National Institute of Allergy and Infectious Diseases

Update

EMBARGOED UNTIL
10:45 am, EDT, Wednesday
June 3, 1987

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EXPRESSION OF HIV GENES BY RECOMBINANT VACCINIA VIRUSES

Dr. Bernard Moss and his colleagues at the National Institute of Allergy and Infectious Diseases (NIAID) are studying important aspects of human immunodeficiency virus (HIV) gene expression in recombinant vaccinia virus. The investigators are using a technique they developed to turn the vaccinia virus, originally used as a vaccine against smallpox, into a vector to express genes from other microorganisms. These studies may lead to a vaccine to prevent acquired immunodeficiency syndrome (AIDS).

Using genetic engineering methods, Dr. Moss is able to construct new kinds of recombinant live virus vaccines by inserting bits of genetic material from other disease-causing agents into the vaccinia virus. The resulting hybrids retain the vaccinia virus's ability to stimulate an immune response.

When certain HIV genes, such as the envelope gene (which contains instructions for proteins that appear on the surface of HIV), are inserted into the recombinant virus, the virus expresses, or produces, proteins that can be used as vaccines to stimulate an immune system against HIV. Vaccines induce the immune system to produce antibodies; in the case of some viral diseases, such as measles, antibodies prevent subsequent infection with the virus. Scientists do not know, however, whether production of antibodies against HIV will prevent AIDS.

In the past year, Dr. Moss and his colleagues have made recombinant viruses that express HIV genes for envelope proteins, gag proteins, and reverse transcriptase (RT). HIV envelope proteins are considered possible candidates for vaccine material since the corresponding proteins of mouse retroviruses can induce protective immunity against mouse leukemia. Gag proteins make up part of the structural core of HIV, and thus may also be candidates for a vaccine to prevent infection with HIV. RT enables HIV to multiply in cells and spread; vaccinia virus that contains the RT gene might be used for drug studies. A drug that prevents production of RT might prevent HIV infection.

Through genetic engineering techniques, Dr. Moss and Dr. Patricia Earl of NIAID inserted the HIV envelope gene into vaccinia virus. Dr. William

London of the National Institute of Neurological and Communicative Disorders and Stroke inoculated the recombinant vaccinia virus into rhesus monkeys and later took blood samples from the monkeys. Drs. Marjorie Robert-Guroff and Robert C. Gallo of the National Cancer Institute showed that the blood sera contained antibody against HIV. This antibody neutralized, or killed, HIV when the sera and HIV were combined in test tubes. Dr. Moss and his colleagues do not know if these antibodies will protect against HIV infection in humans.

Another route being tested for a potential prevention of AIDS is the use of HIV envelope protein by itself as a "subunit" vaccine. A subunit vaccine is one in which the protein itself is inoculated into the body to stimulate an immune response. This differs from a whole virus vaccine in which a vector (such as vaccinia virus) is used to bring the gene that codes for the protein into the body. Once the virus carrying the gene is in the body, the virus produces the immune-stimulating proteins.

Historically, one technical problem has been the production of enough protein for use as a subunit vaccine. Using biotechnology, scientists can insert a gene from one organism into another, which then produces the protein faster, or in larger quantities than the original organism. Sometimes, however, these proteins are not identical to those that would be produced in the original organism, since protein manufacturing conditions vary among organisms. Dr. Moss and his colleagues have now devised a fast yet accurate protein-producing system that makes use of two different recombinant vaccinia viruses simultaneously.

The reseachers combined the best features of bacterial and mammalian production of proteins in one experimental system. In one vaccinia virus they inserted the HIV envelope gene. In the second vaccinia virus, the researchers inserted a gene from a bacteriophage, or virus that infects bacteria, whose product increases expression of another gene, in this case, the HIV envelope gene. When both of these vaccinia recombinants were put in the same human cells in cell culture, perfect envelope proteins were obtained in larger amounts than was previously possible with recombinant vaccinia virus expression systems. Improved production of these proteins is an important step toward testing of subunit vaccines for the prevention of AIDS.

Dr. Moss presented these findings at the III International Conference on AIDS held in Washington, D.C. this week. Other members of his research team are Drs. Thomas R. Fuerst, and Patricia L. Earl, Laboratory of Viral Diseases, NIAID.

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