Study: Cells have a natural defense against HIV

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Scientists here have discovered a previously unknown mechanism that cells use to fight off the human immunodeficiency virus (HIV), the cause of AIDS. The findings indicate that two proteins that normally help repair cellular DNA can also destroy the DNA made by HIV after it enters a human cell. This HIV DNA is essential for the virus to survive and reproduce.

The study was led by researchers at The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC – James) and published in the *Proceedings of the National Academy of Sciences*.

The findings could lead to a possible new strategy for treating HIV infection and AIDS, one that might complement current therapies and would probably be less susceptible to viral drug resistance – an increasingly urgent dilemma for patients and doctors.

Currently, doctors treat people with AIDS using combinations of drugs that target the virus itself. These drugs do not eliminate HIV from the body, but they do block its ability to reproduce and spread, and they restore most people with AIDS to good health.

In time, however, HIV can develop mutations that render those drugs ineffective.

"Our findings identify a new potential drug target, one that involves a

natural host defense," says principal investigator Richard Fishel, professor of molecular virology, immunology and molecular genetics and a researcher with the OSUCCC – James. "HIV treatments that target cellular components should be far less likely to develop resistance."

Fishel's laboratory colleague and first author Kristine Yoder discovered the role of the cellular repair proteins while trying to answer a different question.

Before HIV infects a cell, it carries its genetic material in the form of RNA, or ribonucleic acid. Once inside a cell, the virus makes a copy of its genes in the form of DNA. This DNA copy – known as cDNA – then travels to the cell nucleus. There, it becomes inserted, or integrated, into the cell's DNA. There it is known as a provirus, and it will generate new HIV in an infected patient and eventually cause AIDS.

The process of integration, which is absolutely required for a productive infection, begins with the help of an enzyme, integrase, which is supplied by HIV. But the job is finished by DNA repair enzymes provided by the host cell.

Yoder originally wanted to identify which repair enzymes were involved.

During these experiments, Yoder learned that cells with high levels of two proteins called XPB and XPD had lower levels of HIV provirus in their chromosomes. Both proteins help the cell repair damaged DNA.

Yoder, Fishel and their collaborators then introduced mutations into the genes for the two proteins, which crippled the proteins' ability to repair DNA. When cells with these mutations were then infected with HIV, they showed higher levels of provirus in their chromosomes.

"When we weakened a DNA repair pathway, we got more integration of

the provirus," Yoder says. "This was a total surprise."

Next, the researchers wanted to learn whether the normal cells used in the study had lower proviral levels because they were making less HIV cDNA or because the HIV cDNA was being destroyed before it integrated.

To answer that question, the researchers used antiretroviral drugs known as non-nucleoside reverse transcriptase inhibitors (NNRTIs). These drugs prevent HIV from making the cDNA copy of its RNA genetic material. The researchers exposed newly infected cells to the drugs and then measured changes in the amount of cDNA over time.

These experiments showed that the cDNA was destroyed faster in cells with normal XPB and XPD compared to cells with mutant XPB or XPD. Cells with normal XPB protein lost half their proviral DNA after 4.6 hours, while cells with low levels of the protein lost half after about 7.7 hours. Similarly, cells with normal XPD protein lost half the proviral DNA after 3.5 hours, while cells with mutated protein lost half after five hours.

These experiments also showed that the two proteins destroyed the HIV cDNA before it is integrated into the chromosome.

"Overall, our results indicate that these two DNA repair proteins participate in the destruction of HIV cDNA in cells," Fishel says. "This process reduces the pool of HIV cDNA that can integrate into host chromosomes, thereby protecting cells from infection."

The researchers are now working to learn how the proteins destroy the HIV cDNA. These studies could lead to drugs that might help the proteins destroy more HIV cDNA and in shorter time.

Source: Ohio State University