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Study holds promise for new way to fight HIV

Novel approach may address viral resistance

Researchers have confirmed for the first time the benefit of an innate defense system present in the few patients who remain healthy after years of infection with HIV despite receiving no treatment, according to an article published in the September edition of the Journal of Virology. The study found that the subset of HIV-infected patients referred to as long-term survivors or nonprogressors have higher amounts of a key enzyme in their white blood cells. At the same time, a related biotech company is poised to begin preclinical testing on a drug designed to confer similar protection on most HIV patients.

Approximately five percent of patients with HIV, or human immunodeficiency virus, do not develop AIDS, or do so very slowly. Researchers have been trying for years to understand what sets long-term nonprogressors apart. Past research suggested that such patients maintain higher levels of an enzyme in white blood cells called APOBEC-3G (A3G), and the new study confirmed it in the first experiments on human cells.

Researchers at the University of Rochester Medical Center believe that A3G "edits," or introduces changes in, the HIV genetic code every time the virus copies itself. By doing so, A3G corrupts the HIV gene code and prevents the virus from reproducing. Unfortunately, HIV has evolved to counter A3G with viral infectivity factor (Vif), a protein that "grabs" A3G and tricks the body into destroying it. With the "editing enzyme" gone, HIV is free to overwhelm the immune system, leaving patients vulnerable to AIDS infections that take three million lives per year.

"Unlike nonprogressors, we believe that most people do not make enough A3G to overcome the efforts by Vif to shut it down," said Harold C. Smith, Ph.D., professor of Biochemistry and Biophysics at the University of Rochester Medical Center, co-author of the J. Virology paper and a founder of the biotech company, OyaGen Inc. "Our work supports Michael Malim's seminal discovery while at the University of Pennsylvania,

which suggested that protecting whatever amount of A3G that people do have from Vif represents a new way to attack HIV."

Study Details

For two decades, medical center researchers have worked to determine how families of editing enzymes, including A3G, make changes to DNA and RNA. The immune system recognizes the ability of editing enzymes to cause rapid genetic change and unleashes them on viral DNA. Researchers believe that the enzymes change the HIV genetic code so extensively that the virus loses the ability to code for its own proteins and can no longer reproduce.

To confirm that A3G offers strong protection against HIV, researchers in the current study measured A3G levels in the immune cells of six people not infected with HIV and in 25 patients with the virus. Of those with HIV, eight were long-term nonprogressors and seventeen had normal disease progression. None of those studied were receiving antiretroviral therapy at the time blood was drawn.

In the study, the researchers found that higher levels of A3G closely corresponded to lower HIV viral levels. In addition, higher levels of A3G were closely associated with higher CD4 T cell counts. Unless destroyed by HIV, helper T cells with CD-4 receptors target bodily invaders for full-scale attack by the immune system. Furthermore, the team determined that nonprogressors have the most A3G editing enzyme, followed by those not infected with HIV and lastly by those progressing toward full-blown AIDS.

"Our study is immediately relevant to HIV research in several important areas," said Xia Jin, M.D., Ph.D., assistant professor of Medicine at the medical center and lead author of the J. Virology paper. "In diagnostics, the work will establish a new prognostic marker for AIDS by enabling the measurement of A3G levels in HIV-infected patients. It will also clarify a previously unrecognized mechanism that underlies slower disease progression in long-term nonprogressors. Lastly, the data suggest that protecting A3G from viral attack may be an important new way to treat AIDS and other viral infections," Jin said. A New Approach to HIV Treatment

Smith, with support from the University of Rochester Technology Seed Fund, formed OyaGen in 2003. The biotech startup seeks to exploit a family of 14 editing enzymes and related proteins as novel targets for the development of pharmaceuticals.

While OyaGen's platform technology has the potential to address several disease areas, the first focus is the treatment of HIV. The company's lead drug candidate interferes with ability of Vif to disable A3G. The experimental treatment is based on the work of Hui Zhang, M.D., Ph.D., associate professor of Medicine at Thomas Jefferson University (TJU) and on technology licensed from TJU.

As a dimer, Vif is able to come together like the two arms in a pair of pliers to "grab" A3G. Once attached to A3G, Vif flags it for destruction as part of an otherwise healthy protein recycling process. OyaGen's drug, a Vif Dimerization Antagonist (VDA), prevents the two halves of Vif from linking up and leaves A3G free to "catastrophically mutate" the HIV genetic code. In early experiments, OyaGen's therapeutic has been successful in reducing HIV infectivity.

OyaGen recently completed an initial $1.5 million fundraising round with investors including the technology seed fund and private individuals. The resources will support research and pave the way for safety, toxicology, bioavailability and mode of delivery studies to begin in October. Based on early successes, the company now seeks to raise between $10 million and $30 million to fund pre-clinical trials and to support negotiations with the U.S. Food and Drug Administration on the submission of a new drug application planned for 2006.

In addition, OyaGen in July signed a licensing agreement with the University of Rochester for rights to the technology developed by Smith. The agreement covers novel drug targets with the aim of protecting A3G from viral attack. It also establishes a laboratory in the university's technology incubator space.

"We hope to develop the first drug that solves the problem of viral resistance, where viral strains have changed so quickly that HIV is resistant to current treatments in 40 percent of new cases," Smith said. "Our theory is that if the virus attempts to outsmart our drug by changing Vif, it will leave itself open to attack by A3G. If early studies go as planned, OyaGen may be able to offer a treatment that HIV cannot easily escape."

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