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New Theory on Autoimmune Disease

MAY 01, 2010

Denver, CO — The recent discovery of a protein fragment capable of causing diabetes in mice has spurred researchers at National Jewish Health and the University of Colorado Denver to propose a new hypothesis about the cause of diabetes and autoimmunity in general. In the April 23, 2010, issue of *Immunity*, Drs. Brian Stadinski, John Kappler and George Eisenbarth propose that the unusual and rare presentation of protein fragments (peptides) to the immune system allows autoreactive T cells to escape the thymus and trigger autoimmune disease (abstract). The findings could lead to a new strategy for preventing type 1 diabetes.

"The immune system normally deletes dangerous, autoreactive T cells that recognize 'self" peptides, which are a normal part of the organism," said Dr. Kappler, Professor of Immunology at National Jewish Health. "We believe autoreactive T cells in diabetes and other autoimmune diseases escape destruction in the thymus because they never see these poorly presented peptides there. But the T cells do encounter those peptides elsewhere in the body and trigger an autoimmune attack."

Autoimmune diseases, such as type 1 diabetes, multiple sclerosis and lupus, occur when the immune system turns against its own body. This attack is often led by T cells, which serve as coordinators and effectors of the adaptive immune response. During development the immune system tries to protect against this by subjecting T cells to a stringent selection process in the thymus. Any T cell with receptors that bind to self proteins are destroyed before they can circulate throughout the body. This system does occasionally fail, however, opening the door to autoimmune disease.

It has been a challenge for scientists to identify which peptides the autoreactive T cells bind to when they initiate autoimmune disease. Drs. Kappler, Stadinski and Kathryn Haskins, however, recently reported in *Nature Immunology* (abstract) that they had identified a small piece of the protein chromogranin A as the target for one of the most pathogenic T cells in a mouse model of diabetes. This, in conjunction with other discoveries, led them to a new hypothesis about diabetes and autoimmunity.

Cells display protein fragments, or peptides, on their surfaces. The peptides can be derived from self proteins or infectious organisms. The cells hold these peptides with a special protein, known as MHC in mice, sort of like a hotdog bun (MHC) holding a hotdog (peptide). If a T cell, with its unique receptor, can bind to the combined MHC-peptide pair, it is activated and initiates an immune response against that peptide or cells displaying it.

In the case of the chromogranin A peptide, the researchers found that it binds to MHC in an odd way. Instead of fitting cleanly in the MHC binding groove, it fills only part of the groove, hanging over the side and binding to a different area, much like a foot-long hotdog hanging out one end of a normal-sized bun. The peptide also binds very weakly to the MHC molecule.

Another team of researchers found a similar situation with an animal model of multiple sclerosis; only part of the MHC binding groove is filled and the peptide binds only weakly to MHC. Dr. Kappler and his colleagues suspect that a similar situation may occur in diabetes with a peptide from the insulin protein.

Drs. Kappler, Stadinski and Eisenbarth believe these autoimmune antigens may be important precisely because they bind so oddly and weakly to the MHC molecule. The researchers propose that such unusual binding means that these particular MHC-peptide pairs show up only rarely, or never, in the thymus where T-cell selection occurs. Out in the rest of the body, however, specialized processing of the proteins or high concentrations of the source protein produce enough of those odd MHC-protein complexes for the T cells to find them.

"When these T cells encounter the self protein for the first time in the periphery, they initiate an autoimmune response," said Dr. Kappler.

Diabetes and other autoimmune diseases have been associated with specific, relatively rare forms of MHC molecules. Kappler and his colleagues believe these rare forms of MHC are part of the autoimmune puzzle.

"Other scientists have proposed that the MHC molecules associated with autoimmune diseases bind all peptides weakly," said Dr. Kappler. "We think, however, that the MHC molecules can bind peptides perfectly well, but that their unique shape allows them to weakly bind and present peptides that no other MHC molecules can."

National Jewish Health is the leading respiratory hospital in the nation. Founded 121 years ago as a nonprofit hospital, National Jewish Health today is the only facility in the world dedicated exclusively to groundbreaking medical research and treatment of patients with respiratory, cardiac, immune and related disorders. Patients and families come to National Jewish Health from around the world to receive cutting-edge, comprehensive, coordinated care. To learn more, visit the media resources page.

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