would a lifetime 21% increase in all-cause mortality be an acceptable trade-off for a person with HIV who is deeply invested in HIV cure?
>
> And who will get to decide?

Click here to read the study abstract.

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http://beta.docker.poz.com/article/disabling-ccr5-key-curebut-cost