Medical Xpress

Pitt study points to new opportunities for HIV treatment

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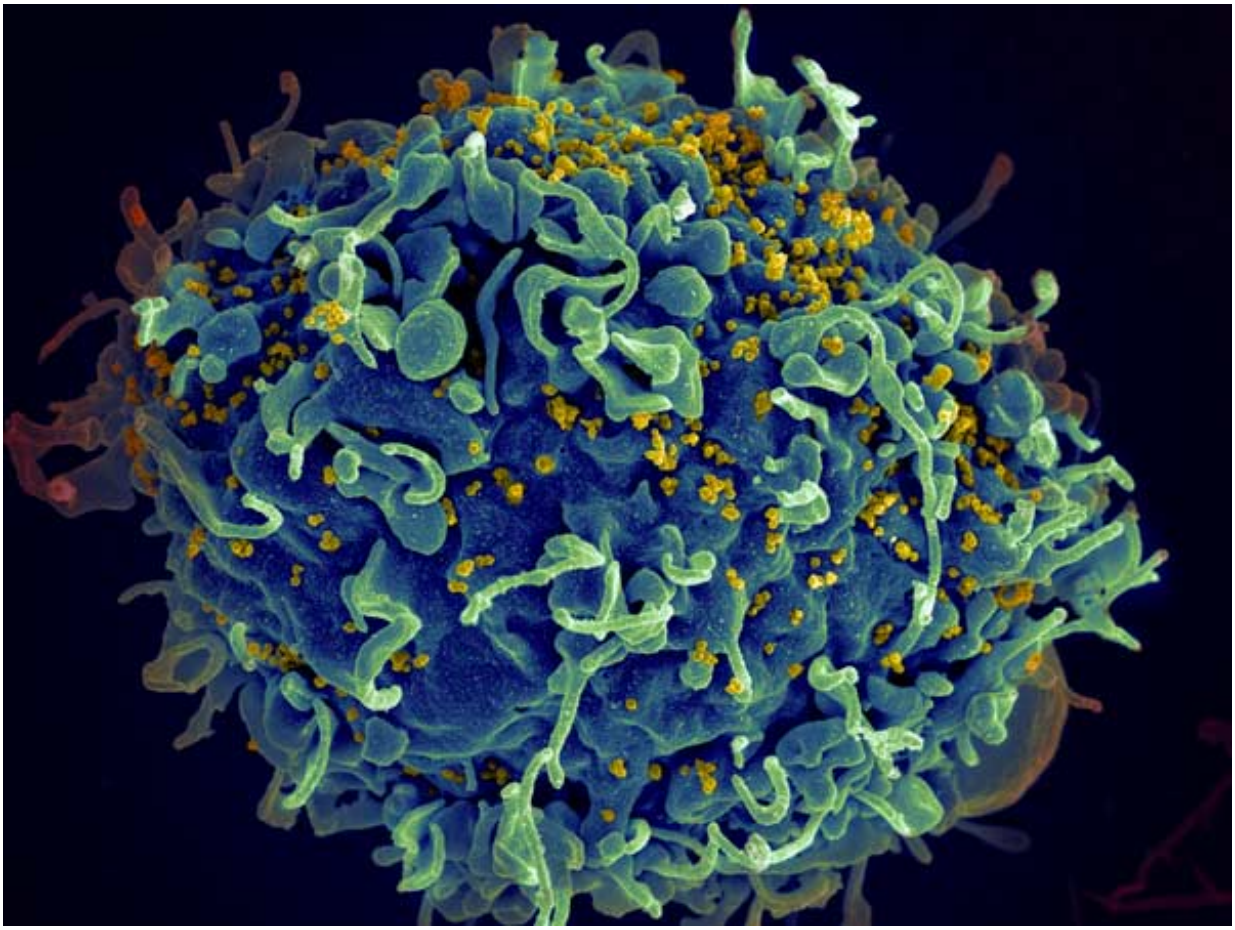

HIV infecting a human cell. Credit: NIH

Sometimes in science, answers come serendipitously, where researchers

aren't expecting to find them. That's what happened to Cristian Apetrei, Ivona Pandrea and their colleagues during a recent study on human immunodeficiency virus, or HIV.

The results point to a new opportunity for HIV treatment and research in humans.

Apetrei and Pandrea are a husband-wife scientist pair, and both have labs at the University of Pittsburgh; scientists from Tulane University in New Orleans, Rush University Medical Center in Chicago, and Los Alamos National Laboratory in New Mexico also contributed to the study.

HIV targets T cells, a group of cells in the body that creates immune responses and fights off foreign pathogens. When HIV infects T cells, it tricks those cells into replicating the genetic code of the virus, which leads to a flood of more HIV particles that can infect other T cells. The virus also has mechanisms to evade the body's immune response, like an intruder wearing a disguise and slipping past bodyguards.

Previous HIV research involved dampening this T cell-mediated inflammation, but these new findings suggest that may not be enough.

The results, published Monday in the journal *JCI Insight*, suggest that HIV treatment might be better targeted at the gut. Research shows one of HIV's first lines of attack is to compromise the gut lining, leading to bacteria entering the bloodstream and a widespread autoimmune response.

The researchers gave African green monkeys infected with simian immunodeficiency virus a discontinued cancer drug called Ontak to knock out T cells that might otherwise try to kill the virus the monkeys were infected with. (SIV is the equivalent of HIV in humans.) Four

monkeys got Ontak over 5 days (there were 5 control monkeys with SIV that did not receive the drug), and researchers measured their inflammation, viral load and other disease markers over a period of 166 days.

Ontak binds to a type of T cell that helps to regulate the immune environment and kills them.

"Now you have a motor running nonstop," said Robbie Mailliard, visiting associate professor in the Department of Medicine and the Division of Infectious Diseases at the University of Pittsburgh, specializing in immunology. "It leads to an explosion of immune activity." Mailliard was not involved in the research.

If HIV is caused by chronic inflammation and immune activity turned all the way up, one might expect these monkeys, who now had less ability to fight off the virus, to get sicker and develop the simian equivalent to AIDS. But they didn't.

The African green monkey, it turns out, has a protective mechanism in its gut that the researchers think is responsible for thwarting deadly disease. In a previous study, Apetrei and colleagues infected the same species of monkey with SIV and then worsened their gut health with a poor diet. Those monkeys did see their disease progress. It seems an impermeable gut lining is the secret.

"It seems that animals with SIV who don't progress (to AIDS) have better inflammation control," said Apetrei, a professor of infectious diseases at Pitt's School of Medicine, professor of infectious diseases and microbiology at Pitt's School of Public Health, and first author on the paper. "We had to shift our interpretation. Why does it behave this way? Because we didn't damage the gut."

"Looking at the "homeostasis of the gut tissue and lining, African green monkeys seem to have some protective mechanism that blocks damage from occurring," said Mailliard.

Possibly, then, scientists could target the inflammation at its source before it becomes widespread in the body.

"The researchers showed that causing a leak in the dam [of the gut] was inducing this whole cascade of events to occur," Mailliard said. "Just squashing immune activation from T cells isn't going to be enough."

Mailliard used the example of traffic control to explain the difference between targeting T cells in the blood and targeting the gut itself, where the source of the problem may lie. "If you wanted to quiet the city down and dampen traffic, you can slow traffic with police officers, but unless you get rid of what's causing that traffic, you're still going to have issues," he said.

Traffic—in this case, molecules in the blood—gives only a snapshot and doesn't tell the whole story. "Who is playing at the stadium? You have to get to where the action is occurring."

In addition to highlighting future steps for HIV treatments, looking deeper into the gut could help those who struggle with dysfunction there, too. Irritable Bowel Syndrome, a common disorder that signals gut dysregulation of some kind, affects 10-15% of the U.S. population—up to nearly 50 million people—per the American College of Gastroenterology.

While many with IBS struggle with inflammation, chronic pain or mental health issues, an IBS diagnosis doesn't home in on the root cause of the problem. Understanding how the lining of the gut becomes leaky and the gut bacteria shift toward harmful could elucidate treatment for more

than just those with HIV.

"A lot of people have IBS and Crohn's disease, and there are not a lot of good treatments," said Apetrei. "These results are exciting, because every step further we try to understand will bring us closer."

The researchers hope to further investigate microbial transplants; Apetrei said they are in the initial stages of looking into the impact of altering the gut microbiome.

Cindy Sears, an infectious disease physician and professor of medicine at Johns Hopkins University specializing in the gut microbiome and immunotherapy, thought the study was "very interesting" but wished barrier function—or how well the gut lining works to prevent leaks—was measured directly.

For a future study, she thinks that scientists could measure the barrier function of people newly diagnosed with HIV using a tracker that could be followed throughout the body. That way, scientists can see more clearly how the disease is impacting gut function.

Sears also said that barrier function is one of the first processes to be disrupted in IBS and is thought to contribute to the development of colon cancer, pointing to a large swath of potential patients benefiting from looking deeper into how gut barrier function and the immune system are linked.

With animal research, there is always a question of extrapolation—while monkeys share 98.8% of our DNA, it's not guaranteed that results will transfer perfectly to humans. The sample size was also small, with nine monkeys in the study. Mailliard said for those who study HIV, this paper can still point to a new direction of research.

"Once the gut is damaged, understanding how to get it back to where it was before the infection is going to be important," he said.

More information: Cristian Apetrei et al, T cell activation is insufficient to drive SIV disease progression, *JCI Insight* (2023). DOI: 10.1172/jci.insight.161111