



National Institute of Allergy and Infectious Diseases

Update

FOR RELEASE
Monday, June 13, 1988

PUBLIC HEALTH SERVICE
Sandy Hecker
(301) 496-5717

AIDS VIRUS BINDING SITE TO CD4 ELUCIDATED

A team of scientists at the National Institute of Allergy and Infectious Diseases (NIAID) have identified more precisely the site at which the AIDS virus binds to the human cell receptor called CD4. Such information is critical to ongoing efforts by scientists to use a soluble form of CD4 (not attached to a cell surface) as a potentially safe and effective treatment for persons infected with the AIDS virus. Dr. Edward A. Berger, senior investigator, NIAID Laboratory of Viral Diseases (LVD), presented the team's findings at the Fourth International Conference on AIDS in Stockholm.

To gain entry into human cells, the outer coat protein of the human immunodeficiency virus (HIV, the cause of AIDS) attaches to CD4. This receptor is found on the surface of immune system cells, such as T4 cells and monocyte/macrophages, as well as on a few other cell types, and makes these cells infectible by HIV. Because HIV attaches to CD4, scientists hypothesize that soluble CD4 could be administered as a treatment to HIV-infected patients. If HIV binds to soluble CD4, rather than to infectible cells, pathogenesis (disease processes) may be prevented. Indeed, test tube studies combining HIV, infectible human cells, and soluble CD4 have been promising.

To use soluble CD4 as a treatment, however, it must not interfere with normal cellular processes. The normal function of CD4 is not completely understood, although it is believed to interact with immune system Major Histocompatibility Complex (MHC) class 2 proteins.

MHC class 2 proteins are involved in communication between cells of the immune system, an important part of normal immune response. They are necessary to stimulate the production of antibodies (protective proteins) as well as to regulate interactions between T cells.

Scientists are determining which region(s) of CD4 interact with HIV. Ideally, soluble CD4 as a treatment would contain only the region(s) that interact with HIV in order to minimize interference with natural CD4 function. Dr. Berger, along with LVD senior scientist Dr. Thomas R. Fuerst, and LVD chief, Dr. Bernard Moss, conducted experiments to elucidate such regions.

Dr. Berger and his colleagues systematically produced a series of different-sized fragments of the CD4 protein and tested each one for the ability to bind to the envelope protein of HIV using a wide range of very specific antibodies as tools. Results demonstrated that a fragment of CD4 consisting of approximately 180 amino acids (protein subunits), or about one-half of the section of CD4 extending outside the cell, contains an active binding site for HIV. The researchers next wanted to determine precisely where within that fragment HIV binds.

LVD guest researcher Dr. Tamio Mizukami, from the Japanese pharmaceutical company Kyowa Hakko Kogyo, Limited, Tokyo, identified sites in the region critical for HIV binding. Using a research technique called site-directed mutagenesis, Dr. Mizukami systematically changed individual components of the 180 amino acid region thought to be important for HIV binding. Those changes, or mutations, which resulted in loss of the fragment's ability to bind to the HIV envelope, enabled identification of sites functionally important for HIV binding. Resulting data localized an area of the 180 amino acid region that is important for HIV binding to CD4. These results are bringing scientists closer to development of AIDS treatments involving the use of soluble CD4.

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