



Update

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AIDS Virus Binding Site on CD4 Determined

Several research groups recently showed that a soluble form of CD4, the receptor by which the AIDS virus enters cells, shows promise as a potential treatment for AIDS. One of the groups identified a region of CD4 that attaches to the human immunodeficiency virus (HIV), the cause of AIDS. Dr. Edward A. Berger and his colleagues at the National Institute of Allergy and Infectious Diseases (NIAID) have independently confirmed and further elucidated this region of CD4. Such information is critical for development of an effective soluble CD4 treatment for HIV-infected persons that has minimal side effects.

To gain entry into human cells, the outer coat protein of HIV (called gp120) attaches to CD4. CD4 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. The presence of CD4 makes these cells infectible by HIV.

Because HIV attaches to CD4, scientists hypothesize that soluble CD4 (CD4 not attached to a cell surface) could be administered 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. CD4's normal function is not completely understood, although it is believed to interact with immune system proteins called 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 required to stimulate the production of antibody (protective proteins) by B cells (another type of immune system cell), as well as to regulate interactions between T cells.

Before CD4 can be used as treatment, scientists must determine which region(s) of CD4 interact with HIV and which interact with the normal cellular proteins. If these are different areas of the CD4 molecule, modified soluble CD4 could be produced to contain only the region(s) that interact with HIV.

Dr. Berger and his colleagues at the Laboratory of Viral Diseases, NIAID, have characterized the HIV binding domain of CD4 by producing various-sized fragments of the CD4 protein. The researchers used a vaccinia virus/bacteriophage T7 (virus that infects bacteria) hybrid system developed in their laboratory that easily and effectively produced these CD4 fragments. The system involves insertion of genetic information coding for CD4 into plasmids (chromosome-like entities found in bacteria) from which CD4 is then produced. The researchers can modify the CD4 genetic information very specifically. The resulting modified CD4 can then be tested for functional changes by using a wide range of very specific antibodies as tools. This provides much information about the function of certain

regions of CD4.

Results of these experiments demonstrated that an approximately 180 amino acid (protein subunit) fragment of CD4 (about one-half of the section of CD4 extending outside the cell) contains an active binding site for HIV. Dr. Berger and his colleagues are currently examining other CD4 fragments and mutants to further pinpoint the HIV binding region. They are also working to produce large quantities of these protein fragments for additional testing of their ability to block HIV infection of cells and their effects on normal immunological function of cellular CD4.

These results are reported by Dr. Berger, along with Drs. Thomas R. Fuerst, and Bernard Moss, Chief, Laboratory of Viral Diseases, NIAID, in the April 1, 1988 issue of Proceedings of the National Academy of Sciences, V85:2357-2361. The article is entitled "A Soluble Recombinant Polypeptide Comprising the Amino-Terminal Half of the Extracellular Region of the CD4 Molecule Contains an Active Binding Site for Human Immunodeficiency Virus."

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