Gene Courier Targets Skin-Tumor Cells

Researchers are reporting another first in the annals of gene therapy: the use of fat-like molecules to deliver DNA with cancer-killing potential into the tumors of people with skin cancer. These preliminary results take scientists one step closer to gene therapy for cancer, they contend.

Last October, genetic engineers used a crippled virus to deliver a therapeutic gene to the nasal cells of three people with the inherited illness cystic fibrosis (SN: 10/23/93, p.260). Some scientists still worry that such altered viruses may cause disease in humans.

Gary J. Nabel, a Howard Hughes Medical Institute researcher at the University of Michigan Medical Center in Ann Arbor, and his colleagues turned to liposomes, artificially produced fat particles that have long been used to ferry toxic chemotherapeutic drugs into human cells. Nabel and his colleagues now show that such molecules can also usher DNA into tumor cells in the human body.

"I think the results are fascinating," comments molecular biologist Joseph Ilan of Case Western Reserve University School of Medicine in Cleveland, Ohio. Ilan's team is using liposomes to courier therapeutic genes to cancers in animals. Ilan, Nabel, and other scientists believe that liposomes may prove safer than viral vectors in the race to deliver therapeutic genes to human cells.

The Nabel team began its landmark experiment by mixing together liposomes and the DNA that makes up the HLA-B7 gene. They picked HLA-B7 because it is part of a class of genes that helps the immune system recognize foreign tissue. The researchers wanted to find out whether HLA-B7 could trigger an immune attack on malignant skin tumors.

They injected the liposome-DNA mixture directly into the cancerous skin tumors of five patients, none of whom had this type of HLA gene. The five volunteers suffered from malignant melanoma, a deadly form of skin cancer that kills some 6,800 people in the United States each year. The recruits had an advanced form of the disease that would not respond to conventional anticancer therapies.

In all five patients, the team found evidence that the HLA-B7 gene had turned on and was directing the production of its protein product. Since none of the recruits had inherited the HLA-B7 gene, any evidence of the protein had to come from the introduced gene, Nabel says.

In addition, the researchers demonstrated evidence of an immune response in two patients. Once the gene is deposited inside the tumor cell, the researchers believe, production of the "alien" protein acts as a red flag to the immune system. Nabel expects that the immune cells will then recognize those tumor cells as foreign and mount an attack.

Only a fraction of tumor cells take up the gene, a technical problem related to the gene-carrying capacity of the liposome, Nabel says. Yet the researchers believe that once immune cells travel to the tumor site, they may kick off a broad-based attack, one that eventually seeks out all malignant cells, not just ones carrying the HLA-B7 gene.

Although this study was not designed to prove the therapy's efficacy, one man showed a dramatic positive response, Nabel's team reports in the Dec. 1 PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES. In that case, a skin tumor that had been injected directly with the experimental mixture completely disappeared, as did several other tumors that were not treated. Nabel thinks revved-up immune cells traveling through the man's bloodstream may have destroyed the uninjected tumors. This same man also had a tumor that did not respond to treatment.

The injections caused no toxic effects, the research group says. However, additional studies are needed to prove the therapy's safety and efficacy. "Five patients simply isn't enough," points out gene therapy researcher R. Michael Blaese at the National Cancer Institute in Bethesda, Md.

This trial and others like it are important because they pave the way for more advanced studies of gene therapy's ability to fight cancer in humans, Blaese adds.

– K.A. Fackelmann

Turning a fly's eye on energetic cosmic rays

The origin of high-energy cosmic rays has long puzzled astrophysicists. Were these electrically charged particles accelerated to extremely high velocities outside the Milky Way or in turbulent, supernova-disturbed regions within our galaxy?

Using two ground-based Fly's Eye detectors to pick up the faint streaks created in the night sky by the passage of energetic cosmic rays plunging through Earth's atmosphere, researchers have now obtained the clearest evidence yet that cosmic rays of the highest energies detectable consist largely of protons that apparently originated outside the Milky Way. Cosmic rays of somewhat lower energy consist mainly of atomic nuclei of such heavy elements as iron. These rays probably originated within our galaxy.

The results reveal a "dramatic transition" from one type of cosmic ray to another at an energy between 10^{18} and 10^{19} electron-volts, Eugene C. Loh of the University of Utah in Salt Lake City and his collaborators report in the Nov. 22 PHYSICAL REVIEW LETTERS. This finding provides clues that may help determine where and how these particles are accelerated to such high energies.

"This paper is extremely interesting," comments Gary P. Zank of the Bartol Research Institute at the University of Delaware in Newark. "The suggestion, made over the years, that the very-high-energy particles are extragalactic in origin is probably nailed down fairly well."

Cosmic rays pierce Earth's atmosphere with sufficient energy to leave a cascade of charged particles in their wake. Because these particles excite nitrogen molecules, the air along these paths through the atmosphere glows with a dim blue light.

The Fly's Eye detector consists of a collection of mirrors and photomultiplier tubes packed together to look like a fly's compound eye. This arrangement allows researchers to monitor the entire night sky for cosmic-ray tracks. Using two such detectors, located 3.4 kilometers apart in the desert near Dugway, Utah, they can deduce the energy of an incoming cosmic ray and determine its arrival direction.

Observing the sky for more than a decade, the Fly's Eye team has accumulated sufficient data to produce a spectrum showing the intensity of cosmic rays at different energies. The researchers interpret an obvious "dip" in the plotted spectrum as evidence that high-energy cosmic rays come in two distinct varieties, with different origins.

The detection of a cosmic ray with an energy of 3×10^{20} electron-volts – the highest energy ever recorded for a cosmic ray – also suggests that these rays can't be relics from the early universe. Because a cosmic ray loses energy through interactions with the background microwave radiation that permeates the universe, this particular ray must have come from a source less than 100 million light-years away.

The new data may help theorists decide whether highly energetic cosmic rays originate in the dense nuclei of galaxies, where tremendous concentrations of stars or even black holes can create environments in which protons can be accelerated to high velocities. The lower-energy findings focus attention on exactly what happens inside supernova remnants to accelerate heavy nuclei.

– I. Peterson

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