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Natural HIV control may rely on sequence of T cell receptor protein

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The rare ability of some individuals to control HIV infection with their immune system alone appears to depend – at least partially – on specific qualities of the immune system's killer T cells and not on how many of those cells are produced. In a *Nature Immunology* paper that has received advance online publication, researchers at the Ragon Institute of Massachusetts General Hospital, MIT and Harvard report that – even among individuals sharing a protective version of an important immune system molecule – the ability of HIV-specific killer T cells to control viral replication appears to depend on the particular sequence of the protein that recognizes HIV infected cells.

"We've known for the past 25 years that HIV-infected people have the immune killer cells that recognize and should be able to destroy virus-infected cells, but in most individuals those cells cannot control infection," says Bruce Walker, MD, director of the Ragon Institute and senior author of the Nature Immunology paper. "What this study shows is that the presence of these cells, also called CD8 T cells, is not enough. It turns out that people who can control HIV on their own make killer cells with T cell receptors – proteins that recognize viral fragments displayed on infected cells – that are particularly effective at killing HIV-infected cells."

It has been known for almost two decades that a small minority – about one in 300 – of individuals infected with HIV are naturally able to suppress viral replication with their immune system, keeping viral loads at extremely low levels. In 2006, Ragon Institute investigator Florencia

Pereyra, MD, established the International HIV Controllers Study (www.hivcontrollers.org/) to investigate genetic and other differences that may underlie this rare ability. Currently more than 1,500 controllers have enrolled in the study.

Several studies have found that particular versions of a molecule called HLA-B, which helps to flag infected cells for destruction by CD8 T cells, are associated with the ability to naturally control HIV infection. But even among individuals who inherit those versions or alleles of HLA-B, only a few are HIV controllers. A 2010 Ragon Institute study published in Science identified five amino acids within HLA-B that appear to affect the ability to control infection, but that study only explained about 20 percent of the difference in viral load between controllers and individuals in whom the infection progressed.

The current study was designed to search for other factors besides HLA-B that contribute to and possibly determine the ability to control HIV infection. Since many things can affect CD8 T cell response, the investigators enrolled only participants known to express the protective HLA-B27 allele. By selecting persons with HLA B-27 who had extremely high viral loads and comparing them to those with B-27 who were able to control virus, the investigators were able to address whether differences in CD8 T cell function were involved. Although this restricted the study population to five HIV controllers and five progressors, the small sample size allowed comprehensive characterization of a broad range of immune cell functions in study participants.

The experiments first confirmed there was no significant difference in the number of HIV-specific CD8 T cells between controllers and progressors but also found significant variability in the protein sequence of all participants' T cell receptors. Tests of particular functional aspects of the CD8 T cell response found that a subset of cells from controllers

were quite efficient at killing infected cells and able to respond to HIV mutations that can allow the virus to escape immune control. No such effective cells were found in samples from progressors. Detailed sequencing of HIV-specific CD8 cells from three controllers and two progressors found that the specific protein sequence of T cell receptors – which affects their structure and ability to recognize infected cells – appears to make the difference.

"A big remaining question is why these particularly effective killer cells are generated in some people but not in others. At this point we don't know why, but now we know what we are looking for," says Walker, a professor of Medicine at Harvard Medical School. "We also need to investigate whether a vaccine can induce production of these effective killer cells. HIV is slowly revealing its secrets, and each revelation helps us focus the search for the next secret, bringing us closer and closer to our goal of conquering HIV." Walker is also a Howard Hughes Medical Institute (HHMI) investigator

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