Insulin peptide may point to a solution for type 1 diabetes

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Researchers at National Jewish Health and the University of Colorado Anschutz Medical Campus have identified the precise protein fragment, or peptide, that can trigger diabetes in mice. The finding, published in the June 15, 2010, issue of the *Proceedings of the National Academy of Sciences*, supports an emerging theory about the origins of autoimmunity, and may lead to new diagnostic and therapeutic strategies in humans.

"Our findings contradict conventional wisdom, which suggests that insulin peptides that are well presented to the immune system trigger diabetes," said John Kappler, PhD, Professor of Immunology at National Jewish Health. "We believe, however, that the peptide we identified triggers diabetes precisely because it is so poorly presented to the immune system."

The immune system tries to delete all T cells that might cause autoimmune disease. During development in the thymus, immature T cells are exposed to "self" protein fragments, which are part of the organism. T cells that recognize and bind to them are destroyed. This process, however, is not foolproof, and autoimmune T cells do occasionally escape.

The development of type I diabetes in mice is associated with one form of MHCII, the molecule that holds and presents peptides to the immune system. Previous research had identified a specific fragment of insulin, consisting of 12 linked amino acids, as the target of the autoimmune attack in type I diabetes. The MHCII molecule, which has a binding

pocket only 9 amino acids long, can bind to and present that insulin fragment in at least four different ways, known as registers. Peptides bound in register present different subsets of amino acids to the T cells that cause diabetes.

Contrary to conventional wisdom, the research team found that the peptide presented in the register that binds most weakly to the MHCII molecule stimulated four different T cells associated with diabetes. Peptides bound in the other registers did not stimulate those T cells.

"Although scientists have been closing in on the cause of type I diabetes, this is the first time that anyone has identified exactly what T cells recognize when they initiate an autoimmune attack in diabetes," said co-author George Eisenbarth, MD, Professor of Immunology at the University of Colorado Anschutz Medical Campus and executive director of the Barbara Davis Center for Childhood Diabetes at the university.

The findings support a theory recently posited by Kappler, Eisenbarth, and Brian Stadinski, PhD, of Harvard Medical School. They believe that poorly presented peptides are more likely to cause diabetes and other autoimmune diseases, because they allow autoimmune T cells to escape deletion. Once they begin circulating in the body, these T cells are stimulated when they encounter high concentrations of the peptide or peptides that have been processed differently outside the thymus.

"This is the third time that a specific peptide and its binding register have been associated with autoimmune disease," said Kappler. "All three have been peptides that are weakly bound to the MHCII molecule."

These findings have a direct link to human disease. Development of the type I diabetes in humans is also associated with a particular form of the MHCII molecule, which has a binding pattern similar to the one in mice.

Kappler and Eisenbarth plan to see if T cells associated with diabetes in humans also bind the same insulin peptide in the same register as the mouse version.

If the peptide does stimulate T cells associated with diabetes in humans, the discovery would suggest potential diagnostic and therapeutic strategies. Detecting and/or blocking that peptide-MHC complex with an antibody could detect early onset of the disease and might be able to slow or block progression of the disease.

Provided by National Jewish Health

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