Stopping HIV transmission with a molecular barrier

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Using a technique that silences genes promoting infection, researchers have developed a novel, topically-applied molecular microbicide capable of preventing HIV transmission. The microbicide is predicted to have long-lasting effects in mice, opening the door to developing an intravaginal microbicide that could protect women against HIV infection potentially for weeks at a time and bolster public health efforts to halt the spread of HIV/AIDS.

The study, led by Lee Adam Wheeler and Judy Lieberman, MD, PhD, of the Immune Disease Institute and the Program in Cellular and Molecular Medicine at Children's Hospital Boston, was published online on May 16 in the *Journal of Clinical Investigation.*

The microbicide takes advantage of a molecular phenomenon called RNA interference (RNAi), in which small pieces of RNA called small interfering RNAs (siRNAs) silence the expression of individual genes with complementary sequences. Originally observed in plants, RNAi was found to be active in mammals only a decade ago, but it is already the focus of many clinical investigations.

Lieberman and Wheeler chose to investigate RNAi's potential to provide a molecular barrier against HIV transmission based on earlier work in her laboratory showing that the phenomenon could be harnessed to prevent herpes simplex virus (HSV) transmission, and also on recent advances in understanding how HIV penetrates the body. "The current model of HIV transmission holds that the virus is localized to the genital

tract for about a week, which could provide a window of opportunity to intervene and prevent the infection from establishing itself throughout the body," said Lieberman. "And last year it was shown that it is possible to prevent HIV transmission, at least to some extent, with a topical vaginal agent using an antiviral drug, thus providing proof-of-principle that a topical strategy could interfere with virus transmission."

In the current study, the researchers used siRNAs that turned off two viral genes and that of one of HIV's two host co-receptors, CCR5. HIV uses CCR5, found on immune cells called T cells and macrophages, to gain entry into an uninfected person's immune cells and establish a foothold within the body. Individuals harboring mutations that deactivate CCR5 are resistant to infection with HIV.

To ensure that the siRNAs would be delivered only to the immune cells targeted by HIV, the research team linked the siRNAs to an aptamer - a second piece of RNA designed to attach to a specific molecule - that binds to HIV's main receptor, CD4, to create CD4 aptamer-siRNA chimeras (CD4-AsiCs).

"By using CD4 as a binding site but knocking down CCR5, we get specificity for the cells targeted by HIV but avoid the risk of interfering with the overall immune response," Lieberman noted.

When tested in vitro using cell lines and blood cells, the CD4-AsiCs bound only to immune cells displaying CD4 on their surface; turned off expression in those cells of the three targeted genes; and prevented HIV replication. In addition, CD4-AsiCs successfully penetrated cultured human cervicovaginal tissues to reach immune cells deep within the tissue layers, silence target gene expression, and prevent HIV infection of the cultures.

To test the effectiveness of this system in vivo, the study team applied

CD4-AsiCs topically within the vaginal canal of female mice with humanized immune systems, and then exposed those mice intravaginally to HIV so as to mimic sexual transmission of the virus. As in the in vitro model, the CD4-AsiCs were able to penetrate through the vaginal walls of these mice to the immune cells within the tissues, deliver the siRNAs to cells displaying CD4, and turn off the expression of the targeted genes. Over the following 12 weeks, none of the mice treated with the siRNAs showed any biological signs of HIV infection, while all of the control mice progressed to full-blown HIV infection.

Lieberman thinks that the RNAi-based microbicide's specificity and duration of action make it attractive for further pharmaceutical development. "The problem with most topical methods for preventing sexual transmission of disease is that you have to use them just before having sex, and compliance is a huge issue," she said. "But our laboratory results show that we can knock down CCR5 expression potentially for weeks, suggesting that we could create a stable viral-resistant state where one would only have to apply the agent every couple of weeks."

According to Wheeler, the method's modularity suggests that its promise is not limited to HIV. "You could basically switch in or out any kind of siRNA or aptamer for any binding target to knock down any gene you would want, be it host or viral." Lieberman added, "Conceivably, one could include siRNAs against multiple viral agents in a cocktail to gain protection from multiple sexually transmitted diseases, including HSV and human papilloma virus."

More information: www.jci.org/articles/view/4587 … f00cbc583fd015db1899

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