Major breakthrough in understanding development of type 1 diabetes

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Joslin researchers have uncovered the action of a gene that regulates the education of T cells, providing insight into how and why the immune system begins mistaking the body's own tissues for targets. The gene, Clec16a, is one of a suite of genes associated with multiple autoimmune disorders, suggesting it is fundamental to the development of autoimmunity. When the researchers turned the Clec16a gene off, mice genetically prone to diabetes were protected from developing the disease.

This discovery is an important step towards understanding the development of type 1 diabetes. The more researchers know about the onset of the disease, the closer they can get to diabetes prevention.

"We think the reason it is associated with so many different diseases is because it plays a function in a very central mechanism," said Stephan Kissler, Ph.D., Investigator in the Section on Immunobiology. "It's nothing that's specific for type 1 diabetes, it's nothing that's specific to multiple sclerosis. The way T cells are selected is something that's common to all these diseases."

The gene plays a role in the process known as autophagy, in which cells digest their own internal proteins and then recycle them onto their cell surfaces. Autophagy occurs in all cells, for example when they are infected with a virus or starved for nutrients. The process is a little different in a special type of cell residing in the thymus, a small organ found behind the breastbone and above the heart. Here, thymic epithelial cells (TECs), or teachers of the immune system, undergo autophagy in order display to T cells which proteins are supposed to be in the body and which should be eradicated.

"Thymic epithelial cells are pretty much the only cells that do this all the time not because they're stressed or because they need to recycle nutrients, but simply because they use that as a way to present to T cells," said Dr. Kissler.

The study, published on May 12 in *Immunity*, showed that the Clec16a gene affected the autophagy process such that it prevented diabetes-prone mice from getting the disease.

"By changing autophagy in TECs you change T cell selection, and by changing T cell selection you change the risk of autoimmune disease," said Dr. Kissler.

They started their series of studies by determining whether or not the Clec16a gene had a noticeable effect on disease course. In one group of diabetes-prone mice they turned off the gene. They let the other group progress naturally.

"Out of more than 40 mice two became diabetic, whereas in the group that didn't have the gene knocked down about 60 percent of the mice became diabetic. So it was a very big difference," he said.

They saw Clec16a made a marked difference, but they didn't know why or in which organ. To narrow things down they started a series of transplant experiments, including spleen and bone marrow. They determined that the gene affected the function of T cells but did so indirectly; Clec16a played a role not in T cell themselves but during their education in the thymus. They confirmed this hypothesis with a thymus transplant.

Dr. Kissler and his team had previously conducted similar experiments on other genes with interesting results, but the Clec16a studies are the most promising so far. "It's the strongest protection [against diabetes] we've seen," he said. "We've never seen something as dramatic before."

Their research also showed that Clec16a plays a role in autophagy of human cells in general. Next, they want to confirm that the same process holds true in a human thymus. "All we know for now is the gene has an effect on human autophagy," said Dr. Kissler. "Is the same true in human thymus? How does that compare to what we've described in the mouse?"

If Clec16a proves to affect the education of human T cells, it would be a big clue in unraveling the mystery of a complicated disease.

Source:
Joslin Diabetes Center