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Restoring the Immune System

HIV disease gradually damages the human immune system, making it more difficult for the body to fight off opportunistic infections. Researchers hope that highly active anti-retroviral therapy (HAART) and other treatments can help people with HIV repair their immune systems and be able to fight disease more effectively. But restoration of immune function still holds many unknowns for scientists, and there is some concern that stimulating immune system cells could actually encourage increased production of HIV in the body.

The immune system has several components, including a range of different kinds of T-lymphocytes that fight invaders. CD4+ T-lymphocytes, also called T-helper cells, orchestrate immune system responses. When the immune system is damaged, the numbers of CD4+ cells can fall, leaving gaps in immune defenses. New CD4+ cells are created in the bone marrow and travel to the thymus where they become fully mature CD4+ cells. New CD4+ cells are also generated when old CD4+ cells make copies of themselves. CD8+ cells (or cytotoxic cells) kill other cells that have already been infected with an invading agent. Cytokines, including interleukin-2 (IL-2), are responsible for relaying messages between immune cells. IL-2 therapy shows promise for helping people with HIV increase CD4+ cell counts and possibly lower their HIV viral load, though further research is needed to understand whether increased CD4+ cell levels after IL-2 treatment will lead to truly improved immune systems and longer life.

Researchers at the Gladstone Institute of Virology and Immunology and elsewhere at UCSF are engaged in wide ranging work to better understand the immune system and how it can be helped to respond more successfully to HIV infection. This work includes research to understand the causes of T-cell cell depletion, factors influencing antiviral activity, the functioning of the thymus, evidence of immune restoration, and use of IL-2 in people with HIV disease.

The Causes of T-Cell Depletion

Researchers are trying to better understand why and how T-cells are depleted as HIV disease progresses. More full knowledge of this process could enable scientists to help the immune system prevent T-cell death and accelerate production of new T-cells.

Several Gladstone/UCSF studies have expanded our understanding of the dynamics of CD4+ cell functioning in HIV disease, documenting increased T-cell production following HAART. Dr. Susan Huang and colleagues at UCSF studied the effects of HAART on 66 HIV positive patients to learn about how therapy affects CD4+ cell counts. The researchers concluded that T-cell deficiency in HIV disease may be largely due to decreased production of CD4+ cells, rather than increased destruction of these cells. The researchers deduced that HAART often leads to increased T-cell counts because it restores and increases production of T-cells and other cells of the immune system.

Dr. Marc Hellerstein and colleagues at Gladstone/UCSF and UC Berkeley used isotope-labeled glucose to measure changes in T-cell life and T-cell production in HIV positive and HIV negative individuals. They found that the survival time of T-cells among HIV-infected individuals was less than one-third that of HIV seronegative subjects. The researchers also established that the immune systems of people with HIV disease did not compensate for this more rapid loss of T-cells by increasing T-cell production rates. However, researchers found that therapy with HAART had a significant effect on T-cell production. Hellerstein noted that after subjects had had their viral replication suppressed by HAART for 12 weeks, the production rates of CD4+ and CD8+ cells were elevated. Like Dr. Susan Huang, they concluded that T-cell production systems are key to understanding HIV disease and a patient's response to antiretroviral therapy (ARV).

Dr. Mike McCune and colleagues at Gladstone/UCSF and UC Berkeley found that multiple

factors, in addition to viral load, affect CD4+ cell levels in people with HIV. Their research emphasizes the importance of considering multiple immune factors particular to each individual, including size of the thymus gland, the elapsed time since initiation of HAART, and the relative abundance of different kinds of T-cells. McCune found increased rates of T-cell production in patients with HIV disease at 12 weeks after initiation of HAART. By 12–36 months of therapy, the rate of cell replacement returned to normal.

This research also concluded that the thymus plays a central role in the production and life of T-cells. In particular, McCune and colleagues found that HIV positive individuals with larger thymus glands had higher levels of one kind of T-cell, and lower turnover rates among the total CD4+ T-cell population. The researchers concluded that HIV disease progression may be closely linked to damage in the T-cell production process and that further understanding of the nature of this damage may aid with improved treatments of HIV disease.

Cell Antiviral Factor

What factors make it possible for CD4+ and CD8+ cells to effectively control HIV infection for a period of time? Dr. Jay Levy and colleagues at UCSF identified the CD8+ cell antiviral factor (CAF), a substance that mediates, at least in part, the antiviral response associated with CD8+ cells. HIV-infected, asymptomatic people and long term survivors of HIV infection have high levels of this CD8+ cell antiviral activity. Levy studied the blood cells in long-term survivors of HIV disease and observed that when their CD8+ cells and CD4+ cells were separated in a culture, the CD4+ cells released high levels of HIV.

When the two kinds of cells were placed together again, no viral replication occurred. What factor makes it possible for CD8+ cells to control HIV infection? The researchers demonstrated that a soluble factor (CAF) released by the CD8+ cells had antiviral activity. In cell culture, they have found that IL-2 can increase this antiviral response of CD8+ cells. Noting research on the ability of IL-2 therapy to stabilize CD4+ cell numbers in patients, the researchers believe that the effect of IL-2 in these cases could be brought about through the induction of CD8+ cell anti-HIV responses and CAF production.

The Role of the Thymus

The thymus plays a critical role in the immune system by generating more CD4+ cells. It was long thought that the thymus ceases to work in older people, leading to gradual degeneration of the immune system. Maintenance of thymic function is one potential approach to stimulating an ongoing effective immune response to HIV disease.

A first step in improving immune function is better understanding of the role of the thymus in people with HIV disease. Dr. Jean-Francois Poulin, working with several researchers at Gladstone/UCSF and elsewhere, used a novel assay to study thymus function. The researchers determined that the thymus, though less functional with age, operates well into adulthood. Given this finding, the researchers concluded that presence or reappearance of T-cells in people with HIV disease may not necessarily mean that the immune system has been reconstituted, but that the thymus, and perhaps other sources, are simply producing T-cells normally.

The thymus's ability to produce T-cells appears to be related to its size. Dr. Mike McCune, working with colleagues at Gladstone/UCSF and the University of Michigan, used computerized tomograph (CT) scans to measure thymic tissue in HIV positive and HIV negative individuals. They found that in HIV positive adults, larger thymus size was associated with higher CD4+ cell counts, even when age and duration of infection were taken into consideration.

McCune concluded that thymic function may be enhanced in some people who are HIV positive, and that the thymus is functional in some but not all adults with HIV disease. The researchers found that abundant thymic tissue is present in many HIV positive adults, and they posited two possible explanations: 1) the thymus may respond to declining CD4+ T-cell counts in people with HIV by maintaining higher than usual functioning; or 2) high prevalence of thymic tissue in older people with HIV can be explained by increased survival rates among adults with larger thymus size.

The dynamics of thymic function still hold many puzzles for researchers. Dr. Kimberly Smith, working with several colleagues, including McCune of Gladstone/UCSF, used CT scans to explore the role of the thymus in immune

reconstitution during HAART. The researchers noted that HIV positive persons with abundant thymic tissue had a more rapid rise of CD4+ T-cells after the initiation of HAART than did individuals with minimal thymic tissue. The researchers were surprised to find that HIV viral load levels were significantly higher at week 48 among those patients with abundant thymic tissue than the group with minimal thymic tissue. These findings suggest there is a complex relationship between the thymus, cellular restoration, and viral replication.

Evidence of Immune Reconstitution

Researchers at UCSF have studied the use of HAART and other treatments to restore immune function in people with HIV disease. Dr. Krishna Komanduri and colleagues at Gladstone/UCSF studied immune reconstitution after treatment with HAART and ganciclovir. Cytomegalovirus (CMV) is the leading cause of blindness in people with AIDS, and studies have identified an important role for CD4+ cells in controlling CMV. Dr. Komanduri and colleagues studied HIV-infected individuals with and without a history of active CMV-associated end organ disease (EOD) and individuals with dormant CMV EOD after ganciclovir therapy and HAART. The researchers found a strong correlation between CMV-associated EOD and loss of CMV-specific CD4+ cells. By contrast, patients *without* CMV-associated EOD, and the majority of patients with *dormant* EOD after HAART showed strong CMV-specific CD4+ cell responses. Komanduri and colleagues concluded that the loss of CMV-specific CD4+ cell responses in HIV-infected individuals who have active CMV EOD can be restored after ganciclovir therapy and HAART.

IL-2 Therapy

Studies of interleukin-2 have shown promise for improving immune function in people with HIV disease. Dr. Frederick Hecht of UCSF, and colleagues from UCSF, Blood Centers of the Pacific, and Harvard University, performed a randomized trial to understand the immunologic effects of using IL-2 together with ARV. Study participants had begun HAART during primary HIV infection (within 12 months of infection). Other IL-2 studies focused on individuals later in the course of HIV disease. Sixteen patients were

randomized into an “early” treatment group that received IL-2 within four weeks of achieving an HIV viral load of less than 500. Those in the “deferred group” received IL-2 48 weeks after achieving viral load under 500. The researchers found that at week 48 of ARV treatment, the mean CD4+ cell count was 1587 in the early IL-2 group and 681 in the delayed group. Hecht and his colleagues concluded that patients with HIV infection can achieve higher CD4+ cell counts when IL-2 is added to HAART.

Dr. James O. Kahn of UCSF was involved in a study headed by Dr. Richard Davey of the National Institutes of Health that followed 82 HIV positive patients to determine whether IL-2 therapy with HAART would provide improved immunological outcomes as compared with HAART alone. In a randomized trial, patients received IL-2 and HAART or only HAART. After one year, those patients receiving IL-2 had CD4+ cell counts 112% higher than they did at the beginning of the study, while those receiving only HAART had seen only an 18% increase in CD4+ cell count. Those receiving IL-2 also had a larger drop in viral load during the study period. Research currently underway will help determine whether enhanced viral suppression and CD4+ cell count increases associated with IL-2 therapy translate into improved clinical outcomes.

AIDS research has led to great strides in understanding the immune system and using several therapeutic approaches to restore immune function. A range of ongoing research at UCSF and elsewhere holds promise for identifying new treatments that can help the immune system repair itself and more effectively fight HIV infection over many years.

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Materials Available

Further information on immune restoration is available on HIV InSite
<http://hivinsite.ucsf.edu>

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