Characterization of Human DNA Topoisomerase II as Autoantigen Recognized by Patients with IDDM

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Autoantibodies against several cytoplasmic autoantigens such as glutamic acid decarboxylase, heat shock protein 65, insulin, and carboxypeptidase H have been identified in the sera of patients with insulin-dependent diabetes mellitus (IDDM). To investigate whether DNA topoisomerase II is an autoantigen in IDDM patients, we have constructed a series of overlapping DNA topoisomerase II fragments that covered the entire length of this enzyme. These framents were used as antigens to screen sea of IDDM patients. We have examined 195 Chinese IDDM patients (mean age 14.2 $\pm$ 7.5 years, age at onset 9.2 $\pm$ 6.4 years, duration 4.6 $\pm$ 3.4 years) and 51 non-diabetic individuals. The results showed that DNA topoisomerase II autoantibodies were detected in 49.2% of IDDM patients. The frequency of anti-topoisomerase II positivity was relatively stable irrespective of gender and disease duration. The patients were older at onset and the prevalence of anti-thyroglobulin /anti-microsomal autoantibodies was twice in IDDM subgroup positive for anti-topoisomerase II than those IDDM who were negative for anti-topoisomerase II. We also characterized the epitopes of DNA topoisomerase II that were recognized by IDDM sera. Those epitopes resided mostly in 3 distinct domains. One residend in

amino acid residues 1-147, another in amino acid residues 286-472, and the third in carboxyl-terminal one-third of DNA topoisomerase II. Intriguingly, we found that these epitopes shared similarity (up to 36% identity and 63.6% homology) to previously identified epitopes of IDDM autoantigens.