*Review Article:*

# Autoimmunity and Pathogenesis of Type 1 Diabetes

MARWA FATHY, M.Sc.*; IBRAHIM I.M. EL ARABY, M.D.*; NANCY M. EL GUINDY, M.D.** and
GHADA M. ANWAR, M.D.**

*The Departments of Pediatrics, Faculties of Medicine, Cairo** and Alexandria & Must Universities**

## Abstract

Type 1A diabetes mellitus results from autoimmune destruction of the insulin-producing beta cells in the islets of Langerhans. This process occurs in genetically susceptible subjects, is probably triggered by one or more environmental agents, and usually progresses over many months or years during which the subject is asymptomatic and euglycemic. Thus, genetic markers for type 1A diabetes are present from birth, immune markers are detectable after the onset of the autoimmune process, and metabolic markers can be detected with sensitive tests once enough beta cell damage has occurred, but before the onset of symptomatic hyperglycemia. This long latent period is a reflection of the large number of functioning beta cells that must be lost before hyperglycemia occurs. Type 1B diabetes mellitus refers to nonautoimmune islet destruction (Type 1B diabetes).

Both genetic and environmental factors contribute to the risk of developing type 1 diabetes mellitus (T1DM). In genetically susceptible individuals, exposure to one or more environmental agents appears to trigger an immune response that ultimately causes destruction of the insulin-producing pancreatic beta cells. Identification of these factors should lead to a better understanding of the pathogenesis of the disease and aid in developing strategies to prevent T1DM.

*They include:*

- Viral infections, particularly enterovirus infections.

- Immunizations.

- Diet, especially exposure to cow's milk at an early age.

- Higher socioeconomic status.

- Obesity.

- Vitamin D deficiency.

- Perinatal factors such as maternal age, history of preeclampsia, and neonatal jaundice. Low birth weight decreases the risk of developing T1DM.

*Key Words:* *Type 1 diabetes – Autoimmunity.*

*Correspondence to:* Dr. Marwa Fathy, The Department of Pediatrics, Faculty of Medicine, Alexandria & Must University

## Introduction

**GENETIC** Susceptibility - Polymorphisms of multiple genes are reported to influence the risk of type 1A diabetes (including, HLA-DQalpha, HLA-DQbeta, HLA-DR, preproinsulin, the PTPN22 gene, CTLA-4, interferon-induced helicase, IL2 receptor (CD25), a lectin-like gene (KIA0035), ERBB3e, and undefined gene at 12q) [1-3]. A meta-analysis of data from genome-wide association studies confirmed the above associations and identified four additional risk loci (BACH2, PRKCQ, CTSH, C1QTNF6) associated with an increased risk of type 1 diabetes [4]. In addition, some loci conferring shared risk for celiac disease (RGS 1, IL 18RAP, CCR5, TAGAP, SH2B3, PTPN2) have been identified [5].

MHC genes - The major susceptibility genes for type 1 diabetes (called IDDM 1 for the MHC locus) are in the HLA region on chromosome 6p [6]. This region contains genes that code for MHC class II molecules expressed on the cell surface of antigen-presenting cells such as macrophages. These MHC molecules consist of alpha and beta chains that form a peptide-binding groove in which antigens involved in the pathogenesis of type 1 diabetes are bound. MHC binding of antigen allows it to be presented to antigen receptors on T cells, which are the main effector cells of the destructive autoimmune process.

Non-MHC genes - Although important, the MHC susceptibility genes are not sufficient to induce type 1 diabetes, suggesting polygenic inheritance in most cases [7]. An important component of the susceptibility to type 1 diabetes resides in certain non-MHC genes that have an effect only in the presence of the appropriate MHC alleles.

Interferon gamma-positive T cells (Th1 cells) appear to be an important mediator of the insulitis in NOD mice, and destruction of the islet cells can be slowed by the administration of anti-interferon gamma antibodies. Interferon gamma-inducing factor (IGIF; also called interleukin-18) and interleukin-12 are potent inducers of interferon gamma, and the progression of insulitis begins in parallel with increased release of these two cytokines [8].

It was initially thought that, in contrast to Th1 cells, Th2 cells (which produce interleukin-4, -5, -10, and -13) protected against the onset and progression of type 1 diabetes. However, Th2 cells also are capable of inducing islet cell destruction and, therefore, the onset and progression of type 1 diabetes are probably under the control of both Th1 and Th2 cells [9].

A more generalizable concept is that type 1A diabetes is prevented by a balance between pathogenic and regulatory T lymphocytes [10]. A major subset of regulatory T lymphocytes termed regulatory T cells (Tregs) express the markers CD4 and CD25 on their surface and lack the IL7 receptor. Tregs generally suppress or downregulate induction and proliferation of effector T cells and are dependent for development upon a transcription factor termed FOXP3. Mutations of FOXP3 lead to lethal neonatal autoimmunity, including type 1 diabetes in neonates. This condition, though extremely rare, it is important to recognize as bone marrow transplantation can reverse it [11].

STAT3 mutations have been identified as a monogenic cause of autoimmunity, including type 1 diabetes [12]. De novo germline activating STAT3 mutations are associated with a spectrum of early-onset autoimmune disease, such as type 1 diabetes, autoimmune thyroid dysfunction, and autoimmune enteropathy. These findings emphasize the critical role of STAT3 in autoimmune disease and contrast with the germline inactivating STAT3 mutations that result in hyperimmunoglobulin E (IgE) syndrome.

## Discussion

*Autoimmunity:*

Children with type 1 diabetes who do not have islet cell or other autoantibodies at presentation have a similar degree of metabolic decompensation as do children who have these antibodies, although those with more of the different types of antibodies appear to have the most accelerated islet destruction and a higher requirement for exogenous insulin during the second year of clinical disease [13]. It is not clear whether these patients had an unusually abrupt onset of autoimmune type 1A diabetes or nonautoimmune islet destruction (type 1B diabetes), though with studies indicating high-risk human leukocyte antigen (HLA) alleles in these individuals, rapid type 1A diabetes in the absence of islet autoantibodies is a possibility.

*Target autoantigens:*

Insulin - The early appearance of anti-insulin antibodies suggests that insulin is an important autoantigen [14]. Direct confirmation of this hypothesis has come from studies in NOD mice. Pathogenic CD8+ T cell clone recognizes an epitope on the insulin B chain and a major target autoantigen for CD4 T cells of NOD mice is insulin peptide B chain amino acids 9 to 23 [15]. Similar T cell responses are found in peripheral lymphocytes obtained from patients with recent-onset type 1 diabetes and from subjects at high risk for the disease have also been reported [16].

Insulin autoantibodies are often the first to appear in children followed from birth and progressing to diabetes, and are the highest in young children developing diabetes. Of note, once insulin is administered subcutaneously, essentially all individuals develop insulin antibodies, and thus insulin autoantibody measurements after approximately two weeks of insulin injections cannot be used as a marker of immune mediated diabetes (type 1A) [14].

Other type 1 diabetes-related autoantigens - As autoimmunity in type 1 diabetes progresses from initial activation to a chronic state, there is often an increase in the number of islet autoantigens targeted by T cells and autoantibodies. This condition is termed "epitope spreading". Several observations indicate that islet autoantibody responses directed to multiple islet autoantigens are associated with progression to overt disease. A number of additional type 1 diabetes-related autoantigens have been identified, which include islet cell autoantigen 69kDa (ICA69), the islet-specific glucose-6-phosphatase catalytic subunit-related protein (IGRP), chromogranin A (ChgA), the insulin receptor, heat shock proteins, the antigens jun-B,16, CD38, peripherin and glial fibrillary acidic protein (GFAP) [17].

*Role of cellular immunity:*

The existence of IgG immunoglobulins directed to epitopes of islet autoantigens implies the influence of T cell participation in the autoimmune response. While the role of autoimmunity in the

pathogenesis of type 1 diabetes and the frequent development of autoantibodies are not in question, there is increasing evidence for a major role of cellular immunity. The occurrence of type 1 diabetes in a 14-year-old boy with X-linked agammaglobulinemia suggests that B cells are not required for the development of the disorder and that the destruction of pancreatic beta cells is mediated principally by T cells [18].

Naturally processed epitopes of islet cell autoantigens represent the targets of effector and regulatory T cells in controlling pancreatic beta cell-specific autoimmune responses [19]. In particular, naturally processed HLA class II allele-specific epitopes recognized by CD4+ T cells, corresponding to the intracellular domain of IA-2, were identified after native IA-2 antigen was delivered to EBV-transformed B cells and peptides eluted and analyzed by mass spectrometry [20].

Molecular mimicry - Initiating factors of the immune response are not well understood. One possibility is molecular mimicry due to homology between GAD and an infectious agent such as Coxsackie B virus. Coxsackie B virus-specific immunoglobulin M (IgM) responses have been found in 39 percent of children with newly diagnosed type 1 diabetes, compared with only 6 percent of normal children [21].

Association with other autoimmune diseases - Patients with type 1 diabetes are at increased risk for developing other autoimmune diseases, most commonly autoimmune thyroiditis and celiac disease.

Type 1 diabetes can be seen with polyglandular autoimmune disease, especially type II, in which adrenal insufficiency, autoimmune thyroid disease, and gonadal insufficiency are the other major components.

Rare syndromes associated with type 1 diabetes have shed important light on pathogenesis. The immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome is associated with neonates developing type 1 diabetes. These infants usually die of overwhelming autoimmunity, in particular, severe enteritis. They have a mutation of a gene termed foxp3, a "master-switch" for the development of regulatory T cells. Studies provide dramatic evidence that regulatory T cells (formerly termed suppressor T cells) have a major physiologic role. The APS-I syndrome (Autoimmune Polyendocrine Syndrome type 1) is caused by a mutation of the AIRE gene (autoimmune regulator). This gene controls expression of a series of "peripheral"

antigens in the thymus, including insulin. It is thought that the gene provides protection from autoimmune disorders, including type 1 diabetes, via its influence on central T cell tolerance [22].

*Prevention of type 1 diabetes:*

The goal of disease prevention is to halt the autoimmune attack on beta cells by redirecting or dampening the immune system. This remains one of the foremost therapeutic goal in T1ADM. Glycemic intensive control and immunotherapeutic agents may preserve beta-cell function in newly diagnosed patients. It may be assessed through C-peptide values, which are important for glycemic stability and for the prevention of chronic complications of this disease [23].

Most strategies to prevent, arrest, or reverse type 1 diabetes target T cells, either directly by altering number or function or indirectly via tolerizing antigens. To date, some interventions seem to preserve some b-cells after onset, but none safely and effectively prevent or reverse the disease [24].

Tolerance/Autoimmunity And the production of type I diabetes Diabetes arises from a breakdown of tolerance to islet antigens, resulting in T cell-driven destruction of the islet cells and concomitant hyperglycemia. This loss of tolerance results in part from a defect in the action of regulatory T cells [25]. It is associated with the mutation of the autoimmune regulatory gene (AIRE), located in chromosome 21 which is important to the regulation of autoimmune mechanisms.Change in this gene results in autoimmune reactions to different antigens expressed in peripheral tissues due to a failure in regulating the presentation of such antigens to the thymus for its recognition as "self-antigens" [26].

*Multiple mechanisms have been invoked to elucidate how insulin -producing cells are destroyed:*

• Directly killing of $\beta$-cells by killer T-cells through a cytotoxic process.

• Release of proinflammatory cytokines, granzyme B, or perforin.

• Possibly, signaling pathways of programmed cell death.

• Proinflammatory cytokines, such as IL-1 $\beta$, IFN-y, and free radicals mediate pancreatic $\beta$-cell death [27].

• Pancreatic $\beta$-cells are highly susceptible to a situation of protein folding imbalance termed endoplasmic reticulum (ER) stress. This unfolded proteins accumulate in the ER as a result of ER stress, triggering apoptosis if this imbalanced

condition is not reversed. Cytokines IL-1 β and IFN-γ induce severe ER stress through NO-mediated depletion of ER calcium and inhibition of ER chaperones, inhibiting β-cell defense and augmenting proapoptotic pathways [28].

*T cell (Tregs) a crucial part of peripheral tolerance and autoimmunuty:*

A recently characterized subset of T cells identified by their cell surface expression of CD4 & CD25 is critical in regulating the function of other immune cells and preventing potentially harmful autoimmune responses and are called regulatory T cells (Tregs). These Regulatory T-cell are present in all normal immune systems and their absence leads to severe autoimmunity. A subset of these cells originates in the thymus; although cells with a similar phenotype can develop in the periphery as well. These cells, are absolutely dependent on interleukin-2 (IL-2) for their growth and survival, although they cannot produce this cytokine themselves [29].

Therapeutic interventions which selectively increase Treg numbers or function would therefore appear to have tremendous potential in type 1 diabetes, but how can Tregs specific for pancreatic antigens be generated? [30].

*Immunology of type 1 diabetes (Recapitulation):*

In the beginning of the autoimmune process against pancreatic beta cells, three or more antigens may be present, but at the end, there are endless antigens which are activating the process. The greater the beta cell lesion, the more antigens are expressed, which will reactivate the process. This explains the natural history of T1ADM: A preclinical stage characterized by a succession of relapses and remissions with interrelation between regulatory T cells (T-regs) and effectors cells, and regeneration of beta cells up to the moment when the percentage of beta cell destruction would no longer allow a proper insulin secretion, resulting in the expression of hyperglycemia [31].

After presenting the antigen by the macrophages to T lymphocytes, at least four types of answer may be induced in the immune system: Th1 (cellular immune response), Th2 (humoral immune response), Th17 (cellular immune response potentialization) and T-regs (which take the control of immune cellular reactions). Nowadays, T 1 DM is considered a T-reg disease, both by its decrease or by its function alteration (e.g., T lymphocytes of Th1 response with Th17 which do not obey the regulation of T-reg cells). This was confirmed by the publication of T1DM cases in individuals who did not produce antibodies through congenital agamaglobulinemia. In such individuals, the Th2 response was absent and thus there was no antibody production [32].

The anti-islet antibodies circulating also express the inflammatory lesion taking place in the pancreas. In T1ADM the most studied autoantibodies are classical anti-islet, glutamic acid decarboxylase antibodies (GADA), anti-tyrosine-phosphatase (IA2/ICA512) antibodies and anti-insulin autoantibodies. The presence of autoimmunity against the pancreatic islets is considered when the individual has one or more antibodies persistent for at least 3 to 6 months [23].

*Apoptosis of CD4+CD25 T Cells in Type 1 Diabetes:*

Yet it has been demonstrated that there is increased apoptosis of Tregs in recent-onset T1D subjects and in subjects at-risk for T1D. This increase in Treg apoptosis was found to correlate with a decline in suppressive potential of these cells. The fact that both hyperglycemic T1D subjects and normoglycemic at-risk subjects showed this phenomenon suggests that Treg apoptosis is more a precursor to, rather than a consequence of diabetes [33].

IL-2, a T-cell growth factor, apart from its effect on Treg activation, there is strong evidence supporting a role for IL-2 in the development and/or function of Tregs. It is understandable that effector T-cells control Treg development and function by secreting several cytokines, including IL-2 and There is evidence for an imbalance in cytokine secretion from effector cells in T1D [34].

*T regulatory cell therapy:*

The discovery of the cells which are involved in β-cell destruction in the pancreas and ways in which they might be inhibited by antigen-specific Treg cells paved the way to trials of using these cells in the treatment of diabetes. Pancreatic β-cells can be killed by effector cells which have been activated in the pancreatic draining lymph node. The mechanisms by which effector cells can kill β-cells includes an MHC class I restricted cytotoxicity by CD8+ T cells, FAS/FASL interaction by both CD4+ T cells and CD8+ T cells and also cytokine-mediated destruction. Treg cells can inhibit these processes through the production of cytokines such as IL-10 and TGF-β. IL-10 secretion by Treg cells may also influence DCs such that they become tolerogenic [35].

*Induction of Tolerance in Type 1 Diabetes via Both CD4-CD25-T Regulatory Cells and T Regulatory Type 1 Cells:*

It was reported that rapamycin combined with interleukin (IL)-10 blocks type 1 diabetes development and induces long-term immune tolerance. Rapamycin mediates accumulation in the pancreas of suppressive CD4-CD25- FoxP3-Tr cells, which prevent diabetes. IL-10 induces Treg-type 1 (Treg 1) cells, which reside in the spleen and prevent migration of diabetogenic T-cells to the draining lymph nodes. These two Treg cell subsets act in concert to control diabetogenic T-cells [36].

*The Effector T Cells of Diabetic Subjects Are Resistant to Regulation via CD4_FOXP3_ Regulatory T Cells:*

In vitro assays using regulatory (Treg) and responder effector (Teff) T cells have shown that suppression is impaired in diabetic subjects. It was established that in type 1 diabetes (T1D) individuals similar levels of impaired suppression were seen, irrespective of whether natural (nTreg) or adaptive Treg (aTreg) were present. It was later found that the aTregs from T1D subjects function normally in the presence of control Teff, and that the T1D Teffwere resistant to suppression in the presence of control aTreg. Thus,Schneider [37] concluded thatthe "defective regulation" in T1D is predominantly due to the resistance of responding T cells to Treg and is a characteristic intrinsic to the T1D Teff.

In this context, Peluso [38] indicated that the mechanisms by which these Teff populations evade suppression have been attributed to multiple factors including the production of cytokines that impede Treg function or changes intrinsic to the Teff. Several different cytokines have been shown to impair Treg function these include: TNF, IL-4, IL-6, IL-12 , IL-7, IL-15 and recently, IL-21.

In addition, cell intrinsic resistance to suppression has been shown to be present in the CD4 memory and Th17 T cells though the mechanisms are yet unknown. One study demonstrated that the level of cell surface glycosylation can influence the sensitivity of Teff to Treg. In another study, it was found that T1D Teffdo not transfer resistance to regulation to control Teff in coculture [39].

*Uncoupling of Proliferation and Cytokines CD4 CD25 T Cells Compartment:*

Strikingly, the CD4+CD25+ compartment from type 1 diabetic subjects had increased proliferative capacity that correlated with increases in select cytokines-IL-17 and TNF- a but not IFN-y. It was found that IL-17 and TNF- a from healthy control subject CD4+CD25- targets can be readily inhibited by type 1 diabetic CD4+CD25+ cells, suggesting that IL-17/TNF- a producers within the CD4+ CD25+ population in type 1 diabetes are particularly resistant to suppression [40].

Honkanen [41] stated that future studies determining the stability of Foxp3 expression, using measures of Foxp3 methylation, and its relationship to IL-17 production in the type 1 diabetic CD4+ CD25+ population will be important. IL-17 is the subject of intensifying study in type 1 diabetes.

## References

1- ATKINSON M.A. and MACLAREN N.K.: The pathogenesis of insulin-dependent diabetes mellitus. N. Engl. J. Med., 331: 1428, 1994.

2- McCULLOCH D.K. and PALMER J.P.: The appropriate use of B-cell function testing in the preclinical period of type 1 diabetes. Diabet Med., 8: 800, 1991.

3- CONCANNON P., RICH S. S. and NEPOM G.T.: Genetics of type 1A diabetes. N. Engl. J. Med., 360: 1646, 2009.

4- COOPER J.D., SMYTH D.J., SMILES AM, et al.: Meta-analysis of genome-wide association study data identifies additional type 1 diabetes risk loci. Nat Genet, 40: 1399, 2008.

5- SMYTH D.J., PLAGNOL V., WALKER N.M., et al.: Shared and distinct genetic variants in type 1 diabetes and celiac disease. N. Engl. J. Med., 359: 2767, 2008.

6- TISCH R. and McDEVITT H.: Insulin-dependent diabetes mellitus. Cell, 85: 291, 1996.

7- DAVIES J.L., KAWAGUCHI Y., BENNETT S.T., et al.: A genome-wide search for human type 1 diabetes susceptibility genes. Nature, 371: 130, 1994.

8- ROTHE H., JENKINS N.A., COPELAND N.G. and KOLB H.: Active stage of autoimmune diabetes is associated with the expression of a novel cytokine, IGIF, which is located near Idd2. J. Clin. Invest, 99: 469, 1997.

9- ALMAWI W.Y., TAMIM H. and AZAR S.T.: Clinical review 103: T helper type 1 and 2 cytokines mediate the onset and progression of type I (insulin-dependent) diabetes. J. Clin. Endocrinol. Metab., 84: 1497, 1999.

10- BLUESTONE J.A. and TANG Q.: Therapeutic vaccination using CD4+CD25+ antigen-specific regulatory T cells. Proc. Natl. Acad. Sci. USA, 101 (Suppl 2): 14622, 2004.

11- WILDIN R.S. and FREITAS A.: IPEX and FOXP3: Clinical and research perspectives. J. Autoimmun, 25: 56-62, 2005.

12- FLANAGAN S.E., HAAPANIEMI E., RUSSELL M.A., et al.: Activating germline mutations in STAT3 cause early-onset multi-organ autoimmune disease. Nat. Genet, 46: 812, 2014.

13- SABBAH E., SAVOLA K., KULMALA P., et al.: Diabetes-associated autoantibodies in relation to clinical characteristics and natural course in children with newly diagnosed type 1 diabetes. The Childhood Diabetes In

Finland Study Group. J. Clin. Endocrinol. Metab., 84: 1534, 1999.

14- ACHENBACH P., KOCZWARA K., KNOPFF A., et al.: Mature high-affinity immune responses to (pro)insulin anticipate the autoimmune cascade that leads to type 1 diabetes. J. Clin. Invest, 114: 589, 2004.

15- NAKAYAMA M., ABIRU N., MORIYAMA H., et al.: Prime role for an insulin epitope in the development of type 1 diabetes in NOD mice. Nature, 435: 220, 2005.

16- ALLEVA D.G., CROWE P.D., JIN L., et al.: A disease-associated cellular immune response in type 1 diabetics to an immunodominant epitope of insulin. J. Clin. Invest, 107: 173, 2001.

17- WINER S., TSUI H., LAU A., et al.: Autoimmune islet destruction in spontaneous type 1 diabetes is not beta-cell exclusive. Nat. Med., 9: 198, 2003.

18- MARTIN S., WOLF-EICHBAUM D., DUINKERKEN G., et al.: Development of type 1 diabetes despite severe hereditary B-cell deficiency. N. Engl. J. Med., 345: 1036, 2001.

19- Di LORENZO T.P., PEAKMAN M. and ROEP B.O.: Translational mini-review series on type 1 diabetes: Systematic analysis of T cell epitopes in autoimmune diabetes. Clin. Exp. Immunol., 148: 1, 2007.

20- PEAKMAN M., STEVENS E.J., LOHMANN T., et al.: Naturally processed and presented epitopes of the islet cell autoantigen IA-2 eluted from HLA-DR4. J. Clin. Invest, 104: 1449, 1999.

21- KO I.Y., JUN H.S., KIM G.S. and YOON J.W.: Studies on autoimmunity for initiation of beta-cell destruction. X. Delayed expression of a membrane-bound islet cell-specific 38 kDaautoantigen that precedes insulitis and diabetes in the diabetes-prone BB rat. Diabetologia, 37: 460, 1994.

22- BARKER J.M. and EISENBARTH G.S.: Autoimmune Polyendocrine Syndromes. In: Immunology of Type 1 Diabetes, Eisenbarth GS (Ed), 2003.

23- SERGIO A.D. and MARILIA B.G.: Etiopathogenesis of type 1 diabetes mellitus: Prognostic factors for the evolution of residual β cell function. Diabetology & metabolic Syndrome, 25: 1758-5996, 2009.

24- KEYMEULEN B., WALTER M., MATHIEU C., et al.: Four-year metabolic outcome of a randomised controlled CD3-antibody trial in recent-onset type 1 diabetic patients depends on their age and baseline residual beta cell mass. Diabetologia, 53: 614-623, 2010.

25- THOMAS D., ZACCONE P. and COOKE A.: The Role of Regulatory T Cell Defects in Type I Diabetes and the Potential of these Cells for Therapy. The Review of Diabetic Studies Thomas, Zaccone, Cooke, Vol. 2, No. 1, 2005.

26- MATHIS D. and BENOIST C.: A decade of AIRE. Nat. Rev. Immunol., 2009.

27- HASKINS K., KENCH J., POWERS K., BRADLEY B., PUGAZHENTHI S., REUSCH J. and McDUFFIE M.: Role for oxidative stress in the regeneration of islet beta cells? J. Investig. Med., 52: 45-49, 2004.

28- CARDOZO A.K., ORTIS F., STORLING J., FENG Y.M., RASSCHAERT J., TONNESEN M., VAN EYLEN F.,

MANDRUP-POULSEN T., HERCHUELZ A. and EIZIRIK D.L.: Cytokines downregulate the sarcoendo-plasmic reticulum pump Ca2+ ATPase 2b and deplete endoplasmic reticulum Ca2+, leading to induction of endoplasmic reticulum stress in pancreatic beta-cells. Diabetes, 54: 452-461, 2005.

29- RANDOLPH D. and FATHMAN G.: CD4+CD25+ regulatory T cells and their therapeutic potential Annu. Rev. Med., 57: 381-402, 2006.

30- JAECKEL E, VON BOEHMER H and MANNS M.P.: Antigen-specific FoxP3-transduced T-cells can control established type 1 diabetes. Diabetes 54: 306-10, 2005.

31- MATTHIAS VON HERRATH, SRINATH SANDA and KEVAN HEROLD: Type 1 diabetes as a relapsing-remitting disease? Nat. Rev. Immunol., 12: 988-94, 2007.

32- GROSS D.M., EARLE K.E., BLUESTONE J.A. and TANG O.: Regulatory T cells and their role in type 1 diabetes. CurrOpin in Endocr, Diabetes and Obesity, 13: 325-31, 2006.

33- GLISIC-MILOSAVLJEVIC S., WAUKAU J., JAILWALA P., JANA S. and KHOO H.J.: At risk and recent-onset type 1 diabetic subjects have increased apoptosis in the CD4+CD25+ T-cell fraction. PLoS ONE, 2: e146, 2007.

34- RABINOVITCH A. and SUAREZ-PINZON W.L.: Roles of cytokines in the pathogenesis and therapy of type 1 diabetes. Cell Biochem. Biophys, 48: 159-163, 2007.

35- THOMAS D., ZACCONE P. and COOKE A.: The Role of Regulatory T Cell Defects in Type I Diabetes and the Potential of these Cells for Therapy. The Review of Diabetic Studies Thomas, Zaccone, Cooke Vol. 2, No. 1, 2005.

36- BATTAGLIA M., STABILINI A., DRAGHICI E., MIGL-IAVACCA B., GREGORI S., BONIFACIO E. and RON-CAROLO M.G.: Induction of tolerance in type 1 diabetes via both CD4-CD25- T Regulatory cells and T Regulatory type 1 cells. Diabetes, 55: 1571-1580, 2006.

37- SCHNEIDER A., RIECK M., SANDA, PIHOKER C., GREENBAUM C. and BUCKNER J.H.: The effector T cells of diabetic subjects are resistant to regulation via CD4-FOXP3- regulatory T cells. The Journal of Immunology, 181: 7350-7355, 2008.

38- PELUSO I., FANTINI M.C., FINA D., CARUSO R., BOIRIVANT M., MacDONALD T.T., PALLONE F. and MONTELEONE G.: IL-21 counteracts the regulatory T cellmediated suppression of human CD4- T lymphocytes. J. Immunol., 178: 732-739, 2007.

39- TOSCANO M.A., BIANCO G.A., ILARREGUI J.M., CROCI D.O., CORREALE J., HERNANDEZ J.D., ZWIRNER N.W., POIRIER F., RILEY E.M., BAUM L.G. and RABINOVICH G.A.: Differential glycosylation of TH1, TH2, and TH-17 effector cells selectively regulates susceptibility to cell death. Nat. Immunol., 8: 825-834, 2007.

40- O'CONNOR R.A., TAAMS L.S. and ANDERTON S.M.: Translational mini-review series on Th17 cells: CD4 T helper cells: functional plasticity and differential sensitivity to regulatory T cell-mediated regulation. Clin. Exp. Immunol., 159: 137-147, 2010.

41- HONKANEN J., NIEMINEN J.K. and GAO R.: IL-17 immunity in human type 1 diabetes. J. Immunol., 185: 1959-1967, 2010.

# المناعة الزاتية والتسبب
# فى مرض السكرى من النوع الأول

مرض السكر ينشأ من انهيار التسامح لمستضدات جزيرة، مما أدى إلى قيام الخلايا اللمفاوية بتدمير خلايا البنكرياس ناتجاً عن ذالك ارتفاع نسبة السكر فى الدم. التحمل الجينى يوضح أن تعدد الأشكال لجينات متعددة يؤثر على خطر الإصابة بمرض السكرى من النوع A۱ (بما فى ذلك HLA-DQalpha و HLA-DQabeta و HLA-DR وPreproinsulin وجين PTPN22 و CTA-4 و هيلكس الناجم عن الإنترفيرون ومستقبل IL2 CD25، وهو جين يشبه الليكتين KIA0035، وجين ERBB3e.

المفهوم القابل للتعميم هو أن المرض السكرى من النوع الأول يتم منعه من خلال التوازن بين الخلايا الليمفاوية التائية الممرضة والتنظيمية. مجموعة فرعية من الخلايا الليمفاوية التائية التنظيمية تسمى الخلايا التائية التنظيمية (Tregs) تعبر عن العلامات CD4 و CD25 على سطحها وتفتقر إلى المستقبلات IL7. تقوم Tregs عموماً بقمع أو خفض تنظيم الحث وانتشار الخلايا التائية المستجيبه وتعتمد على التطور على عامل النسخ المسمى FOXP3. تؤدى طفرات FOXP3 إلى مناعة ذاتية قاتلة لحديثى الولادة، بما فى ذالك مرض السكرى من النوع الأول عند حديثى الولادة.

العلاج بالخلايا التنظيمية مهد اكتشاف الخلايا التى تشارك فى تدمير خلايا بيتا β فى البنكرياس والطرق التى يمكن من خلالها تثبيطها بواسطة خلايا Tregs الخاصة بمستضد الطريق لتجارب استخدام هذه الخلايا فى علاج مرض السكرى. يمكن قتل خلايا βالبنكرياس بواسطة الخلايا المستجيبة التى تم تنشيطها فى العقدة الليمفاوية التى تصريف البنكرياس. تتضمن الآليات التى يمكن من خلالها لخلايا المستجيب أن تقتل خلايا β فئة MHC من الدرجة الأولى التى تقيد السمية الخلوية بواسطة خلايا CD8+T، وتفاعل FAS/FASL بواسطة كل من خلايا CD4+T وخلايا T CD8+ وايض التد مير بواسطة السيتو كين. يمكن لخلايا Treg أن تمنع هذه العمليات من خلال انتاج السيتو كينات مثل IL10 و TGF. قد يؤثر افراز IL10 بواسطة خلايا Treg أيضاً على DCs بحيث تصيح مسببة للتحمل.