Despite countless changes, original HIV infection lurks within

June 29 2010

Scientists have been surprised to learn that, despite thousands of changes that viruses like HIV undergo in rapid fashion to evade the body's immune system, the original version that caused the infection is still present in the body months later.

The finding, published in the June issue of the Journal of Virology, is the result of an uncommonly detailed look at the cat-and-mouse action that takes place in an organism shortly after infection. The work is aimed at understanding the earliest stages of infection by HIV more thoroughly, to help scientists develop ways either to quash the infection outright or to develop a vaccine to prevent infection.

The research, which was conducted by scientists at the University of Rochester Medical Center, is based on an analysis of more than 100,000 genetic snippets of a virus known as SIV, or simian immunodeficiency virus, which infects monkeys and is a close cousin of HIV.

While HIV has flummoxed scientists for nearly three decades, that's certainly not because our immune system fails to respond. Rather, within two or three weeks of infection, the onslaught of immune cells puts the virus on the run to such an extent that the virus must mutate rapidly to evade the body's defenses.

HIV changes quickly and continually, creating thousands and thousands of mutated versions of itself in a process called "viral escape." The virus changes; the immune cells hunting it down change in response; and the

virus changes again, and so on, in a kind of molecular arms race.

"Viral escape is a significant phenomenon in HIV - it's what allows HIV to elude the immune system," said Ha Youn Lee, Ph.D., the assistant professor in the Department of Biostatistics and Computational Biology who led the project.

"The dynamics in the earliest stage of infection by HIV are incredibly complex, and understanding what happens is crucial for developing a vaccine," Lee added.

To do the study, Lee's team applied a mathematical model to data originally gathered by David O'Connor, Ph.D., at the University of Wisconsin at Madison, who studies how SIV evolves. Lee's team analyzed the genetic features of three key sections of the SIV genome as they changed during the first few months of infection in eight macaque monkeys, part of an effort to quantify how quickly the process of viral escape occurs.

The research took advantage of a method known as ultradeep sequencing, which provides hundreds or thousands of glimpses of a single genetic change, compared to approximately 50 or so looks using conventional methods.

"This new technology is very exciting," said Lee. "It allows us to look at the earliest stages of infection in more depth than we could otherwise, and to quantify exactly what is going on in the body. If we can understand it more completely, we can fine-tune vaccines under development."

As expected, the team found that immune cells known as CD8+ T-lymphocytes, also known as cytotoxic T cells, are a powerful force in the life of SIV when it first causes infection. While scientists have known

that the CD8 attack on the virus is strong, the latest work quantifies the body's response. They found that the original portions of the virus degrade 400 times faster in response to CD8 cells than they would have if those cells weren't a factor - what scientists call significant "selective pressure" on the virus.

The team also found that SIV creates such mutants in response to the assault by CD8 cells at about the same rate as HIV does.

But the most striking finding is that the original viral genetic sequences are still present in the body months after the initial infection, at a time that scientists call the "viral set point," which occurs about two to five months after infection. It's a signal of just how difficult it is for the body to eradicate HIV from the body - key portions of the virus have managed to survive despite the immense immune assault.

"It's a surprise that the original virus stays in the body so long," said Stephen Dewhurst, Ph.D., professor of Microbiology and Immunology and one of the study authors.

"We know that the virus confronts such a strong response from the body's immune system that the virus evolves quickly to cope with it. Yet, the virus is able to establish a reservoir somewhere in the body, where it continues to reproduce and does not have to respond to the threat from the immune system," Dewhurst added.

Provided by University of Rochester Medical Center