War of the viruses: Could ancient virus genes help fight modern AIDS?

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(PhysOrg.com) -- Almost 30 years into the AIDS epidemic, scientists have yet to find an effective vaccine against HIV, the virus that destroys the immune system and causes AIDS. HIV is perhaps the most adaptive virus ever seen, not only evading the immune system, but also antiviral medicines.

Because this genetic slipperiness also makes the virus a difficult target for vaccine makers, a University of Wisconsin-Madison scientist is embarking on a brand-new effort to sidestep this evasive behavior.

Jonah Sacha, an immunologist and assistant scientist in the UW-Madison AIDS Vaccine Research Laboratory at the Wisconsin National Primate Research Center, thinks he may have identified a stable molecule on the outside of HIV-infected cells. If so, it may be possible to create a vaccine to "teach" the human immune system to destroy these cells and prevent HIV from escaping and reproducing. "It's analogous to teaching a bull to ignore the 'red cape' and go instead for the 'matador' portion of the virus," Sacha says. "Even though the cape may vary, the matador does not."

Sacha, who also has an appointment in the Department of Pathology and Laboratory Medicine at the UW-Madison School of Medicine and Public Health, acknowledges that success is something of a long shot, but his proposal has now attracted a $100,000 exploratory grant from the Bill and Melinda Gates Foundation, announced today (Oct. 20).

The new strategy is rooted in the fact that ancient retroviruses like HIV have, over the eons, inserted their genes into the chromosomes of our animal ancestors. This viral DNA now comprises "an astounding 8 percent" of the entire human genome, Sacha says.

Viruses such as HIV that insert themselves into host chromosomes, called retroviruses, were discovered at UW-Madison in the 1970s. Unlike most viruses, which exploit their host's biochemistry to make viral proteins, retroviruses join their host's genome, which is then forced to produce viral proteins along with human proteins.

"It's especially gratifying to be doing this work at UW-Madison, where Howard Temin won the Nobel Prize for helping to discover retroviruses," says Sacha.

Sacha's strategy focuses on retrovirus genes that entered the chromosomes of our ancestors millions of years ago. Most of these so-called endogenous retroviruses are inactive, either because they carry defects or are somehow stifled by the human cells they reside in.

Less than two years ago, however, Douglas Nixon of the University of California at San Francisco and Brad Jones at the University of Toronto discovered that the cells of AIDS patients carry proteins made by these adopted retroviruses. When HIV replicates in a cell, it somehow triggers the old retroviruses to make viral proteins. These proteins are then transported to the cell surface, becoming markers that could allow the immune system to destroy the infected cell.

This process is how the body normally rids itself of viruses and the cells they infect. Teaching the immune system to recognize foreign proteins is a core strategy for vaccination.

As a first step toward producing an AIDS vaccine, Sacha, working in the

laboratory of David Watkins, a professor of pathology at UW-Madison, will explore whether ancient viral proteins appear on the cells of rhesus macaques, monkeys that can be infected by a virus similar to HIV.

Sacha hopes that attacking these viral proteins instead of HIV proteins would sidestep a key roadblock to vaccination: So many strains of HIV have evolved that vaccine makers could be forced to make a nearly infinite number of vaccines. And if an effective vaccine was distributed, the evasive virus would probably mutate to evade control, Sacha adds. "There is an amazing error rate in HIV replication, and if you put selective pressure on the virus, it almost always escapes from that pressure."

All of this shape-shifting "has caused immunologists to look for stable targets on HIV," Sacha says, "but it's been a real struggle. Even the recent vaccine trials in Thailand, which showed partial effectiveness, worked only against the strain of HIV circulating in that region. Using that approach, it might be necessary to build multiple vaccines for use against the different strains of HIV in different areas of the world."

A similar, if less drastic, shape-shifting problem, explains why a new influenza vaccine is needed every year.

Another benefit of attacking proteins produced by old viral genes rather than HIV is that it should not force HIV to evolve resistance, Sacha says. "Any way you can circumvent the ability of the virus to escape is helpful. This approach does not put direct pressure on the virus, and we believe it will change slowly if at all."

It's not clear if the ancient viral genes play a role in causing the immune decline in AIDS. "We don't know, but the body is already fighting HIV," says Sacha. "It looks like it could instead become a war on two fronts. I think that retroviruses from inside and outside the body could be

working together."

Although incorporating genes from other organisms sounds odd, scientists believe that both mitochondria — which provide energy to cells — and chloroplasts — which perform photosynthesis in plants — lived independently before they were "adopted" by their parent organisms.

A similar repurposing may have been applied to the ancient viral genes, Sacha adds. "In some cases, the body has harvested these viruses and begun taking advantage of them." Viral proteins are involved in forming the placenta and controlling when human genes make proteins. For these reasons, any vaccine experiments that emerge from Sacha's studies must first be explored in animals.

The story of the ancient retroviruses is new to science, but old to biology, Sacha concludes. "This incorporation of retroviral genes has happened many times before in primate evolution. Some members of this family of genes were even inserted before humans and monkeys split off into separate lineages. I think this has been happening the entire time we have been evolving. But we can expect more surprises as we watch HIV interact with these ancient retroviruses."

Provided by University of Wisconsin-Madison (news : web)