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Research findings open new front in fight against AIDS virus

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A research group supported by the National Institutes of Health (NIH) has uncovered a new route for attacking the human immunodeficiency virus (HIV) that may offer a way to circumvent problems with drug resistance. In findings published today in the online edition of the *Proceedings of the National Academy of Sciences*, the researchers report that they have blocked HIV infection in the test tube by inactivating a human protein expressed in key immune cells.

Most of the drugs now used to fight HIV, which is the retrovirus that causes acquired immune deficiency syndrome (AIDS), target the virus's own proteins. However, because HIV has a high rate of genetic mutation, those viral targets change quickly and lead to the emergence of drug-resistant viral strains. Doctors have tried to outmaneuver the rapidly mutating virus by prescribing multi-drug regimens or switching drugs. But such strategies can increase the risk of toxic side effects, be difficult for patients to follow and are not always successful. Recently, interest has grown in attacking HIV on a new front by developing drugs that target proteins of human cells, which are far less prone to mutations than are viral proteins.

In the new study, Pamela Schwartzberg, M.D., Ph.D., a senior investigator at the National Human Genome Research Institute (NHGRI), part of NIH; Andrew J. Henderson, Ph.D., of Boston University; and their colleagues found that when they interfered with a human protein called interleukin-2-inducible T cell kinase (ITK) they inhibited HIV infection of key human immune cells, called T cells. ITK

is a signaling protein that activates T cells as part of the body's healthy immune response.

"This new insight represents an important contribution to HIV research," said NHGRI Scientific Director Eric D. Green, M.D., Ph.D. "Finding a cellular target that can be inhibited so as to block HIV validates a novel concept and is an exciting model for deriving potential new HIV therapies."

When HIV enters the body, it infects T cells and takes over the activities of these white blood cells so that the virus can replicate. Eventually, HIV infection compromises the entire immune system and causes AIDS. The new work shows that without active ITK protein, HIV cannot effectively take advantage of many signaling pathways within T cells, which in turn slows or blocks the spread of the virus.

"We were pleased and excited to realize the outcome of our approach," Dr. Schwartzberg said. "Suppression of the ITK protein caused many of the pathways that HIV uses to be less active, thereby inhibiting or slowing HIV replication."

In their laboratory experiments, the researchers used a chemical inhibitor and a type of genetic inhibitor, called RNA interference, to inactivate ITK in human T cells. Then, the T cells were exposed to HIV, and the researchers studied the effects of ITK inactivation upon various stages of HIV's infection and replication cycle. Suppression of ITK reduced HIV's ability to enter T cells and have its genetic material transcribed into new virus particles. However, ITK suppression did not interfere significantly with T cells' normal ability to survive, and mice deficient in ITK were able to ward off other types of viral infection, although antiviral responses were delayed.

"ITK turns out to be a great target to examine," said Dr. Schwartzberg,

noting that researchers had been concerned that blocking other human proteins involved in HIV replication might kill or otherwise impair the normal functions of T cells.

According to Dr. Schwartzberg, ITK already is being investigated as a therapeutic target for asthma and other diseases that affect immune response. In people with asthma, ITK is required to activate T cells, triggering lung inflammation and production of excess mucus.

“There are several companies who have published research about ITK inhibitors as part of their target program,” Schwartzberg said. “We hope that others will extend our findings and that ITK inhibitors will be pursued as HIV therapies.”

Source: National Human Genome Research Institute