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Researchers genetically engineer immune cells into potent weapons for battling HIV

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By outfitting immune-system killer cells with a new pair of genes, scientists at the Albert Einstein College of Medicine of Yeshiva University transformed them into potent weapons that destroy cells infected with HIV, the virus that causes AIDS. Their novel strategy of genetically engineering immune cells to redirect their infection-fighting ability toward killing HIV-infected cells could lead to an entirely new approach for combating AIDS and other viral diseases. The findings appear in the March issue of the *Journal of Virology*.

After someone is infected with HIV, a subgroup of their immune cells known as CD8 cytotoxic T lymphocytes, or CTLs, recognize cells infected with HIV and kill them before they become HIV-producing factories. This CTL activity initially keeps the infection in check.

But then—largely because these CTLs may not bind tightly enough to the infected cells or because HIV mutates so rapidly—the virus typically evades and ultimately overpowers the immune system, leading to an increase in viral load that, in the absence of drug therapy, results in AIDS. However, a very small percentage of HIV-infected people known as elite controllers manage to suppress HIV infection for many years.

“Certain of the CTLs of elite controllers may be genetically equipped to bind tightly to HIV-infected cells and destroy them and thereby suppress the infection indefinitely,” says Dr. Harris Goldstein, senior author of the study and Director of the Einstein/Montefiore Center for AIDS Research. “Our idea,” says Dr. Goldstein, “was first to identify the elite

controllers' "super" CTLs and to isolate the genes that enable these cells to bind tightly to HIV-infected cells and kill them efficiently; then we would transfer these genes into CTLs that do not recognize HIV-infected cells and convert them into potent killers of those cells."

After infecting a cell, HIV instructs it to make viral proteins. Tiny bits of these proteins, known as peptides, are displayed on the surface of the infected cell—the cell's way of signaling the immune system that it is infected. Detecting virus-infected cells so they can then be eliminated is the job of CTLs and the protein molecules, known as T-cell receptors, that jut from their surface.

If a CTL's T-cell receptor has the right amino acid sequence, it will recognize the HIV peptide on the infected cell as foreign--prompting the CTL to multiply and attack the infected cell. But all too often, this battle between activated CTLs and HIV-infected cells ends badly. Why, then, are super CTLs of elite controllers so effective in killing HIV-infected cells"

The explanation, the Einstein researchers postulated, is that these CTLs express T-cell receptors that either have a knack for recognizing viral peptides that tend not to mutate, or they bind extremely tightly to HIV-infected cells, enabling the elite controllers to keep their HIV infections under control.

A CTL's T-cell receptor, which is as unique for each CTL as a person's fingerprint, consists of two "chains," alpha and beta. To obtain the blueprint for making exceptionally potent HIV-specific T-cell receptors, the researchers isolated the genes that code for each of the two "chains" from the potent HIV-specific CTL. Then, as a way to efficiently insert both genes into "naïve" CTLs (from people not infected with HIV), they developed an efficient delivery system in which the genes were combined and packaged inside a special type of virus, called a lentivirus.

The lentiviruses then inserted these genes into the chromosomes of naïve CTLs obtained from a naïve donor's blood and reprogrammed them into potent HIV-specific CTLs.

"We demonstrated that these genetically reprogrammed CTLs have very strong activity in terms of killing HIV-infected cells in both test tubes and an animal model," says Dr. Goldstein. In some of the animal studies, for example, the researchers injected mice with both HIV-infected human cells and with reprogrammed naïve CTLs into which the HIV-recognizing T-cell receptor genes had been inserted using the lentiviral delivery system. One week later, when the researchers looked for HIV-infected human cells in the animals, they found that the infected cells had virtually been eliminated.

Dr. Goldstein notes that this study was done using genes for just a single CTL T-cell receptor. "To make this strategy even more effective, we're now in the process of isolating a "cocktail" of CTL receptor genes that are specific for many different HIV peptides—an approach analogous to today's combination drug therapy for treating HIV infection," says Dr. Goldstein. "Ultimately, we'd like to remove CTLs from patients, convert them into potent HIV-specific CTLs by inserting a variety of HIV-specific CTL receptor genes, and then re-infuse these fresh, genetically reprogrammed CTLs back into patients. By reinforcing the immune system in this way, we hope to turn the tide of battle against HIV in favor of people infected with the virus."

Source: Albert Einstein College of Medicine