Type 1 diabetes may result from good genes behaving badly

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New research from Stanford University scientists suggests that type 1 diabetes, an autoimmune disease that develops in children and young adults, may not be due to bad genes but rather to good genes behaving badly.

Because type 1 diabetes typically runs in families, scientists have looked for inborn genetic errors or gene variants passed on from generation to generation. Although this search has failed to find a single type 1 diabetes gene, many candidate type 1 diabetes susceptibility genes have been identified. These susceptibility genes, located in a region known as the major histocompatibility complex (MHC), help the body distinguish its own cells and tissues from those that are foreign.

Studies in identical twins, however, reveal that the situation is more complicated: often one twin develops type 1 diabetes while the other twin remains disease-free. This pattern of good luck/bad luck led researchers at Stanford to examine whether genetically at-risk individuals respond differently to environmental stimuli. In some cases, the immune system will respond in a benign fashion, while in other cases it will begin an inflammatory response that can ultimately lead to diabetes. The critical difference between health and disease might thus reside not in an individual's genetic blueprint but in how those genes are "expressed"--that is, how the translation of genetic information into proteins or RNA is switched on and off.

In a study supported by the National Institute of Allergy and Infectious

Diseases, (NIAID) part of the National Institutes of Health, the Stanford team, led by C. Garrison Fathman, M.D., studied differences in gene expression between two groups of mice. The first group, non-obese diabetic mice, spontaneously develop type 1 diabetes. The second group, mice genetically identical to the first group except for their MHC genes, do not develop the disease.

The researchers looked at gene expression in three different tissues in the diabetic and non-diabetic mice at separate times after birth. In the first few weeks of life, they found an explosion of changes in gene expression in the pancreatic lymph nodes, spleen and circulating blood cells of the diabetic mice compared with those in the non-diabetic mice. At 8 weeks, this activity had quieted down. But several weeks later, when the mice were 12 weeks old, a second explosion of changes in gene expression occurred in the diabetic mice in all three tissues examined: pancreatic lymph nodes, spleen and blood cells.

According to Dr. Fathman, the results suggest that type 1 diabetes may not result from genetic mutations but from differences in how normal genes and gene variants are turned on and off during disease progression. In addition to identifying altered genes that may indicate potential avenues for therapeutic or preventive treatments, the authors also found patterns of coordinated gene expression that may prove useful as biomarkers of disease onset or progression.

Citation: K Kodama et al. Tissue- and age-specific changes in gene expression during disease induction and progression in nod mice. *Clinical Immunology* DOI: 10.1016/j.clim.2008.07.028 (2008).

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