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## Less Discriminating Immune Cells Help Control HIV

For many years, AIDS researchers have sought to understand why a few HIV-positive individuals – termed “elite controllers” – have the ability to keep the virus at harmlessly low levels for decades. Now, Howard Hughes Medical Institute researcher Bruce Walker and colleagues appear to have gained important insight into one factor that contributes to enhanced control of HIV in these individuals. It turns out that elite controllers carry an especially adaptable type of T cell that keeps better pace with the virus’s ability to mutate and evade attack. These T cells can effectively kill or cripple HIV.

Elite controllers are a subset of the estimated one in 100 HIV-positive people called “long-term nonprogressors,” who don’t develop full-blown AIDS, or do so only after many years – even though they take no antiviral drugs. Elite controllers – estimated at about one in 300 HIV-positive people – maintain such low levels of the virus that it is undetectable, or nearly so.

Walker and his MIT colleague Arup Chakraborty report in an advance online publication in *Nature* on May 5, 2010, that elite controllers are genetically predisposed to make large numbers of unusually versatile T cells, the armed defenders that recognize and kill HIV-infected cells in the blood.

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Instead of being narrowly tuned to recognize a single viral identifier on the surface of an infected cell, these T cells are cross-reactive, meaning they can also bind to mutated variants of that identifier, which is a fragment of a protein produced by the virus itself. As a result, elite controllers' T cells can

quickly spot and attack rapidly mutating HIV viruses that would evade the immune defenses of the average person. Chakraborty and Walker, using computational modeling and experimental data, show that the ability to do this stems from how T cells are educated in the thymus, an organ that all T cells have to visit in order to become fully licensed killers.

“We believe these cross-reactive T cells enable the immune system to keep up with the mutations in HIV that occur every time the virus replicates,” Walker explains. “That’s why if the viruses do escape from the immune system [in the elite controllers], they survive in a crippled form” that poses less threat.

The study revealed that these super T cells are more abundant in people born with a protein on the surface of their cells called HLA-B57. This is one version of a family of molecules called human leukocyte antigens (HLA), which sit on the surface of cells and communicate to T cells. When a virus has invaded the cell, HLA molecules display fragments of viral protein to alert the immune system of an infection. Carrying HLA-B57, which is found in about 10 percent of the population, has previously been associated with good outcomes in HIV-positive individuals.

Walker says cross-reactive T cells are probably present in people without HLA B57, too, but at numbers that are too low to effectively overtake HIV. “We think these cross-reactive T cells exist in small numbers in people with other HLA types,” he says. “What we’d like to do is fish these out with a vaccine to get them active so they will see the virus. We don’t know how to do that right now.”

Walker is co-senior author of the *Nature* paper along with Arup Chakraborty of the Massachusetts Institute of Technology, who is a chemist, physicist, and computational scientist who studies basic immunology. Through the Ragon Institute, a newly established, privately funded institute of MGH, MIT, and Harvard, Walker has been casting a wide net to recruit collaborators from outside the HIV-AIDS research community who have a fresh view and different kinds of expertise. He asked Chakraborty to brainstorm with him on the elite controller enigma.

The physicist/immunologist was struck by the observation that most elite controllers are prone to autoimmune problems caused by mistaken immune attacks on the person’s own tissues and organs, including psoriasis and hypersensitivity reactions. Was this more than a coincidence?

Chakraborty proposed that the answer to both puzzles might lie in the thymus gland, a small organ in the chest. One of its jobs is to teach immature T cells to respond only to foreign proteins and ignore the host’s own “self” proteins.

Each of the millions of T cell types is equipped with a surface receptor tuned to recognize a specific peptide. As part of their schooling, “student” T cells

are exposed to fragments of the body's own proteins. "To become part of the army, each T cell has to pass two tests," explains Chakraborty. "First, it must recognize and bind to at least one self-peptide-HLA complex on the surface of cells." If the T cell doesn't do this, it is eliminated. "But second," Chakraborty says, "it must not bind *too* strongly to any 'self' peptide in the body, because of the danger of autoimmunity." These T cells, too, are eliminated.

Chakraborty used computational methods to model the selection process in the thymus. The computer modeling showed that T cells that encountered the smallest number of self-peptides in the thymus became the most cross-reactive to viral mutations that are a characteristic of HIV; those that encountered and recognized the largest number turned out to be the least able to do this.

When the computer model matched these findings to different HLA types and experimental data, the pieces fell into place. Immune armies whose development is influenced by HLA-B57 molecules have larger squads of T cells that are more cross-reactive because the young T cells encountered fewer self-peptides during their thymic education. These T cells are predicted to bind more strongly in a few key places to peptides on an HIV-infected cell – giving them more viral-controlling potency. Further, they are predicted to recognize mutants of those peptides – giving them an edge over the virus's evolution. Both of these predictions are supported by published data.

Finally, the researchers applied these findings to data previously gathered on 1,110 elite controllers and 628 "progressors" whose blood contained large amounts of virus. The findings were as predicted: Smaller numbers of self-antigens encountered in the thymus and a greater proportion of cross-reactive T cells correlated with HLA types of individuals who strongly controlled the virus. And larger numbers of self-antigens encountered, along with smaller ratios of cross-reactive T cells correlated with HLA types of people whose HIV infection progressed rapidly.

The findings also provide an explanation for the vulnerability of elite controllers to having autoimmune reactions. Because the T cells are more cross-reactive, they are prone to over-respond and mistakenly attack self-peptides in normal tissues of an individual.

Walker and Chakraborty are continuing to explore the details of how the cross-reactive T cells so rapidly and forcefully seek out and kill HIV-infected cells. They are optimistic that what they find could help in the search for an elusive vaccine for preventing HIV disease.