Autoantigens and type I diabetes

Pseudo type II diabetes (latent insulin-dependent diabetes mellitus). Clinical, biochemical, immunogenetic and immunological parameters

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Type I (insulin-dependent) diabetes mellitus (IDDM) is typically characterized by a rapid onset of clinical symptoms at a young age, insulin dependency, proneness to ketosis as well as the presence in the peripheral blood of islet-specific autoantibodies and cell-mediated immunity towards islet components. There is a strong association with a HLA DR3/DR4 haplotype in Caucasians and especially with non-Asp at position 57 of the HLA DQβ chain across different races. By contrast, type 2 (non-insulin-dependent) diabetes mainly affects adipose individuals and its prevalence rises with increasing age. Type 2 diabetes is mainly due to insulin resistance and a defect in insulin secretion. It has a slow onset of symptoms which can be controlled by oral hypoglycaemic drugs.

Over the past few years we have learned that some individuals who clinically appear to have type 2 diabetes fail to respond to oral hypoglycaemic drugs after several months or a few years and eventually require insulin. Several groups, including our own, have shown that such a rapid secondary failure mainly affects non-obese adults who are islet cell antibody-positive or who show an impaired stimulated insulin or C-peptide response to secretagogues such as glucagon. This form of diabetes has been denominated as pseudo-type 2 diabetes, latent IDDM, or type 1 1/2 diabetes.

Antibodies to the 64 kD islet cell protein have attracted full attention in diabetes research since it has been shown that they recognize the enzyme glutamic acid decarboxylase (GAD) which is also present in the brain. GAD exists in at least two isoforms with Mr 65,000 and 67,000 respectively. By producing human monoclonal autoantibodies with cytoplasmic islet cell antibody (ICA) reactivity, we have shown that at least a fraction of ICA is directed towards GAD_{65}. We and others have also shown that GAD_{65} is the major GAD isoform recognized by patients with IDDM.

While the titres and the prevalence of ICA rapidly decrease after the onset of IDDM, GAD antibodies usually persist over a long period of time. Using brain homogenates (containing GAD_{65} and GAD_{67}) it has been shown recently that GAD antibodies may be found in a substantial portion of patients with type 2 diabetes. Using an ELISA technique with baculovirus-expressed GAD_{65} protein as an antigen, we now assessed the significance of antibodies to GAD_{65} as a predictive marker to indicate the future development of diabetes in initially healthy adult individuals and of future insulin dependency in patients with type 2 diabetes. These results are discussed in detail.