

## Autoimmunity in type 1 diabetes: Antibodies and cellular immune responses

Priv.-Doz. Dr. med. Nanette C. Schloot, Institut für Klinische Diabetologie, Deutsches Diabetes- Zentrum, Leibniz- Zentrum für Diabetesforschung an der Heinrich-Heine Universität Düsseldorf und Klinik für Stoffwechselkrankheiten am Universitätsklinikum Düsseldorf. [schloot@ddz.uni-duesseldorf.de](mailto:schloot@ddz.uni-duesseldorf.de)

Type 1 diabetes is a chronic immune mediated disease that appears predominantly in children and younger patients but can affect all ages. About 10-20% of all patients with diabetes have type 1 diabetes or LADA, that is latent autoimmune diabetes in adults.

During disease process insulin producing  $\beta$ -cells are almost irreversibly destroyed by a cellular immune response directed against islet cell autoantigens (IC) such as insulin (I), glutamat decarboxylase (GAD), protein tyrosine phosphatase like antigen IA2 and zinc transporter ZNT8.

Antibodies (A) with specificity towards these proteins, namely ICA, IAA, GADA, IA2A and ZNT8A appear early in the disease process and accompany chronic islet destruction. Islet antibodies are the gold standard for risk determination in pre-diabetic conditions. Furthermore, in case of need for the clarification of diagnosis of type 1 diabetes, these antibodies are positive in more than 90% of affected patients and thereby can help to ensure diagnosis. Whereas the classical ICA that are measured by fluorimetric assays are still measured in some laboratories, biochemical assays for determination of GADA, IA2A and IAA are currently applied in clinical practice as they are relatively easy to standardize and are available as commercial kits. Recent data on IA2 $\beta$  antibodies and ZNT8A help identifying subjects with progressive disease process (IA2 $\beta$ , ZNT8) and can help to identify additional antibody positive subjects in case of ZNT8.

Whereas the pathogenic role of antibodies is not yet fully elucidated, islet antigen reactive T-lymphocytes play a pivotal role in islet destruction either by CD8+ mediated cytotoxicity or indirectly by cytokine release and cytokine mediated toxicity, released by CD4+ T- lymphocytes. T-regulatory cells do play an important role in shifting the immune response towards destruction or protection from disease development. Several experimental approaches are currently performed to assess islet antigen directed lymphocyte responses. Proliferation, tetramer assays, ELISPOT assays as well as T cell cloning are means to assess and characterize diabetogenic T-lymphocytes. Although T-lymphocyte reactivity as well as systemic cytokine concentrations have been shown to be altered in patients with type 1 diabetes and correlate with disease activity, assays are used mainly as surrogates for clinical studies in patients with type 1 diabetes undergoing immune-intervention therapies to hold the disease process or to better understand pathogenesis.

Current efforts of the immunology of diabetes society (IDS) aim on standardizing T-lymphocyte assays to enable more laboratories to perform robust assays. Equivalent standardization assays for islet cell antibodies have been initiated many years ago and are successfully performed every 1.5 years during the DASP (Diabetes Antibody Standardization Program) workshops.

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