Camouflaged grafts elude immune detection

Two immunologists have devised a novel strategy for sneaking donor tissue past the body's immune system. Instead of subduing the system's watchdogs, they pretreat the tissue to mask its foreign "scent."

Like trained security dogs, T-lymphocytes roam the body and detect intruding foreign cells, which they quickly attack and kill. But in the June 21 SCIENCE, researchers report avoiding rejection of human cells grafted into mice by camouflaging the cells with antibodies.

Denise Faustman and Chuck Coe of Massachusetts General Hospital in Boston successfully transplanted human pancreatic islets or liver cells into 25 mice after treating the tissues with antibody fragments that bind harmlessly to HLA class I antigens – the molecules that alert the patrolling T-cells to a foreign presence. With their telltale antigens concealed, the graft cells effectively became invisible to the immune system.

Ordinarily, physicians give transplant recipients powerful, immunity-suppressing drugs to help prevent rejection of the new tissue. However, weakening the immune system can expose a patient to deadly infections. Seeking safer alternatives, immunologists have recently focused on HLA class II antigens and other nonlethal ways of blocking T-cells, but their experiments have yielded only partial success. The latest approach, focusing on HLA-I, has startled and delighted researchers in the field.

"I'm surprised. It's very intriguing to use an antibody to class I. It makes sense, though," says pathologist Paul Lacy of Washington University in St. Louis.

"That's really exciting," says Gerald Nepom, an immunologist at the Virginia Mason Medical Center in Seattle. The Boston experiments provide a "dramatic illustration" of the new approach, he notes, because the researchers chose a strain of mice known for its relatively strong immune system.

Faustman says her work stemmed from studies in the 1980s showing that T-cells recognize and lock onto specific parts, or epitopes, of their target cells. It seemed an obvious step to try and hide those areas, she says.

She and Coe tried several approaches. In one, they incubated the insulin-producing pancreatic cells called islets with a solution of antibodies that bind to a wide range of epitopes. In another, they used an antibody fragment that binds only to the HLA-I sites. The HLA-I strategy proved just as effective as the broader approach, suggesting a key role for the HLA-I antigen.

In the HLA-I trial, the researchers confirmed the function of the grafted islet cells at 30 and 200 days by measuring human C peptide, an insulin-processing product not normally found in mice. They also confirmed the presence of the islets and the absence of attacking T-cells at each stage. Grafts of liver cells yielded similar success, they report.

Furthermore, says Faustman, the pretreated cells apparently "educated" the mouse immune system to ignore undisguised HLA-I antigens in subsequent transplants. Such tolerance is vital to the long-term survival of a transplant, since the antibody masks will eventually wear off, Lacy notes.

Although human trials probably won't begin for another five years or so, Faustman believes the HLA-I approach has great potential. "We think it's very applicable for cellular transplantations, and possibly for whole organs," she says. Transplanting just islets would be a great boon for insulin-dependent diabetics, she says, and successful grafts of protein-producing muscle cells could help those with muscular dystrophy. She also plans to experiment with central-nervous-system cells involved in Parkinson's disease.

Whole organs, such as kidneys and lungs, pose extra difficulties, but pretreating them might at least reduce the need for immunosuppression. "The concept we're working on is treating the graft so you don't have to use the terrible drugs on the patient," Faustman says. – *J. Travis*

Glowing evidence of gene-altered arteries

One of summer's delights is the pulsing glow of hundreds of fireflies dotting the dusky sky. New research suggests that this same power source can help light the way to a gene therapy for coronary artery disease.

A 1989 report of the first successful transfer of a bacterial gene into the leg arteries of live animals (SN: 6/17/89, p.373) took molecular biologists one step closer to the prospect of a gene therapy for humans who suffer from clogged arteries. Researchers have now added a luminous twist to such experiments, this time inserting dog arteries with the gene coding for luciferase – the enzyme that gives the firefly its "fire."

In one experiment, Judith L. Swain and her colleagues at Duke University Medical Center in Durham, N.C., anesthetized seven dogs and surgically exposed the femoral arteries of the legs. They then inserted catheters and flushed the arteries with a solution containing luciferase genes. The enzyme's glow, they reasoned, would signify gene activation. After three days, they removed the tissue and exposed it to a light-measuring device.

In six of the animals, the glow-meter readings indicated that the altered femoral tissue contained 1 to 77 picograms of luciferase, averaging about 20 picograms. This showed that the gene had traveled through the cell membrane and "turned on," directing the canine cell to secrete the firefly enzyme, Swain's group reports in the June CIRCULATION. In a separate experiment, the team transferred the luciferase gene into the coronary arteries of two dogs, later detecting 28 and 32 picograms of the enzyme.

While no one proposes injecting firefly genes into people, the study does brighten hopes that scientists may someday inject human coronary arteries with genes that code for powerful clot-dissolving proteins such as tissue plasminogen activator (TPA), Swain says. The inserted genes might turn artery cells into miniature TPA factories that churn out enough of the drug to prevent the blood clots that can trigger a heart attack, she adds.

People undergoing angioplasty, in which doctors use a tiny balloon to open clogged arteries, might be prime candidates for such gene therapy, Swain suggests. Although physicians currently give angioplasty patients intravenous injections of TPA, this doesn't always prevent the arteries from later reclogging or developing clots. Swain cautions, however, that a gene therapy to keep human arteries open will take many more years to develop. – *K.A. Fackelmann*

Pigs make human pigment

Genetic engineers have created the first pigs carrying the human gene for hemoglobin, the oxygen-carrying pigment in red blood cells. The feat may help scientists create an inexpensive, disease-free substitute for human blood, say researchers at DNX Corp. of Princeton, N.J., the biotechnology firm that developed the transgenic swine.

John Logan of DNX presented data on one of the three pigs this week at the World Congress on Cell and Tissue Culture, held in Anaheim, Calif. Ten to 20 percent of this pig's hemoglobin is the human variety, he says.

Logan also outlined a simple method for breaking open red blood cells and separating the swine and human hemoglobins – a crucial step toward producing a human blood substitute.

DNX President Paul Schmitt notes that isolated hemoglobin stores at room temperature for six months to a year, significantly longer than whole blood. The company plans to pasteurize the hemoglobin, a process that reduces the risk that a blood substitute will harbor disease-causing microbes.

DNX must complete animal testing and conduct human trials before the pig-produced pigment can obtain federal approval, Schmitt adds. □