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Structure of a Human Insulin Peptide- HLA-DQ8 Complex and Susceptibility to Type 1 Diabetes

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The major histocompatibility complex (MHC) is an important susceptibility locus for many human autoimmune diseases. The structural and functional properties of HLA-DR molecules that are associated with susceptibility to several autoimmune diseases, such as rheumatoid arthritis and multiple sclerosis, have been defined. Recently, progress has been made in explaining functional and structural characteristics of HLA-DQ molecules that confer susceptibility to type 1 diabetes and celiac disease. The class II Major Histocompatibility Complex (MHCII) glycoproteins HLA-DQ8 and HLA-DQ2 in humans are the major risk factors for increased susceptibility to type 1 diabetes and celiac disease ($I\text{-}A^{g7}$ in the non-obese diabetic mouse (NOD) are to type 1 diabetes). In type 1 diabetes autoimmune destruction of pancreatic islets is preceded by the appearance of autoantibodies and autoreactive T cells to a number of islet antigens including insulin and glutamic acid decarboxylase (GAD). The relationship of these autoimmune reactions to the initiation and progression of disease is undefined. Using X-ray crystallography, we have determined the 3-dimensional structure of DQ8 complexed with an immunodominant peptide from insulin. We have analyzed the size and composition of the peptide binding pockets of DQ8 relative to $I\text{-}A^{g7}$ and to models that we have constructed of DQ2 and MHCII molecules associated with either low risk (DQ7) or dominant protection (DQ6). A marked

similarity of the DQ8, DQ2, and I-A^{g7} peptide binding pockets suggests that diabetes is caused by the same antigen-presentation event(s) in humans. Correlating type 1 diabetes epidemiology and MHCII sequences with the DQ8 structure suggests that other structural features of the P9 pocket in addition to position 57 contribute to susceptibility to type I diabetes.