A trait of the rare few whose bodies naturally control HIV: 'Trained' immune cells

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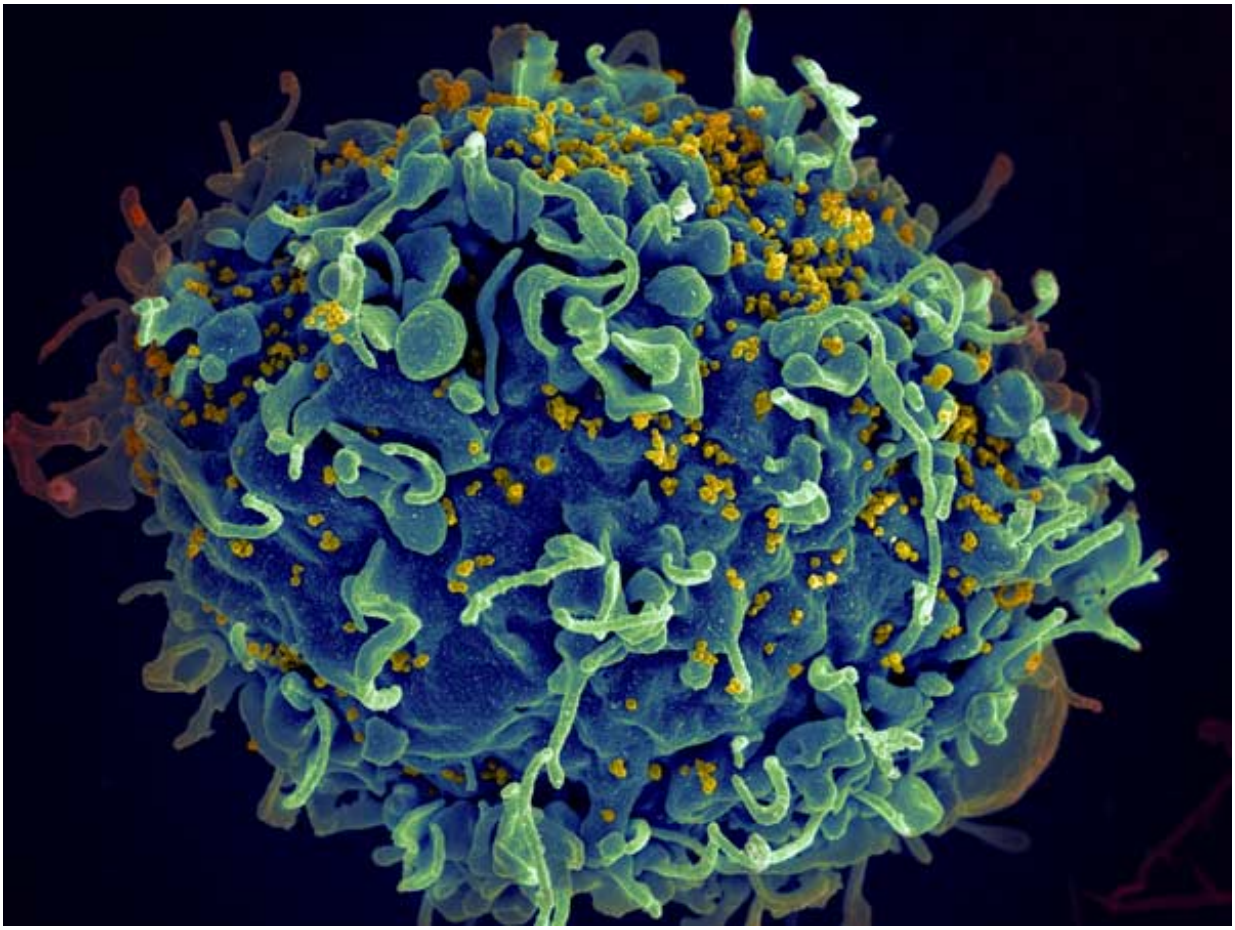

HIV (yellow) infecting a human immune cell. Credit: Seth Pincus, Elizabeth Fischer and Austin Athman, National Institute of Allergy and Infectious Diseases, National Institutes of Health

Immunity often calls to mind the adaptive immune response, made up of antibodies and T cells that learn to fight specific pathogens after infection or vaccination. But the immune system also has an innate immune response, which uses a set number of techniques to provide a swift, non-specialized response against pathogens or support the adaptive immune response.

In the past few years, however, scientists have found that certain parts of the innate immune response can, in some instances, also be trained in response to infectious pathogens, such as HIV. Xu Yu, MD, a Core Member of the Ragon Institute of MGH, MIT and Harvard, and colleagues recently published a study in the *Journal of Clinical Investigation* which showed that elite controllers, a rare subset of people whose immune system can control HIV without the use of drugs, have myeloid dendritic cells, part of the innate immune response, that display traits of a trained innate immune cell.

"Using RNA-sequencing technology, we were able to identify one long-noncoding RNA called MIR4435-2HG that was present at a higher level in elite controllers' myeloid dendritic cells, which have enhanced immune and metabolic states," says Yu. "Our research shows that MIR4435-2HG might be an important driver of this enhanced state, indicating a trained response."

Myeloid dendritic cells' primary job is to support T cells, which are key to the elite controllers' ability to control HIV infection. Since MIR4435-2HG was found in higher levels only in cells from elite controllers, Yu explains, it may be part of a learned immune response to infection with HIV. Myeloid dendritic cells with increased MIR4435-2HG also had higher amounts of a protein called RPTOR, which drives metabolism. This increased metabolism may allow the myeloid dendritic cells to better support the T cells controlling the HIV infection.

"We used a novel sequencing technology, called CUT&RUN, to study the DNA of these cells," says postdoctoral fellow Ciputra Hartana, MD, Ph.D., the paper's first author. "It allowed us to study epigenetic modifications like MIR4435-2HG, which are molecules that bind to the DNA and change how, or if, the DNA is read by the cell's machinery."

The team found that MIR4435-2HG might work by attaching to the DNA near the location of the RPTOR gene. The bound MIR4435-2HG would then encourage the cell's machinery to make more of the RPTOR protein, using the instructions found in the RPTOR gene. This type of epigenetic modification, a trained response to HIV infection, would allow the myeloid dendritic cells to stay in an increased metabolic state and therefore provide long-term support to the T cells fighting the virus.

"Myeloid dendritic cells are very rare immune cells, accounting for only 0.1-0.3% of cells found in human blood," says Yu. "We were fortunate and thankful to have access to hundreds of millions of blood cells from the many study participants who have donated their blood to support our HIV research. These donations were key to making this discovery."

Understanding exactly how elite controllers' immune systems can control HIV is a key part of HIV cure research. If scientists can understand how elite controllers suppress this deadly virus, they may be able to develop treatments that allow other people living with HIV to replicate the same immune response, removing the need for daily medication to control the virus and achieving what is known as a functional cure.

More information: Ciputra Adijaya Hartana et al, Long noncoding RNA MIR4435-2HG enhances metabolic function of myeloid dendritic cells from HIV-1 elite controllers, *Journal of Clinical Investigation* (2021). DOI: 10.1172/JCI146136

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