An Assessment of HIV Research in the Last Three Years

Jennifer Baure

Writer's comment: Writing was always difficult for me, and I dreaded writing papers and essays. When I took ENL 102B (Writing in the Disciplines: Biological Sciences) taught by Jared Haynes, I found that with a helpful teacher and an interesting topic, writing could be quite effortless and even enjoyable. One of the assignments in ENL 102B was to write a review paper about any subject. I chose to write about HIV because the virus is extremely complex and fascinating. When I was looking up primary research articles, I discovered that research topics were so extensive that it was difficult for me to find at least six articles on a particular area. Therefore, this paper covers a multitude of subjects instead of focusing on a specific one.

—Jennifer Baure

Instructor's comment: Jennifer wrote this literature review for my Advanced Composition course, English 102B: Writing in the Biological Sciences, in the fall of 2003. The assignment asks the students to find, read, and understand a group of articles clustered around a research area of their choice, then to synthesize the information so that a reader could quickly grasp the present state of research in that area. Jennifer's review examines the most recent advances in research into HIV infection. Her introduction lays out some of the problems faced by HIV researchers and indicates the general areas that her paper will be reviewing. While the review assumes a certain level of knowledge on the part of the reader (the assignment asked that it be aimed at undergraduate biology students), it explains the research clearly and indicates the significance of the findings being reviewed. Even a reader with little background in science could learn from this review, a feature of Jennifer's writing that made her paper stand out.

—Jared Haynes, University Writing Program

Introduction

Human Immunodeficiency Virus, or HIV, is a retrovirus that gradually weakens the immune system and may result in the immune system debilitating disease AIDS. Since society has learned how HIV is acquired, people act more cautiously to prevent contracting the potentially deadly virus. In addition, there have been great advances in HIV research that have helped develop treatments that effectively prevent HIV from progressing to AIDS. The spread of HIV has decreased in some parts of the world; however, HIV and AIDS remain significant problems in most countries.

Unfortunately, many details of HIV infection remain unknown. HIV reduces the number of T-cells, but it is not known how HIV accomplishes this. HIV eventually can result in AIDS, but it is not known how this occurs and why some patients with HIV quickly progress to AIDS while others can live for decades without any progression to the fatal disease. Because more than 30 classes of HIV exist in the world (Ly et al., 2001), finding one effective treatment for HIV has been difficult. In the last three years, HIV researchers have focused not only on discovering the mechanism HIV uses to cause immunodeficiency and on hindering that mechanism through current treatments but also on developing vaccines to prevent HIV infection.

How HIV Causes Immunodeficiency

Effects of HIV on T-cells

Immunological experiments have isolated specific HIV viral proteins and observed their effect on T-cells. The HIV-produced protein Viral Protein R (Vpr), in particular, has been studied extensively. Vpr has been found in the serum and cerebrospinal fluid of HIV infected patients. Lum et al. (2003) observed both mutated and wild type Vpr functions in HIV patients. They noticed that many HIV-infected patients had long-term nonprogressive (LTNP) HIV, meaning the patients would remain healthy without therapy. Because they found that a large percentage of LTNP patients had the Vpr mutation, they attributed the lack of immunodeficiency to those mutations. Lum et al. observed that functional, or wild type, Vpr caused more CD4+ T-cells to undergo apoptosis than non-functional, or mutated, Vpr. Vpr must play a major role in T-cell apoptosis.

There is evidence that HIV-1 not only induces apoptosis of T-cells but also causes the proliferation of large numbers of new T-cells

(Hellerstein et al., 2003). Hellerstein et al noted that patients infected with HIV-1 produced three times as many new T-cells as uninfected patients; however, more T-cells died in a shorter amount of time. In the same experiment, Hellerstein and his colleagues used two radioactive isotopes, deuterated water and ^{2}H-glucose, to differentiate between effector T-cells and memory T-cells; they observed that HIV-1 affects each cell type. Patients infected with HIV produced twice as many new effector T-cells and half as many memory T-cells as control patients. These results show that HIV induces T-cell apoptosis as well as their uncontrollable growth; the virus also differentiates between effector T-cells and memory T-cells, disrupting the balance between the two cell types.

How the Body Responds to HIV

When the immune system is first infected with HIV, it produces antibodies against it. One of the best ways to identify HIV in the blood is to do a combination assay that detects both HIV and its antibody (Ly et al., 2001). Many cells work together to produce this antibody. The innate immune system leukocytes (monocytes, dendritic cells, etc.) are the first cells to attempt to defend against HIV. When those cells fail, T-cells and the antigen-presenting cells communicate. T-cells produce CD40 ligand (CD40L) that bind to CD40 receptors on antigen-processing cells. Cotter et al. (2001) demonstrated that macrophages in contact with CD40L, as opposed to macrophages without any contact with CD40, increased cytokine production as well as decreased HIV retroviral activity. In response to HIV infection, CD40L binds to the CD40 receptor to induce the release of cytokines, which have been shown to inhibit HIV-1 function (Cotter et al., 2001).

Unfortunately, macrophages consistently releasing large amounts of cytokines may distress the immune system. If an excess of cytokines is released, monocyte dysfunction may occur (Amirayan-Chevillard et al., 2000). In patients with HIV, Amirayan-Chevillard et al. (2000) reported an increase in monocytes expressing the surface protein CD16 and a decrease in beneficial monocyte activity. They also demonstrated that a decrease in macrophage cytokine activity caused a decrease in HIV replication. The body's own immune response to HIV may aid in eventual immune system deterioration.

Treatments

How Current Treatments Work

Researchers are studying how treatments work against HIV and determining how to slow down HIV pathogenesis. Several types of effective treatments are available for HIV patients. Anti-retroviral therapies, or ART, prevent HIV replication. Protease inhibitors and inhibitors of HIV reverse transcriptase (RT) are two types of antiretroviral therapies. Amirayan-Chevillard et al. (2000) observed that both RT inhibitors and protease inhibitors prevented HIV replication by decreasing the production of certain cytokines.

ART has been shown to treat HIV-infected patients effectively. T-cells of HIV-infected patients on long-term ART reproduced less and lived longer than the T-cells of untreated HIV-infected patients (Hellerstein et al., 2003). In addition, patients treated with ART produced more memory T-cells than untreated HIV-infected patients, maintaining the balance between numbers of long-lived and short-lived T-cells (Hellerstein et al., 2003).

Highly active antiretroviral therapy (HAART) is a combination of one HIV protease inhibitor and two HIV RT inhibitors. Amirayan-Chevillard et al. (2003) studied how HAART affects HIV replication. They found that HAART decreased production of cytokines TNF, IL-1β, IL-6, and IL-10. HAART not only effectively decreased cytokine production and HIV replication but also decreased the number of monocytes expressing the CD16 surface protein, better regulating monocyte/macrophage response.

Vaccine Research

Researchers have exposed rats and human T-cells, in vitro, to HIV viral proteins. Friedman et al. (2000) utilized the *Listeria monocytogenes* bacterial vectors expressing HIV genes *gag* and *nef*. They observed a strong cytotoxic T-cell response in both the attenuated and wild type bacteria and found that the attenuated bacteria triggered little T-cell apoptosis. T-cells can quickly react to viral proteins expressed by attenuated bacteria.

Because utilizing live but weakened strains of pathogens has been successful at building good immune responses to certain infections, like polio, some researchers have considered using live attenuated strains of HIV to build up an effective immune response against wild type HIV. Blower et al. (2001) predicted that using less pathogenic HIV strains for

vaccination can eliminate the wild type strain of HIV in a certain region, and the attenuated HIV strain will become more prevalent. Unfortunately, they found that in some cases even the attenuated strains could result in AIDS. (Blower et al., 2001).

Conclusion

Currently, HIV research has been dispersed among different areas of study. Although the results have been informative, future research should support some of the studies mentioned and focus on a specific area of HIV to study. The study by Hellerstein et al. (2003) can guide further studies on HIV and its effects on memory T-cells and effector T-cells. Since memory T-cells help defend the body against common antigens, memory T-cell reduction along with the abnormal growth of new effector T-cells may be the cause of immune system deficiency due to HIV. With the successful method designed by Hellerstein et al., future studies could give more insight into why HIV infects these two cell types differently. Perhaps there are slight differences in effector and memory T-cell plasma membranes, and HIV recognizes only certain domains on the plasma membrane.

In addition, researchers should further study HIV Vpr and other viral proteins. Researchers may be able to discover how Vpr induces T-cell apoptosis. Vpr probably works with other viral proteins to cause T-cell apoptosis. Immune responses to these viral proteins can be induced through bacterial vectors or other methods. Current research is promising, but due to the lack of knowledge about HIV mechanisms and the growing number of different HIV strains, many years of study will be required before researchers can gain a solid understanding of HIV infection.

References

Amirayan-Chevillard, N., H. Tissot-Dupont, C. Capo, C. Brunet, F. Dignat-George, Y. Obadia, and J.L. Mege. 2000. Impact of highly active anti-retroviral therapy (HAART) on cytokine production and monocyte subsets in HIV-infected patients. *Clinical and Experimental Immunology* 120: 107–112.

Blower, S.M., K. Koelle, D.E. Kirschner, and J. Mills. 2001. Live attenuated HIV vaccines: Predicting the tradeoff between efficacy and safety. *Proceedings of the National Academy of Sciences of the United States of America* 98 (6): 3618-3623. URL:http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=30702.

Cotter, R.L., J. Zheng, M. Che, D. Neimann, Y. Liu, J. He, E. Thomas, and H.E. Gendelman. 2001. Regulation of Human Immunodeficiency Virus Type 1 infection, chemokine production, and CCR5 expression in CD40L stimulated macrophages: Immune Control of Viral Entry. *Journal of Virology* 75 (9): 4308–4320. URL: http://jvi.asm.org/cgi/content/full/75/9/4308.

Friedman, R.S., F.R. Frankel, X. Zhan, J. Lieberman. 2000. Induction of Human Immunodeficiency Virus (HIV)-specific CD8 T-cell responses by *Listeria monocytogenes* and a hyperattenuated *Listeria* Strain engineered to express HIV antigens. *Journal of Virology* 74 (21): 9987–9993. URL: http://jvi.asm.org/cgi/content/full/74/21/9987.

Hellerstein, M.K., R.A. Hoh, M.B. Hanley, D. Cesar, D. Lee, R.A. Neese, and J.M. McCune. 2003. Subpopulations of long-lived and short-lived T cells in advanced HIV-1 Infection. *Journal of Clinical Investigation* 112 (6): 956–966. URL: http://www.pubmedcentral.gov/articlerender.fcgi?tool=pmcentrez&artid=193663.

Lum, J.J., O.J. Cohen, Z. Nie, J.G. Weaver, T.S. Gomez, X. Yao, D. Lynch, A.A. Pilon, N. Hawley, J.E. Kim, Z. Chen, M. Montpetit, J. Sanchez-Dardon, E.A. Cohen, and A.D. Badley. 2003. *Vpr* R77Q is associated with long-term nonprogressive HIV infection and impaired induction of apoptosis. *Journal of Clinical Investigation* 111 (10): 1547–1554 URL: www.pubmedcentral.gov/articlerender.fcgi?artid=155040.

Ly, T.D., L. Martin, D. Daghfal, A. Sandridge, D. West, R. Bristow, L. Chalouas, X. Qiu, S.C. Lou, J.C. Hunt, G. Schochetman, and S.G. Devare. 2001. Seven Human Immunodeficiency Virus (HIV) antigen-antibody combination assays: evaluation of HIV seroconversion sensitivity and subtype detection. *Journal of Microbiology* 39 (9): 3122–3128. URL: jcm.asm.org/cgi/content/full/39/9/3122.