Ancient Virus Sheds Light on Modern HIV Infection

June 21 2007

Human resistance to a retrovirus that infected chimpanzees and other nonhuman primates 4 million years ago ironically may be at least partially responsible for the susceptibility of humans to HIV infection today.

These findings, reported by a team of researchers at Fred Hutchinson Cancer Research Center in the June 22 issue of *Science*, provide a better understanding of this modern pandemic infection through the study of an ancient virus called Pan troglodytes endogenous retrovirus, or PtERV1.

"This ancient virus is a battle that humans have already won. Humans are not susceptible to it and have probably been resistant throughout millennia," said senior author Michael Emerman, Ph.D., a member of the Human Biology and Basic Sciences divisions at the Hutchinson Center. "However, we found that during primate evolution, this innate immunity to one virus may have made us more vulnerable to HIV."

Evidence of human immunity to this ancient retrovirus first emerged with the sequencing of the chimpanzee genome. "When the chimp genome was sequenced, a team of scientists at the University of Washington led by Evan Eichler found the largest difference overall between the chimp and human genomes was the presence or absence of PtERV1," Emerman said. "Chimps have 130 copies of PtERV1 and humans have none."

It is believed that retroviruses have been entering the genome for many millions of years, and so humans share many retroviral DNA fragments with their primate cousins. Such vestiges of primitive infection, rendered inactive by eons of genetic mutation, make up about 8 percent of the human genome.

Innate protection against PtERV1 in humans could be credited, the researchers believe, to the presence of an ancient, rapidly evolving antiviral defense gene called TRIM5a, which produces a protein that binds to and destroys the virus before it can replicate within the body.

"We know that PtERV1 infected chimps, gorillas and old-world monkeys 4 million years ago but left no traces of having infected humans. Our theory is that this is because humans had this innate viral defense system," Emerman said.

To test their hypothesis, Emerman and co-authors Harmit Singh Malik, Ph.D., an evolutionary biologist and an assistant member of the Center's Basic Sciences Division, and Shari Kaiser, a graduate student in Emerman's laboratory, used DNA sequences from the chimp genome to reconstruct a small part of the PtERV1 virus.

They reassembled about one-fifth of the virus by taking dozens of PtERV1 sequences and aligning them to create an "ancestral" sequence, teasing out areas of commonality between them. They then used this information to make a partial viral genome. During reconstruction the viral segment was debilitated, enabling only one round of infection in cells. Working with cells in the laboratory, the researchers found that the human antiviral protein TRIM5a effectively neutralizes this extinct retrovirus, which never successfully fixed into the human genome.

"However, while TRIM5a may have served humans well millions of years ago, the antiviral protein does not seem to be good at defending

against any of the retroviruses that currently infect humans, such as HIV-1," Emerman said. "In the end, this drove human evolution to be more susceptible to HIV." For example, the researchers found that changes in TRIM5a that make it better at fighting HIV actually inhibit its ability to stop PtERV1 and vice versa, which indicates that this antiviral gene may only be good at fighting off one virus at a time.

Uncovering the story of TRIM5a's role in battling one ancient retrovirus while increasing human susceptibility to modern-day HIV "is a lot like doing archaeology -- figuring out how humans have become who we are today and why we are or are not susceptible to modern viruses that presently circulate," Emerman said.

In fact, this emerging area of research, which seeks to better understand modern infections by studying ancient viruses, is known as "paleovirology." "Ultimately," said co-author Malik, "if we want to understand why our defenses are the way they are, the answers inevitably lie in these ancient viruses more so than the ones that have affected us only recently, such as HIV."

Source: Fred Hutchinson Cancer Research Center