

New study challenges link between HLA class I hyperexpression in pancreas and type 1 diabetes

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The cause of type 1 diabetes remains unknown. Several studies using immunohistochemistry (IHC) have independently reported hyperexpression of human leukocyte antigen (HLA) class I on pancreatic islet cells in young patients with recent-onset type 1 diabetes. Investigators have therefore suggested that HLA hyperexpression may be an important first step in the development of type 1 diabetes. However, a new study in *The American Journal of Pathology* challenges these findings and reports that results differ when quantitative molecular techniques are applied instead of IHC. The investigators suggest that the previously reported model may require reexamination.

"IHC is the most commonly used method to display protein expression in tissues. However, the pattern of expression in composite tissues, such as the pancreas, should be interpreted with caution because obtained results critically depend on the accessibility of the epitope(s) recognized by the primary antibody. Availability of epitopes on proteins in tissue sections varies markedly between tissues, type of fixation, and staining technique," says Oskar Skog, PhD, of the Department of Immunology, Genetics, and Pathology of Uppsala University (Sweden).

According to Dr. Skog and his co-investigators, the clinical manifestations of [type 1 diabetes](#) result from the loss of insulin-producing beta cells in the portion of the pancreas known as the endocrine (hormone-secreting) pancreas. However, the pancreas also

contains exocrine tissue that produces digestive enzymes secreted into the small intestine. Researchers studied both endocrine and exocrine pancreatic tissue to see whether the findings were specific to the tissue directly affected by type 1 diabetes.

The investigators, who are members of The Diabetes Virus Detection (DiViD) Study, analyzed fresh pancreatic tissue from living, newly-diagnosed type 1 diabetic patients, instead of relying on commonly studied post-mortem tissue. Previous reports were confirmed using IHC, showing pronounced and distinct hyperexpression of HLA class I, especially in endocrine tissue compared to exocrine tissue. When quantitative molecular techniques were used, such as Western blot analysis, flow cytometry, real-time quantitative polymerase chain reaction (PCR), or RNA sequencing analyses, no differences were observed in the levels of HLA class I expression between endocrine and exocrine [tissue](#) in patients with recent-onset type 1 diabetes. In addition, no differences were found between samples from type 1 diabetic and non-diabetic subjects.

Further investigation found no important differences in messenger RNA expression for the major histocompatibility complex class 1-specific enhanceosome and related transcription factors in isolated islets, and no differences in the expression of cytokines known to up-regulate HLA expression.

"Islet hyperexpression of HLA class I has been suggested to be an important step in the development of type 1 diabetes by providing a so-called fertile field for pre-existing autoreactive T cells. Our findings suggest that this model may need revision," notes Dr. Skog. "The results presented by our study provide important clues for a better understanding of how this complex disease develops."

Type 1 diabetes, previously known as [juvenile diabetes](#), is characterized

by destruction of [pancreatic beta cells](#), resulting in an absence of insulin. It accounts for 5% to 10% of diabetes cases in the world. Some, but not all, cases of type 1 diabetes can be attributed to an autoimmune reaction that is influenced by genetic and environmental factors. The genes of the HLA system, which are located on chromosome 6, encode antigenic glycoproteins that are present on the surface of most cells in the body, including B cells, T cells, and fibroblasts. Individuals with certain variants of HLA genes are at heightened risk of developing autoimmune diseases, including type 1 [diabetes](#), psoriasis, and reactive arthritis. The HLA complex helps the immune system differentiate the body's proteins from those of foreign invaders such as viruses and bacteria. The class I region of the HLA complex includes the HLA-A, -B, and -C genes; these loci code for the heavy chain of the HLA-class I molecules.

More information: "Expression of HLA Class I in Endocrine and Exocrine Pancreatic Tissue at Onset of Type 1 Diabetes," by Oskar Skog, Stella Korsgren, Anna Wiberg, Angelika Danielsson, Bjørn Edwin, Trond Buanes, Lars Krogvold, Olle Korsgren, Knut Dahl-Jørgensen. (DOI: [dx.doi.org/10.1016/j.ajpath.2014.09.004](https://doi.org/10.1016/j.ajpath.2014.09.004)), *The American Journal of Pathology*, Volume 185, Issue 1 (January 2015).

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