



Update

EMBARGOED UNTIL
2:45 pm, EDT, Monday
June 1, 1987

Sandy Hecker
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AREA OF HIV ENVELOPE IDENTIFIED AS CRITICAL FOR INFECTIVITY

By altering one small component of an outer, or envelope, protein of the human immunodeficiency virus (HIV), National Institute of Allergy and Infectious Diseases (NIAID) scientist Ronald L. Willey and his colleagues made a mutant HIV that is non-infectious. The mutant virus was able to bind to CD4, the natural receptor for HIV that is present on a subset of T cells called T4 cells, the immune system cells the virus preferentially infects. Unlike normal HIV, however, the mutant virus was unable to gain entry into T4 cells, a step necessary for the initial phase of HIV infection. This finding demonstrates that, in addition to binding to the CD4 receptor, another step is necessary for HIV to successfully infect immune cells. Additional research showed that the non-infectious HIV was later able to regain its infectivity through additional self-created alterations in a different region of its envelope protein.

The surface of HIV is studded with two types of proteins called envelope proteins. The larger of these two proteins, called gp 120, makes contact with a CD4 receptor during early stages of infection. To determine if specific areas of the gp 120 protein are required for infectivity, Mr. Willey and others looked at the protein's precise chemical construction. They compared samples of HIV isolated from different people and found that, in all the viruses, certain regions of the gp 120 envelope protein are very similar, termed "constant regions," while others vary from one HIV isolate to the next.

In all HIV samples analyzed to date, one of these constant regions contains 4 sites (recognized by their chemical structure) where sugar molecules could attach to the envelope protein. Although scientists do not know what role the sugar molecules might play in HIV infection, the fact that these sites are always found in the same places indicates that these sites are likely to be important.

To determine if disruption of any of these sites could prevent HIV from infecting T cells, the investigators changed each site, one at a time. Loss of each of three sites had no effect on HIV infectivity, but the fourth change prevented HIV from getting into a T4 cell. Further tests showed that in other respects the mutant virus was normal, and it was still able to bind

to the T4 cell receptor. Before this and related research, scientists thought that once HIV attached to the CD4 receptor, infection of the T4 cell followed automatically. The new findings indicate that other processes in addition to HIV attachment to its T4 cell receptor may be necessary for HIV to infect cells and spread. This information provides insight into how HIV infection might be prevented.

Surprisingly, when the non-infectious mutant was tested for infectivity a month later, the researchers found that in three out of nine cases, it was infectious. Analysis of the revertant gp 120 protein showed that the site changed by the scientists was still there, but in addition there was a new alteration. One possible explanation for regained infectivity is that the second change altered the shape of the HIV envelope, thereby permitting the mutant to enter the cell. The appearance of the revertant may indicate the existence of a process by which the virus can change its outer proteins. This process could be important in enabling HIV to escape the immune system, and to go on to infect other cells.

Discovery and understanding of the basic, or molecular, mechanisms that allow HIV to infect cells is important for developing strategies for the successful treatment and prevention of AIDS. The research described here has defined a functionally important region of the HIV envelope that has to be intact to permit infection. These findings raise the possibility of genetically engineering proteins that would interfere with HIV infection of T4 cells.

Ronald L. Willey presented these findings at the III International Conference on AIDS held in Washington, D.C., this week. The research team also included Drs. Theodore Theodore, and Malcolm A. Martin, Chief, Laboratory of Molecular Microbiology, NIAID; and Drs. Daniel J. Capon, and Laurence A. Lasky, Genentech.

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Update

FOR IMMEDIATE RELEASE
June 1, 1987

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NIAID INTERNATIONAL COLLABORATION IN AIDS RESEARCH (ICAR)

The National Institute of Allergy and Infectious Diseases (NIAID) will award grants of up to \$500,000 of direct costs per year to fund collaborative research on AIDS between U.S. and foreign scientists. The NIAID International Collaboration in AIDS Research (ICAR) program will provide up to \$5 million dollars during its first year (1988) to American institutions, which will then sponsor AIDS research in countries where the disease is epidemic or endemic. Seventy to eighty percent of the research will be conducted in foreign countries.

Under the ICAR program, U.S. experts in virology, epidemiology, medicine, public health and other scientific disciplines will spend 6 months to 2 years in foreign countries helping scientists develop research facilities and projects and become self-sufficient investigators. Some foreign scientists and technicians will obtain additional training in U. S. institutions.

The ICAR program will emphasize research in epidemiology, particularly on perinatal and pediatric AIDS infections, heterosexual transmission, and natural history of disease. Scientists are especially interested in what factors may make people more vulnerable to AIDS, such as infection with parasitic or other diseases.

U.S. and foreign scientists will also study the variability of the AIDS virus from different parts of the world and how these variations might relate to changes in transmission of the disease and its clinical course. They will also investigate related human and animal viruses to find clues about how the AIDS virus evolves and changes its structure and why it can cause disease.

Studies will be aimed at improving and protecting the health of the people in these countries by developing rapid, inexpensive diagnostic tests and instituting blood-screening programs. Scientists also will be searching for better methods of treatment and for vaccines to prevent infection with the AIDS virus.

As many as 10 million people worldwide may be infected with human immunodeficiency virus (HIV), formerly called HTLV-III, or LAV. Infection has been reported in more than 130 countries. As many as two-thirds or more of those infected with the virus may develop the disease.

In the United States, most cases of AIDS have occurred among homosexual and bisexual men and intravenous drug users. In other countries, patterns of transmission vary. In Africa, where several million people are infected, AIDS affects equal numbers of males and females. It is spread primarily through heterosexual activity, by transfusion of contaminated blood that has not been tested for evidence of the virus, by injections with contaminated and unsterilized needles, and from infected mothers to newborn babies during pregnancy or childbirth. As in the United States and Europe, AIDS in Africa primarily affects very young children and young adults.

The ICAR program will fund these collaborative efforts with program project grants--designed for broad multidisciplinary programs consisting of three or four related research projects. Research reports will be co-authored by American and foreign scientists and published in scientific journals.

The NIAID grants to fund foreign research are expected to serve as seed money to begin these programs, and foreign scientists will be encouraged to also seek other sources of funding for their research.

Applications for the ICAR grants are due no later than September 15, 1987. Further information about this program is available by writing to:

Dr. Harold Ginzburg
Chief, Epidemiology Branch
NIAID AIDS Program
National Institute of Allergy and Infectious Diseases
Westwood Building, Room 3A12
Bethesda, Maryland 20892.

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Update

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ALPHA INTERFERON PROMISING IN TREATMENT OF EARLY AIDS INFECTION

Scientists at the National Institute of Allergy and Infectious Diseases (NIAID) have reported promising results from two studies using alpha interferon in patients in the early stages of infection with human immunodeficiency virus (HIV), the retrovirus that causes AIDS.

Dr. Joseph A. Kovacs, NIAID, presented data from clinical trials demonstrating that alpha interferon showed anti-retroviral activity in AIDS patients whose only symptom was Kaposi's sarcoma and in HIV-infected patients with no symptoms.

Alpha interferon, a naturally occurring protein produced in quantity through recombinant technology, has been used in a number of AIDS patients as a treatment for Kaposi's sarcoma. Tumor regressions have been seen in up to 50 percent of these patients, but scientists have not known whether the results reflect an anti-tumor effect alone or whether the alpha interferon acts against the AIDS virus itself. In laboratory studies conducted by Dr. Martin Hirsch and colleagues at Massachusetts General Hospital, Boston, alpha interferon has shown anti-retroviral activity.

Dr. Kovacs and his colleagues used alpha interferon to treat 14 patients with Kaposi's sarcoma. Patients received daily subcutaneous injections of the drug, beginning at 35 million units per day and reduced as necessary. After 9 to 11 weeks of therapy, partial remissions of tumors were seen in 7 patients, and 4 of these 7 patients went on to complete remission of their tumors. The other 7 patients experienced progressive disease or adverse effects. Responses were closely correlated with patients' T4 lymphocyte counts; all of the patients who experienced tumor remissions had T cell counts of more than 100 cells per cubic millimeter in peripheral blood from the beginning of the study.

Viral cultures, a measure of HIV activity in the body, were done every two weeks. When cultures from the patients treated with alpha interferon were compared with those from another group of Kaposi's sarcoma patients at a similar stage of HIV infection, the interferon-treated patients had considerably less viral activity.

In the second study, which is still ongoing, the investigators used alpha interferon in asymptomatic patients who were seropositive (had antibody to the AIDS virus), and who were viral culture positive. None

(more)

had a history of opportunistic infection or evidence of significant immunologic abnormality, as shown by T4 lymphocyte counts of at least 400 cells per millimeter of peripheral blood.

The patients in this study were randomized to receive either 35 million units of recombinant alpha interferon or placebo for 12 weeks. Dr. Kovacs reported data from 6 patients who received interferon and 10 who received placebo. HIV cultures were performed every two weeks. At the end of 12 weeks, 50 percent of the interferon treated patients were culture negative (showed no evidence of HIV), compared to only 20 percent of the patients on placebo.

"While the data from the two studies are not statistically significant, because of the small numbers of patients studied, they do suggest that alpha interferon may have an in vivo effect in patients whose HIV infection has not yet resulted in severe immunologic destruction," Dr. Kovacs concluded. Further studies of alpha interferon in similar patient groups are being conducted at the NIAID, he added, including a study combining alpha interferon and AZT, and patient recruitment is continuing.

Co-authors of the study, which was presented at the Third International Conference on AIDS, are Dr. H. Clifford Lane, Dr. Henry Masur, Ms. Betsey Herpin, Dr. Judith Feinberg, and Dr. Anthony S. Fauci.

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Update

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FUNCTIONAL ANALYSIS OF THE HIV A (SOR) GENE PRODUCT

The process by which the human immunodeficiency virus (HIV), the cause of AIDS, spreads in the body is of great interest to AIDS researchers. Dr. Klaus Strebel of the National Institute of Allergy and Infectious Diseases (NIAID) and his colleagues are studying the function of a HIV gene called "A," (or "sor") that may play a role in the spread of HIV.

In viral infections, a viral particle will infect a cell, use the cell to make additional copies of itself (new viral particles), and then each of these new viruses will leave the cell and go on to repeat the cycle in another cell. In general when a viral particle is released from one cell it is termed "free virus" until it finds a new cell to infect. Infection by free viral particles accounts for the spread of most human viral diseases such as influenza, polio, and the common cold.

Dr. Strebel and his colleagues created a mutant HIV that lacks the A gene and compared its infectivity with normal HIV. Unlike normal HIV, free viral particles lacking the A gene were not able to infect other cells. HIV lacking the A gene could only spread to T4 cells that were in actual contact with the cell the mutant virus was leaving.

The researchers showed that loss of the A gene had no other effects on the virus. Despite lack of the A gene, when the mutant HIV were artificially introduced into cells, the viruses were able to make viral proteins, and to replicate, that is, make additional copies of themselves. The fact that the HIV mutant could only spread cell-to-cell suggests to the scientists that this mode of spread is likely to occur in normal HIV, though this has not been formally demonstrated.

Scientists have previously suspected that HIV could be spread cell-to-cell; this might explain the chronic infection that exists in persons with AIDS despite the presence of antibodies against HIV, and the fact that little if any free virus can be detected in people with AIDS. If HIV passes directly from one cell to the next, it will not be vulnerable to a protective component of the immune system called antibodies, which could destroy it.

These results indicate that the A gene is required for production of infectious free viral particles, and have implications for development of antiviral drugs and AIDS vaccines. In addition, HIV lacking the A gene may be a useful model system for quantifying cell-to-cell spread of HIV as well as for testing the effectiveness of new drugs to prevent cell-to-cell spread of HIV.

Dr. Strebel presented these findings at the III International Conference on AIDS held in Washington, D.C. this week. The research team included Drs. Strebel and Malcolm A. Martin, Chief, Laboratory of Molecular Microbiology, NIAID, and Dr. Thomas Folks, Laboratory of Immunoregulation, NIAID, and Dr. David Cohen, National Institute of Diabetes, Digestive and Kidney Disorders, National Institutes of Health; Dr. Daryl Daugherty, University of Michigan; and Dr. Kathleen Clouse, Georgetown University.

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