



Selective Killing of Autoimmune Cells Suggests Therapy for Type 1 Diabetes

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BOSTON, Aug. 25 -- Laboratory studies of type 1 diabetes and other autoimmune diseases show that boosting levels of tumor necrosis factor (TNF) or its receptor activity selectively destroys autoreactive T cells, suggesting a possible cure for the diseases, investigators here reported.

Administration of TNF or a receptor agonist to isolated T-cells led to the death of a subpopulation of autoreactive CD8 cells to insulin, Denise Faustman, M.D., Ph.D., of Massachusetts General Hospital, and colleagues reported online in *Proceedings of the National Academy of Sciences*.

CD4 cells and other populations of autoreactive CD8 cells proved invulnerable to TNF- or agonist-induced death.

Action Points

- Explain to patients that the study suggests that neutralizing specific cells implicated in type 1 diabetes and other autoimmune diseases may offer a new approach to treatment.
- Note that the findings were based on laboratory studies of blood samples, not a randomized, clinical trial.

Using an animal model of type 1 diabetes, the investigators had previously shown that TNF-triggered cell death led to regeneration of normal pancreatic islet cells to replace those destroyed by autoreactive T-cells.

"With chronic diseases such as diabetes and other forms of autoimmunity, most therapies have traditionally used nonspecific immunosuppression, because it was thought that the rare autoreactive T cells could not be identified, much less selectively killed," the authors said.

"A defective NF signaling pathway, which leads to cell death, now provides, at least *in vitro*, a unique opportunity in human [autoimmune] diseases to kill only autoreactive T cells"

Noting that anti-TNF therapy has become a mainstay of treatment for rheumatoid arthritis and Crohn's disease, both autoimmune disorders, the authors said, "an expanding body of research in animal models . . . suggests the opposite strategy may be warranted."

Genetic and functional studies have implicated deficiencies in TNF levels or signaling pathways in human autoimmunity, suggesting that therapy to raise levels of the immunoregulatory cytokine or restore normal signaling may have a role in human autoimmune diseases.

Continuing their investigation of TNF's role in autoimmunity, Dr. Faustman and colleagues studied blood specimens from 675 patients with type 1 diabetes, from patients with other autoimmune diseases, and from 512 healthy individuals.

The investigators isolated CD4 and CD8 T cells from the blood samples. In a series of experiments, TNF or an agonist to TNF receptor 2 was added to the samples.

Two different cell-death assays demonstrated that a subpopulation of CD8 cells succumbed to the cytokine and the receptor agonist. CD4 cells and other CD8 subpopulations were unaffected.

The researchers subsequently traced the activated T cells involved in type 1 diabetes to an autoreactive CD8 subpopulation that specifically targets insulin, which is a known autoantigen.

"This study shows that autoreactive T cells, although rare, can be selectively destroyed in isolated human blood," the authors concluded. "TNF and TNF [receptor 2] agonist may offer highly targeted therapies, with the latter likely to be less systemically toxic."

The results also support an ongoing phase I clinical trial involving patients with type 1 diabetes treated with bacillus Calmette-Guerin, which transiently elevates TNF levels.

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