'Silencing' HIV with small bits of RNA

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Researchers have shown that they can effectively tackle HIV-1 with small bits of gene-silencing RNA by delivering them directly to infected T cells, the major targets of the virus. While earlier studies had shown such a strategy could fight against many viruses including HIV-1, the new study in mice with human blood cells, so-called humanized mice, is the first to demonstrate an effective approach to systemic delivery in a living animal.

The researchers, led by Premlata Shankar of Texas Tech University Health Sciences Center and Sang-Kyung Lee of Hanyang University in Korea, reported their findings online as an immediate early publication on August 8th in *Cell*, a Cell Press journal.

" RNA interference has great potential as an antiviral treatment," said Premlata Shankar of Texas Tech University Health Sciences Center. "Using a delivery method for T cells, we now show that siRNA treatment can dramatically suppress HIV infection. This is nice proof of principle that it could be used as a therapeutic strategy. We think it has real promise, but there is a lot more to be done."

" No one had demonstrated before that HIV infection can be stopped in vivo, not just in cell lines but in animal models. It implies it might work in humans," added Priti Kumar of Harvard Medical School and Hanyang University.

Small interfering RNAs (siRNAs), as they are called, can effectively silence specific genes by ridding cells of messenger RNA before it is

translated into functional proteins. Many previous studies had shown the effectiveness of RNAi in suppressing HIV replication in cell lines as well as in primary human T cells and macrophages.

"The challenge is delivery to the right cell [within a living animal]," Shankar said. "How do you get it in, especially into T cell where HIV infects? It's a big challenge."

In the new study, the researchers found a way. They combined part of an antibody that targets a surface molecule on T cells to an "oligo-9-arginine" peptide that allows the construct to attach and deliver siRNA to T cells.

Another impediment to studies of this kind had been the lack of a suitable small animal model that simulated HIV infection, the researchers said. In other words, mice can't normally get HIV. A recent development made that problem easier. Study co-author Leonard Schultz of The Jackson Laboratory and Dale Greiner from the University of Massachussets created an immunodeficient mouse that takes engraftments of human blood or stem cells well, yielding mice with human blood cells that are prone to HIV infection.

The researchers treated immunodeficient mice transplanted with human white blood cells with siRNAs targeting CCR5, a coreceptor on blood cells that allows the virus to enter, challenged them with HIV and then treated them further with a mixture of CCR5 siRNA and two siRNAs aimed at conserved HIV genes. In untreated mice, HIV-infected CD4 T cell levels dropped sharply. In contrast, in three out of four antiviral siRNA-treated mice, CD4 T cell levels remained essentially normal even four weeks after infection, they report.

" When treated with the siRNA mix, the infected mice looked almost like uninfected controls," Shankar said. "They had negligible levels of

virus and their CD4 counts were maintained."

They then took a different approach. Rather than transplanting the mice with human blood cells, they injected newborn mice with human stem cells taken from umbilical cord blood. That way, the human blood cells develop in the mouse itself, such that the rodents' immune system doesn't recognize them as foreign, more closely mimicking the situation in humans. In that case as well, they found, the siRNA treatment dramatically cut the viral load.

The treatment also suppressed the virus and restored CD4 T cell counts in mice reconstituted with HIV-infected peripheral human blood cells. The finding provides evidence that the strategy has potential against an established HIV infection, in which multiple HIV "quasispecies" are likely to be present.

Further study will examine whether the method can also be used to target siRNAs to other cell types important to HIV infection.

" The availability of a preclinical animal model for HIV infection, as shown in this study, should allow rapid testing of these strategies, as well as other potential problems, such as viral escape and toxicity, that have to be resolved before RNAi therapy can be translated for clinical use," the researchers said.

Ultimately, Kumar said, siRNA therapy might be important as an adjunct or addition to the highly active antiretroviral therapy (HAART) used today.

Source: Cell Press

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