National Institute of Allergy and Infectious Diseases

Update

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MOUSE MODEL OF HIV LATENCY DEVELOPED

Animal models for human disease are often critical for finding treatments, cures, and ways to prevent the disease. Chimpanzees infected with human immunodeficiency virus (HIV), develop antibodies (protective proteins produced by the immune system) against the virus, but fail to develop disease. Dr. John M. Leonard of the National Institute of Allergy and Infectious Diseases (NIAID) and his colleagues have created a mouse model of one phase of HIV infection called the latent (resting) phase. In this phase HIV is present in the infected cell's genetic material, but is not replicating itself.

In humans, HIV is transmitted principally by exposure to HIV-infected immune cells in blood and blood products exchanged between individuals during sexual intercourse or through sharing of contaminated needles and syringes by intravenous drug users. Using special genetic probes, scientists can detect that one out of roughly 100,000 infectible cells in infected individuals are actively producing viral particles. It is unlikely that the AIDS epidemic could be sustained by so few cells producing viral particles when a relatively small amount of blood or blood products can transmit HIV infection. Scientists think that HIV infect cells in an inactive, or latent form that can not be detected with presently available laboratory techniques.

The Federal Centers for Disease Control (CDC) reported in 1986 (five years after AIDS was first recognized) that 20 to 30 percent of persons infected with HIV went on to develop AIDS or related illnesses within five years of infection. That is, the remaining 70 to 80 percent of infected people (as demonstrated by the presence of antibodies against HIV) continue to harbor the AIDS virus in their cells in a latent state and are in good health. According to the CDC, this currently represents roughly 2 million Americans. Since typical exposure to HIV is characterized by months to years of apparently latent infection prior to the development of AIDS or related conditions, researchers are trying to determine what causes the activation of latent HIV that results in disease progressing to clinical symptoms, collapse of the immune system, opportunistic infections, and death. Understanding the latent state could lead to treatment strategies that might prevent latent HIV from being activated.

To create their mouse model, Dr. Leonard and his colleagues started with a switch-like region of the HIV genetic material called the LTR, which when activated, controls the HIV genes and causes production of more HIV. The scientists attached the LTR to an "indicator" gene, which makes a

product only when the LTR is activated, or switched on. The indicator gene codes for production of a protein that can be easily detected when present. Because the indicator gene is not normally found in mice, the scientists know that if its product is present, the LTR has been switched on. Conversely, if there is no product present the LTR has not been activated.

Dr. Leonard and his colleagues injected this LTR/indicator gene construct into fertilized mouse eggs. A percentage of the mice grew up with a copy of the LTR/indicator gene in every nucleated cell (only nucleated cells contain genetic material) of their bodies. Because their cells contain genetic material from another organism in addition to their own, they are called transgenic mice.

The researchers examined 14 different types of tissue from the mice, including heart, eye, liver, blood, thymus, and spleen. In each type of tissue they looked for the indicator gene product in order to determine whether or not the LTR had been activated in the tissue, and if activated, how much of the indicator gene product had been made. Dr. Leonard and his colleagues found that the highest level of LTR activity was in thymus tissue. This was particularly interesting because thymus tissue contains many T cells, a type of immune system cell that HIV preferentially infects.

The scientists could also do tests to determine what factors (termed "cofactors") might stimulate an inactive LTR into an active state. Dr. Leonard and his colleagues obtained two immune system cell types called monocytes and T cells from the blood of the transgenic mice. Initially, no indicator gene product was present in these cells, meaning that the LTR was switched off. But when the scientists added growth factors to these cells (growth factors normally activate immune cells for immunological duty), the LTR's were switched on. One hypothesis is that HIV can be activated when the immune cell it occupies is stimulated in response to an immunological threat. In another experiment the researchers infected two types of immune system cells (called T cells and macrophages) with adenovirus, polyomavirus, or mouse cytomegalovirus and found that the viruses caused up to a 50-fold increase in activation of the LTR.

This research is providing information about the inactive state of the LTR in mice, a model for understanding latent HIV infection in humans. Unidentified factors that activate latent HIV might contribute to disease progression in infected individuals. Dr. Leonard and his colleagues have developed a safe and convenient living model to test the HIV stimulating capacity of a variety of factors. Ultimately, this knowledge may be applied toward finding a treatment to prevent development of AIDS in people who are latently infected with HIV.

Dr. Leonard presented these findings at the III International Conference on AIDS held this week in Washington, D.C. The research team included Drs. Leonard, Howard E. Gendelman and Malcolm A. Martin, Chief, Laboratory of Molecular Microbiology, and Drs. Jaspal Khillan and Heiner Westphal, National Institute of Child Health and Human Development, National Institutes of Health; Dr. Akio Adachi, Kyoto University, Japan; and Dr. Monte S. Meltzer, Walter Reed Army Institute of Research.

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