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Well-armed immune cells help long-term non-progressors contain HIV

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To help develop an effective HIV vaccine, researchers are trying to better understand how the immune systems of a small minority of HIV-infected people known as long-term non-progressors (LTNPs) contain the virus naturally. CD8+ T cells, which kill cells infected with HIV, enable LTNPs to control HIV, but it has been unclear how CD8+ T cells mediate that control so effectively. A new report shows that the ability to stockpile two molecular weapons makes the HIV-specific CD8+ T cells of LTNPs superior cellular killers.

Lead author Stephen Migueles, M.D., senior author Mark Connors, M.D., and colleagues at the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health, used cutting-edge technology to examine individual CD8+ T cells for their killing prowess.

The study included new techniques to measure how many HIV-infected cells each CD8+ T cell destroys, and how rapidly. In laboratory experiments, the scientists found that CD8+ T cells taken from LTNPs efficiently killed HIV-infected cells in less than 1 hour. In contrast, the CD8+ T cells of progressors, or individuals who do not contain the virus without antiretroviral therapy, killed HIV-infected cells inefficiently, even when the CD8+ T cells were present in high numbers or came from progressors being successfully treated with antiretroviral therapy.

When CD8+ T cells kill HIV-infected cells, a protein, perforin, made by the CD8+ T cells punches holes in the infected cells. Then a second

protein, granzyme B, penetrates those holes and causes the cells to die. Previously, the researchers found that HIV-specific CD8+ T cells of progressors, unlike those of LTNPs, make little perforin when they encounter an HIV-infected cell. It remained unclear, however, whether this deficiency explained why HIV-specific CD8+ T cells of progressors are poor killers.

The current study demonstrates a direct relationship between the quantity of both perforin and granzyme B that CD8+ T cells accumulate over time and the ability of CD8+ T cells to eliminate HIV-infected cells. This discovery significantly advances the understanding of the cellular mechanisms unique to LTNPs that explain why their immune systems, unlike those of the majority of HIV-infected people, can control HIV without antiretroviral therapy.

According to the NIAID scientists, their results also suggest that an HIV vaccine might control virus replication if it could stimulate HIV-specific CD8+ T cells to robustly stock and rapidly deliver perforin and granzyme B to HIV-infected cells.

Publication: SA Migueles et al. Lytic granule loading of CD8+ T cells is required for HIV-infected cell elimination associated with immune control. Immunity DOI 10.1016/j.immuni.2008.10.010 (2008).

Source: National Institute of Allergy and Infectious Diseases