Cutting Edge: Unusual NK Cell Responses to HIV-1 Peptides Are Associated With Protection Against Maternal-Infant Transmission of HIV-1


PURPOSE OF THE STUDY. To investigate the role of specific T cell responses in maternal-fetal HIV-1 transmission.

METHODS. CD3\(^{-}\) cell responses to HIV-1 peptide were measured in HIV-infected mothers and their infants at birth and at 6 to 10 weeks after delivery. Samples from the mother-child cohort were stimulated with HIV-1 synthetic peptides in pools representing Gag, Pol, Nef, envelope, and regulatory protein regions. A positive peptide-induced CD3\(^{-}\) response was defined as >3% of cells expressing cytokine at a level at least twofold above background levels. Additional HIV-infected women were recruited to determine whether CD3\(^{-}\) HIV-responding cells expressed markers for B cells, monocytes, T cells, or natural killer (NK) cells.

RESULTS. In the cohort of infected mothers, 54% and 22% had CD3\(^{-}\) responses to envelope and regulatory peptides, respectively. These same regions were targeted to a lesser degree in their infants (21% and 5% had CD3\(^{-}\) responses to envelope and regulatory peptides, respectively). Twenty-eight (57%) of 49 nontransmitting mothers and 13 (30%) of 44 exposed uninfected infants had detectable, HIV-specific, CD3\(^{-}\) responses. In comparison, 1 (7%) of 15 transmitting mothers and 1 (6%) of 18 infected infants had these responses. When both the mother and the infant had HIV-specific CD3\(^{-}\) responses, none of the infants became infected. One of the 22 responder mothers with a nonresponder infant transmitted HIV to her infant, and 2 of the nonresponder mothers with responder infants transmitted HIV to their infants. HIV-specific CD3\(^{-}\) cells were identified as NK cells on the basis of cell surface markers.

CONCLUSIONS. Mothers and infants who have CD3\(^{-}\) NK cells that respond to HIV-1 peptides are substantially less likely to transmit and to acquire infection, respectively. CD3\(^{-}\) NK cells respond with high specificity and strength to HIV-1 peptides from envelope and regulatory protein regions. This finding highlights the importance of innate immunity in preventing maternal-fetal transmission of HIV-1.

CONCLUSIONS. HIV-exposed infants and offers a possible marker for transmission risk. Although future studies need to be conducted, it is possible not only that this robust immune response to specific HIV-1 proteins may serve as a predictor of possible vertical transmission but also that a decrease in these cell numbers may serve as a marker of disease progression. In addition, the HIV-1-specific CD3\(^{-}\) cell population may serve as a possible target for future immunotherapy for HIV infection.

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


PURPOSE OF THE STUDY. Since the discovery of RNA interference within mammalian cells in 2001, RNA interference has become a significant bench research tool and presents a new therapeutic modality against viral infections and cancer. The purpose of this study was to determine whether a novel method for delivery of small interfering RNAs (siRNAs) to T cells can suppress HIV viral infection.

STUDY POPULATION. A humanized mouse model of AIDS was used to demonstrate in vivo effects.

METHODS. A CD7-specific antibody conjugated to a peptide was used to deliver siRNA to target cells in mice reconstituted with human lymphocytes or CD34\(^{+}\) stem cells. Anti–chemokine receptor 5 (viral coreceptor) complexed with antiviral siRNAs was also used in HIV-infected mice.

RESULTS. Treatment controlled viral replication, prevented disease-associated CD4\(^{+}\) T cell loss, suppressed endogenous virus, and restored CD4\(^{+}\) T cell counts. In addition, it was demonstrated that antiviral siRNAs could be delivered to naive T cells and effectively suppress viremia.

CONCLUSIONS. siRNA therapy for HIV infection seems to be feasible in a preclinical animal model.

REVIEWER COMMENTS. The annual rate of new HIV infections around the globe was 2.7 million in 2007, with 14% of these cases (370,000 cases) occurring in children <15 years of age (1013 cases per day). RNA interference holds considerable potential for antiviral therapy, but delivering effective quantities of siRNAs into the right target cells in vivo represents a considerable challenge. Several small clinical trials using siRNAs are currently underway. This study represents a significant advance for 2 reasons: (1) the findings heighten the prospect of a new HIV-1/AIDS therapy and (2) this study provides a
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