

Cellular ‘Garbage Disposal’ Linked to Type 1 Diabetes

Chemical reactions create novel proteins that can trigger autoimmune disease

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DENVER — Researchers at National Jewish Health and the University of Colorado Anschutz Medical Campus have shown that chemical reactions inside cellular organelles known as lysosomes can produce novel proteins capable of triggering type 1 diabetes. Identifying the proteins that trigger type 1 diabetes provides an important clue to the origins of the disease and suggests potential targets for treatment and prevention of the disease.

The lysosome is a small structure inside cells with enzymes that break down old, misshapen or excess proteins into their amino-acid building blocks for reuse. It is often called the ‘garbage disposal’ or ‘recycling center’ of the cell. National Jewish Health Professor of Biomedical Research John Kappler, PhD, and his colleagues report in the *Journal of Experimental Medicine* that, in addition to breaking down proteins, enzymatic reactions in the lysosome sometimes also fuse protein fragments into novel proteins. Dr. Kappler and his colleagues showed some of these new proteins stimulate T cells known to be major drivers of type 1 diabetes.

“These novel fusion proteins are not like any others in the human body, so T cells recognize them as foreign, potentially harmful invaders and attack them,” said Dr. Kappler. “We believe that initiates an inflammatory process in the pancreas that destroys beta cells and the body’s ability to produce insulin.”

Type 1 diabetes is an autoimmune disease in which the immune system attacks and destroys insulin-producing beta cells in the pancreas. Lack of insulin reduces the body’s ability to use sugar for energy and leads to harmful high levels of sugar in the blood. Type 1 diabetes is different from type 2 diabetes, which is initiated by a different mechanism that does not involve the immune system.

Scientists have known for decades that immune cells known as T cells orchestrate the misguided autoimmune attack that causes type 1 diabetes. They have isolated specific T cells that participate in that attack. They have not, however, identified the specific protein fragments that stimulate these T cells into action.

Over the past decade, Dr. Kappler and others have shown that alterations to naturally occurring proteins produce novel proteins that stimulate pathogenic T cells. Exactly how those alterations occur has remained a mystery. In the current paper, they showed that a process known as transpeptidation fuses protein fragments in the lysosome into novel proteins.

In the laboratory, Dr. Kappler and his colleagues combined lysosomal enzymes and beta cell proteins in concentrations and conditions similar to those that exist in beta cell lysosomes. They found that one protease, cathepsin L, fuses protein fragments into hundreds of novel proteins, some of which are capable of strongly stimulating the pathogenic T cells involved in type 1 diabetes.

“We have known for several years that diabetes is triggered by novel proteins found in beta cells,” said Dr. Kappler. “We have now shown that transpeptidation in the lysosome can create the novel proteins that trigger diabetes.”



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