Scientists learn how common virus reactivates after transplantation

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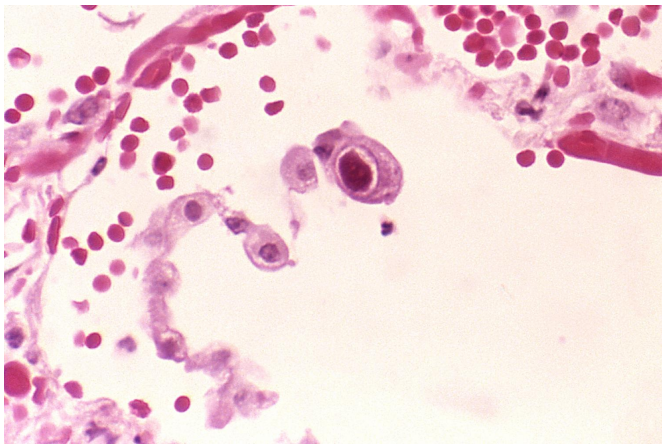

Cytomegalovirus. Credit: CDC/Dr. Edwin P. Ewing, Jr. (PHIL #958), 1982.

A new study in *Science* challenges long-held theories of why a common virus—cytomegalovirus, or CMV—can reactivate and become a life-threatening infection in people with a compromised immune system, including blood cancer patients undergoing bone marrow transplantation.

The discovery, to be published in *Science*'s Jan. 18 issue, used a newly developed mouse model and could pave the way for cheaper, safer therapies to protect patients from CMV.

"This is a big deal for the bone marrow transplantation field," said Dr. Geoffrey Hill, the paper's senior co-author and director of Hematopoietic Stem Cell Transplantation at Fred Hutchinson Cancer Research Center. "Our study shows for the first time that antibodies can play a dominant role in controlling CMV reactivation. This is turning dogma on its head."

Previous research on CMV reactivation has focused on T cells, the celebrated disease fighters of the immune system. There had been occasional hints that antibodies produced by immune system B cells played some role against CMV, but it seemed to be a supporting role. Clinical trials using antibodies to fight the virus were disappointing, Hill said.

But Hill and his research team found that strain-specific antibodies made from B cells are responsible for keeping CMV suppressed in mice, without the need for any other immune cells.

A future therapy could work by collecting the CMV-thwarting antibodies from patients who have been exposed to the virus and who are undergoing bone marrow transplant. The antibodies would be purified and multiplied in the lab, then returned to the patient after transplant.

At Fred Hutch, Hill and colleagues are now pursuing clinical studies to test the approach.

"Most people don't see any symptoms of the virus because their healthy immune systems keep CMV in check," Hill said. "But it can roar back to life in anyone with a compromised immune system, and the results can be life-threatening."

BACKGROUND

CMV, a type of herpes virus, infects at least half of adults by age 40. The virus can cause life-threatening complications such as pneumonia, hepatitis and gastroenteritis and has plagued allogenic transplant patients for decades. CMV infection is the most common complication of bone marrow transplantation. Just over 8,000 people in the United States received allogenic transplants in 2017 for blood cancers, including leukemias and lymphomas, and other blood disorders, according to the Center for International Blood & Marrow Transplant Research.

"Just having been exposed to the virus in the past predicts a worse outcome, despite new antiviral

medications. It's a major problem," said Hill, who cares for patients at Seattle Cancer Care Alliance, the Hutch's clinical care partner.

To find out the fuller story, Hill, who worked at the QIMR Berghofer Medical Research Institute until 2018, and Mariapia Degli-Esposti at the Lions Eye Institute in Perth, Australia, created the first animal model of CMV reactivation. They infected mice with CMV so that the animals experienced the primary infection followed by virus dormancy, as a person would. Three months later, the researchers gave the mice a bone marrow transplant, effectively wiping away their immune systems and replacing them with new donor marrow.

In a series of experiments looking at the roles of different types of immune cells, the team found that B cells played a critical role in controlling CMV. That is, transplanted mice that had no pre-existing B cells and thus lacked antibodies saw CMV spring back to life within 10 days of the transplant.

The group then looked into different strains of the virus, since CMV exists in many related but differing forms and can change over the course of infection. The researchers used eight different strains of CMV and found mice given the antibody from the same strain of the virus that they were exposed to previously were protected completely from CMV coming back.

Since earlier clinical trials had used antibodies from pooled sources, the strain-specific CMV protection had been hidden.

More information: J.P. Martins el al., "Strain-specific antibody therapy prevents cytomegalovirus reactivation after transplantation," *Science* (2019). science.sciencemag.org/cgi/doi … 1126/science.aat0066

"B cells, CMV, and stem cell transplant," *Science* (2019) science.sciencemag.org/cgi/doi … 1126/science.aav9867

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