Medical Xpress

Scientists identify new cellular receptor for HIV

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A cellular protein that helps guide immune cells to the gut has been newly identified as a target of HIV when the virus begins its assault on the body's immune system, according to researchers from the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH).

“The identification of this new receptor opens up new avenues of investigation that may help further elucidate the complex mechanisms of the pathogenesis of HIV infection,” says NIAID Director Anthony S. Fauci, M.D., chief of the Institute’s Laboratory of Immunoregulation (LIR) and senior author of the new study.

Several other immune cell receptors bind to HIV. Most important among these, the CD4 molecule, identified as an HIV receptor in 1984, functions as the principal receptor for HIV. The CCR5 and CXCR4 molecules, discovered in 1996, serve as co-receptors that HIV uses to enter its target cells. In the new study, which appears online Feb. 10, 2008 in *Nature Immunology*, NIAID scientists identify a cell adhesion molecule known as integrin alpha 4 beta 7 as another potentially important receptor for HIV.

Early in the course of HIV infection, the virus rapidly invades and replicates in gut-associated lymphoid tissue (GALT), the immune cells of the gut. Once seeded with HIV, the gut is rapidly depleted of CD4+ T cells, the main target of HIV, triggering the process that ultimately leads to AIDS.

“In the very early days of infection, it is in the GALT where most of the damage caused by HIV occurs,” says Elena Martinelli, Ph.D., a lead author of the paper and a fellow in Dr. Fauci’s laboratory. “The gut is where the virus really takes hold. We found that integrin alpha 4 beta 7, whose natural function is to direct T cells to the GALT, is also a receptor for HIV. It is very unlikely that this is a coincidence.”

Dr. Martinelli, along with Claudia Cicala, Ph.D., James Arthos, Ph.D., and their colleagues found that the gp120 protein, part of the HIV envelope, binds to integrin alpha 4 beta 7 on CD4+ T cells, which promotes the formation of a stable junction, or synapse, between neighboring cells.

“A synapse is a junction that allows two cells to adhere in a stable way,” says Dr. Arthos. “Many viruses have found a way to trick cells into forming these stable junctions. Now it appears that HIV can also trigger synapse formation.”

Specifically, a short piece of the HIV gp120 protein in a region known as the V2 loop recognizes the alpha 4 chain of the integrin molecule on host cells. This stretch of the V2 loop is similar to part of the naturally occurring molecules that bind integrin alpha 4 beta 7. Thus, it appears that HIV is mimicking the natural molecular partners, or ligands, that normally bind to the receptor. The authors note, however, that some HIV isolates react more strongly to integrin alpha 4 beta 7 than others.

“The ability of a particular virus to bind to integrin alpha 4 beta 7 may determine whether it will have a major impact in targeting the gut lymphoid tissue,” says Dr. Fauci. “This finding could be a significant determinant in the pathogenic mechanisms that lead to AIDS.”

As part of the natural homing process, integrin alpha 4 beta 7 binds to its natural ligands and activates a protein known as LFA-1. According to

Dr. Arthos, HIV can co-opt this process by mimicking the cells' alpha 4 beta 7 receptor natural ligands. When HIV gp120 protein binds to the alpha 4 beta 7 receptor it facilitates the formation of a synapse. Thus, HIV tricks an infected cell into binding to an uninfected cell, enabling HIV to readily gain access to the uninfected cell.

"While this study provides important new information concerning the various mechanisms by which HIV debilitates the human immune system, it also raises new questions and challenges that our laboratory and others will pursue," notes Dr. Cicala.

Source: National Institute of Allergy and Infectious Diseases