HIV Can Convert T Cells From Helpers to Killers

CD4 helper cells that transform into CD8 killer cells may make up a previously unrecognized part of the HIV reservoir.

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Some CD4 T cells infected with HIV can take on the characteristics of CD8 cells, according to a study published in Science. The researchers found that this transformed population of induced CD8 cells can still harbor latent HIV and contributes to the viral reservoir, which has implications for functional cure strategies.

Antiretroviral therapy can keep HIV suppressed indefinitely, but the virus inserts its genetic blueprints into host cells and establishes a long-lasting viral reservoir that is impervious to the drugs and usually invisible to the immune system, making a true cure nearly impossible.

HIV enters immune cells via the CD4 receptor on the cell surface along with a second coreceptor, either CCR5 or CXCR4. Most T cells carrying the CD4 receptor are “helper” cells that coordinate the adaptive immune response, while cells bearing the CD8 receptor are cytotoxic “killer” cells that destroy virus-infected and cancerous cells. It has traditionally been assumed that CD4 and CD8 cells generally maintain a stable identity over time and that the HIV reservoir primarily consists of dormant CD4 cells, but the new research suggests that the picture is more complex.

HIV’s accessory proteins—Nef, Vif, Vpu and Vpr—play a role in viral persistence, spread and immune system evasion. Nef and Vpu are known to reduce, or downregulate, CD4 expression on infected T cells, but the fate of these T cells is not well understood.

Jinfeng Cai, PhD, of the Institute of Human Virology at Sun Yat-sen University in China, and colleagues looked at the characteristics and evolution of CD4 cells collected from six people in China with acute HIV infection who had not started antiretroviral therapy, 80 HIV-positive people on treatment with viral suppression (72 in China and eight in St. Louis) and blood donated by healthy HIV-negative people.

Unexpectedly, the researchers found that a subset of latent CD4 cells can directly convert to induced CD8 cells by upregulating CD8 receptor expression. They demonstrated that Vpr increases production of transforming growth factor-beta1 (TGF-beta1), which in turn activates a signaling pathway essential for such CD8 cell reprogramming. The researchers noted that neither Nef nor

Vpr alone could transform T cells, which requires both CD4 downregulation and CD8 upregulation. “Both viral factors were required simultaneously, restricting conversion to HIV-1-infected cells,” they wrote.

The induced CD8 cells shared T-cell receptor sequences with their CD4 cell precursors, offering evidence for HIV-driven CD4-to-CD8 conversion. HLA class II-restricted CD8 cells—typically only a feature of CD4 cells—were detected in both treated and untreated people with HIV but not in blood from HIV-negative donors. Cai’s team observed that the converted CD8 cells did not have the same killing capacity as conventional cytotoxic T cells. Further analysis revealed that the induced CD8 cells primarily arose from regulatory CD4 T cells, which suppress excessive immune responses—for example, autoimmune responses against the body’s own tissues).

Although HIV does not usually infect normal CD8 T cells, converted CD8 cells from both untreated people with HIV and those with viral suppression were shown to harbor transcriptionally active viral RNA or intact proviral DNA, which has the potential to produce new virus if antiretrovirals are stopped. What’s more, the HIV DNA integration site was the same in CD4 cells and some CD8 cells in three people, suggesting the latter were indeed previously CD4 cells.

“Collectively, these findings uncover a viral mechanism of host-cell reprogramming, demonstrate that CD8+ T cells constitute a previously overlooked component of the HIV-1 reservoir and broaden our understanding of latent reservoir heterogeneity, an essential consideration for future cure strategies,” the study authors concluded. “Future studies should explore the role of induced CD8 T cells in tissue reservoirs and evaluate whether targeting this population could contribute to a functional cure for HIV-1.”

This research also raises a larger question, Robin Orozco, PhD, of the Department of Molecular Biosciences at the University of Kansas, noted in an accompanying editorial. “How do we, and how should we, define a T-cell subset, and what assumptions should we make about that cell’s biology purely on the basis of the surface markers?” she asked. “Continued work in this area is of importance as investigators across the field of immunology continue to use surface markers to identify cell subsets and make assumptions about their functionality.”

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