MedicalXpress

Zinc finger proteins put personalized HIV therapy within reach

June 30 2008

Researchers at the University of Pennsylvania School of Medicine and collaborators are using minute, naturally occurring proteins called zinc fingers to engineer T cells to one day treat AIDS in humans.

The Penn researchers and colleagues from Sangamo Biosciences, Richmond, CA, who developed the zinc finger technology, report in an advanced online issue of *Nature Biotechnology* the first steps towards the goal of using modified T cells from an HIV-infected person for their own treatment. They showed that, using the zinc fingers, they could reduce the viral load of immune-deficient mice transplanted with engineered T cells.

"By inducing mutations in the CCR5 gene using zinc finger proteins, we've reduced the expression of CCR5 surface proteins on T cells, which is necessary for the AIDS virus to enter these immune system cells," explains first author Elena Perez, MD, PhD, Assistant Professor of Pediatrics at Penn. "This approach stops the AIDS virus from entering the T cells because it now has an introduced error into the CCR5 gene."

Some people are born with a mutation on their CCR5 gene and therefore do not have a working CCR5 receptor on the surface of their T cells. These rare individuals are immune to HIV infection and seemingly are not affected by the non-functional CCR5 protein. The zinc finger approach aims to mimic this natural immunity.

Perez performed the research while a postdoctoral fellow in the lab of

senior author Carl June, MD, Director of Translational Medicine at the Abramson Family Cancer Research Institute, and a Professor of Pathology and Laboratory Medicine at Penn. Perez is also an attending physician with the Children's Hospital of Philadelphia in the Division of Allergy and Immunology.

Normally, zinc fingers bind to different bases in the DNA sequence to regulate the activity of genes. The zinc fingers used in this experiment were designed to bind to specific DNA sequences in the CCR5 gene. The CCR5 protein is one of the two cell-surface receptors needed for HIV to gain entry into a T cell in order to replicate.

In this study, the zinc finger protein brings a DNA enzyme to the CCR5 gene to cut a portion of its sequence, but due to the repair process a new mutation arises in the CCR5 protein, rendering it non-functional. Without a functional CCR5 protein on the cell's surface, HIV cannot enter, presumably leading to resistance to HIV infection.

The researchers demonstrated this process in cell culture and in a mouse model. For the animal part of the study, the investigators used healthy human CD4 T cells and added DNA that expresses the zinc fingers, which modifies the CCR5 co-receptor. They grew the engineered cells in tissue culture flasks and transferred them into immune-deficient mice infected with HIV. "We followed them over time and showed that those mice that received the zinc-finger-treated cells showed less viral load than controls and improved CD4 counts," says Perez.

Source: University of Pennsylvania