Autoimmunity

Etiology and Pathogenesis of Type 1 Diabetes

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Summary

An increasing bulk of evidence suggests that type 1 (insulin-dependent) diabetes mellitus is an autoimmune disease with a strong immunogenetic background. 1st-degree relatives of type 1 diabetic patients, especially HLA-identical individuals, bear an increased risk to develop the disease. The autoimmune reactions are pronounced at the onset of disease where an infiltration of islets with T and B lymphocytes, plasma cells and macrophages can be observed. Autoreactive T lymphocytes play a crucial role among effector mechanisms which finally lead to a selective destruction of pancreatic beta cells. Disease-specific autoantibodies (Ab) include cytoplasmic islet cell Ab (ICA), islet cell surface Ab (ICSA), Ab to the 64KD islet cell protein and Ab to insulin (IAA). As ICA can be detected months or years before the onset of clinical disease, testing of individuals at risk or population screening programs can help to recognize subclinical insulitis. High titers of ICA and high levels of IAA, as measured by radioimmunoassay, indicate a high risk for progression to type 1 diabetes. A blunted first phase insulin response in the i.v. glulcose tolerance test is the most sensitive sign of an irreversible metabolic deterioration. It is likely that immunotherapy at a prediabetic state will be more efficious than its initiation after the clinical manifestation of diabetes. However, the appropriate immunotherapeutical strategies are yet to be worked out.

Key-Words: *Type 1-Diabetes, Etiology, Pathogenesis, Autoimmunity*

Introduction

Type 1 (insulin-dependent) diabetes mellitus (IDDM) is brought about by a process causing a selective destruction of the insulin-producing beta cells of the pancreas. Although the etiology and the exact pathogenetic mechanisms leading to type 1 diabetes are still unknown, it has now become evident that the disease develops on a genetic background, there is strong evidence for an underlying viral infection and autoimmune phenomena directed to islet cells are largely recognized. There are also some data suggesting nutritional or toxic factors. Some important observations indicating a role for autoimmunity in IDDM are listed in Table 1. The analysis of the autoimmune phenomena associated with IDDM give new insights into the disease process and allow to draw conclusions as to the relevant pathogenetic events leading to the disease. It is the aim of this paper to update the present knowledge on the contribution of autoimmunity to type 1 diabetes and to highlight some recent advances which may be relevant to a

Table 1 Observations indicating a role for autoimmunity in Type 1 diabetes mellitus (IDDM).

Associated autoimmune diseases and/or autoantibodies
Infiltration of pancreatic islets with mononuclear cells
Aberrant expression of HLA class II molecules β cells
Detection of humoral autoimmune reactions
– cytoplasmic islet cell antibodies (ICA)
– antibodies to the 64KD islet cell protein
– islet cell surface antibodies (ICSA)
– cytotoxic islet cell antibodies
– insulin autoantibodies (IAA)
Effectiveness of Cyclosporin A therapy in IDDM

molecules. It was now suggested that CD4-positive activated T cell clones isolated from a patient with type 1 diabetes are able to lyse HLA-compatible islet cells expressing HLA class II antigens (*De Bernardinis, Londei, James, Lake, Wise* and *Feldmann* 1988). This mechanism may be crucial to the disease process and these data are compatible with the fact that only beta cells are destroyed in type 1 diabetes.

The role of viral infection

Although the initial event leading to the cellular infiltration of islets and aberrant HLA class II expression is as yet unknown, chronic beta cell specific viral infections are major candidates since alpha interferon, which is usually produced by cells in response to viral infection, has been found to be present in the beta cells of newly diagnosed type 1 diabetic patients (*Foulis, Farquharson* and *Meager* 1987). Increased IgM anti-Coxsackie B4 and/or B5 antibodies, indicating recent infection, were detected in 30 % of newly-diagnosed type 1 diabetic children in England, Austria and Australia whereas these antibodies were present in only 6 % of controls (*Banatvala, Bryant, Schernthaner, Borkenstein, Schober, Brown, De Silva, Meuser* and *Silink* 1985). The presence of these antibodies was correlated with the detection of complement-fixing islet cell antibodies (*Schernthaner, Banatvala, Scherbaum, Bryant, Borkenstein, Schober* and *Mayr* 1985).

In the above studies there was no excess of rubella, choriomeningitis virus (CMV) and mumps. In another survey, performed in Finland, it was shown that anti-mumps antibodies were persistently increased in diabetic patients (*Hyoty, Huupponen* and *Leinikki* 1985). However, in the latter survey long-standing cases were tested so that it is hard to attribute the antibody findings to an initiating or a precipitating event.

The demonstration that apparently normal beta cells have an impaired function following infection by CMV (*Oldstone, Souther, Rodriguez* and *Lampert* 1985) may explain why some cases of ketosis-prone insulin-dependent diabetes in children who died soon after diagnosis were found to have completely normal looking beta cells on histology.

Humoral autoimmunity in type 1 diabetes

Cytoplasmic islet cell antibodies (ICA) are detected in 70–90 % of newly-diagnosed IDDM patients. Their prevalence decreases to 50 % after one year and to 7 %–10 % in long-standing cases (*Lendrum, Walker, Cudworth, Theophanides, Pyke, Bloom* and *Gamble* 1976). ICA are found in less than 1 % of normal controls. ICA detected by the indirect immunofluorescence test or by the protein A method react with a ganglioside antigen of the islets (*Colman, Nayak, Campbell, Ramesh, Jain* and *Eisenbarth* 1988). Cytoplasmic ICA are exclusively of the IgG type whereas islet cell surface antibodies (ICSA) may also contain the IgM specificity. ICSA including cytotoxic antibodies have been mostly determined on non-human substrates such as the RINm5F rat insulinoma cell line (*Daneman, Sochett, Pak* and *Yoon* 1988). The correlations of ICSA test results with the clinical state are variable in different assays.

Four International Workshops have been held to improve the precision of ICA measurement. The first workshop revealed extreme variations in the results, even when identical methods were used. Therefore, a serum exchange programme was developed where the influence of test methods and reagents as well as interassay and intraassay variations were evaluated (*Gleichmann* and *Bottazzo* 1987). A substantial improvement of the test was now obtained by including dilutions of individual sera distributed to the participating laboratories, using each laboratory's standard curve and converting results to units (*Bonifacio, Lernmark* and *Dawkins* 1988). ICA results should now be expressed in terms of units" rather than titers". This will allow to compare test results obtained by different laboratories around the world.

Besides the above specificities, sera from IDDM patients contain antibodies reacting with an islet cell protein. These antibodies precipitate a 64,000 dalton islet cell antigen. It has been shown that they are present in more than 70 % of newly-diagnosed IDDM patients (*Baekkeskov, Landin, Kristensen, Srikanta, Bruining, Mandrup-Poulsen, de Beaufort, Soeldner, Eisenbarth, Lindgren, Sundquist* and *Lernmark* 1987), but they do not parallel the ICA test results (*Christie, Landin-Olsson, Sundquist, Dalquist, Lernmark* and *Baekkeskov* 1988). Similarly, islet cell antibodies detected by an ELISA system (*Scherbaum, Seißler, Hedderich, Boehm, Specker* and *Pfeiffer* 1989) or antibodies to the so-called polar antigen of

The detection of ICA is crucial for the prediction of later development of IDDM. High ICA titers and the presence of complement-fixing ICA indicate a high risk for IDDM. All non-diabetic 1st-degree relatives of IDDM patients in whom ICA = 80 JDF units were detected, developed IDDM within nine years of follow-up (*Tarn, Thomas, Dean, Ingram, Schwartz, Bottazzo* and *Gale* 1988). ICA of low titer may be fluctuating and have a minor predictive value. In follow-up studies ICA-negative relatives have a cumulative risk below one per cent.

Recently the value of IAA has been investigated in detail for the prediction of IDDM. Relatives who are positive for ICA as well as IAA, as determined by RIA (RIA-IAA), seem to be more at risk than those with ICA alone. In retrospective studies the detection of antibodies to the 64KD islet cell protein was found to be typical for the prediabetic state in children (*Riley* 1988). However, the determination of the latter antibodies is very laborious and it will not be suitable as a screening test until easier methods will be available for this specificity.

The intravenous glucose tolerance test (ivGTT) with the determination of the first phase insulin response provides the most sensitive parameter for the detection of an impaired beta cell function in the preclinical state of type 1 diabetes. A reduction of the first phase insulin response below the first percentile of normals indicates a 95% risk to progress to overt IDDM within the next 6 months (*Soeldner, Srikanta, Eisenbarth* and *Gleason* 1986). It is important to note that this only applies to ICA positive individuals, since the impaired ivGTT is also a sensitive sign of early type II diabetes (*Vialettes, Mettei-Zecaco, Badier, Ramahandridona, Lassmann-Vague* and *Vague* 1988). There has been no report of a case so far where a blunted insulin response to i.v. glucose below the first percentile should have been restored in prediabetic patients. Further immunological studies are required to provide more insight into the early events leading to the disturbance of beta cell function. This may also facilitate specific approaches towards immunotherapy of type 1 diabetes.

Acknowledgements

W. A. S. is supported by grants from the Deutsche Forschungsgemeinschaft (Sche 225/3-2 and Sche 225/6-1), and by a grant from the regional government of Baden-Württemberg.

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future progress towards immunotherapy and prevention of type 1 diabetes.

The genetic predisposition

Type 1 diabetes is strongly correlated with the presence of the HLA types DR3 and/or DR4. Over 90 % of the cases have one of the two genes, or both (*Bertrams* and *Baur* 1984). However, it is important to mention that only the HLA DR3/DR4 heterocygous genotype is increased in frequency. We now know that the structure of the HLA DQß chain is crucial for type 1 diabetes: the presence of aspartic acid at position 57 of the DQß chain protects against the disease (*Todd, Bell* and *McDevitt* 1987). However, this does not apply to Japanese patients who also do not show an increase of DR3, but they have an increased frequency of DR4 and DRw9. Chinese lack the increase of DR4. These data show that we are still not looking at the "diabetogenic genes", but at linked markers. This notion can also be derived from the fact that identical twins of type 1 diabetic patients have a concordance rate of 30 % to 50 % whereas less than 20 % of HLA identical siblings become diabetic over the years (*Barnett, Eff, Leslie* and *Pyke* 1981).

Histopathology of the Pancreas in Type 1 Diabetes

At the onset of type 1 diabetes an infiltration of the islets of Langerhans with mononuclear cells is a common feature. Insulitis has been observed in 78 % of recent onset cases, but it is not usually seen in the pancreas of long-standing IDDM. Mostly the beta cell mass rapidly decreases with the duration of disease, but surviving beta cells can still be found in type 1 diabetics of prolonged duration. The alpha, delta, and pp cells always remain intact (*Gepts* and *De Mey* 1978).

The suspicion that insulitis in type 1 diabetes is mediated by an autoimmune attack to insulin secreting beta cells is supported by the fact that the infiltration is patchy and usually affects one of four islets containing insulin, but only 1 % of islets which are insulin deficient (*Foulis, Liddle, Farquharson, Richmond* and *Weir* 1986). The infiltrates consist of a mixture of mononuclear cells including T helper cells, T suppressor cells, B lymphocytes and also macrophages. The exocrine pancreas is only rarely involved in this process.

Aberrant expression of HLA class II molecules on beta cells

Major histocompatibility complex (MHC) antigens play an important role in the discrimination between self and nonself. While T cell subsets expressing MHC class I (A, B, C) antigens have cytolytic activity and mediate graft rejection (*Swain* 1983), MHC class II (DR, DP, DQ) antigens are crucial to facilitate recognition between cells of the immune system (*Benacerraf* 1985). In particular, T helper cells cannot initiate an immune response to an antigen unless the antigen is presented to them by a cell expressing HLA class II molecules. It has been demonstrated in a series of papers that there is an aberrant expression of HLA class II antigens by insulin containing beta cells in type 1 diabetes (*Bottazzo, Dean, McNally, Swift* and *Gamble* 1985). It can now be speculated that the presence of these HLA class II molecules can convert the target cell into a functional antigen presenting cell and it may thus amplify an immune response. It is also possible that HLA class II expression on these somatic cells appears secondary to lymphocytic infiltration which has been shown on thyroid follicular cells (*Khoury, Greenspan* and *Greenspan* 1988).

Cellular immunity in type 1 diabetes

At the clinical onset of type 1 diabetes the number of activated T lymphocytes is increased in the circulation, pointing to a stimulation of the immune system. Furthermore, an increased cytotoxic activity against islet cells as well as an increased killer cell activity have been described. The data on mixed lymphocyte cultures, mitogen stimulation of lymphocytes, as well as on the number and distribution of circulating T suppressor and T helper cell subsets are divergent (*Drell* and *Notkins* 1987). This may be due to the fact that the cells producing the local islet inflammation are only poorly represented in the blood. Also, different groups of patients were investigated in these studies and most of the reagents and tests are not clearly standardized, so that different immunological parameters are actually measured.

The mechanism by which islet beta cells are destroyed in type 1 diabetes is still unknown. It was shown in a recent report that the majority of T cells activated in vivo express the CD4 antigen. CD4-positive (helper) T cells are generally not cytotoxic and recognize antigens in association with HLA class II

Table 2 Influence of biochemical treatment on various islet cell antibody reactivities.

Pretreatment	Result of antibody test		
	ICA (IFL test)	ELISA-ICA	Antibodies to polar antigen
Acetone	+	+	+
Neuraminidase digestion	–	–	–
Methanol extraction	–	–	–
Pronase digestion	+	–	–
Glycolipid absorption	–	+	+

RINm38 rat insulinoma cells (*Dotta, Nayak, Appel, Bonner-Weir* and *Eisenbarth* 1989) do not reflect the cytoplasmic ICA test results. Some important biochemical features of these antibodies are given in Table 2.

Autoantibodies to insulin (IAA) may be detected in 30%–50% of newly-diagnosed IDDM patients before insulin therapy has been initiated (*Palmer, Asplin, Clemons, Lyen, Tatpaty, Raghu* and *Pacquette* 1983; *Wilkin, Hoskins, Armitage, Rodier, Casey, Dias, Pyke* and *Leslie* 1985). With solid phase assays (ELISA) and fluid phase assays (RIA) different reactivities are measured (*Sodoyez-Goffaux, Koch, Dozio, Brandenburg* and *Sodoyez* 1988). ELISA-IAA may be positive in one third of healthy first-degree relatives of IDDM patients and of polyendocrine autoimmune cases or even in cystic fibrosis without diabetes. The IAA-RIA are usually positive in young children at diagnosis of IDDM (*Karjalainen, Salmela, Ilonen, Surgel* and *Knip* 1989) and they seem to be of dictive value for future development of IDDM in healthy relatives (*Eisenbarth* 1988).

In addition to the islet cell-related autoimmune phenomena, some interesting new specificities have been recognized in IDDM. One of them is an antibody to cytoplasmic components of adrenal medullary cells which is mainly detected in ICA-positive sera, but it does not reflect a cross-reactivity of ICA with the adrenal medulla (*Scherbaum, Mogel, Boehm, Hedderich, Glück, Schernthaner, Bottazzo* and *Pfeiffer* 1988). Also antibodies to sympathetic ganglia have been found in IDDM patients and it has been speculated that they are responsible for an impaired postural blood pressure regulation in diabetic patients (*Rabinowe, Brown, Watts, Kadrowske* and *Vinik* 1989).

Type 1-diabetes and associated organ-specific autoimmunity

Type 1 diabetes may appear as a feature of polyendocrine autoimmunity (*Scherbaum, Youinou, Jouquan, Pujol-Borrell, Bercovici* and *Bottazzo* 1986). It may be associated with autoimmune Addison's disease and also with autoimmune thyroid diseases. Some patients with IDDM were also found to have acquired myasthenia gravis, autoimmune central diabetes insipidus, pernicious anaemia or other organ-specific autoimmune diseases (*Doniach* and *Bottazzo* 1981). The detection of autoantibodies to endocrine organs in IDDM patients is even more frequent than the full-blown disease. Thyroid antibodies are present in 30%, and parietal cell antibodies in 5%–8% of IDDM patients (*Betterle, Zanette, Pedini, Presotto, Rapp, Monciotti* and *Rigon* 1984). In contrast to these frequent antibodies, the incidental detection of high titers of the rare antibodies to adrenal cortex is associated with a significant risk to acquire the corresponding disease, i.e. adrenocortical failure (*Scherbaum* and *Berg* 1982).

Who is at risk to develop IDDM?

Patients with organ-specific autoimmune diseases, especially with autoimmune Addison's disease, bear an increased risk for IDDM. Furthermore, some women in whom gestational diabetes has been diagnosed acquire classical IDDM later in their life (*Freinkel, Metzger, Phelps, Simpson, Martin, Radvany, Ober, Dooley, Depp* and *Belton* 1986). Some adults may be primarily diagnosed as type II diabetics, but when they are treated with oral antidiabetic drugs, a secondary failure with insulin dependency becomes apparent after some months. Such patients can be identified by a positive ICA test result. We were able to show that these individuals have similar HLA characteristics as classical IDDM, indicating that they are in fact IDDM cases with slow onset (*Boehm, Scherbaum, Schöffling, Kühnl, Althoff, Manfras, Usadel* and *Trucco* 1989).

About 15% of patients with type 1 diabetes have a family history of IDDM. Therefore, first-degree relatives have been extensively studied as a group at risk to develop IDDM. It has been calculated that 50% of the risk is conferred by the HLA region. However, HLA typing of family members is expensive and laborious so that is remains restricted to scientific studies.

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