Thymus of the Essence

A new view of how HIV does its damage

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What causes the catastrophic loss of CD4 cells in HIVers? Unlock this, and a whole new world of therapies might well open up. A likely key is in research into the poorly understood thymus, the chest gland believed to churn out mature, or "functional," T-cells (T for *thymus*, including CD4 and CD8) after their initial production as immature, or "stem," cells by the bone marrow. *POZ* contributing editor Mike Barr checked in with thymus-study pioneer Joseph "Mike" McCune, MD, PhD, of the Gladstone Institute of Virology and Immunology at the University of California at San Francisco. Famous for his 1988 breakthrough development of a mouse with a human immune system, McCune coauthored one of this year's most exciting AIDS papers—on the vicissitudes of the thymus—and is blazing immunologic trails likely to yield unique advances in disarming HIV.

Mike Barr: What about your recent findings surprised you most?

Mike McCune: Until recently, it was generally believed that the thymus shuts down in adults—after producing a lifetime's worth of T-cells. Now, in adults with HIV, the absence—or the virus' destruction—of this organ would mean that new T-cells could not be produced to replace those killed by HIV. Surprisingly, our study found—through CAT scans of the thymus and T-cell analysis—not only that some adults have substantial thymic tissue, but that many people with HIV have more, not less, of it than their HIV negative peers.

So in HIVers the thymus "turns on" to compensate for the loss of T-cells, but eventually the virus gets the better of it?

That's our working hypothesis. As long as the bone marrow and the thymus can keep up with T-cell loss, the immune system won't collapse. But once those production systems are significantly damaged by HIV, all bets are off. That's why we believe, unlike some researchers, that AIDS is a problem more of "regenerative failure"—the inability to make new T-cells—than of "accelerated destruction" of mature T-cells.

So HIV attacks immune cells from both ends—the source (bone marrow and thymus) and the periphery (bloodstream and lymph system)?

That's one way to look at it. Now, there are two fascinating instances of retroviral infection in

which this may not happen. One involves SIV, a virus that causes an AIDS-like illness in monkeys. In the infected rhesus macaque, T-cells go away, and the animal dies. But in the sooty mangabey, SIV causes T-cell depletion only slowly, if at all. We're studying whether SIV has "learned" how to kill the mature cells in the periphery but not the immature ones still at the source.

The second instance is in people with HIV whose HAART is "failing." Many have high viral loads but still maintain high CD4 counts. We hypothesize that, as in the SIV-infected sooty mangabey, the HIV strains in these people have evolved and can now kill mature CD4 cells in the periphery but not immature cells in the bone marrow or thymus. So even with lots of virus, the immune system doesn't collapse.

What does this mean for treating PWAs?

With better tests, we may find that patients fall into subgroups requiring different therapies. Those with no thymic function and few CD4s may not be able to rebuild an *effective* T-cell system after the virus is suppressed with HAART. Already there are reports of people with post-HAART CD4 increases who nonetheless get opportunistic infections. These people may have any number of defects: a lack of stem cells coming into the thymus from the bone marrow, an absence of thymic tissue to "teach" developing T-cells how to function, or an inability of the bloodstream and lymph system to provide feedback to the thymus to churn out more T-cells.

Does such "feedback" actually exist?

We don't yet know. It's generally believed that the thymus operates without any control by the periphery, but we are reevaluating that premise. A good analogy would be to erythropoietin (EPO), a protein produced by the kidney that is responsible for stimulating the bone marrow's production of red blood cells. People with kidney disease develop low red counts because they don't make enough EPO. But we don't give them transfusions of red cells or bone-marrow cells—we give them EPO. So we're testing whether similar factors might stimulate T-cell production in the thymus. Support for this comes from two directions: data showing that two steroid hormones, cortisol and testosterone, cause the thymus to shrink; and, conversely, anecdotal reports that human growth hormone and insulin-like growth factor might promote thymic function.

What about treatments for people who lack thymic function?

It depends on what's missing. If HIV has destroyed the bone marrow, a transplant might provide the missing stem cells needed by the thymus. If the thymus is destroyed, a thymic tissue transplant might help. Finally, in those missing thymic feedback, certain substances may restore that loop. What's exciting is that our new methods for studying the thymus provide us with a powerful flashlight—you point it at different places to see different parts of the biology. This is the most likely path to better therapies for an HIV-damaged thymus.

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