# Defensive protein killed ancient primate retroviruses, research suggests

December 12 2008

(PhysOrg.com) -- Retroviruses are the worst sort of guest. Over eons, these molecular parasites have insinuated themselves into their hosts' DNA and caused a ruckus. The poor hosts can't even be rid of the intruders by killing them, because they stubbornly remain after death.

As much as eight percent of the human genome is littered with a "fossil record" of extinct retroviruses that we have inherited from our ancestors — human and otherwise — who were the original victims of the viruses. That record allows scientists to study what may have killed these ancient viruses, providing clues for fighting those that plague us today, like HIV.

Now researchers from Rockefeller University have revived two groups of long-dead primate retroviruses to study whether defensive proteins that have rapidly evolved in humans and other primate species could kill them. They found that one protein, called TRIM5α, was disappointingly useless. But by scrutinizing the remnants of the extinct viruses found in the reference genomes of chimpanzees and rhesus monkeys, investigators discovered unmistakable signs that a different protein — APOBEC3 — was likely the exterminator. The research was published in PLoS Pathogens.

"It's a little like finding a fossilized skeleton with a spear through its head. You can be fairly sure of how that individual died," says Paul Bieniasz, an associate professor and head of the Laboratory of Retrovirology and a scientist at the Aaron Diamond AIDS Research Center. "In this case, we can even do tests to show that the spear wasn't

put there after the individual died. The DNA evidence is clear on that point."

The investigators reanimated parts of retroviruses that had worked their way into the DNA of old-world primates within the past few million years. They know the rough timeline because the viruses are not found in humans, who diverged from chimps about six million years ago. The goal is to explain why these ancient viruses did not cross over into humans as HIV has and to identify what in humans has defended against them.

Working with pieces of the extinct retroviruses preserved in primate DNA, the researchers compelled a related modern retrovirus, found in mice, to produce the same proteins as its ancient relatives. Bieniasz, postdoctoral fellow David Perez-Caballero and graduate fellow Steven Soll found that one defensive protein — TRIM5α — did not stop the hybrid viruses from infecting other cells, contrary to another lab's recent findings. Analyzing many of the DNA "fossils" of the retroviruses, however, the researchers found unique mutations that would have caused the viruses to stop reproducing, mutations that are caused by APOBEC3. They showed that the mutations responsible for inactivating the retroviruses varied in both a virus- and species-dependent manner.

So far, the Bieniasz lab has established that APOBEC3 is involved in fighting the retroviruses but not that it singularly killed all of them, or that it is necessarily responsible for preventing the viruses from crossing into humans, who have APOBEC3 proteins of their own.

That's what the researchers would like to show next, but it doesn't come easy. "When you're dealing with something that happened millions of years ago, it's tough to demonstrate an extinction event in the laboratory," Soll says.