

IMMUNE CELL ENTRY INTO THE PANCREATIC ISLETS KEY TO UNDERSTANDING TYPE 1 DIABETES ORIGINS MEMPHIS, TENNESSEE, OCTOBER 8, 2009

St. Jude Children's Research Hospital (Memphis, Tennessee) investigators have discovered how destructive immune cells gain access to insulin-producing cells and help cause diabetes.

The finding points to possible new strategies to halt or prevent type I diabetes.

Working in mice, researchers demonstrated that to enter key areas of the pancreas known as the islets of Langerhans, immune cells known as T cells must recognize a marker on the surface of insulin-producing cells housed there. T cells play a key role in regulating immune response. Once inside the islets, T cells trigger the inflammation that can lead to destruction of the insulin-producing beta cells. The result is type I diabetes.

The report answers a fundamental question about the role of T cell entry and accumulation in the islets in development of type I diabetes, a disease that affects as many as 250 million people world-wide. The research appears in the October 16 edition of the journal *Immunity*. Dario Vignali, Ph.D., is the paper's senior author and vice chair of the St. Jude Immunology department.

The St. Jude results contradict a widely held theory that only a small percentage of T cells that infiltrate the islets were actively involved in causing type I diabetes. The old scenario held that most of the T cells found in the islets were recruited to the site by a small number of specialized T cells. Those recruited or bystander T cells were thought to play no role in causing diabetes. Furthermore, it was thought that any T cell could gain access to the islets.

"The new research argues that every T cell in the islet is important. What these T cells recognize that allowed them to gain access to the islets may provide us with clues as to what might be needed to prevent diabetes," Vignali said. "Understanding the molecular differences between the T cells in the islets and the T cells in the periphery might also start to tell us a lot about what it takes to make a T cell attack the beta cells and cause diabetes."

Without insulin to turn food into fuel for cells, type I diabetes develops and people are left dependent on insulin injections, an insulin pump or in rare cases a pancreas transplant. Unlike the more common form of the disease, known as type II diabetes, type I diabetes usually affects children and is sometimes called juvenile diabetes. Another 7 million new cases are diagnosed annually worldwide. Even with treatment, patients with type I diabetes are at risk for blindness, kidney failure and other complications.

"This paper also presents a new clinical intervention strategy—blocking T cells from even getting into the islet cells in the first place," Vignali added.

If any T cell could enter the islets, then it would be less likely that there were any "special rules" for entering islets and thus nothing unique about entry into the islets that might be targeted by treatment, he explained.

Understanding how T cell access to islets is controlled also raises hopes for developing a therapy to re-educate the immune system to tolerate rather than attack the beta cells. The St. Jude research points to a new route into islet cells.

For this study, scientists used a technique Vignali's laboratory developed in 2006. The technique allows researchers to quickly modify T cell production in mice. Normally mice make millions of T cells that can recognize many different cells and microorganisms. Each T

cell carries on its surface a receptor that recognizes and binds to just one specific antigen, or marker, on the surface of the T cell's intended target.

The modification technique allowed researchers to create strains of mice with only two types of T cells, each with different receptors. One population carried a receptor that recognized the insulin-producing beta cells and could cause diabetes. The other group was programmed to recognize a different antigen. Researchers reported they could not induce the latter group of T cells to enter the islets.

Then investigators created and tracked T cells with three types of receptors—receptors from T cells with a proven ability to enter islet cells and cause diabetes, those able to enter islets and cause inflammation, but not diabetes, and a third group of receptors with no connection to type 1 diabetes or islet cells. The scientists reported that none of the T cells, even those with a demonstrated ability to cause diabetes in mice, could induce bystander T cells to enter the islet cells.

Finally, investigators tracked T cells carrying receptors from mice that naturally developed type 1 diabetes. They created mice with 17 new T cell receptors, five from the spleen of diabetic mice and 12 from T cells isolated in the islets of those diabetic mice. If the islets control T cells entry, then islets in the new mouse strains would be infiltrated by T cells with islet-derived, but not spleen-derived, receptors.

That is what happened. “About 70 percent of the receptors that came from the islets could mediate T cell migration back into the islets, while none of the receptors that came from the spleen could do likewise,” Vignali said. The islet-derived receptors were also linked to rapid development of diabetes, with one-third causing diabetes during the 10-week study.

Vignali said it is unclear if the findings will hold true for other autoimmune diseases, such as rheumatoid arthritis or Crohn's disease. The authors noted that the structure, location and other factors might make the islet cells unique.

Greig Lennon, Maria Bettini and Amanda Burton, of St. Jude, shared first authorship on this study. The other authors were Erica Vincent and Paula Arnold of St. Jude, and Pere Santamaria of the University of Calgary, Alberta, Canada.

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For further information please visit www.diabetesresearchfoundation.asn.au or contact Sherl Westlund on 08 9224 1006.