Mouse study suggests diabetes prevention

Boston researchers have identified two types of immune-system cells with opposing effects that determine whether or not diabetes-prone mice will develop the disease. By injecting the mice with a toxin that targets the cell type that destroys the body's insulin factories, they have tipped the balance in favor of the insulin-protective cell type, halting diabetes onset.

The work points to a possible preventive treatment for people at high risk of insulin-dependent (Type I) diabetes and adds to the evidence linking the disease with a misdirected immune-system attack, the researchers say.

Vicki E. Kelley of Harvard Medical School and her colleagues began their study after reports that certain T-cells – a class of immune-system cell – invade the insulin-producing islet cells in the pancreas of prediabetic mice. The invasion causes insulitis, or inflammation of the islets, which appears to be a necessary first step for the development of diabetes in both mice and humans. But Kelley noted that some prediabetic mice remained healthy despite insulitis. With Terry Strom of Harvard and John R. Murphy of Boston University, she theorized that a molecular tug-of-war with another group of T-cells – acting as islet-cell preservers – might explain the phenomenon.

The researchers removed and cultured the T-cells involved in the earliest stages of islet invasion, reasoning that those cells might have the most potency for triggering or preventing diabetes. They isolated and cloned a subgroup of these cells featuring some unusual properties: They belonged to a class known as CD4, and they triggered diabetes when injected into other prediabetic mice. The investigators also cloned another type of T-cell – members of a class called CD8, many of which suppress immune function. When they injected prediabetic mice with CD8 cells and with spleen cells known to accelerate diabetes onset, the mice did not develop the disease. In contrast, prediabetic mice injected only with the spleen cells developed diabetes within three weeks.

"Our work demonstrates that a delicate balance between autoaggressive T-cells and those which suppress immune reactions determines whether autoimmunity is limited or progresses to diabetes," Kelley reported this week at a National Kidney Foundation science writers' briefing in New York City. Diabetes accounts for about 25 percent of all kidney failure.

Strom and Murphy established that the insulitis-associated CD4 cells produce a chemical called interleukin-2 and also have surface receptors for it. Knowing that interleukin-2 stimulates these cells to multiply – and presumably to attack islet cells – they used some genetic sleight-of-hand to thwart the invasion process. They created a hybrid of diphtheria toxin and interleukin-2 that binds exclusively to CD4 cells possessing the receptor and kills them.

Kelley, Strom and Murphy found the toxin prevented prediabetic mice from developing the disease, even though they had first injected these mice with aggressive islet-destroying immune cells taken from mice with full-fledged diabetes. Kelley says the treated mice retained functioning immune systems after toxin therapy ended – an important consideration for human therapy.

She notes that researchers at M.D. Anderson Hospital in Houston have begun a clinical trial of the hybrid diphtheria toxin's potential for destroying adult leukemia and lymphoma cells possessing interleukin-2 receptors. Trials in diabetes-prone humans may begin later this year, she adds. Such studies have become feasible in recent years with the discovery that certain indicators in blood can help identify people at risk of diabetes (SN: 7/18/88, p.389).

"We are now at the stage where we can identify people at risk," says immunologist George S. Eisenbarth of the Joslin Diabetes Center in Boston. "The question is whether the interleukin-2 toxin is the most effective treatment."

– R. Cowen

Cholesterol-cancer clues

Heart disease risk decreases with increasing blood levels of the so-called "good" cholesterol, or high-density lipoprotein (HDL). On average, women in the United States have higher HDL levels than men – which may help explain women's lower rate of heart disease. But mounting evidence also suggests that higher-than-average HDL levels in women may signal an increased risk of breast cancer.

HDL levels may one day help physicians identify women at high risk for breast cancer, says Norman F. Boyd of the Ontario Cancer Institute in Toronto, who coauthored a review paper on HDL's link to breast cancer in the March 21 JOURNAL OF THE NATIONAL CANCER INSTITUTE. He adds, however, that more studies are needed to establish that link.

The researchers noted strong evidence that women living in the United States and Northern Europe have higher HDL levels and breast cancer rates than women in Asia. Women who have never been pregnant and those of above-average socioeconomic status generally have high HDL levels. Moreover, HDL rises with increasing alcohol and fat intake – two dietary factors thought to increase breast cancer risk. Existing data conflict on whether HDL and breast cancer risk rise with estrogen replacement therapy, oral contraceptive use or obesity.

Preliminary studies have suggested that higher HDL levels correlate with a family history of breast cancer and with mammograms indicating abnormal cell growth thought to increase breast cancer risk. In addition, the researchers note, two studies have shown that HDL stimulates the growth of various tumor cells *in vitro*, including breast cancer. *– C. Decker*

Japanese satellite begins orbiting moon

A Japanese legend tells of Hagoromo, a robe that transported a beautiful princess from the moon to Earth and back. Hagoromo means "feather garment," and it is also the name newly given to a Japanese spacecraft that entered lunar orbit on March 19, making Japan the third nation to reach the moon.

The lunar orbiter was deployed from another craft, called Hiten, launched from Earth on Jan. 24 (SN: 3/3/90, p.138). Their separation occurred less than 1 second from the scheduled time, when Hiten was 16,422.4 kilometers from the moon – only 2.2 km from the distance planned by officials at Japan's Institute of Space and Aeronautical Sciences (ISAS).

Hagoromo carries no scientific instruments, although it has a camera that photographed both the moon and Earth around the time of deployment, deliberately overexposing the pictures to make each "limb," or edge, clearly visible as a navigational aid for positioning the two craft. Hiten, meanwhile, remains in an Earth-circling orbit.

Hiten also bears the mission's only scientific instrument, a detector to count tiny meteoroids. It had already counted several within a day of Hagoromo's release, says ISAS Director-General Jun Nishimura, who adds that the data are now being calibrated to indicate each micrometeoroid's mass and velocity.

Shortly after Hagoromo's deployment, ground controllers changed Hiten's orbit from an ellipse varying between 442,000 and 727,000 km from Earth to a smaller, more eliptical one varying between 11,000 and 116,000 km. Nishimura says the orbit change is essentially a practice run for a similar maneuver with a Japanese satellite called Geotail. Scheduled for launch in 1992, Geotail is a NASA/ISAS cooperative project to study the tail region of Earth's magnetic field. *– J. Eberhart*