

Suspected cause of type 1 diabetes caught 'red-handed' for the first time

Scientists at Washington University School of Medicine in St. Louis working with diabetic mice have examined in unprecedented detail the immune cells long thought to be responsible for type 1 diabetes.

Researchers were able to examine the immune cells from isolated insulin-making structures in the pancreas known as the islets of Langerhans. They caught the immune cells, known as dendritic cells, "red-handed": carrying insulin and fragments of insulin-producing cells known as beta cells. This can be the first step toward starting a misdirected immune system attack that destroys the beta cells, preventing the body from making insulin and causing type 1 diabetes.

The results, reported online in *The Proceedings of the National Academy of Sciences*, push scientists a step closer to finding ways to treat this condition.

"Now that we've isolated dendritic cells from the pancreas, we can look at why they get into the pancreas and determine which of the materials that they pick up are most critical to causing this form of diabetes," says senior author Emil R. Unanue, M.D., the Paul and Ellen Lacy Professor of Pathology. "That may allow us to find ways to inhibit dendritic cell function in order to block the disorder."

The American Diabetes Association estimates that 1 million to 2 million Americans suffer from type 1 diabetes, which is also called juvenile diabetes because it frequently develops in children.

Patients require insulin injections to survive because the immune system has destroyed the islets of Langerhans, which contain the body's only beta cells. The insulin these cells make is required for the critical task of regulating blood sugar levels.

Scientists detected dendritic cells in the islets years ago. Dendritic and other antigen-presenting cells are the sentinels of the immune system: They pick up bits of protein from around the body and present them to lymphocytes to initiate an immune system reaction. The lymphocytes lead immune attacks against foreign invaders like bacteria and viruses and eliminate them, clearing infections. But when interaction between an antigen-presenting cell and a lymphocyte leads to a part of the body being mistakenly identified as alien, the resulting attack harms the body, causing autoimmune diseases.

Although dendritic cells' presence in the islets and their ability to summon immune attacks made them likely suspects in type 1 diabetes, they were challenging to isolate from the pancreas for closer examination.

"They're very tiny and there are only about 5 to 10 of them per islet, each of which contains approximately a thousand cells," explains Unanue. "So the senior postdoctoral researcher in the lab who did this work, Boris Calderon, had to develop some sophisticated cellular assays to pick them up."

Calderon, M.D., found indications that the cells were carrying granules of insulin and pieces of proteins from beta cells on their cell surfaces. To test whether this cargo carried by the dendritic cells had the potential to trigger an immune attack on beta cells, Calderon exposed the dendritic cells to lymphocytes taken from diabetic mice. The lymphocytes were activated by the dendritic cells of the islets and switched into attack mode.

In a separate line of research, Unanue's lab has learned that dendritic cells in the pancreas may normally have beneficial effects on the health of beta cells. They've shown that when dendritic cells are absent from the pancreas, the beta cells are smaller, an indication that they're not as healthy.

"We think these dendritic cells aren't in the pancreas by accident," says Unanue. "We believe that in the normal individual they help maintain the health of beta cells. But in a person with autoimmune diabetes, they appear to start the problems that destroy beta cells."

The key distinction likely lies in a group of proteins called the major histocompatibility complex (MHC). Two decades ago, Unanue and Paul Allen, Ph.D., the Robert L. Kroc Professor of Pathology and Immunology, showed that the MHC provides the stage on which antigen-presenting cells show bits of protein or peptides to other immune system cells. Scientists believe autoimmune conditions like type 1 diabetes are caused by differences in what the MHC binds to and how it presents that material to immune attack cells.

In support of this theory, Unanue's laboratory and that of Michael Gross, Ph.D., Washington University professor of chemistry, have collaboratively shown that the genes that encode the MHC proteins in the diabetic mouse are unique and bind to a set of very characteristic peptides.

Source: Washington University School of Medicine

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