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CONTACT: Cathy Reynolds, cathy.reynolds@ttuhsc.edu, (915) 545-6527
Patricia Williams, patricia.williams@ttuhsc.edu, (915) 545-6426

HARVARD AND TEXAS TECH RESEARCHERS HALT SPREAD OF HIV WITH RNAi

FINDINGS:
Using a novel method to deliver small molecules called siRNAs into T cells, researchers dramatically suppressed HIV in the first-ever animal model that mirrors progression of the disease in humans. The siRNAs knocked down three key genes and kept the infection from spreading in mice containing human immune cells infected with the virus.

RELEVANCE:
This study demonstrates that siRNAs can control the spread of HIV among cells in an animal model. Although labs must verify the findings in other animal models before attempting clinical trials, siRNAs may eventually supplement or replace the harsh drug cocktails currently prescribed to patients with HIV, reducing the side effects of treatment.

PRINCIPAL INVESTIGATORS:
Premlata Shankar conducted this work while she was a junior investigator at the Harvard Medical School-affiliated Immune Disease Institute and an assistant professor at Harvard Medical School. Shankar is now a professor at Texas Tech University Health Sciences Center in El Paso, where she is co-director of the Center of Excellence for Infectious Diseases at the Paul L. Foster School of Medicine.

Formerly a postdoctoral researcher at the Immune Disease Institute, Sang-Kyung Lee is an assistant professor in Hanyang University's Department of Bioengineering and Hanyang Fusion Materials Program.

CITATION:
Cell. Online Aug. 7, 2008.

FUNDING:
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BOSTON, Mass. (Aug. 7, 2008) -- Hopes languished last September when a promising candidate HIV vaccine failed to work. Despite this setback, many researchers still believe immunization is possible, and a new study suggests they're correct--at least at the cellular level.

Working in mice infected with HIV, a team used a method called RNA interference to knock down three genes in T cells, protecting them from the virus. This method seemed to prevent HIV from jumping between cells in the mice.

"For the first time, we've used RNAi to dramatically suppress HIV infection in an organism," says corresponding author Premlata Shankar, who conducted the work while she was a junior investigator at the Harvard Medical School-affiliated Immune Disease Institute and an assistant professor at Harvard Medical School. Shankar is now a professor at Texas Tech University Health Sciences Center in El Paso.

Although labs must verify the findings in other animal models before attempting clinical trials, this method--published online Aug. 7 in Cell--may eventually supplement or replace the harsh drug cocktails currently prescribed to patients with HIV, reducing the side effects of treatment.

When the Nobel Prize in Physiology or Medicine was awarded in 2006 for the discovery of RNAi, the judges speculated that it might "lead to novel therapies in the future." Researchers hoped to flood specific cells in patients with short interfering RNAs (siRNAs), molecules that silence genes by disrupting the protein templates they produce. But scientists weren't sure how to deliver the siRNAs exclusively into relevant cell types within an organism.

In collaboration with Sang-Kyung Lee of Hanyang University, Shankar's lab overcame this obstacle, delivering siRNAs directly into T cells, which are targeted by HIV. The team used an apparatus analogous to a truck equipped with GPS and a trailer hitch to haul the siRNAs to their destination. The truck--in this case, a single-chain antibody developed by Georg Fey of the University of Erlangen in Germany--homed to a protein found exclusively on the surface of T cells. The trailer hitch--an oligo-9-arginine--pulled siRNAs along for the ride.

This new antibody delivery vehicle lends itself to mass production in a dish. The team built thousands of these carriers for use in experiments, loading them with siRNAs targeting three key genes. One encodes a human protein called CCR5, which dots the surface of T cells and allows HIV to gain entry. The others encode proteins produced by the virus within cells upon infection.

Shankar's protege and first author Priti Kumar mixed the siRNAs with the antibody carriers and injected them into the veins of mice that harbor human T cells rather than their own. These mice serve as an animal model of HIV. After being infected with the virus, the mice mirror progression of the disease in humans.

Developed by study co-authors Leonard Shultz of the Jackson Laboratory and Dale Greiner of the University of Massachusetts, these mice lack their own immune systems, so they tolerate tissue from other species. The team injected the mice with human blood stem cells, which divided time and again, building a human immune system in their hosts. When infected with HIV, the synthetic immune system seemed to respond as it would in humans, since T cell levels followed the same pattern in both species.

Kumar's siRNAs halted T cell destruction in the mice, essentially stopping the virus in its tracks.

"Both prophylactic and therapeutic regimens proved successful," said Kumar. "Apparently, the siRNAs kept HIV from entering most T cells and kept it from replicating when it managed to slip inside."

Kumar and Shankar caution that labs need to confirm the findings in other animals, tweak the dosage, and tinker with the siRNA delivery vehicle before attempting clinical trials. In addition, the molecules degrade with time, so periodic shots may be necessary to maintain cellular immunity, precluding large-scale vaccination.

"I'm not saying we've developed tomorrow's therapy, but this is a major step forward," says Shankar. "We've used a small animal model for HIV and proven that RNAi works in that model."

John Rossi, a pioneer in RNA-based therapeutics who was not part of the study, hopes labs will use the new animal model to compare the side effects of potential and existing therapeutic regimens.

"The number one problem with the current antiretroviral drug regimens is toxicity," says Rossi, a professor at the Beckman Research Institute of the City of Hope. He wonders if siRNAs will eventually enable doctors to lower the doses of existing drugs in patients. Perhaps siRNAs will one day supplement or replace harsh antiretrovirals.

"Overall, I see this work as an exciting proof of principle," says Rossi. "This is a strategy that can be developed for clinical applications in humans."

FULL CITATION :

Cell. Online Aug. 7, 2008.

"T Cell-Specific siRNA Delivery Suppresses HIV-1 Infection in Humanized Mice."

Priti Kumar (1,9), Hong-Seok Ban (2,9), Sang-Soo Kim (1), Haoquan Wu (1), Todd Pearson (3), Dale Greiner (3), Amale Laouar (1), Jiahong Yao (1), Viraga Haridas (1), Katsuyoshi Habiro (4), Yong-Guang Yang (4), Ji-Hoon Jeong (5), Kuen-Yong Lee (2), Yong-Hee Kim (2), Sung Wan Kim (5), Matthias Peipp (6), Georg H. Fey (7), N. Manjunath (1, 10), Leonard D. Shultz (8), Sang-Kyung Lee (2), and Premlata Shankar (1,10).

The authors all contributed to this work. Professor Shankar's present address is as follows: Department of Biomedical Sciences, Center of Excellence for Infectious Diseases, Paul L. Foster School of Medicine, Texas Tech University Health Sciences Center, El Paso, TX, 79905, 915-545-6527.