Researchers increase understanding of genetic risk factor for type 1 diabetes

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As part of their ongoing research on the role of genes in the development of type 1 diabetes, Joslin Diabetes Center scientists, in collaboration with scientists at the University of Würzburg, have demonstrated how a genetic variant associated with type 1 diabetes and other autoimmune diseases influences susceptibility to autoimmunity. The findings appear in the upcoming issue of *Diabetes*.

Recent studies of the human genome have identified genetic regions associated with autoimmune diseases such as type 1 diabetes. Joslin scientists in the Section of Immunobiology seek to understand how genes that are most widely associated with various autoimmune diseases contribute to disease risk.

One of these genes is PTPN22, which plays a role in lymphocyte (immune cell) function. A PTPN22 variant (or mutation) has been implicated as a risk factor for type 1 diabetes and several other autoimmune disorders. PTPN22 is involved in the formation of a key protein known as lymphoid tyrosine phosphatase (LYP), which helps control the activity of T and B cells in the immune system. The PTPN22 mutation generates a variation of LYP with a different molecular structure.

Most studies of the PTPN22 disease variant have suggested that this variant is a gain-of-function genetic mutation that enhances LYP activity and lessens the activity of T and B cells, which increases susceptibility to autoimmunity. "When immune cells are less reactive during the maturation phase of their development, the cells can evade mechanisms that help protect against autoimmunity," says study lead author Stephan Kissler, PhD, of the Section of Immunobiology. However, one study which analyzed data from humans and genetically modified mice suggested that the LYP variant associated with type 1 diabetes is a loss-of-function mutation that reduces LYP activity.

To help resolve the conflicting data, Joslin scientists conducted studies with a unique mouse model developed by Dr. Kissler's graduate student and co-author, Peilin Zheng. Using a technology that combines RNA interference, a method to silence gene expresson, with lentiviral transgenesis, a method to genetically modify animals, the scientists can manipulate gene activity in the most widely used mouse model for type 1 diabetes, the nonobese diabetic mouse (NOD). In this study, the

researchers were able to easily turn off and on the PTPN22 gene in the NOD mouse. "We are the first to use this approach in the NOD mouse model," says Dr. Kissler. "It provides a very powerful way to study the contribution of PTPN22 to disease."

When PTPN22 was turned off in mice, mimicking a loss-of-function mutation, the researchers observed an increase in regulatory T cells and a decreased risk of autoimmune diabetes. "This is the first study conducted on the diabetic mouse model that supports the LYP gain-of-function hypothesis," says Dr. Kissler. "Our work should help to resolve the controversy."

By providing additional data that suggests the potential therapeutic value of PTPN22 manipulation, the study may further the development of new therapeutic options that inhibit LYP to reduce or prevent autoimmunity. "Our goal is to treat autoimmunity. Inhibiting LYP in patients may increase regulatory immune cells and could confer protection against autoimmunity, but it remains to be tested if our promising findings in this mouse model are reflected in humans," says Dr. Kissler.

The Joslin scientists are following up on this study to deepen understanding of how inhibiting PTPN22 affects T and B cells.

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