

Potential diabetes treatment selectively kills autoimmune cells from human patients

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In experiments using blood cells from human patients with diabetes and other autoimmune disorders, Massachusetts General Hospital (MGH) researchers have confirmed the mechanism behind a potential new therapy for type 1 diabetes. A team led by Denise Faustman, MD, PhD, director of the MGH Immunobiology Laboratory, showed that blocking a metabolic pathway regulating the immune system specifically eliminated immune cells that react against a patient's own tissues.

Faustman and her colleagues previously discovered a technique that reversed type 1 disease in a mouse model. The current study, which will appear in the *Proceedings of the National Academy of Sciences* and has been released online, is the first demonstration of this strategy in human cells and supports the viability of a clinical trial that is currently underway.

"Our studies in mice showed that we could selectively kill the defective autoimmune cells that were destroying insulin-producing islets," says Faustman. "These results show that the same selective destruction can occur in humans cells and connect what we saw in our animal studies with the protocol we are pursuing in our Phase I clinical trial."

Type 1 diabetes and other autoimmune diseases are caused when the body's immune cells mistakenly attack an individual's own cells. In several studies over the past decade, Faustman's team showed that triggering the expression of the immune-system modulator tumor necrosis factor (TNF) in diabetic mice led to the death of the T cells

responsible for destroying insulin-producing pancreatic islets. After receiving this treatment, the animals were able to regenerate healthy islet cells that produced normal levels of insulin, effectively curing the animals' diabetes.

The current study used T cells from more than 1,000 patients with type 1 diabetes, other autoimmune disorders and healthy controls. First the researchers found that treatment with TNF killed CD8 T cells, the immune system's "killer" cells, from diabetic patients but not CD4 "helper" T cells. TNF treatment also induced the death of CD8 T cells from other autoimmune disease patients but had no negative effect on cells from healthy controls.

Since TNF interacts with immune cells through two different receptors – TNFR1 and TNFR2, which activate different signaling pathways – the researchers next tested several TNF agonists, substances that mimic the molecule's actions. One of those TNF agonists acts through TNFR1, which is expressed on all T cells, and three act through TNFR2, only found on subpopulations of T cells. While neither the TNFR1 agonist nor two of the three substances that activate the TNFR2 pathway had any significant effects, a third TNFR2 agonist induced cell death in particular CD8 cells from patients with diabetes and other autoimmune disorders. As with TNF treatment, no cell death occurred in cells from healthy participants.

Further experiments with blood samples from several diabetic patients revealed that the population of CD8 T cells responsible for the autoimmune destruction of pancreatic islets consistently died after treatment with the TNFR2 agonist, while similar cells from a non-diabetic proliferated. However, CD8 cells from diabetic participants that were targeted against two common viruses were not killed by exposure to the TNFR2 agonist, confirming that the protocol only leads to the death of T cells responsible for an autoimmune reaction.

The clinical trial based on Faustman's earlier studies is testing whether use of bacillus Calmette-Guerin (BCG), a generic drug that temporarily elevates TNF levels, will reduce autoimmune T cells in patients with type 1 diabetes. The current Phase 1 trial, which has been approved by the FDA and is directed by David M. Nathan, MD, director of the MGH Diabetes Center, focuses on determining the optimal dose and timing of BCG administration. More information on the 18-month trial, which began in March, is available at <http://www.faustmanlab.org/> and at <http://www.massgeneral.org/news/releases/031308faustman.html> .

Source: Massachusetts General Hospital

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