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New monkey model for AIDS offers promise for medical research

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HIV-1, the virus responsible for most cases of AIDS, is a very selective virus. It does not readily infect species other than its usual hosts – humans and chimpanzees. While this would qualify as good news for most mammals, for humans this fact has made the search for effective treatments and vaccines for AIDS that much more difficult; without an accurate animal model of the disease, researchers have had few options for clinical studies of the virus.

New work from Paul Bieniasz's Laboratory of Retrovirology at The Rockefeller University and the Aaron Diamond AIDS Research Center and Theodora Hatziioannou's Laboratory, also at Aaron Diamond, may help fill this gap. In research described today in *Science*, they announce that they have coaxed a slightly modified form of the HIV-1 virus to not only infect pigtailed macaques, a species of monkey, but to cause full blown AIDS in the primates, a first.

"HIV-1 only causes AIDS in humans and chimpanzees, but the latter are not a practical model and are no longer used for HIV/AIDS research. Our goal has been to figure out how HIV-1 could cause disease in a new host," Bieniasz says. "By accomplishing this with macaques, we have taken a step toward establishing a new model for AIDS that can be used universally in prevention and treatment research."

Although pigtailed macaques have fewer defenses against HIV-1 than most other primates—they lack an antiviral protein that fights off the virus—the researchers still had to alter both the virus and the macaque

immune system in order to induce AIDS.

They bolstered the virus with a defense-disabling protein made by Simian Immunodeficiency Virus (SIV), a relative of HIV-1. Then they encouraged the modified HIV strain to adapt to its new host by passing it from one monkey to another, resulting in six generations of infected monkeys and an adapted virus. Even so, the monkeys' immune systems were still able to control the HIV-1 infection. So, the researchers temporarily weakened their immune systems by depleting a type of white blood cell, known as a CD8 T-cell, that destroys virus-infected cells.

"When we depleted their CD8 cells, the infected monkeys developed disease closely mirroring that of human patients. For example they contracted AIDS-defining conditions including pneumocystis pneumonia, a textbook example of an opportunistic infection in AIDS," says Hatziioannou. "Because it replicates what happens when HIV-1 compromises a human patient's immune system, our approach could potentially be used in the development of therapies and preventative measures for human patients."

In fact, if fully developed, the macaque model will offer a substantial improvement for research. Often, HIV therapy and prevention research relies on SIV, a viral relative of HIV-1, since SIV can cause AIDS-like disease in nonhuman primates. However, SIV doesn't always behave the same way HIV-1 does. "We still have one major hurdle to overcome: If we could get HIV-1 to cause AIDS without depleting the CD8 cells, we could replace models that make use of SIV for this research."

This work and previous research in the lab has also illuminated the process by which HIV-1 and other members of the lentivirus family can colonize a new host like the macaques. It turns out that evading or fighting off the antiviral proteins produced by the new host's cells is key.

"This new model for HIV-1 infection is the result of years spent exploring scientific questions about how the virus interacts with a host's antiviral defenses. These kinds of basic insights will enable us to continue to improve this model," Hatziioannou says.

More information: "HIV-1–induced AIDS in monkeys," by T. Hatziioannou et al. www.sciencemag.org/lookup/doi/ … 1126/science.1250761

Provided by Rockefeller University