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HIV patients 'cured' by their own unique biology may harbor secrets to end the global scourge

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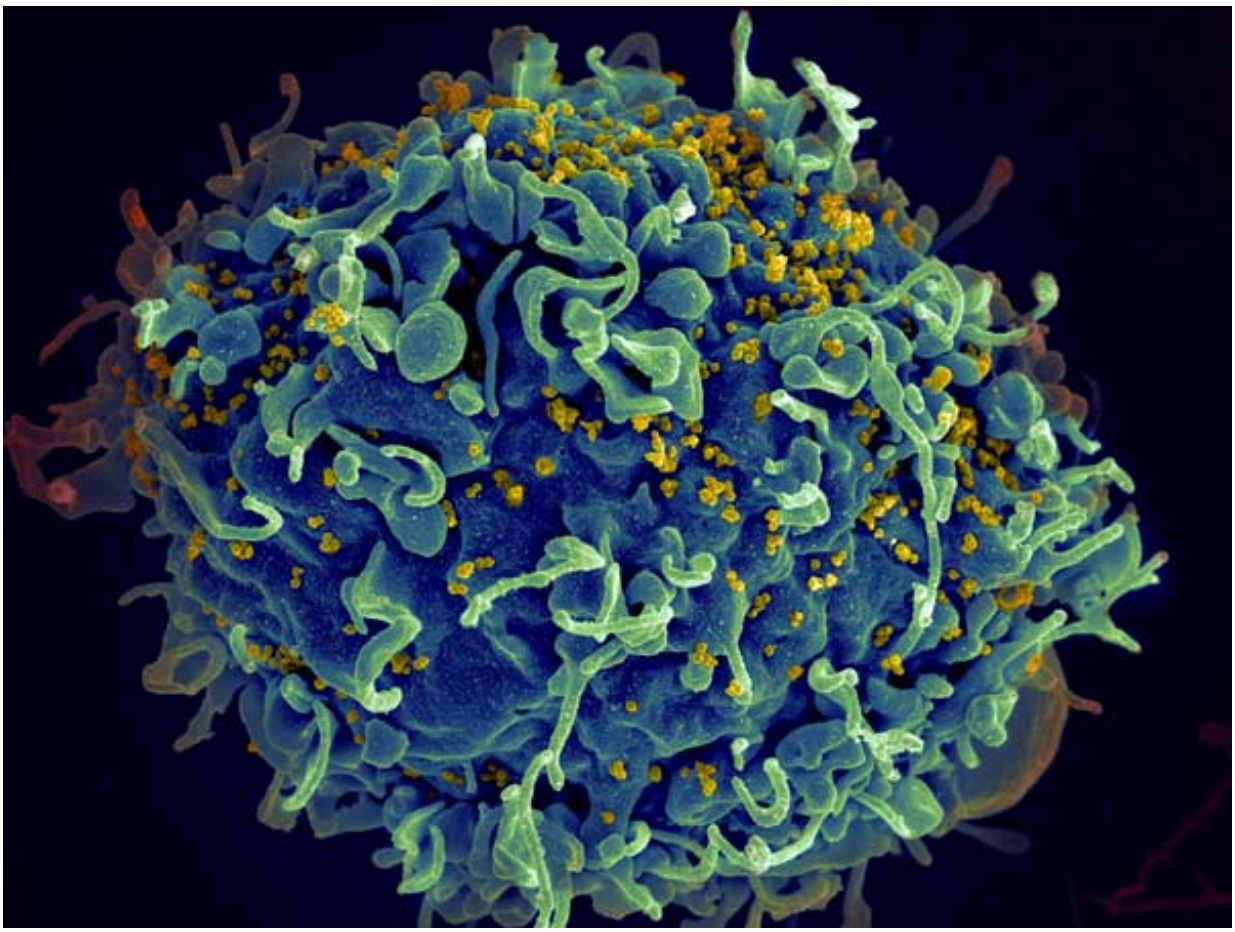

HIV (yellow) infecting a human immune cell. Credit: Seth Pincus, Elizabeth Fischer and Austin Athman, National Institute of Allergy and Infectious Diseases, National Institutes of Health

Some people diagnosed with HIV are able to eradicate the virus without antiretroviral medications or even stem cell transplants, possessing the ability to naturally suppress the virus and achieve a medically verifiable cure.

Scientists call this small population elite controllers, a moniker that reflects their unique ability to keep one of the most notorious viruses at bay.

Two of these patients have garnered fame in the scientific literature in recent months, each known mostly by a code name: the San Francisco Patient, and another called the Esperanza Patient. Both are women who have been spotlighted in medical journals and at scientific conferences for having eradicated HIV from their bodies.

Beyond those two celebrated examples, new research from the Ragon Institute in Boston has zeroed in on a larger group of elite controllers—58 altogether—who have also been able to keep the virus at bay by virtue of their distinct biological capabilities. The elite controllers were compared with 42 HIV patients on antiretroviral therapy, people who represent the vast majority of those diagnosed globally with HIV.

Writing in *Science Translational Medicine*, immunologists at the institute report that they have uncovered a deep well of new clues that point to elite controllers' unusual ability to eradicate the virus. One reason is a powerful immune response, but another centers on where latent viral genetic sequences are stranded in the human genome. These sequences tend to be in tucked into chromosomes in remote regions where they're less likely to replicate, but more likely to be found by immune forces.

The research is opening a new window of understanding into what it means to be infected with HIV, a virus that is estimated to affect 38 million people globally. Millions worldwide have died since the HIV

pandemic began 40 years ago.

Most patients take antiretroviral drugs for life to hold the virus in check, but elite controllers can handily subdue HIV for long periods without the need for medications. Although the San Francisco Patient was infected in 1992, she has kept the virus at bay for decades. Her existence—and that of other elite controllers—defies the long-held dogma that HIV infection is invariably for life.

The new findings join a growing body of work that may eventually lay the groundwork for future pharmaceutical interventions to help the vast majority of HIV patients eliminate the virus based on principles scientists are learning from elite controllers, people who have achieved so-called "sterilizing cures."

"Increasing evidence suggests that durable drug-free control of HIV-1 replication is enabled by effective cellular immune responses," lead author, Dr. Xiaodong Lian wrote along with his colleagues.

Lian and other members of the team studied what they call the subtle "footprints" of the immune system that reveal how elite controllers are able to eliminate HIV infection without medication. Data from their experimental work suggest that viable human immunodeficiency viruses in elite controllers may face greater pressure from immune system cells. As a result, the viruses are unable to dodge the immune system's formidable army.

The Boston-based team knew going into the research that the immune system is a veritable arsenal capable of powerful antiviral activity. However, for most people infected with HIV the immune response is severely crippled, which is why antiretroviral drugs are critical to survival. The drugs work by stopping the virus from replicating.

"We comprehensively tracked [the] effects of antiviral immune responses on intact and defective proviral sequences from elite controllers," Lian asserted in the report, referring to the viral state in which HIV inserts its genetic material into the DNA of a host cell.

The word "proviral" is not only key to understanding what Lian and colleagues were studying, but is also crucial to understanding the permanence of HIV infection in the vast majority of people who contract the virus and rely on antiretroviral drugs. A provirus is a genetic sequence that has integrated itself into the host's DNA. This act of stealth allows the virus to remain latent—and hide in the body.

Rather than replicating as a freely circulating virus, HIV insidiously replicates when the host cell replicates, which means when the cell is quiescent and not replicating, neither is HIV. And because the proviral sequence has insinuated itself into the host's DNA, the immune system isn't alerted to HIV's presence during this provirus period of latency.

Indeed, when HIV integrates into the host's genetic machinery by placing copies of its genome into the DNA of the host, it's creating what is known as a viral reservoir.

Lian and the Ragon Institute team found that for elite controllers, HIV infection functions differently, a conclusion they drew by studying both intact and defective proviruses because both were present in the chromosomes of elite controllers.

They also found that controllers' proviruses had fewer mutations than those in people who require antiretroviral therapy. Mutations often evolve to help the virus escape recognition by T cells. Another finding reported by the Ragon team revealed that proviruses in elite controllers were more likely to be sequestered in chromosomal regions where they don't easily replicate, but can be handily detected by immune system

patrollers.

Findings such as these have helped immunologists—those at the Ragon Institute as well as others around the world—highlight differences between elite controllers and people who require lifelong antiretroviral therapy.

"Recent studies have begun to unravel pronounced differences between persisting viral reservoirs in elite controllers and most antiretroviral-treated individuals," Lian wrote.

All of the new findings are helping to peel away some of the mystery underlying the phenomenon of elite control. The Ragon Institute reported in the journal *Nature* last year that the San Francisco Patient, an elite controller, had no intact proviral sequences in her genome. She is completely HIV free. Based on the Ragon Institute's research, this suggests the San Francisco Patient's immune system may have completely eliminated the woman's HIV reservoir. Scientists refer to this rare occurrence as a "sterilizing cure."

Two other patients, the late Timothy Brown of California, widely known as the Berlin Patient, and Adam Castillejo of the United Kingdom, who has been dubbed the London Patient, were both declared cured of HIV. Both men, however, had undergone stem cell transplants for cancer, which resulted in their immune systems eliminating virus. Brown died in 2020 after cancer of the blood aggressively rebounded. Neither the San Francisco Patient nor the Esperanza Patient has undergone a stem cell procedure, also known as a bone marrow transplant, which provides patients with a new blood supply.

Like the San Francisco Patient, the Esperanza Patient, an elite controller from Argentina, had no intact HIV proviruses when scientists studied an astounding 1.19 billion blood cells and 500 million tissue-related cells. A

report on her case was published last month by Ragon Institute scientists in the *Annals of Internal Medicine*.

All of the findings suggest there ultimately may be an "actionable path to a sterilizing cure" for patients who are unable to do this on their own, institute scientists said, summing up their research on the Esperanza Patient. More work, these experts say, lies ahead.

"A broad consensus exists that elite, drug-free control of HIV-1 replication is—in most cases—mediated by host immune factors. However, elite control may not simply occur because of the presence of potent antiviral immune responses to suppress ongoing viral replication," Lian and colleagues concluded.

"We performed simultaneous assessments of individual proviral sequences and their corresponding chromosomal locations to generate a comprehensive analysis of the proviral reservoir landscape of intact and defective proviruses from elite controllers. These investigations demonstrated an atypical reservoir profile of intact proviruses in elite controllers."

More information: Xiaodong Lian, et al, Signatures of immune selection in intact and defective proviruses distinguish HIV-1 elite controllers, Science Translational Medicine (2021) DOI: 10.1126/scitranslmed.abl4097