MedicalXpress

Viral recombination another way HIV fools the immune system

July 21 2008

When individuals infected with HIV become infected with a second strain of the virus, the two viral strains can exchange genetic information, creating a third, recombinant strain of the virus. It is known that the presence of multiple viral strains, called superinfection, frequently leads to a loss of immune control of viral levels. Now a study from the Partners AIDS Research Center at Massachusetts General Hospital (PARC/MGH) shows that how and where viral strains swap DNA may be determined by the immune response against the original infecting strain. Their report will appear in the *Journal of Experimental Medicine* and has been released online.

"The implication that recombination events are selected by immune responses identifies a new mechanism for the virus to escape the patient's immune system, which would present additional challenges to vaccine design," says Hendrik Streeck, MD, PhD, of PARC/MGH, one of the paper's lead authors. "This finding also has worldwide implications for the development of more complex strains of HIV."

Part of the immune system's response against HIV is carried out by HIV-specific CD8 T cells, also called cytotoxic T lymphocytes (CTLs), which can identify and kill virus-infected cells. Previous PARC/MGH research showed that the effectiveness of the CTL response varies depending on which version or allele of an immune system molecule called HLA Class I an individual has inherited. The current study was undertaken to investigate why an HIV-positive research participant known to have a powerfully protective Class I allele called HLA-B27 began to experience

rapid increases in viral levels much sooner than would have been expected.

An examination of blood samples from this individual revealed that his immune response against HIV had predictably controlled the virus for about a year and a half after he was first diagnosed. The effective CTL response was primarily directed against a short segment of the Gag protein typically targeted in HLA-B27 patients.

Analysis after the abrupt increase in viral levels showed that the patient had become infected with a second strain of HIV, and two months later it was found that the two strains had exchanged portions of their Gag sequences initially targeted by his CTLs, allowing the virus to escape from that immune response. The patient's viral loads stabilized for a while but rose again several months later, when it was found that a second HIV mutation that more effectively evades control by HLA-B27 had developed, possibly in response to a second recombination of viral sequences.

"The first Gag recombination event facilitated escape from the primary immune response, shortly after which the immune response recovered to recognize this mutant strain," Streeck explains. "After the second recombination event and emergence of a more potent mutation, there was a dramatic reduction in the CTL response against both versions, leading to a significant increase in viral loads."

Todd Allen, PhD, of PARC-MGH, the study's senior author adds that, while recombination itself appears to be a random event, recombinant strains that are better able to evade the immune system are likely to become dominant through natural selection. He also stresses that even patients whose immune systems can partially control HIV should avoid a secondary infection that could lead to the development of an uncontrollable, recombinant viral strain.

Streeck notes, "Given the growing frequency of recombinant HIV strains worldwide, we need to better understand how immune system pressures may be driving their development and also determine how frequently patients exposed to a second strain of HIV become superinfected." He is a research fellow in Medicine at Harvard Medical School, where Allen is an associate professor of Medicine.

Source: Massachusetts General Hospital