Scientists identify a gene that may block HIV

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Scientists at the Harvard Medical School in the United States have identified a human gene, known as TRIM5-alpha, which is capable of preventing the Human Immunodeficiency Virus (HIV) from replicating inside cells. While the discovery, announced in February, is unlikely to lead to any immediate medical breakthrough, it is an important step in understanding the life cycle of HIV and has the potential to enable the future development of a drug to block HIV infection.

The research involved investigating the genetic structure of the rhesus monkey. Scientists have long known that there is a genetic factor in primates that blocks HIV infection. Not long after HIV was discovered in 1983, researchers found that, with the exception of chimpanzees (the closest relatives to humans), HIV infects no other species. Since then, research has been underway to identify the gene or genes responsible for preventing HIV infection and to investigate possible medical applications.

The latest discovery involved investigating each of the 40,000 genes of the rhesus monkey. This type of experiment would have been virtually impossible a decade ago but huge advances in genetic techniques made in the course of research such as the Human Genome Project have enabled the far more efficient pinpointing of genes.

Scientists at the Harvard Medical School's Dana-Farber Cancer Institute in Boston, Massachusetts designed the particularly innovative experiment. Joseph Sodroski, an AIDS researcher, headed the investigation, and Matthew Stremlau, a Harvard Medical School PhD candidate, was the head author of the scientific paper published in *Nature* at the end of February.

According to 27-year-old Stremlau: "It was like looking for a needle in a haystack." He first made a library of the 40,000 genes in the monkey's genome. Each gene was then inserted into human cells that would normally become infected if exposed to HIV. The virus was then added to the cells to observe whether the gene had made them resistant to infection.

To identify the infected cells, the Harvard team modified the HIV virus to emit a green fluorescent light. In other words, infected cells glowed bright green. Dr Sodroski explained: "Cells carrying the gene for TRIM5-alpha didn't get infected, no matter how much HIV you put on them. They remained dark. It is really potent in blocking HIV."

The TRIM5-alpha gene produces a protein that is thought to be part of the body's immune system, which targets foreign bodies and blocks their ability to infect. The human version of the TRIM5-alpha protein is not identical to that found in monkeys and not as effective in preventing HIV infection.

Commenting on possible future applications of the finding, Sodroski said: "Perhaps this protein could be induced to greater activity, thereby increasing the level of resistance to HIV infection."

It is also possible that the potency of TRIM5-alpha protein may differ among individuals. For many years, scientists have investigated particular groups of people, including some Kenyan prostitutes, who remain HIV-free for decades despite regular exposure to the virus. The latest finding may provide a possible explanation: the TRIM5-alpha protein in these people may be more effective in combating the virus.

The role of TRIM5-alpha in preventing HIV infection is not fully understood. However, scientists believe that the protein may "chop up" the HIV capsid and stop the virus from "uncoating". The capsid is a strong protein sheath that surrounds and protects the genetic material of the virus. When a virus enters and infects a cell, it sheds this protective coat so that the genetic material can replicate new viruses.

Sodroski found that the TRIM5-alpha protein interrupts this "uncoating" process. "Over the years, we've leaned quite a bit about how HIV enters cells. More recently, we've developed a picture of the late stages of the viral lifecycle, as it leaves the cell. However, the steps between virus entry and conversion of the viral RNA into DNA have been a black box," he explained.

According to Anthony Fauci, director of the US

National Institute of Allergy and Infectious Diseases, the discovery "opens new avenues for intervening in the early stages of HIV infection before the virus can gain a toehold."

The protein produced by the TRIM5-alpha gene is the first example of an agent that functions inside individual cells to prevent infection. Other elements of the body's immune system, such as antibodies and white blood cells, operate in the blood system to destroy foreign bodies.

The existence of other TRIM molecules has been recognised for a number of years but their functions have been unknown until now. "What we're really uncovering is the first example of a natural system of defence that may be operating against other viruses besides HIV," Sodroski explained. "We're looking at 'example one' here, and I highly doubt it will be the only example in nature."

HIV belongs to a group of viruses known as retroviruses. Retroviruses are particularly insidious infectors as they use the inner "factory" of the host cells to reproduce themselves, killing the host and spreading throughout the body. Mammals have lived with retroviruses throughout their long evolution, but to avoid the detrimental effects, may have developed a large number of genes to inhibit their replication.

"There's an exploding number of these genes [like TRIM5-alpha] that so far as we know have these antiviral activities," said Dr. Stephen Goff, a professor of biochemistry and biophysics at Columbia University. "Presumably they evolved for that reason."

The latest discovery therefore opens up a large new field of research. It may lead to the identification of other genes and proteins that act against particular viruses and may provide the basis for the development of new means for combating debilitating and deadly diseases.