New strategy to halt HIV growth: Block its sugar and nutrient pipeline

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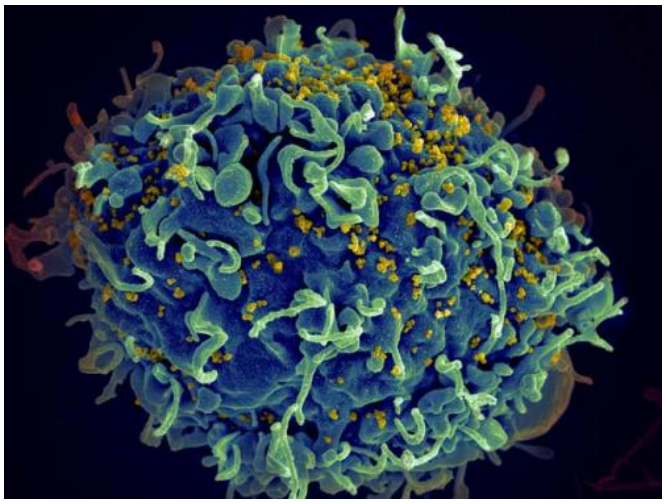

HIV, the AIDS virus (yellow), infecting a human immune cell. Credit: Seth Pincus, Elizabeth Fischer and Austin Athman, National Institute of Allergy and Infectious Diseases, National Institutes of Health.

HIV has a voracious sweet tooth, which turns out to be its Achilles' heel, reports a new study from Northwestern Medicine and Vanderbilt University.

After the virus invades an activated immune cell, it craves sugar and nutrients from the cell to replicate and fuel its wild growth throughout the body.

Scientists discovered the switch that turns on the immune cell's abundant sugar and nutrient pipeline. Then they blocked the switch with an experimental compound, shutting down the pipeline, and, thereby, starving HIV to death. The virus was unable to replicate in human cells in vitro.

The discovery may have applications in treating cancer, which also has an immense appetite for sugar and other nutrients in the cell, which it needs to grow and spread.

The study will be published May 28 in *PLOS Pathogens*.

"This compound can be the precursor for something that can be used in the future as part of a cocktail to treat HIV that improves on the effective medicines we have today," said corresponding study author, Harry Taylor, research assistant professor in medicine at Northwestern University Feinberg School of Medicine.

"It's essential to find new ways to block HIV growth, because the virus is constantly mutating," said Taylor, also a scientist at Northwestern Medicine's HIV Translational Research Center. "A drug targeting HIV that works today may be less effective a few years down the road, because HIV can mutate itself to evade the drug."

HIV needs to grow in a type of immune cell (CD4+ T cell) that is active, meaning it is already responding to pathogens in the blood. Activation increases the T cell's supplies of sugar and other critical nutrients needed for both cell and virus growth.

Until now, no one knew the first step that signaled a newly activated T cell to stock up on sugar and other nutrients. Those nutrients become the building blocks of genetic material the cell and the virus need to grow.

Northwestern and Vanderbilt scientists figured out that first step in stocking the T cell's pantry involved turning on a cell component called phospholipase D1 (PLD1). Then they used an experimental compound to block PLD1 and shut down the pipeline.

This is believed to be the first time scientists have targeted the virus's ability to pilfer the cell's pantry to stop its growth. A related approach was attempted in the 1990s but the drugs used sometimes killed healthy cells and had serious side

effects in HIV patients.

The Northwestern team's new approach is a gentler, non-toxic way to block HIV access to the cell's "pantry."

New strategy could reduce organ damage

The approach has additional benefits beyond the initial goal of preventing HIV from reproducing.

The compound also slowed the proliferation of the abnormally activated immune cells, the study found. Current HIV medications stop HIV growth but do not affect the abnormal excess activation and growth of immune cells triggered by HIV.

The excess immune cell growth is believed to contribute to the life-long persistence of HIV and leads to excess inflammation that causes premature organ damage in HIV patients—even when the virus is suppressed by current medicines.

"Perhaps this new approach, which slows the growth of the immune cells, could reduce the dangerous inflammation and thwart the life-long persistence of HIV," Taylor said.

HIV's hunt for sugar and world domination

When HIV enters the bloodstream, it searches out active CD4+ T cells, the commanders-in-chief of the immune system. These active cells are already responding to other pathogens or allergens in the blood and are guzzling glucose and amino acids from the blood, which they need to churn out the building blocks of DNA. The cells' factories are at full throttle, making these building blocks to produce an army of soldiers to fight that cold that has just started to give you a sore throat or the chills.

When HIV finds an active CD4+ T cell, it hijacks the cell's glucose supply and factory to build millions of copies of itself and invade other cells.

"It's a monster that invades the cell and says 'feed me!' " Taylor said. "It usurps the entire production line."

Cancer cells crave sugar, too

The idea to test this compound for HIV evolved from Taylor's relationship with chemists at Vanderbilt University, where he was on faculty before he joined Northwestern in 2012.

Taylor knew his Vanderbilt colleagues had identified a compound in their massive screening for potential drugs that block the growth of breast cancer cells. The compound stopped breast cancer cells from spreading by blocking PLD1. Taylor and his Vanderbilt colleagues wondered if blocking this same enzyme in the CD4+ T cell would cut off HIV's use of the cell's nutrient supply and slow the invading HIV.

That's exactly what their study shows. In vitro, the compound shut off the glucose and other nutrients and prevented HIV from having enough building blocks of DNA to make the genetic material it needed to reproduce.

Now, Taylor wants to identify even more compounds for development into future medicines that will limit re-stocking of the cell's pantry to starve HIV—without harming cells.

"This discovery opens new avenues for further research to solve today's persisting problems in treating HIV infection: avoiding virus resistance to medicines, decreasing the inflammation that leads to premature aging, and maybe even one day being able to cure HIV infection," said Dr. Richard D'Aquila, director of Northwestern's HIV Translational Research Center. He also is the Howard Taylor Ricketts Professor of Medicine at Feinberg and a physician at Northwestern Memorial Hospital.

Provided by Northwestern University