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Starve a virus, feed a cure? Findings show how some cells protect themselves against HIV

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A protein that protects some of our immune cells from the most common and virulent form of HIV works by starving the virus of the molecular building blocks that it needs to replicate, according to research published online in *Nature Immunology*.

The finding comes from an international team of researchers including scientists from the University of Rochester Medical Center, NYU Langone Medical Center, several institutions in France – and a graduate student who is a political refugee from Africa and is now at work in a Rochester laboratory, intent on helping his people who have been devastated by the HIV epidemic.

While researchers hope the work will one day lead to a way to make anti-HIV drugs more effective by increasing their potency against the virus, they're also excited about its implications for our knowledge of other pathogens, such as herpes viruses, which use the same machinery within our cells that HIV does to replicate.

"The findings may explain why certain anti-HIV drugs used today are more effective under some circumstances and not others," said Baek Kim, Ph.D., professor of Microbiology and Immunology at the University of Rochester Medical Center and one of three corresponding authors of the paper. "It also provides new insights on how many other viruses that afflict people operate in the body."

The work centers on a protein known as SAMHD1, which is found in white blood cells known as macrophages and related cells known as dendritic cells. Last year scientists discovered that the molecule makes it difficult for HIV-1 to infect macrophages – cells that specialize in gobbling up and destroying invaders like viruses.

Now researchers have discovered that the molecule cuts off the supply line of the raw material that HIV needs to create DNA and replicate. That raw material, dNTP, comprises the building blocks of DNA, and without it, HIV can't recreate its DNA in our cells.

The team found that SAMHD1 destroys most of these building blocks, making it nearly impossible for HIV-1 to replicate itself where SAMHD1 resides – the macrophages. Instead, HIV-1 uses the macrophage as a safe haven, surviving in patients for years as it dodges the immune system as well as the drugs designed to kill it. It's thanks largely to its ability to hide out in the body that HIV is able to survive for decades and ultimately win out against the body's relentless immune assault.

The team also discovered how a protein in the other common type of HIV – HIV-2, which is found mainly in Africa – knocks out SAMHD1. They found that the protein Vpx destroys SAMHD1, clearing the way for HIV-2 to infect macrophages. While scientists have known that HIV-2 needs Vpx to infect macrophages, they hadn't known precisely why.

Interestingly, while one might think that a virus that is able to replicate itself in crucial cells like macrophages might be more dangerous than one that cannot, that's not the case with HIV. HIV-2 is actually less virulent than HIV-1.

"We don't know precisely how SAMHD1 and Vpx affect the virulence

of HIV-1 and HIV-2, but it's something we're actively exploring," said Kim. "In this case, the ability of HIV-2 to replicate more quickly in macrophages does not help it become more virulent."

One possibility is that, like a starving man who becomes more and more desperate for food, the virus – when faced with a shortage of raw materials – puts its mutation gear into overdrive, creating more mutations in an effort to circumvent the pathway blocked by SAMHD1. Such constant mutations are one feature of HIV that makes it so challenging to treat patients.

"It makes sense that a mechanism like this is active in macrophages," said Kim. "Macrophages literally eat up dangerous organisms, and you don't want those organisms to have available the cellular machinery needed to replicate. And macrophages themselves don't need it, because they don't replicate. So macrophages have SAMHD1 to get rid of the raw material those organisms need to copy themselves. It's a great host defense.

"The work suggests new ways to target virus replication in macrophages, a critically important cell population that serves as a key reservoir of virus infection and a contributor to HIV-induced disease," added Kim.

At Rochester, Kim was joined in the research by graduate student Waaqo Daddacha, one of two first authors of the paper. A native of the Oromia region of Ethiopia, Daddacha came as a political refugee to the United States. He started out as a computer programmer, then decided to pursue HIV research as a way to help his homeland, where the rate of HIV is one of the highest in the world. As an undergraduate in Minnesota, he visited several laboratories around the nation that focus on HIV, eventually settling on the Kim lab, which he joined four years ago.

"Back home, many people are infected with HIV, and many people are

dying because of it. I wanted to contribute to help solve the problem, and that's why I decided to pursue HIV research," said Daddacha, who still has family in Oromia. In Kim's lab he is focusing on understanding drug resistance among HIV patients and on finding ways to limit resistance to make the drugs more effective in patients.

Provided by University of Rochester Medical Center