

Unexpected find opens up new front in effort to stop HIV

January 23 2011

HIV adapts in a surprising way to survive and thrive in its hiding spot within the human immune system, scientists have learned. While the finding helps explain why HIV remains such a formidable foe after three decades of research – more than 30 million people worldwide are infected with HIV – it also offers scientists a new, unexpected way to try to stop the virus.

The work by researchers at the University of Rochester Medical Center and Emory University was published Dec. 10 in the [Journal of Biological Chemistry](#).

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. One of the virus's favorite hiding spots is an immune cell called a macrophage, whose job is to chew up and destroy foreign invaders and cellular debris.

For more than 15 years, Baek Kim, Ph.D., has been fascinated by HIV's ability to take cover in a cell whose very job is to kill foreign cells. In the last couple of years Kim, professor of Microbiology and Immunology at the University of Rochester Medical Center, has teamed with Emory scientist Raymond F. Schinazi, Ph.D., D.Sc., director of the Laboratory of Biochemical Pharmacology at Emory's Center for AIDS Research, to test whether the virus is somehow able to sidestep its usual way of replicating when it's in the macrophage.

The pair found that when HIV faces a shortage of the molecular machinery needed to copy itself within the macrophage, the virus adapts by bypassing one of the molecules it usually uses and instead tapping another molecule that is available.

Normally, the virus uses dNTP (deoxynucleoside triphosphate, the building blocks for making the viral genetic machinery) to get the job done, but dNTP is hardly present in macrophages – macrophages don't need it, since they don't replicate. But macrophages do have high levels of a closely related molecule called rNTP (ribonucleoside triphosphate), which is more versatile and is used in cells in a variety of ways. The team found that HIV uses primarily rNTP instead of dNTP to replicate inside macrophages.

"The virus would normally just use dNTP, but it's simply not available in great quantities in the macrophage. So HIV begins to use rNTP, which is quite similar from a chemical perspective. This is a surprise," said Kim. "The virus just wants to finish replicating, and it will utilize any resource it can to do so."

When the team blocked the ability of the virus to interact with rNTP, HIV's ability to replicate in macrophages was slashed by more than 90 percent.

The work opens up a new front in the battle against HIV. Current drugs generally target dNTP, not rNTP, and take aim at the infection in immune cells known as CD4+ T cells. The new research opens up the possibility of targeting the virus in macrophages – where the virus is out of reach of most of today's drugs.

"The first cells that HIV infects in the genital tract are non-dividing target cell types such as macrophages and resting T cells" said Kim. "Current drugs were developed to be effective only when the infection

has already moved beyond these [cells](#). Perhaps we can use this information to help create a microbicide to stop the [virus](#) or limit its activity much earlier."

Kim notes that a compound that targets rNTP already exists. Cordycepin in an experimental compound, derived from wild mushrooms, that is currently being tested as an anti-cancer drug. The team plans to test similar compounds for anti-HIV activity.

"This significant breakthrough was unappreciated prior to our paper. We are now exploiting new anti-HIV drugs jointly based on this novel approach that are essentially not toxic and that can be used to treat and prevent HIV infections," said Schinazi, who has developed several of the drugs currently used to treat HIV patients.

Provided by University of Rochester Medical Center

Citation: Unexpected find opens up new front in effort to stop HIV (2011, January 23) retrieved 20 April 2024 from <https://phys.org/news/2011-01-unexpected-front-effort-hiv.html>

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