

UT pathologists believe they have pinpointed Achilles heel of HIV

July 15 2008

Human Immunodeficiency Virus (HIV) researchers at The University of Texas Medical School at Houston believe they have uncovered the Achilles heel in the armor of the virus that continues to kill millions.

The weak spot is hidden in the HIV envelope protein gp120. This protein is essential for HIV attachment to host cells, which initiate infection and eventually lead to Acquired Immunodeficiency Syndrome or AIDS.

Normally the body's immune defenses can ward off viruses by making proteins called antibodies that bind the virus. However, HIV is a constantly changing and mutating virus, and the antibodies produced after infection do not control disease progression to AIDS. For the same reason, no HIV preventative vaccine that stimulates production of protective antibodies is available.

The Achilles heel, a tiny stretch of amino acids numbered 421-433 on gp120, is now under study as a target for therapeutic intervention. Sudhir Paul, Ph.D., pathology professor in the UT Medical School, said, "Unlike the changeable regions of its envelope, HIV needs at least one region that must remain constant to attach to cells. If this region changes, HIV cannot infect cells. Equally important, HIV does not want this constant region to provoke the body's defense system. So, HIV uses the same constant cellular attachment site to silence B lymphocytes - the antibody producing cells. The result is that the body is fooled into making abundant antibodies to the changeable regions of HIV but not to its cellular attachment site. Immunologists call such regions superantigens. HIV's cleverness is unmatched. No other virus uses this

trick to evade the body's defenses."

Paul is the senior author on a paper about this theory in a June issue of the journal *Autoimmunity Reviews*. Additional data supporting the theory are to be presented at the XVII International AIDS Conference Aug. 3-8 in Mexico City in two studies titled "Survivors of HIV infection produce potent, broadly neutralizing IgAs directed to the superantigenic region of the gp120 CD4 binding site" and "Prospective clinical utility and evolutionary implication of broadly neutralizing antibody fragments to HIV gp120 superantigenic epitope."

First reported in the early 1980s, HIV has spread across the world, particularly in developing countries. In 2007, 33 million people were living with AIDS, according to a report by the World Health Organization and the United Nations.

Paul's group has engineered antibodies with enzymatic activity, also known as abzymes, which can attack the Achilles heel of the virus in a precise way. "The abzymes recognize essentially all of the diverse HIV forms found across the world. This solves the problem of HIV changeability. The next step is to confirm our theory in human clinical trials," Paul said.

Unlike regular antibodies, abzymes degrade the virus permanently. A single abzyme molecule inactivates thousands of virus particles. Regular antibodies inactivate only one virus particle, and their anti-viral HIV effect is weaker.

"The work of Dr. Paul's group is highly innovative. They have identified antibodies that, instead of passively binding to the target molecule, are able to fragment it and destroy its function. Their recent work indicates that naturally occurring catalytic antibodies, particularly those of the IgA subtype, may be useful in the treatment and prevention of HIV

infection," said Steven J. Norris, Ph.D., holder of the Robert Greer Professorship in the Biomedical Sciences and vice chair for research in the Department of Pathology and Laboratory Medicine at the UT Medical School at Houston.

The abzymes are derived from HIV negative people with the autoimmune disease lupus and a small number of HIV positive people who do not require treatment and do not get AIDS. Stephanie Planque, lead author and UT Medical School at Houston graduate student, said, "We discovered that disturbed immunological events in lupus patients can generate abzymes to the Achilles heel of HIV. The human genome has accumulated over millions of years of evolution a lot of viral fragments called endogenous retroviral sequences. These endogenous retroviral sequences are overproduced in people with lupus, and an immune response to such a sequence that resembles the Achilles heel can explain the production of abzymes in lupus. A small minority of HIV positive people also start producing the abzymes after decades of the infection. The immune system in some people can cope with HIV after all."

Carl Hanson, Ph.D., who heads the Retrovirus Diagnostic Section of the Viral and Rickettsial Disease Laboratory of the California Department of Public Health, has shown that the abzymes neutralize infection of human blood cells by diverse strains of HIV from various parts of the world. Human blood cells are the only cells that HIV infects.

"This is an entirely new finding. It is a novel antibody that appears to be very effective in killing the HIV virus. The main question now is if this can be applied to developing vaccine and possibly used as a microbicide to prevent sexual transmission," said David C. Montefiori, Ph.D., director of the Laboratory for AIDS Vaccine Research & Development at Duke University Medical Center. The abzymes are now under development for HIV immunotherapy by infusion into blood. They

could also be used to guard against sexual HIV transmission as topical vaginal or rectal formulations.

"HIV is an international priority because we have no defense against it," Paul said. "Left unchecked, it will likely evolve into even more virulent forms. We have learned a lot from this research about how to induce the production of the protective abzymes on demand. This is the Holy Grail of HIV research -- development of a preventative HIV vaccine."

Source: University of Texas Health Science Center at Houston

Citation: UT pathologists believe they have pinpointed Achilles heel of HIV (2008, July 15) retrieved 20 March 2024 from <https://medicalxpress.com/news/2008-07-ut-pathologists-achilles-heel-hiv.html>

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