Diabetes Stopped Before It Starts

For years, researchers have recognized insulin-dependent diabetes as the aftermath of the body's immune defenses turned against itself. This autoimmune attack destroys the pancreas' insulin-producing beta cells, upsetting forever the body's innate ability to regulate sugar.

Two research groups now report in the Nov. 4 NATURE that an enzyme involved in the production of an intercellular messenger somehow provokes critical immune-system aggression, which then snowballs into a full-scale offensive involving not just antibodies but also the immune system's T-cells. More important, their experiments demonstrate that in mice specially bred to develop diabetes, treatment can prevent this escalation from ever occurring, comments Pietro De Camilli, a Howard Hughes Medical Institute investigator at Yale University.

To tease out the trigger for this autoimmune response, both groups tested mice from birth onward for the development of T-cells directed against substances in beta cells known to be targets for antibodies. When the mice reached about 4 weeks of age, both teams observed that glutamate decarboxylase (GAD) began activating T-cells.

The T-cells begin reacting to a different enzyme when the mice reach 2 months of age, and in 3-month-old mice, other T-cells target insulin, reports Daniel L. Kaufman of the University of California, Los Angeles, and his colleagues.

GAD converts the amino acid glutamate into GABA, a key messenger between nerve cells and, to a lesser degree, between pancreatic cells. Because most of the body's supply of GAD exists in the brain, sequestered from the immune system, the body may not recognize GAD as part of itself, Kaufman suggests. He and his colleagues had shown that a piece of GAD closely resembles a virus that has been associated with diabetes. At first, only that piece sets off the T-cells, but eventually other parts elicit a response, and finally many components of the beta cell become T-cell targets, says Kaufman.

"It's like a snowball effect: You get an initial snowball that grows and becomes an avalanche until the whole beta cell is destroyed," he explains.

Kaufman and his colleagues injected human GAD into the veins of 17 3-week-old mice before the mice had developed any sign of an autoimmune response. In 75 percent of these mice, the GAD made peace, in a sense, with the T-cells by helping the immune system realize that GAD belongs to the body's own chemical repertoire, says Kaufman. Those mice never got diabetes, even though they are bred to do so. Because of the similarities between the development of diabetes in these mice and in people, Kaufman hopes GAD tolerance can be induced in people.

The second team followed a slightly different treatment strategy. Roland M. Tisch and his colleagues at Stanford University Medical Center injected mouse GAD into the thymuses of nine 3-week-old mice. Six of these mice remained diabetes-free, the Stanford group reports. However, these six still made antibodies against GAD, indicating that some immune-system activity continued, says Stanford's Hugh O. McDevitt. Their results also suggest that other, still unknown proteins may precede GAD in this cascade of events. "[GAD] may not be the first or even the most important antigen," says McDevitt.

"Clearly, [these results] are very important in terms of prevention of insulin-dependent diabetes," comments Joan T. Harmon of the National Institute of Diabetes and Digestive and Kidney Diseases in Bethesda, Md. "This may be the only place that we can truly prevent [the development of the disease]."

However, De Camilli cautions that diabetes may arise in a different manner in some people and that the treatment may have undiscovered, long-term drawbacks. Also, such an approach would require a precise way to identify a diabetes-prone person very early, before the T-cell response got started, he adds. "Clearly, there are many other things that have to be tested," says McDevitt. —*E. Pennisi*

Chemical pathway links stars, meteorites

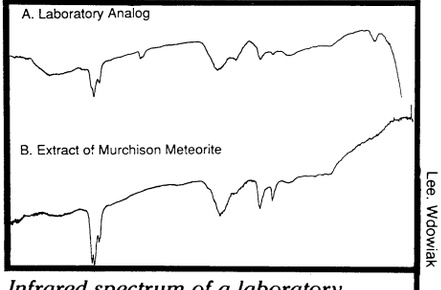
When Thomas J. Wdowiak and Wei Lee zapped a laboratory mixture of hydrogen gas and naphthalene with 9,400 volts, they were seeking to simulate the chemical processes that occur in dusty regions of interstellar space. But their experiment failed to produce any of the hydrocarbon compounds they had hoped for. To add insult to injury, the high-voltage simulation left a yellow-brown residue on their glass discharge tube.

To choose the right solvent for removing the residue, the researchers identified the unwanted material by taking its infrared spectrum. To Wdowiak's surprise, the pattern of light absorption looked strangely familiar. Searching through recently published data, he and Lee discovered that the spectrum closely resembles that of organic material extracted from the Murchison meteorite, which fell to Earth in 1969.

"This is the best match between the spectrum of a particular meteorite and that of a sample synthesized in the laboratory that I've ever seen," notes Louis J. Allamandola, an infrared astrophysicist at NASA's Ames Research Center in Mountain View, Calif.

Wdowiak and Lee, researchers at the University of Alabama at Birmingham, describe their serendipitous study in the Nov. 1 ASTROPHYSICAL JOURNAL LETTERS. They say their work suggests a chemical pathway between meteorites and stars.

Naphthalene, notes Wdowiak, ranks as the simplest of a group of organic molecules known as polycyclic aromatic hydrocarbons (PAHs), many of which are found in interstellar space and the outer atmosphere of old, carbon-rich stars.



Lee, Wdowiak

Infrared spectrum of a laboratory residue resembles that of the Murchison meteorite.

Meteorites also contain PAHs and another group of hydrocarbons known as alkanes. Researchers have suspected that interstellar organic molecules provide the raw materials for the hydrocarbons in meteorites, but they weren't sure of the chemical pathway.

Wdowiak says the new study indicates that PAHs, which are more durable than alkanes, supply both types of hydrocarbons found in meteorites such as Murchison. Traveling through space, the interstellar PAHs would retain their chemical identity until they encountered ionized hydrogen, believed to be plentiful during the formation of the solar system. Wdowiak suggests that the combination of intense outbursts from the young, energetic sun and the presence of ionized hydrogen created conditions similar to those in his high-voltage experiment. He speculates that some of the interstellar PAHs transformed into alkanes and were later incorporated into meteorites as they formed, producing a spectrum like the one detected in the laboratory residue. —*R. Cowen*