Progress Reported on Mouse Models for AIDS

Animal models for AIDS were lacking before and the new "AIDS mice" may facilitate research on the incurable disease

IN THIS ISSUE OF *Science*, three groups of researchers report progress toward developing mouse models for studying AIDS. The availability of such models should facilitate researchers' efforts to understand the disease and produce vaccines to protect against it and drugs to treat it.

The lack of convenient animal models has long hampered AIDS research. Human immunodeficiency virus 1 (HIV-1), the virus that causes AIDS, naturally infects only humans and chimpanzees, and the chimpanzees do not get sick as a result.

How accurately the mouse models mimic human AIDS is still under investigation, however. In addition, the research of one group, that from the National Institutes of Health (NIH), received a setback when a laboratory accident killed almost all the mice that they had produced (*Science*, 16 December, p. 1502).

This group, which includes Malcolm Martin of the National Institute of Allergy and Infectious Diseases and Abner Notkins of the National Institute for Dental Research, have been using gene transfer to introduce the HIV genome directly into the cells of living mice (p. 1665). The initial goal, Martin says, was to produce a model for AIDS virus latency.

When HIV-1 infects a cell, its RNA genome is copied into DNA, which can insert itself into the host cell genome, allowing the virus to be maintained in the cells, often in inactive form, for long times. Mice that have the HIV genome incorporated in the DNA of their cells would mimic this situation and could be used to identify factors that activate the latent virus, as well as for exploring how HIV produces its pathological effects.

Perhaps even more important, such animals may be useful for testing drugs that might be able to prevent or terminate HIV activation. Up to a million and a half people may already be infected with the AIDS virus in the United States alone, and such drugs are badly needed.

All of the original mice that acquired the HIV genome in the NIH experiments apparently had it in latent form, as none of these animals appeared to suffer any ill effects as a result of the presence of the HIV genes. But somewhat unexpectedly, the transgenic progeny of one of the female mice became ill spontaneously and died within a month of birth. ("Transgenic" is the term for animals carrying foreign genes.)

The symptoms of these animals, including growth retardation, enlarged spleens and lymph nodes, inflammatory infiltrates in their lungs, and a psoriasis-like skin condition, were similar to those seen in AIDS patients. Moreover, the animals' tissues made infectious HIV particles. The mice did not appear to develop the infections that afflict AIDS patients, however.

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Why the mice in only this one transgenic line produced HIV particles and got sick, whereas the animals in the other lines did not, is unclear, but Martin thinks that the illness was caused by the activity of the AIDS virus. "Much of the pathology is similar to what you see with HIV infection," he points out.

Martin and his colleagues had begun experiments to see whether they could induce the activity of the AIDS virus in the asymptomatic transgenic mice when the accident killed all but three of the animals in their experiment. The researchers will now have to make more mice carrying the HIV genome. "We would have had to do that anyway, even if we hadn't had the debacle," Martin says. Nevertheless, the research has been set back by as much as 6 months.

The other two groups reporting their results in this issue are using a different approach to making mouse models for AIDS, namely, the introduction of a human immune system into immune-deficient mice. Earlier this year, Mike McCune, Irving Weissman, and their colleagues at Stanford University School of Medicine described a method for doing this (*Science*, 23 September, p. 1632).

They implant human lymphoid tissue, either fetal thymus glands or lymph nodes or both, together with human fetal liver cells in mice with a genetic defect that prevents the maturation of the animals' own immune cells. The fetal liver serves as a source of human stem cells while the human thymus and lymph node tissue provide the proper environments for the stem cells to mature into functional immune cells.

According to McCune, the infection of macrophages and T lymphocytes, which are thought to be the primary targets of the AIDS virus, is likely to be occurring within human lymphoid organs. But human beings cannot be infected with a deadly virus in order to study its effects, and the Stanford workers turned to the mice instead.

They have now shown (p. 1684) that HIV-1 can infect the cells of human lymphoid organs that have been implanted in mice. "It's the first deliberate infection of human lymphoid organs with HIV. At the least, this system may prove to be a realistic model of acute infection by this virus," McCune says.

The transgenic mice essentially represent a late stage in the HIV life cycle, after the viral genome has integrated in the cellular genome, but the mouse model developed by McCune and his colleagues can be used for studying the earliest events in HIV infection as well as the more advanced stages of infection. "In the Stanford model, you have the advantage of being able to look at the entire life cycle of HIV," Martin comments. This may be especially advantageous for testing vaccines or drugs that might interfere with the initial stages of HIV infection.

Finally, Suzanne Kamel-Reid and John Dick of the Hospital for Sick Children and the University of Toronto report (p. 1706) that they have engrafted mice with human myeloid cells, which produce macrophages and also red blood cells. They did this by injecting human bone marrow, which carries the stem cells that give rise to those cell types, into mice with three separate mutations that reduce the populations of killer cells that might otherwise prevent the foreign grafts from taking.

These mice might be used to develop models for any disease affecting the myeloid lineage, including genetic anemias such as sickle cell anemia, leukemias, and of course AIDS. "While we don't have lymphoid cells in our animals yet, the macrophage is clearly an important factor in AIDS," Dick says. The Toronto workers hope that they can eventually combine their method with one similar to that developed by McCune and Weissman to give complete reconstitution of the human myeloid and lymphoid systems in mice. ■ JEAN L. MARX