Fetal AIDS mimicked in brain-cell culture

Scientists have created the first successful tissue-culture model of the nervous system damage incurred by fetuses from mothers infected with the AIDS virus, or HIV. Knowledge gained from the novel system, which includes all types of fetal brain cells and permits their interaction, may eventually help researchers develop ways to treat or prevent the infection *in utero*, says study leader William D. Lyman, a neuropathologist at Albert Einstein College of Medicine in New York City.

Fetal nervous tissue in culture develops in a way that mimics normal human development, and once infected with HIV, it shows a pathology similar to that seen in fetuses infected in the mother's womb, Lyman reported at last week's meeting in New Orleans of the Federation of American Societies for Experimental Biology.

Lyman cultured brain tissue from 13- to 21-week-old fetuses aborted by uninfected women, and compared what he saw to his previous observations of nervous tissue from fetuses aborted by HIV-infected women. The latter work was presented last June at the International Conference on AIDS in Stockholm. HIV genetic material was found in those tissues.

Although other scientists have developed cell-culture systems to study HIV infection of the nervous system, none has used organized human brain tissue of more than one cell type to represent normal nervous system development. And no previous research could reproduce signs of severe AIDS infection in tissue culture, says neurologist Richard W. Price at Memorial Sloan-Kettering Cancer Center in New York City.

Scientists have found HIV in white blood cells in the brain and have suspected that brain cells can be infected, but Price says previous studies have not convincingly revealed whether HIV directly targets the major cell types in the brain – neurons, astrocytes and oligodendrocytes. Lyman's studies indicate that in the fetal brain HIV may directly infect and injure brain cells. He reports that infected tissue cultures showed cell death and disruption of the normal nervous tissue arrangement similar to what occurs *in utero* and reminiscent of some aspects of the neuropathology seen in cases of pediatric AIDS. In addition, Lyman found that the tissue-culture cells accumulated excess fluid, a sign of inflammation.

The clinical symptoms of pediatric AIDS also suggest to Lyman that HIV directly damages the nervous system. "The vast majority of children born with congenital HIV infection exhibit retarded neurological development," Lyman says. They speak late, walk late and always perform among the lowest 2 percent for their age in tests of cognitive skills, he notes.

In addition, many children who develop AIDS-related neurological disease suffer from a deformity of facial features, called AIDS embryopathy, that "is suggestive of a pathologic event occurring very early on in pregnancy that affects cells that go into making up, amongst other things, the nervous system," Lyman says. He notes that the defects are similar to other facial deformities originating early in a pregnancy.

If brain cells are infected, it is important to know which cell types might harbor the virus, says neuropathologist Leroy R. Sharer of the University of Medicine and Dentistry of New Jersey in Newark. Lyman and his team are now using the cell-culture system to address that question and to determine how the infection varies as a function of fetal age, time of infection, amount of virus and pathway of infection. They are also looking at which HIV types are the most pathogenic.

The severity of pediatric AIDS, Lyman says, probably depends on when the fetus is exposed to the virus, the amount and type of HIV and the genetic makeup of the fetus itself. Lyman hopes that what he learns from his *in vitro* system will ameliorate the effects of pediatric AIDS, which by 1991 will have struck approximately 10,000 children in the United States, he says. His system also could be used to explore how a given drug or treatment taken during pregnancy affects the fetal nervous system, he adds.

– I. Wickelgren

Chemically fingerprinting DNA damage

Researchers have accomplished the first precise structural identification of chemical changes that occur when a foreign substance chemically binds to DNA. These changes, known as adducts, are widely suspected as a primary instigator of many cancers. While scientists in the past rounded up and counted suspect adducts, this is the first time anyone has "fingerprinted" individual suspects for an unambiguous chemical identification.

Carcinogens can generate an array of different adducts. Miral Dizdaroglu and his colleagues, working at the National Institute of Standards and Technology in Gaithersburg, Md., focused on a type known as DNA-protein crosslinks.

DNA naturally wraps around protein in nucleosomes, a chromosome's smallest unit. The researchers took pairings of this DNA and protein, and exposed them to an intense dose of hydroxyl radicals – chemically reactive water-molecule fragments. In both the DNA and the protein, the hydroxyl radicals spawned new radicals, or reactive molecular fragments containing an unpaired electron. Seeking to find mates for their unpaired electrons, these linked up with adjacent biological material, yielding more than a dozen species of DNA-protein crosslinks.

Though Dizdaroglu generated his hydroxyl radicals by exposing water to gamma rays, radiation is but one of many carcinogens suspected of causing biological damage through free radicals, such as the hydroxyl radical. For this reason, Dizdaroglu believes his free-radical-induced changes simulate those wrought by many toxic agents.

Using a combination of gas chromatography and mass spectrometry, the research team separated different types of adducts and identified their chemical structure. The results, reported in Seattle last week at the annual meeting of the Radiation Research Society, showed that both of the DNA bases studied – thymine and cytosine – readily transform to adducts, as do most of the protein's amino acids. Dizdaroglu is now looking to see if the same adducts occur in living cells damaged by hydroxyl radicals.

"This is a real breakthrough," comments biochemist Nancy Oleinick, who studies radiation-generated DNA damage at Case Western Reserve University in Cleveland. Radiation creates a broad spectrum of damage, including adducts. Because no one adduct tends to occur in large numbers, she says, researchers seeking them have been limited to "characterizing the sequences of DNA and the types of proteins that are involved in forming these adducts" – essentially identifying the general communities of chemicals available to interact. Now, she says, Dizdaroglu has been able "to unequivocally identify individual chemical species." Moreover, his data show that the DNA-protein adducts form by covalently crosslinking – something scientists had inferred but never directly demonstrated before, says Anne Cress of the Arizona Cancer Center in Tucson.

Researchers can now begin developing DNA probes to seek and count specific adducts – even to scout for adducts within individual genes, thereby determining which of the genes, if any, are targeted or are especially susceptible to injury by particular toxic agents, Cress says. The new findings also hold out hope that scientists will be better able to correlate toxic-substance exposures to the diseases they cause by analyzing how well the body repairs the newly identified adducts.

For all these reasons, Cress believes Dizdaroglu "has really given us an important new tool."

– J. Raloff