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Type 1 diabetes triggered by 'lazy' regulatory T-cells

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A research team led by Dr. Ciriaco A. Piccirillo of McGill University's Department of Microbiology and Immunology has discovered that in some individuals, the specialized immunoregulatory T-cells that regulate the body's autoimmune reactions may lose their effectiveness and become "lazy" over time, leading to the onset of type 1 diabetes. The study – conducted on non-obese diabetic (NOD) mice, which were genetically engineered to model human diabetes – was published in the January 2008 edition of the journal *Diabetes*.

In diabetes mellitus, or type 1 diabetes, insulin-producing beta islet cells in the pancreas are attacked and destroyed by the body's own immune system. Patients must inject insulin on a regular basis or risk diabetic shock and death, and are also at increased risk for numerous secondary health problems, including blindness, heart attack and stroke.

"The genetic and cellular mechanisms by which the immune system goes out of control and destroys the islets has been an enigma and an area of great interest over the last few decades," said Dr. Piccirillo, Canada Research Chair in Regulatory Lymphocytes of the Immune System, and a leading figure in this research area. "For the last several years, it's been postulated that non-functional regulatory T-cells are the critical mechanism, and this study proves it."

Regulatory CD4+ T-cells, whose development and function is dictated by the Foxp3 gene in mice and humans, "have the primary function of pouring a cold shower on inflammatory responses," explained Dr.

Piccirillo. “They suppress and regulate the function of various immune responses to microbes, tumors, allergens and transplants.” While the diabetes-susceptible NOD mice actually generate normal numbers of Foxp3 T-cells over their lifetimes, Dr. Piccirillo and his colleagues discovered that the T-cells’ functional potency declined with age, leaving potential autoimmune responses in the pancreas unchecked.

It is likely, the researchers say, that certain genetic predispositions, coupled with the possible contribution of external environmental factors or infections, could potentially alter regulatory T-cell function in susceptible individuals and trigger a full-scale diabetic autoimmune reaction in the pancreas.

“Once they start, these immune responses are like a fire that goes unchecked by firemen, or a car going downhill without brakes,” said Dr. Piccirillo. Moreover, he said, this discovery not only elucidates the mechanism by which type 1 diabetes is triggered, but it also points the way to the development of new immune system-based therapies for a whole range of diseases.

“We believe that these regulatory cells may represent a kind of master switch, and by understanding how they are made, how they function and how they survive, we may be able to stop disease from occurring.”

Source: McGill University