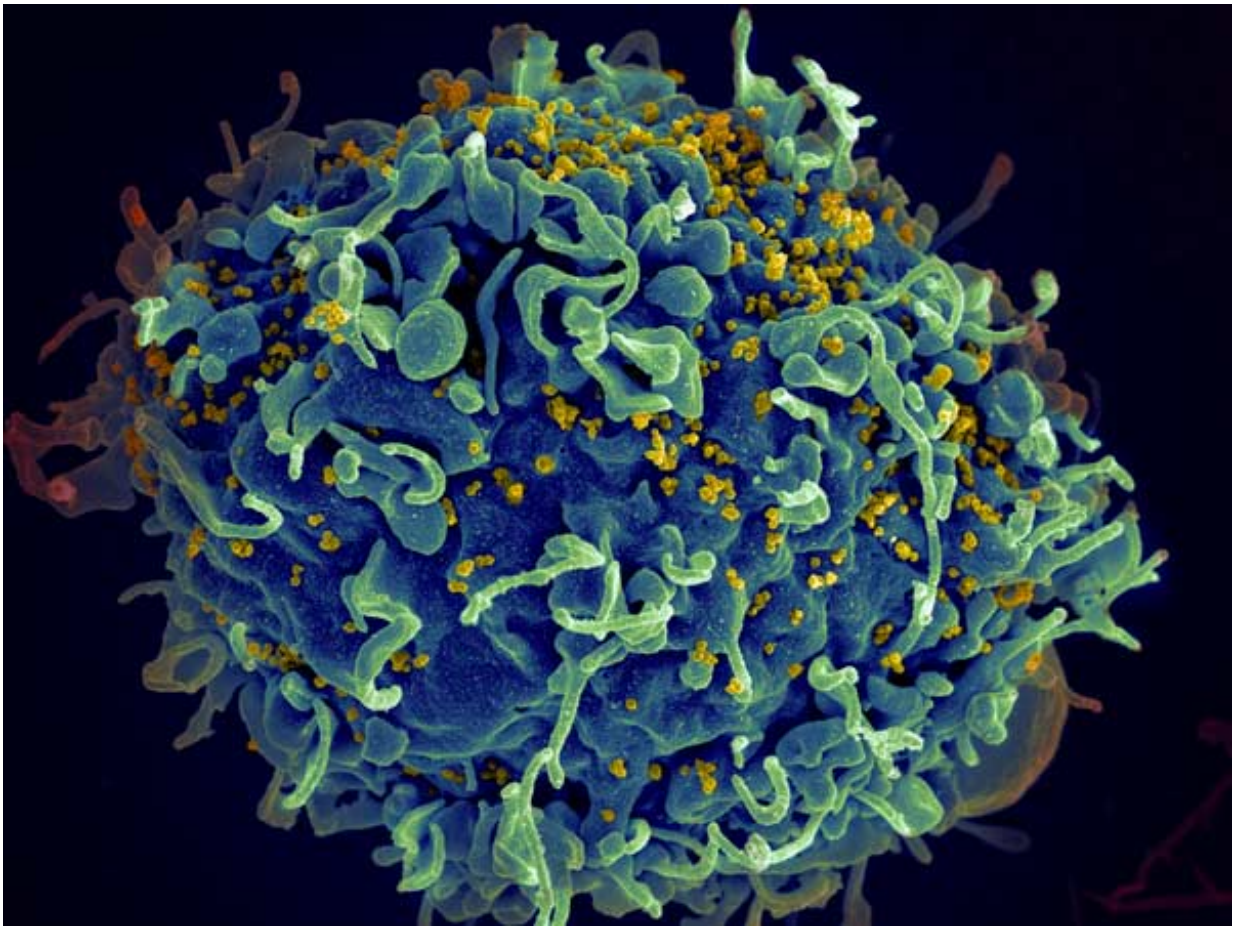
MedicalXpress

New evidence: Defective HIV proviruses hinder immune system response and cure

April 19 2017



HIV infecting a human cell. Credit: NIH

Researchers at Johns Hopkins and George Washington universities

report new evidence that proteins created by defective forms of HIV long previously believed to be harmless actually interact with our immune systems and are actively monitored by a specific type of immune cell, called cytotoxic T cells.

In a report on the study, conducted on laboratory-grown human cells and published April 12 in the journal *Cell Host and Microbe*, the investigators say their experiments show that while defective HIV proviruses—the viral genetic material—cannot create functional infectious HIVs, a specific subset called "hypermutated" HIV proviruses creates proteins that cytotoxic T cells recognize as HIV.

HIV proviruses can outnumber functional HIV 1000 copies to one and the faulty proteins they create can complicate efforts to measure a patient's viral load, exhaust immune systems, shield functional HIV from attack by natural means or drugs, and seriously complicate the development of a cure. Researchers believe that if they can exploit the "hypermutated" form of these proviruses, it could help them eliminate more of the defective HIV proviruses and develop a cure for HIV infection.

"The virus has a lot of ways, even in its defective forms, to distract our immune systems, and understanding how they do this is essential in finding a cure," says Ya Chi Ho, M.D., Ph.D., instructor of medicine at the Johns Hopkins University School of Medicine, and the lead study investigator.

In the study, the scientists collected nine different defective HIV proviruses from six people infected with HIV, then transfected cultures of human immune cells with them in the laboratory. They grew and tested the transfected cells for markers of HIV proliferation—such as RNA and proteins—and found that all of them were capable of creating these components despite their mutations.

"The fact that defective proviruses can contribute to viral RNA and protein production is concerning, because it means that the measurements of HIV load in infected patients may not be as accurate as we thought. Part of the count is coming from defective viruses," says Ho.

After verifying that defective HIV proviruses created HIV proteins, the researchers then tested whether human immune system cells could biologically recognize and interact with those proteins. The group again transfected cells in the lab with 6 different types of defective HIV provirus taken from patients. In collaboration with Dr. R. Brad Jones, Ph.D., co-first author of the paper and assistant professor of microbiology, immunology and tropical medicine at the George Washington School of Medicine and Health Sciences, Ho's team matched cytotoxic T lymphocytes, the immune cells responsible for recognizing and destroying HIV, from the corresponding patient to the infected cells.

The researchers observed that cells containing a the "hypermutated" HIV can be recognized by an infected patient's cytotoxic T cells.

"If we identify and find a way to use the right protein, perhaps one of those expressed by the "hypermutated" HIV we found in this study, we could create a potent vaccine which could boost the immune system enough to eliminate HIV altogether," says Ho.

However, defective HIV proviruses can distract the immune cells from attacking fully infectious normal HIV. "The cytotoxic T lymphocytes' ability to identify and target the real threat appears to be greatly impaired, because they may attack proteins from defective proviruses instead of the real thing," says Ho.

Ho believes that further information about the mutant proviruses could

give scientists the tools to target them, get around them, and create a cure for HIV—a long elusive goal for virologists.

More information: *Cell Host and Microbe* (2017). www.cell.com/cell-host-microbe … 1931-3128(17)30118-X

Provided by Johns Hopkins University School of Medicine