HIV: More Tricks Up Its Sleeve

Two studies reported this week suggest the AIDS-causing virus, HIV, may create much of its biologic havoc not only by destroying the body's immune cells, but also by interfering directly with the function of other cells. One report provides the first evidence that HIV may by itself be carcinogenic. The other indicates that a protein found on the viral surface can — without any help from the rest of the virus — kill nerve cells. This could provide an explanation for AIDS dementia in patients who show no signs of immunosuppression.

A number of malignancies can occur with AIDS, including Kaposi's sarcoma and B-cell lymphoma. But until now, no evidence indicted HIV itself as a cause of any of these cancers. Rather, scientists have hypothesized that such cancers result when an already immunocompromised person is infected by some other carcinogenic virus or is exposed to other known carcinogens.

Using gene transfer techniques, Jonathan Vogel and his colleagues at the National Cancer Institute in Bethesda, Md., along with researchers at the University of California, Davis, created a line of mice whose cells had permanently incorporated a critical HIV regulatory gene called *tat*. In the AIDS virus, *tat* helps regulate the expression of other HIV genes. The researchers wanted to know if *tat* might also be capable of directly regulating gene expression in mammalian cells.

By splicing the *tat* gene into mouse embryo cells, they created three lines of mice that continuously expressed *tat* protein in their skin cells. After four months, microscopic examination of the skin cells from these mice showed cellular changes similar to those seen in the early stages of Kaposi's sarcoma. At 12 to 18 months of age, 10 male mice, or about 15 percent of the male mouse population, developed skin tumors. Others showed a propensity for spontaneous bleeding into the skin. Microscopic analysis again revealed many similarities between the mouse tumors and those seen in Kaposi's sarcoma — all the more significant, the researchers say, because Kaposi's-like lesions are not seen in mice.

"It is unlikely that these tumors resulted from a dysfunction of the immune system, because we have not detected *tat* gene expression in any of the lymphoid [immune system] tissues, nor have we detected changes in either the absolute number of T-cells or the ratios of the T-cell subsets," the researchers report in the Oct. 13 NATURE. "Regardless of the mechanism, the ability of the HIV *tat* gene to induce tumors in mice would suggest that HIV is a cancer-causing virus."

The researchers note a number of mysteries along with their findings. Only the male transgenic mice developed tumors, despite equivalent levels of *tat* expression in females. They suggest the difference may be due to hormonal influences. Equally interesting, none of the tumor cells themselves showed evidence of *tat* gene expression. It's possible, the researchers say, that *tat* levels in the skin tumor cells are simply too low to be detected, or that the *tat* gene remains dormant in tumor cells and so is undetectable by the researchers' methods. On the other hand, the gene's apparent absence may mean *tat* is simply in nearby cells where it codes for a diffusible protein that, in conjunction with other genetic events, can cause cancer at a distance.

In a second study reported in the same issue of NATURE, researchers at the National Institutes of Health in Bethesda tested the effects of an HIV envelope protein, gp120, on cultured brain cells isolated from fetal mice. Brain cells, like immune system cells, have so-called CD4 receptors on their outer membranes, which serve as "docking sites" for HIV's gp120 glycoprotein.

While neuropsychiatric deficits, including early memory loss and progressive dementia, often accompany AIDS, scientists have remained uncertain whether these effects result directly from HIV infection of nerve cells. Douglas E. Brenneman and his co-workers found that gp120 alone could bind and kill mouse neurons.

Moreover, they showed that a hormone called vasoactive intestinal peptide (VIP) — which shares many of the same genetic sequences found in gp120 — can prevent neuronal death when nerve cells are exposed to gp120, perhaps by blocking gp120 binding to nerve cells.

Some researchers consider VIP a key player in the body's response to AIDS. Scientists know VIP is important for neuronal survival in cell culture. And it has structural similarities to another substance, peptide T, which in ongoing studies shows some evidence of protecting AIDS patients from dementia — and perhaps from HIV's immunocompromising effects.

On the basis of their findings, Brenneman and his colleagues suggest that gp120 — which can be produced and secreted by HIV-infected white blood cells — may in some patients travel to the brain, where it can cause neuronal abnormalities even without obvious sign of infection there.

Might VIP prove effective as an AIDS therapy? "VIP will not pass the blood-brain barrier," says Brenneman; thus it would be difficult to get into the brain. "A potential solution would be to somehow increase VIP production [in the brain] or get a VIP-like molecule into the system." Although many scientists are skeptical, Brenneman suggests that peptide T — with its structural similarities to VIP and its ability to cross the blood-brain barrier — may be that substance.

Phase I safety trials of peptide T are underway at the University of Southern California. — *R. Weiss*

Truth in testing

New research adds fuel to the debate about the value of widespread screening for HIV antibodies in the general population. With the rate of AIDS-causing HIV infection so low in most segments of society, critics argue that the low but persistent rate of false positive results inherent in the screening test makes large-scale screening more trouble than it's worth. It would be far more efficient, they say, to test only populations known to be at high risk.

Much of the debate hinges on one critical question: Just how high *is* the rate of false positives using the antibody tests available today? One answer comes from the U.S. military, where applicants are routinely screened for HIV infection. In a study described in the Oct. 13 NEW ENGLAND JOURNAL OF MEDICINE, 135,187 military applicants from rural counties in states with a low incidence of AIDS were tested for HIV antibodies. Using extremely stringent criteria developed by the Army — which included three different backup tests to confirm any initial positives — the screening program came up with only one false positive.

The researchers, led by Donald S. Burke of the Walter Reed Army Institute of Research in Washington, D.C., conclude that "a screening program for HIV infection in a low-prevalence population can have an acceptably low false positive rate."

They acknowledge that lower test volume and different rules for test interpretation in civilian programs might well result in higher levels of false positives.

The cost of testing was about $19 per person, one of the researchers told SCIENCE NEWS. Critics of widespread or mandatory testing contend the real costs of screening — and counseling — civilians may be much higher, and that a low false positive rate alone should not determine public policy. □