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Discovery in how HIV thwarts the body's natural defense opens up new target for drug therapies

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Natural killer cells are major weapons in the body's immune system. They keep the body healthy by knocking off tumors and cells infected with viruses, bombarding them with tiny lethal pellets. But natural killer cells are powerless against HIV, a fact that has bedeviled science for over 20 years.

Now, researchers at Rush University Medical Center have discovered the reason why.

The study, posted online this week in the prestigious peer-reviewed journal *Cell Host & Microbe*, marks the "beginning of a fascinating story that will shed new light on an important but still poorly understood aspect of the interaction of HIV with natural killer cells," according to an editorial in the journal.

"With this information, we now have a major new target for drug therapies that could potentially stop HIV and allow the body's natural killer cells to do what they are designed to do – protect the body from this lethal virus," said Edward Barker, PhD, associate professor of immunology and microbiology at Rush University and lead author of the study.

HIV, like any virus, is bent on producing progeny. It infects a cell, replicates itself over and over, and spreads throughout the body by using

its "accessory" proteins to both take over the machinery of the cells it inhabits and thwart the arsenal of immunological cells that might destroy it.

Oddly, some of these proteins work at cross purposes. One, the Vpr protein, initiates what is called DNA damage repair, stopping the host cell in its tracks so that the virus can take over. But that action also sends a message to the cell surface that something is amiss. A ligand, called ULBP, is sent to the surface of the cell, which the prowling natural killer cells recognize and latch onto – the initial steps just before moving in for a kill.

Meanwhile, another protein produced by HIV prevents the cytotoxic T cells of the immune system from homing in on the HIV-infected cell and obliterating it. But this same protein also provokes the natural killer cells into action by shutting down an inhibitory mechanism that would hold the killer cells back.

If all worked as it should to protect the body from HIV, the natural killer cells would start firing their lethal pellets. But they don't, and that is what has puzzled scientists for so long.

"The barrel of the shotgun is loaded, but the trigger still has to be pulled," said Barker.

Barker and his colleagues now know why the trigger is not pulled: because yet another protein, called NTB-A (for Natural killer T-cell and B-cell Antigen), has virtually disappeared from the surface of the infected cell. Without NTB-A in place, the natural killer cells don't start firing the guns.

The culprit, the researchers found, is a protein made by HIV called Vpu, which holds NTB-A inside the cell and prevents it from reaching the cell

surface.

When the researchers altered the Vpu protein, allowing NTB-A to migrate to the cell membrane, the natural killer cells blasted the HIV-infected cells – proof that both the ULBP ligand and NTB-A are needed before the natural killer cells will start shooting.

Barker said that the finding is extremely exciting not only because it resolves a longstanding puzzle in how HIV is able to evade the body's innate immune response but also because it opens up new possibilities for combating HIV.

Provided by Rush University Medical Center