

BETA CELLS IN TYPE 1 DIABETES: VICTIMS OR ACTIVATORS OF T CELL RESPONSE?


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The hallmark of type 1 diabetes is the specific destruction of pancreatic beta cells. This common disease affects 0.5% of the population in developed countries and 5 to 10% of people originally diagnosed as type 2 diabetics have a less severe form of the disease called Latent Autoimmune Diabetes of Adults (LADA). A large body of evidences both from experimental and clinical origins has suggested that this specific beta cell loss results from an autoimmune-mediated phenomenon [1, 2]. This chronic process may take several years and is associated with insulinitis, when most of the islets are invaded by mononuclear cells, including dendritic cells and T lymphocytes. However, despite a correlation between peripheral markers such as anti-GAD or anti-IA2 antibodies and beta cell destruction, *in vivo* analysis of insulinitis in type 1 diabetics of recent onset has revealed a fraction of patients without autoimmune patterns [3]. In addition, several important issues remain unsolved nearly 40 years after the first discovery of islet cell infiltration figures in the pancreas of a type 1 diabetic patients by Willy Gepts [4]. Among these unsolved questions, stand the characterization of an hypothetical triggering factor of the autoimmune reaction, the putative roles played by environmental or genetic factors in regulating its progression and the final effector mechanisms leading to beta cell destruction. Face with these difficulties, animals models, in particular the non-obese diabetic (NOD) mouse and transgenic derivatives of it, have provided extensive knowledge on the very early phases of the process and on the complex interactions between genes and T cell function [5]. However, transfers of animal data to the human

situation remain to be evaluated due to the important heterogeneity of the genetic background. Physiological, metabolic and immune-mediated destructions of beta cells may be crucial key events that may initiate or control the progression to disease.

■ THE ROLE OF BETA CELLS IN T CELL EDUCATION

Both CD4+ helper and CD8+ cytotoxic T cells respond to several antigens that are synthesized by pancreatic beta cells, including peptides derived from insulin, glutamic acid decarboxylase (GAD) and tyrosine phosphatases IA-2 and IA2- β [6]. Antigen expression may be increased at least in rodents during the first weeks of age, since beta cell size has been shown to be increased, leading to higher peripheral levels of insulin and to early influx of macrophages [7]. The primary role of virus infection in the precipitation of type 1 diabetes has been re-discussed recently through the damage of pancreatic tissue, causing release and presentation of sequestered islet antigens [8]. Naïve beta cell specific T cells do have the capacity to access to the islets but circulate through blood and lymphoid organs. Activation generally occurs after T cells encounter APCs which display beta cell antigens in draining lymph nodes [9]. The importance of target antigens in maintaining T cell function has been largely proven in experimental models of diabetes. Beta cell deprived NOD mice have been shown to be unable to maintain immune competence. Splenocytes from alloxan-treated NOD mice harboring diabetogenic T cells were unable to transfer the disease in naïve irradiated recipients in contrast to untreated age-matched controls. In contrast, ability to transfer sialitis was unchanged suggesting a tissue specific phenomenon [10]. Using TCR-B2.5 transgenic mice with a repertoire highly skewed for a diabetogenic T cell clone, P. Hoglund *et al* have demonstrated the importance of APCs from pancreatic lymph nodes in controlling T cell activation [11]. Using an OVA transgenic mouse system, the

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same authors demonstrated that numbers of mature APCs in PLNs were clearly determinant for T cell activation, which may explain why insulinitis could not occur before 10 days of age despite the presence of specific autoreactive T cells in the spleen of newborn mice. In a model of oral tolerance in NOD mice using CTB-insulin conjugate, we have also demonstrated that functioning beta cells were also important key determinants of T cell homing using streptozotocin-treated NOD mice harboring a functioning islet graft under the kidney capsule [12]. In this model, we observed a change in regulatory T cell migration patterns from pancreatic to renal lymph nodes, thus demonstrating that beta cells were clearly important factors for peripheral T cell activation in both autoreactivity and tolerance.

■ BETA CELL DEATH AS INITIATOR OF T LYMPHOCYTE ACTIVATION

Many groups have shown a physiological wave of beta cell death that occurs before 15 days of age in the islets of juvenile rodents. This significant death rate was first postulated on the basis of mathematical studies taking into account beta cell division, change in cell volume, and evolution of cell mass [13]. Interestingly, NOD mice have an increase wave of beta cell death in comparison to C57/BL6 mice [14]. The significance of such wave of beta cell death remains unknown. An interesting hypothesis is that beta cell antigens released by apoptotic cells may be potent activation signal for APCs, in particular dendritic cells. Local activation of APCs may be followed by its migration to PLN where presentation to naïve beta cell specific T cells may occur. Beta cells have also been shown to be susceptible to the combinatory action of inflammatory cytokines secreted in the vicinity of the islets by mononuclear cells, such as IL1- β and IFN γ . An extensive literature reviewed in [15] has provided some insights into the mechanisms of action. Using gene expression arrays from beta cell lines exposed *in vitro* to inflammatory cytokines, it has been shown recently that such cytokines decrease the expression of several genes that impair beta cell specialized functions, reduce beta cell mass and upregulate stress response genes [16]. More surprisingly, beta cells exposed to cytokines may also increase the expression of genes coding for chemokines and adhesion molecules involved in T cell homing and activation, thus providing an acceleration of T cell influx to the islets.

■ METABOLIC BETA CELL DEATH AS PART OF BETA CELL MASS DECLINE

The cell death receptor Fas is also able to signal apoptosis *via* an intracellular death domain after inter-

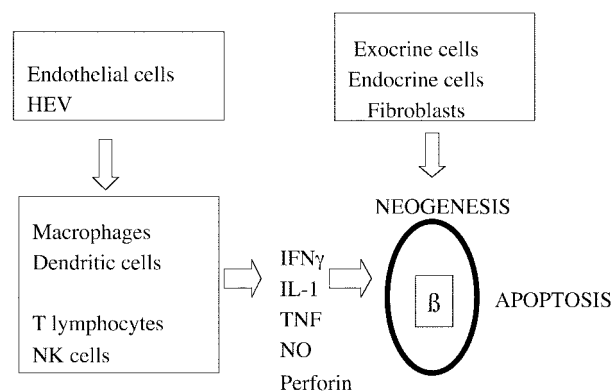


FIG. 1. Beta cells in type 1 diabetes.

action with Fas-ligand expressing T cells as well as neighboring beta cells. *In vitro* exposure of human islets to high concentrations of glucose induced Fas expression specifically on beta cells leading to cell apoptosis [17]. The role for glucose in regulating Fas expression on beta cell membrane may support the clinical evidence that tight glucose control limits beta cell destruction in type 1 diabetic patients as well in patients undergoing islet cell transplantation. Moreover, the possibility to induce beta cell apoptosis in the absence of infiltrating T cells may provide interesting clues for the pathogeny of LADA. In this particular form of diabetes in adults, there is no clear evidence of the duration of the pathogenic process. In the absence of prospective follow-up, it is generally thought that LADA patients have escaped an acute form of the disease in infancy with a very slow autoimmune form of beta cell destruction. An alternative hypothesis, could that autoimmunity may a secondary phenomenon that occurs in genetically predisposed individuals after an increase in blood glucose levels.

■ DIVERTING THE IMMUNE REACTION BY MODIFICATIONS OF THE BETA CELLS

Reintroducing living beta cells in an immune host is thought to be one of the major limitations of islet cell transplantation in type 1 diabetic patients. Several studies including a recent one [18], have shown a sudden rise in specific antibody titers several days or weeks after the islet graft procedure, arguing for the presence of memory T cells long after the clinical onset of the disease. By modifying the structure of the beta cells by long term culture of islet-derived insulin secreting cells, Ramiya *et al.* [19] have been able to obtain a successful islet graft in diabetic NOD mouse that induced long term insulin independence. This experiment provides an additional evidence for the

importance of beta cells and its antigen expression in controlling the level of T cell response.

■ CONCLUSION

Many evidences indicate that beta cells are not passive bystanders of their own destruction. Regulating the expression of autoantigens and controlling the level of beta cell apoptosis under physiological or stress conditions may be important clues for preventing the disease in at risk individuals.

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