New research shows HIV can lie dormant in the brain

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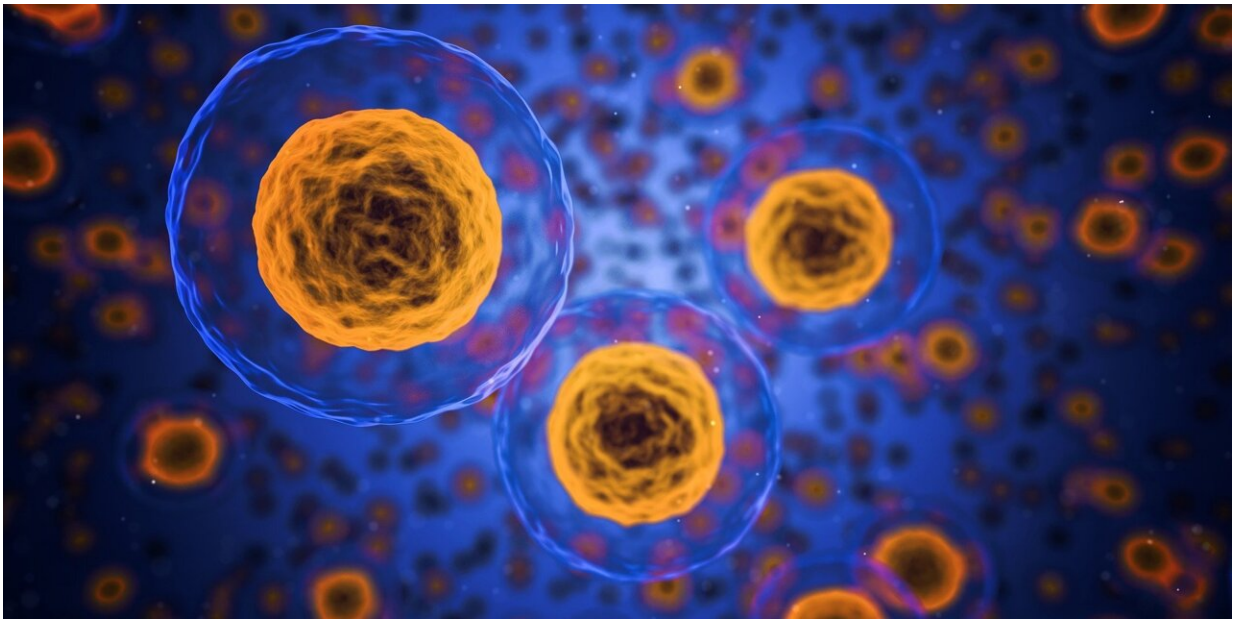

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As a part of its life cycle, the human immunodeficiency virus-1 (HIV) inserts a copy of its DNA into human immune cells. Some of these newly infected immune cells can then transition into a dormant, latent state for a long period of time, which is referred to as HIV latency.

Although current therapies, such current antiretroviral therapy (ART), can successfully block the virus from replicating further, it cannot

eradicate latent HIV. If treatment is ever discontinued, the virus can rebound from latency and reignite the progression of HIV infection to AIDS.

Scientists from the HIV Cure Center at the UNC School of Medicine, University of California San Diego, Emory University, and University of Pennsylvania have been searching for where exactly these latent cells are hiding in the body. New research published in the *Journal of Clinical Investigations* confirms that microglial cells—which are specialized immune cells with a decade-long lifespan in the brain—can serve as a stable viral reservoir for latent HIV.

"We now know that microglial cells serve as a persistent brain reservoir," said first author Yuyang Tang, Ph.D., assistant professor of medicine in the Division of Infectious Diseases and member of the UNC HIV Cure Center. "This had been suspected in the past, but proof in humans was lacking. Our method for isolating viable brain cells provides a new framework for future studies on reservoirs of the central nervous system, and, ultimately, efforts towards the eradication of HIV."

Latent HIV

HIV is a tricky and unique virus to study. During infection, the virus specifically targets the key coordinators of the immune response, which are called CD4+ lymphocytes. Over time, the virus kills enough CD4+ cells to cause immunodeficiency. .

Past research has shown that latent HIV can hide within a few of the surviving CD4+ T cells throughout the body and the bloodstream. However, other viral reservoirs have been suspected to hide within the central nervous system (CNS) in people with HIV receiving effective ART.

Unlike peripheral blood cells, it is extremely difficult to access and analyze brain tissues for the study of HIV reservoirs. Since these types of cells cannot be safely sampled in people taking ART, the potential viral reservoir in the brain has remained an enigma for many years.

Extracting Pure Brain Tissue

The team first studied the brains of macaques with the simian immunodeficiency virus (SIV), a virus that is closely related to HIV, from the Yerkes National Primate Research Center at Emory University to get a better understanding of how to extract and purify viable cells from primate brain tissue.

Researchers used physical separation techniques and antibodies to selectively remove cells that were expressing microglial surface markers. Then, they isolated and separated the highly pure brain myeloid cells from the CD4+ cells that were passing through the brain tissue.

Using these techniques, researchers then obtained samples that were donated by HIV+ people who were enrolled in "The Last Gift" Study at the University of California San Diego (UCSD). As a part of this unique and important effort, altruistic HIV+ people, who are taking ART but suffering from other terminal illnesses, will their bodies to further the HIV research project.

"The samples are from people living with HIV, who are on therapy but facing a fatal disease of some kind," said the co-author David Margolis, MD, the Sarah Kenan Distinguished Professor of Medicine, Microbiology & Immunology, and Epidemiology. "They were willing to not just donate their bodies to science, but also participate in the research program in the months leading up to their death. It's an extraordinary program that made this critical research possible."

Future Projects

Now that the researchers know that latent HIV can take refuge in microglial cells in the brain, they are now considering plans to target this type of reservoir. Since latent HIV in the brain is radically different from the virus in the periphery, researchers believe that it has adapted special characteristics to replicate in the brain.

"HIV is very smart," said senior author Guochun Jiang, Ph.D., assistant professor in the UNC Department of Biochemistry and Biophysics and member of the UNC HIV Cure Center. "Over time, it has evolved to have epigenetic control of its expression, silencing the virus to hide in the brain from immune clearance. We are starting to unravel the unique mechanism that allows latency of HIV in brain microglia"."

NF-κB signaling is one of the critical signaling pathways that controls HIV expression elsewhere in the body. When NF-κB signaling is "turned off", HIV enters latency in the peripheral blood. However, latent HIV in the brain is not impacted by the activation of NF-κB signaling. Researchers are unsure why that is, but once an answer is found, they will be one step closer to knowing how to selectively target and eradicate the virus in the brain or peripheral blood.In addition to understanding the inner workings of the brain reservoir, the researchers are also trying to determine the true size of the latent HIV brain reservoir.

"It is very hard to know how big the reservoir is," said Margolis, who is also the director of the UNC HIV Cure Center. "The problem with trying to eradicate HIV is like trying to eradicate cancer. You want to be able to get it all, so it won't come back."

More information: Yuyang Tang et al, Brain microglia serve as a persistent HIV reservoir despite durable antiretroviral therapy, *Journal of Clinical Investigation* (2023). DOI: 10.1172/JCI167417

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