

Beneficial autoimmunity in Type 1 diabetes mellitus

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The trigger that leads to the pathogenesis of type 1 diabetes is currently unknown. It is well established that the pathophysiology of the disease is biphasic. In the first stage, leukocytes infiltrate the pancreatic islets in a response that does not cause damage. In the second phase, which occurs only in diabetes-prone individuals and strains, autoreactive T cells acquire aggressive potential and destroy the majority of the pancreatic islets. Rodents and humans exhibit a physiological ripple of apoptotic β -cell death shortly after birth, which induces an adaptive autoimmune response towards islet-antigens, both in diabetes-prone non-obese diabetic (NOD) mice and in mice that do not develop diabetes. Here, we propose that the early T cell-mediated autoimmune response towards islet-antigens is physiological, purposeful and beneficial.

Tissue homeostasis is dependent on balanced immunity towards self

Type 1 diabetes (T1D) is an autoimmune disease that affects >5.3 million people worldwide. Per year, >218 000 people develop the disease and its incidence in 0–14 year old children in the UK is increasing 2.5% per year. In spite of the vast scientific research devoted to this disease, our understanding of the trigger that, in susceptible individuals, produces the aggressive attack by immune cells on the pancreatic β -cells, is currently limited [1]. During the early phase of this biphasic autoimmune disease, a benign autoimmune response towards the islets is observed. Surprisingly, during this neonatal early phase, immune activation is protective, whereas the suppression of this response accelerates and exacerbates the impairment in glucose homeostasis in various animal models. In addition, neonatal islet-specific T-cell priming is not a unique property of the spontaneously diabetic non-obese diabetic (NOD) genetic background but also occurs in B6.H2^{g7} mice, which carry the whole MHC I and II haplotype of NOD mice but do not develop diabetes [2].

In this Opinion, considering the view of ‘beneficial autoimmunity’ that was previously established in the field of central nervous system (CNS) injury and degeneration [3,4], we attempt to propose a new scenario for the

induction phase of T1D. We propose that T1D occurs in those individuals that fail to mount a well controlled protective autoimmune response towards the damaged pancreatic tissue at the neonatal stage. Consequently, T1D-prone individuals (i) do not benefit from a physiological protective mechanism, which counters neonatal β -cell death by promoting processes of apoptotic β -cell clearance and repair of the damaged islets; and (ii) are devoid of the postnatal local T-cell activation that subsequently results in the recruitment of islet antigen-specific T cells into the pool of peripheral regulatory T (Tr) cells. Thus, a balanced cooperative activity among islet antigen-specific effector and Tr cells is required to overcome the injurious conditions induced by neonatal β -cell death, while avoiding both extensive tissue damage and autoimmune pathology.

Autoimmunity as a response against an endogenous threat to homeostasis

‘Beneficial autoimmunity’ defines autoimmunity as a physiological defense mechanism and autoimmune disease as a malfunction of this mechanism [5,6]. This protective response is triggered by tissue damage and degeneration and its purpose is to restore and maintain homeostasis. It has been suggested that the existence of T cells reactive to tissue-specific self-antigens in most healthy individuals is not a result of escaping negative selection but is a purposeful selection, providing a means of immune-mediated homeostasis [4,7]. In the case of a pathogen-free degenerative process (e.g. internal injury or degeneration), a well regulated autoimmune response towards tissue-specific self-antigens prevents further tissue damage without the induction of autoimmune pathology [8,9]. A large body of evidence, in various models of CNS injury, supports the assertion that CNS injury induces a physiological protective autoimmune response [10] and that boosting this response by vaccination with self-antigens associated with the injured tissue can improve the outcome of morphological and functional injury [9,11–13].

This view also suggests a role for this immune activation towards self in the formation of active tolerance through the induction of peripheral Tr cells [5,7,14]. Accordingly, neonatal immune activation towards tissue-specific self-antigens promotes the recruitment of naïve

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T cells into the pool of peripheral Tr cells, and thus provides life-long tissue maintenance, providing the individual with an optimal balance between self-reactive effector and Tr cells. This balance enables a tightly restrained level of homeostatic immune activity toward self without the induction of an autoimmune disease. Thus, active tolerance does not represent non-responsiveness to self-antigens but a dynamic state in which the coordinated function of self-reactive effector and Tr cells enables protective autoimmune activation following substantial tissue damage, without induction of an autoimmune disease.

Neonate β -cell apoptosis: an injury to an indispensable tissue

The postnatal origin of pancreatic β -cells and the role of growth and differentiation factors in regulating β -cell mass remain controversial [15,16]. Recent findings by Dor *et al.* suggest that no new islets are formed during adult life and that pre-existing β -cells, rather than pluripotent stem cells, are the only source of new β -cells during adult life and after pancreatectomy [16]. Weaning represents the point at which newborns, whose insulin levels are now independent of maternal insulin, are exposed to exogenous nutrients. In neonates, the risk of hypoglycemia as a result of hyperinsulinism is high, and it is therefore possible that, similar to within the neonatal brain, programmed cell death has a part in determining the final number of insulin production units (islets).

The essential adjustment of islet number to insulin requirements results in extensive apoptotic β -cell death, which occurs shortly after birth in rodents, pigs and humans [17–19]. Trudeau *et al.* showed that: (i) a massive neonatal wave of β -cell apoptosis occurs in normal developing mice and rats, peaking at 14 days of age, and (ii) diabetes-prone NOD mice display a dysfunction in immune-mediated clearance of apoptotic β -cells [19]. These authors suggest that this remodeling phase, in which up to 60% of the β -cells die, might trigger autoimmune diabetes [19]. Turley and colleagues confirmed that a ripple of physiological β -cell death occurs at 2 weeks of age in all mouse strains and showed that this β -cell death results in the induction of an effective autoimmune response towards the islets [2].

In both mice and humans, it is well established that MHC genes are related to diabetes susceptibility. However, B6.H2 g7 mice, which carry the MHC I and II haplotype of NOD mice, do not develop diabetes. Turley *et al.* demonstrated that neonatal β -cell death results in dendritic cell (DC)-mediated T-cell priming towards β -cell antigens in both NOD and B6.H2 g7 mice. They therefore suggest that priming of potentially diabetogenic T cells is a physiological process common to multiple mouse strains and is not a unique property of the NOD genetic background [2]. Hence, NOD mice are diabetes-prone not because they mount an islet antigen-specific T cell-mediated autoimmune response but rather owing to a malfunction in this response.

An alternative scenario for the induction phase of T1D

Autoreactive T cells and benign autoimmune responses are normal occurrences in healthy individuals [20]. We

propose that the trigger for the pathology of T1D arises from a malfunctioning of purposeful protective autoimmunity. The role of such an adaptive autoimmune response is to orchestrate the local innate immune response (which clears out toxic substances and dead cells) to produce trophic factors essential for the maintenance and repair of damaged pancreatic tissue and also to recruit naïve T cells into the pool of peripheral Tr cells. The pathology of T1D can result from a malfunction in one of two different steps of this process (or in both). (i) The inability of diabetes-prone strains to mount a beneficial autoimmune response. As a result, a self-propagating process of β -cell degeneration eventually leads to the complete destruction of the islets. According to this hypothesis, T1D might be considered a degenerative, rather than an autoimmune, disease and destructive autoimmunity is a later occurrence, resulting from excessive tissue damage and inflammation. This hypothesis is supported by the immune dysfunction observed in diabetes-prone individuals and mouse models (Box 1). (ii) The inability of diabetes-prone strains to control the physiological response (onset, intensity and duration), possibly owing to their failure to induce peripheral antigen-specific Tr cells as a consequence of neonatal autoimmune activation. Without appropriate regulation, for example, by activation-induced interleukin-10 (IL-10)-producing type-1 Tr cells, this immune response might turn into a destructive response, producing an autoimmune pathology [21,22].

Interestingly, it has been recently proposed that increased β -cell death in the adult is an important factor contributing to β -cell loss and the onset of type 2 diabetes [23]. This suggestion is in line with the view that the pancreatic islet tissue requires well controlled autoimmune

Box 1. Diabetes-associated immune dysfunctions

In line with our suggestion that diabetes is initiated by the inability to correctly mount a protective autoimmune response, macrophages and DCs show numerous abnormalities in the NOD mouse, BB rat and T1D patients, such as defective differentiation from bone-marrow precursors, impaired maturation, enhanced arachidonic acid and NF- κ B metabolism, altered cytokine secretion and abnormal expression of the Fc γ receptor gene (Fc γ RII), which is involved in phagocytosis [49,50]. Bouma *et al.* have recently reported that NOD mice display severely impaired recruitment of macrophages, DCs, monocytes and granulocytes to sites of inflammation, in addition to an increased IL-10:IL-1 β ratio at these sites [51]. Homo-Delarche and Drexhage recently suggested that macrophages, DCs and lymphocytes have a role in pancreas and islet development and that a defective function of immune cells generates an aberrant islet morphogenesis in T1D-prone individuals or animals. Therefore, they hypothesize that T1D pathology might result primarily from the defective immune cell function [50]. The secretion of IL-2 by activated effector T cells is crucial for the proliferation and function of Tr cells and for the induction of tolerance [52]. However, Tr cells do not produce endogenous IL-2, and their function therefore depends on locally activated IL-2-producing Th1 cells. Interestingly, it has been demonstrated that, in T1D patients, peripheral T cells are defective in secreting Th1 (IFN- γ and IL-2) cytokines [53,54], which might result in defective Tr-cell proliferation and function. Thus, autoimmune pathology might result primarily from the inability to mount a neonatal Th1-mediated response, which would enable the subsequent induction, proliferation and function of islet antigen-specific Tr cells, as well as the cooperative activity of autoreactive effector and regulatory T-cell subsets in mediating tissue homeostasis and peripheral tolerance.

protection throughout life [5]. Protective autoimmune responses are concealed, unless their malfunction produces a visible autoimmune (e.g. T1D, multiple sclerosis) or degenerative (e.g. type 2 diabetes, Alzheimer's disease) pathology.

We therefore suggest the following scenario: (i) a massive ripple of physiological β -cell death occurs coinciding with weaning; (ii) β -cell death triggers priming of T cells by DCs, towards self-antigens associated with the damaged tissue; (iii) activated T cells home to the site of β -cell-injury in the pancreas; and (iv) in diabetes-prone strains and individuals, a defective immune response eventually produces the autoimmune pathology (Figure 1). However, strains not prone to diabetes are able to adequately mount and regulate this response, mostly as a result of subsequent induction of islet antigen-specific Tr cells, and attain a favorable balance in the activity of self-reactive effector T and Tr cells. Therefore, aggressive islet inflammation is an outcome, and not the initial cause, of β -cell death.

Immunosuppression is diabetogenic whereas immune activation is protective

Currently, a protective islet antigen-specific T cell-mediated response has not been demonstrated in young non-autoimmune-prone mice or humans. However, a large body of evidence indicates that manipulation of the local islet antigen-specific immune response affects both

spontaneous and chemically induced diabetes. Numerous immunostimulatory protocols prevent the development of diabetes [24], including treatment with the non-specific immunostimulatory agents, complete Freund's adjuvant (CFA) or bacillus Calmette–Guerin (BCG) vaccine [25], or with autoantigen-specific vaccine (Table 1). Serreze *et al.* demonstrated that the ability of these non-specific immunostimulatory agents to inhibit diabetes development in NOD mice is dependent not on a Th1 to Th2 cytokine shift but on the presence of the Th1 cytokine interferon- γ (IFN- γ) [26]. This finding agrees with the observation that the controlled activity of autoimmune Th1 cells is beneficial following CNS injury [4]. Hugues *et al.* demonstrated that young NOD mice injected with a single low-dose of streptozotocin (STZ), a drug that is rapidly metabolized by β -cells and eventually induces their death, are protected from spontaneous diabetes and β -cell apoptosis is necessary for this protection. Therefore, they propose a model in which apoptosis of pancreatic β -cells induces the development of regulatory T cells, leading to the tolerization of self-reactive T cells and protection from diabetes [27]. These findings are in line with observations made in CNS injury models, showing that survival of retinal ganglion cells in rats is significantly higher when the optic nerve injury is preceded by another unrelated CNS injury, owing to induction of a well controlled protective immune response by the earlier injury [10]. According to this view, minor islet damage in

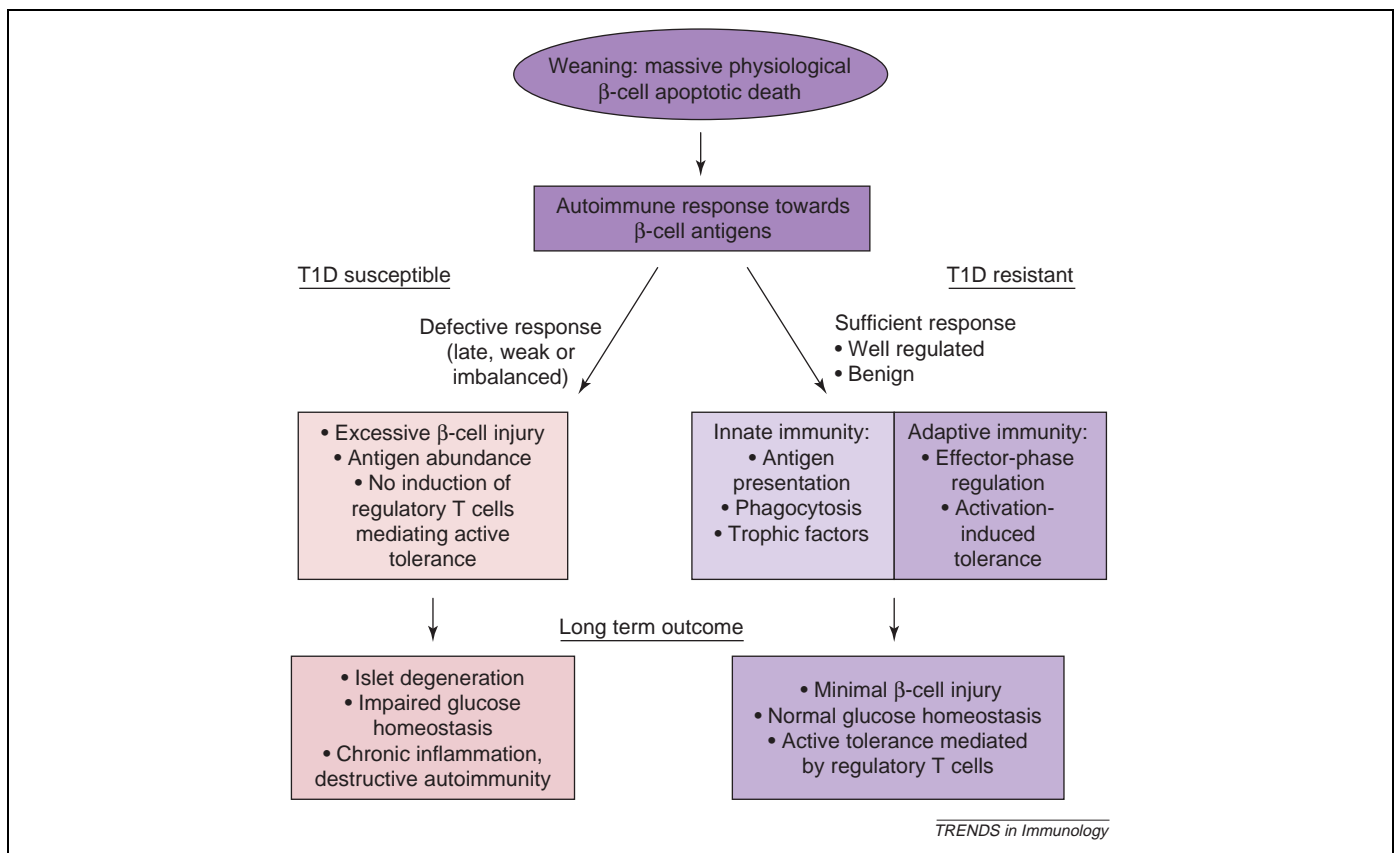


Figure 1. Neonatal β -cell death promotes a physiological autoimmune response to antigens associated with apoptotic β -cells. In healthy (T1D resistant) individuals, a sufficient adaptive response is mounted, mediating innate processes of maintenance and damage control and subsequently inducing Tr cells. Islet-specific Tr cells generate peripheral active tolerance by preventing further activation of autoimmune T cells, excluding cases of considerable tissue damage later in life. In diabetes-prone (T1D susceptible) individuals, this early benign response is defective. Excessive islet damage and the absence of tolerance induction result ultimately in a destructive autoimmune response.

Table 1. Immunostimulatory treatments that prevent diabetes

Autoantigen non-specific	Refs	Autoantigen-specific	Refs
Virus infection	[24]	Immunization with STZ-treated islets	[28]
<i>Schistosoma mansoni</i> infection	[24]	DC vaccination with insulin	[55]
<i>Mycobacterium avium</i> or <i>Mycobacterium bovis</i> infection	[24]	DNA vaccination with insulin B chain	[56]
BCG vaccination	[25]	DNA vaccination with GAD65	[57]
CFA vaccination	[25]	Immunization with insulin or GAD65 in incomplete Freund's adjuvant	[59]
Empty plasmid DNA or CpG oligonucleotide vaccination	[58]	Vaccination with insulin- or pro-insulin-derived peptides	[60]
CD3 antibody	[47]	Passive transfer of GAD65-reactive T cells	[43]
Vitamin D3	[61]		
Heat shock protein 60 (P277) peptide vaccination	[58,60]		

young NOD mice stimulates a protective autoimmune response, which results in prevention of diabetes. Similarly, in line with observations that active immunization with self-antigens that are associated with damage to a specific tissue promotes the recovery of this tissue from injury [4], Rayat *et al.* have shown that active immunization with STZ-treated islets protects young NOD mice from developing spontaneous diabetes [28].

Local expression of transgene-encoded cytokines in the pancreatic islets is a useful method to test the effect of specific cytokines on diabetes onset. Interestingly, in some cases, the result of local cytokine expression is not in accordance with the expected biological activity [29] (Table 2). Systemic overexpression of the immunomodulatory cytokine IL-10 in 4-week-old NOD females ameliorates diabetes through the induction of Tr cells [30]. By contrast, transgenic NOD mice expressing IL-10 in the islets display prominent pancreatic inflammation and accelerated diabetes induction [31], whereas transgenic (not prone to diabetes) Balb/c mice expressing IFN- γ in the pancreatic β -cells are resistant to STZ-induced diabetes [32]. A later report described immune activation and recruitment of antigen-presenting cells (APCs) to the pancreas in transgenic Balb/c mice whose islets express granulocyte-macrophage-colony stimulating factor (GM-CSF). Surprisingly, the advanced immune cell infiltration in these mice not only did not harm the islets but it also protected pancreatic function by delaying the onset of STZ-induced diabetes [33]. Accordingly, local expression of transgene-encoded tumor necrosis factor- α (TNF- α) prevents diabetes onset in NOD mice [34]. Conflicting effects of TNF- α have been observed in different animal models. Thus, systemic administration of TNF- α inhibits diabetes in both the NOD mouse and the BB (Bio-Breeding) rat model [35], whereas in a transgenic model of virally induced diabetes [RIP-LCMV (rat insulin promoter-lymphocytic choriomeningitis virus)], it abrogates the ongoing autoimmune process when induced late, but not early, during

Table 2. Protective and destructive expression of transgene-encoded cytokines in pancreatic islets of animal models of diabetes

Prevention or attenuation of T1D	Refs	Induction or aggravation of T1D	Refs
TNF- α	[34]	IL-10	[31]
IFN- γ	[32]	IFN- β	[62]
GM-CSF	[33]	IFN- α	[62]
IL-4	[62]	TNF- α	[36]
Transforming growth factor- β	[62]		

pathogenesis [36]. Interestingly, viral mimicry has a role in the acceleration of ongoing disease but not in the initiation of autoimmune diabetes [37]. These findings support the idea that locally confined postnatal stimulation of islet reactive T cells prevents diabetes onset.

Search for the T-cell subset that prevents diabetes

T cells have a protective role in various diabetes models [38]. Notably, diabetes onset in NOD females is accelerated by thymectomy at weaning, which results in significant T-cell depletion [39]. Antigen-specific autoreactive T cells can acquire *in vivo* diabetogenic or protective effector function, depending on the site and context of the initial priming event. Akhtar *et al.* isolated splenic β cell-reactive Th1 clones from unprimed NOD mice. Interestingly, these autoreactive clones prevent diabetes after adoptive transfer into 4-week-old NOD mice [40]. Homann *et al.* isolated insulin B chain-specific autoreactive CD4⁺ T cells from protected and diabetic mice that were fed porcine insulin, and demonstrated that these cells locally suppress diabetogenic T-cell responses against an unrelated self-antigen (bystander suppression) in the RIP-LCMV model [41]. These observations demonstrate the beneficial role autoreactive T cells have in the prevention of destructive autoimmunity.

Glutamic acid decarboxylase (GAD)65 has been suspected to be one of the initial autoantigens targeted in the early course of T1D. Absence of GAD65 expression in the thymus and predominant expression in a peripheral tissue supports its role in autoreactivity [42]. Tarbell *et al.* [43] generated transgenic NOD mice expressing a T-cell receptor (TCR) specific for a GAD65 peptide. Interestingly, these mice do not develop diabetes. Furthermore, activated GAD65-specific T cells significantly delay the onset of diabetes in NOD.SCID (severe combined immunodeficiency) mice, when adoptively transferred along with diabetogenic NOD spleen cells. Therefore, GAD65-specific T cells have disease protective capacity and are not pathogenic [43]. These findings are in line with a previous demonstration that transgenic BDC2.5 NOD mice, which express a TCR derived from a diabetogenic β -cell-reactive T-cell clone, show dramatic islet infiltration by autoreactive T cells but rarely develop diabetes [44]. Thus, similar to what is observed in experimental autoimmune encephalomyelitis (EAE)-susceptible strains following CNS trauma, autoimmune T cells can, under certain conditions, be beneficial [3,8].

Gonzalez *et al.* found that a mutation of the TCR α locus, which blocks the differentiation of $\alpha\beta$ T cells, significantly

accelerates diabetes in BDC2.5 transgenic NOD mice [45]. A mutation of recombination-activating gene 1 (*RAG-1*^{-/-}), which prevents the maturation of $\alpha\beta$ T, $\gamma\delta$ T and B cells, results in severe acceleration and exacerbation of diabetes in these B/R^o mice. Interestingly, transfer of splenocytes from young NOD donors into B/R^o mice completely abrogates diabetes when performed on day 10 or 15 of age, although not later. Moreover, CD4⁺ T cells depleted of CD25⁺ Tr cells or of CD45RB^{lo} Tr cells (a T-cell subset that includes Tr cells that mediate tolerance *in vivo*) could protect with the same dose response profiles as total CD4⁺ T cells. Autoreactive BDC2.5 T cell-mediated protection from diabetes does not involve clonal deletion or anergy, rather, the full activation of these cells tempered the aggressiveness of the insulinitic lesion and the extent of β -cell destruction [45]. These findings indicate that T cells prevent diabetes in neonate mice primarily by performing an effector, rather than a suppressive, function.

You *et al.* [46] have recently confirmed the protective effect of CD4⁺ T-cell transfer into 10-day-old T cell-deficient NOD mice. Moreover, they found that infusion CD4⁺ T cells, which express L-selectin (CD62L, a surface marker that has been associated with T-cell migration), however, not of CD4⁺CD25⁺ Tr cells, prevents diabetes onset in these mice [46]. The authors therefore suggest that CD4⁺CD62L⁺ is a specific subset of Tr cells, which prevents diabetes. However, the suppressive function of these cells has not been demonstrated *in vitro* or *in vivo*. Collectively, these findings suggest that the transfer of islet antigen-specific naive (CD4⁺CD45RB^{high}CD62L⁺) T cells protected 10- and 15-day-old NOD mice from diabetes by performing their effector function in the context of neonatal β -cell apoptosis. Subsequent to their activation at the site of antigen presentation, these cells enable the induction, proliferation and activation of antigen-specific Tr cells. Finally, You *et al.* showed that the 145 2C11 anti-CD3 antibody, previously shown to prevent diabetes induction in NOD mice in a T cell-dependent manner [47], has no effect when injected into newborn NOD BDC2.5 immune-deficient mice, indicating that the mode of action of this antibody does not involve depletion or inactivation of effector T cells but rather T-cell stimulation. Salomon *et al.* showed that spontaneous diabetes is exacerbated in mice rendered deficient of CD28 co-stimulation [48]. They also showed that these mice have a profound decrease in the number of CD4⁺CD25⁺ Tr cells. These findings suggest that the CD28–B7 co-stimulatory pathway is essential for maintenance of homeostasis through the induction of Tr cells.

Collectively, these observations are supportive of our claim that the local activation of self-reactive Th1 cells, and secretion of Th1 cytokines, are required at the neonatal phase for prevention of excessive tissue damage, and subsequently for the establishment of a favorable balance in the activity of self-reactive effector T and Tr cells, which mediate the dynamic state of active tolerance.

Concluding remarks

The rationale for this viewpoint is not to deny the role of a detrimental autoimmune response in the pathogenesis of

T1D. Numerous papers describe the destruction of the pancreatic islets by infiltrating immune cells. Nevertheless, we propose that pathogenic autoimmunity results from a malfunction in the immune mechanism by which neonatal islet specific T-cell priming reconciles tissue homeostasis and active tolerance.

Animal models of disease do not always accurately correspond to the relevant human pathology. We are aware of the fact that most of the findings reviewed here rely on experiments performed in animals. The NOD mouse model is special because it is the only model of a spontaneous autoimmune disease. The evidence for a β -cell abnormality in this model is inconclusive and it seems that immune dysfunction determines the pathology. Transgenic models, which display accelerated and exacerbated diabetes might prove advantageous for addressing specific questions regarding overt disease. However, these models might differ notably from the human pathology in focusing on destructive autoimmune pathology and neglecting the early phase of protective autoimmunity. Better understanding of the protective role of autoimmunity might promote the development of novel therapies for both degenerative diseases and autoimmune diseases, which result from imbalanced activity of effector T and Tr cells.

The perception of autoimmunity as the protective mechanism of the body, and of autoimmune disease as a failure of protective autoimmunity, calls for a different therapeutic strategy for autoimmune diseases. It argues in favor of early preventive therapies based on immunomodulation, rather than immunosuppression, with the object of maximizing the beneficial component rather than eliminating the protective aspects of immunity towards self.

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