Journal of Autoimmunity 31 (2008) 301–305

Contents lists available at ScienceDirect

Journal of Autoimmunity

journal homepage: www.elsevier.com/locate/jautimm

A new role for an old player: Do B cells unleash the self-reactive CD8+ T cell storm necessary for the development of type 1 diabetes?

Eliana Mariño, Shane T. Grey*

Gene Therapy & Autoimmunity Group, Arthritis and Inflammation Program, Garvan Institute of Medical Research, 384 Victoria St., Darlinghurst, NSW 2010, Australia

Keywords:
Autoimmunity
B cells
CD8+ T cell
Diabetes

A B S T R A C T

Type I diabetes mellitus is an autoimmune disease mediated by a selective immune-mediated destruction of the insulin containing beta cells within the pancreatic islets of Langerhans. T cells reactive to beta cell-derived antigens are critical for the pathogenesis of type I diabetes, indeed treatments that target T cells are currently in clinical trials. CD8+ T cells may play a particularly crucial role in the onset of hyperglycaemia, as they can mediate beta cell destruction late in the pathogenesis of diabetes. However, the precise steps by which beta cell-reactive CD8+ T cells are activated are poorly understood. In this review we speculate on the possibility that B cells are essential for the activation and expansion of pathogenic CD8+ T cells that cause final beta cell destruction. We also discuss the involvement of different B cell subsets in the aetiology of diabetes.

1. Introduction

Type I diabetes mellitus is an autoimmune disease marked by insulin deficiency and hyperglycaemia for which there is no known cure. Insulin deficiency is caused by a selective immune-mediated destruction of the insulin containing beta cells within the pancreatic islets of Langerhans. Many lines of evidence support the concept that type I diabetes is an autoimmune disease. Indeed, progression to or protection from type I diabetes is associated with certain MHC alleles, the most significant diabetes susceptibility genes being the MHC class II alleles HLA-DQB1 and HLA-DRB1, and the MHC class I alleles HLA-B and HLA-A [1,2]. Moreover, type I diabetes can be transferred by bone marrow transplantation [3], and conversely, diabetes development can be slowed by treatment with immunosuppressive drugs such as anti-CD3 monoclonal antibody and cyclosporine [4]. However, a detailed understanding of the exact processes underlying the development of type I diabetes from the study of human subjects has remained elusive, due to the lack of suitable bio-markers, an inability to directly monitor the pancreatic beta cells, and the shortage of predictive markers to indicate development of the autoimmune response and diabetes onset. Thus, much of what is known currently stems from the study of animal models of human type I diabetes. In this regard, study of the non-obese diabetic (NOD) mouse, which mimics many features of human type I diabetes [5], has greatly enhanced our understanding of the pathogenesis of type I diabetes. One important aspect that has come to light from the study of the NOD model is the role of CD4+ and CD8+ T cells, specific for beta cell derived antigens, as important mediators of beta cell destruction, a process essential for diabetes pathogenesis. Thus, transfer or elimination of CD4+ or CD8+ T cells can precipitate or prevent diabetes, respectively, providing strong support for the concept that type I diabetes is a T cell mediated autoimmune disease. However, major questions remain concerning the precise steps by which T cells reactive to beta cell antigens are activated, expanded and then recruited to the pancreas, and to the mechanisms they utilize to destroy the beta cells. It is self-evident that therapies designed to prevent these processes could potentially provide powerful treatments for the cure of type I diabetes.

2. B cells and the pathology of type I diabetes

Whilst T cells may represent the final arbitrators of beta cell destruction, there is evidence that B cells also may play a prominent role in the aetiology of type I diabetes [6]. Perhaps the most important evidence relates to a long recognised feature of human subjects with type I diabetes, that is the presence of serum autoantibodies specific for beta cell derived antigens. The molecular targets of these so called islet cell antibodies (ICA) include insulin, glutamic acid decarboxylase (GAD) and the tyrosine phosphatase-like molecules IA-2/IA-2β [7]. The presence and titres of particular autoantibodies, together with assessment of the presence or absence of HLA-susceptibility genes, are currently the best predictive markers for future development of type I diabetes. Significantly, many of the autoantigens recognized by the ICA, particularly insulin and GAD, are also the targets for self-reactive T cells,

* Corresponding author. Tel.: +61 2 9295 8104; fax: +61 2 9295 8404.
E-mail address: s.grey@garvan.org.au (S.T. Grey).

0896-8411/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.jaut.2008.04.001

demonstrating a strong link between the molecular targets of both the T and B cell autoimmune response [8]. While these data provide evidence for the activation of B cells, they do not explicitly indicate whether B cells are a principal player, necessary for diabetes pathogenesis or are rather activated secondary to the inflammatory events occurring during the primary autoimmune assault. While a healthy debate rages on this topic [5,6], it is quite likely that type I diabetes represents a syndrome in which multiple immune and non-immune pathways can differentially impact upon disease progression in each individual. Thus, while B cells may not be necessary for the development of type I diabetes in every human subject [9], the overall predictive value of autoantibodies suggests B cells would have some importance in the aetiology of diabetes for a significant proportion of cases.

The concept that B cells are important players in diabetes pathogenesis is more strongly supported from studies on the NOD mouse. In the NOD model, B cells infiltrate the pancreas during the early stages of insulitis and, as in human subjects, circulating autoantibodies, specific for beta cell auto-antigens are readily detected [6]. Significantly, genetic or antibody-mediated ablation of B cells in NOD mice is protective, thus crossing a mutation that prevents B cell development onto the NOD background to generate NOD.$Ig\mu^{null}$ mice, prevents diabetes [10]. In addition, treatment of NOD mice with anti-CD20 antibodies to mediate B cell elimination can also markedly reduce diabetes incidence [11]. Collectively, studies in both human subjects with type I diabetes, as well as NOD mice, provide evidence that B cells are important for the development of spontaneous diabetes, but are also potential therapeutic targets for the treatment of type I diabetes.

3. B cells can perform an antigen presenting cell function in type I diabetes

If B cells are necessary for diabetes development, as indicated by studies on the NOD mouse model, what is their function? There is evidence to indicate that B cells are involved in multiple aspects of the processes culminating in type I diabetes. Of particular importance for this discussion, numerous studies have demonstrated that B cells can provide T cell help as antigen presenting cells, and are required for the optimal expansion of diabetogenic T clones [12–14]. In contrast, B cells do not appear to be required as an important effector cell for beta cell destruction in the NOD model. T cells transferred from diabetic NOD mice to B cell deficient recipients can still precipitate diabetes, whereas transfer of antibodies alone to NOD mice cannot mediate beta cell destruction [12]. However, these studies should not be interpreted to indicate autoantibodies have no pathogenic role. Indeed, one report has suggested that beta cell specific autoantibodies are necessary to prime the maternal environment, setting the scene for later diabetes development in susceptible progeny [15]. More pertinently, autoantibodies may allow efficient capture of beta cell autoantigens to enable the selection and or activation of self-reactive T cells by antigen presenting cells [16]. Indeed, surface expression of autoantibodies may be important in facilitating the antigen capture and presenting capability of B cells themselves [17,18].

The current paradigm of how B cells participate in the pathogenesis of type I diabetes as antigen presenting cells indicates the presentation of autoantigen to CD4+ T cells in a MHC class II restricted fashion [6]. While this is a popular concept, the supportive evidence is not unequivocal. Major conceptual support for MHC class II mediated B cell antigen presentation is considered to have been provided by studies utilizing B cell deficient NOD mice, which typically exhibit a low frequency of spontaneous diabetes. In these studies, while diabetes can be precipitated following reconstitution with splenic B cells carrying the NOD MHC haplotype IAg7, diabetes is not restored when NOD mice are reconstituted with MHC class II deficient B cells [19]. However, there are some important caveats to the interpretation of these experiments. Since MHC class I is in strong linkage disequilibrium with MHC class II, the introduction of the MHC class II knockout mutation also alters the MHC class I alleles present in NOD mice. This is a critical point, as disruption of the MHC class I gene is sufficient to prevent diabetes in NOD mice [20]. Perhaps more direct evidence for B cell mediated and MHC class II dependent antigen presentation comes from studies with islet specific CD4+ T cells expressing the BDC2.5 clonotypic TCR [21] and those reactive to GAD. The expansion of both BDC2.5 transgenic T cells and GAD-reactive CD4+ T cells is severely impaired *in vivo* in B cell deficient NOD mice [12,19]. Thus, these data demonstrate that B cells can act as drivers of CD4+ T cell activation through MHC class II dependent interactions. However, they do not necessarily indicate that B cell help is limited to providing support for pathogenic CD4+ T cells. Indeed, we speculate that an additional and perhaps overlooked role for B cells in the pathogenesis of type I diabetes may be as antigen presenting cells required for the activation of self-reactive CD8+ T cells.

4. CD8+ T cells can mediate beta cell killing

There is strong supportive evidence to indicate that CD8+ T cells are important in the pathogenesis of type I diabetes. This includes studies showing that CD8+ T cells contribute to the insulitic lesion in NOD mice and that NOD mice deficient in MHC class I due to lack of β-2 microglobulin do not develop diabetes. It is postulated that CD8+ T cells could destroy insulin producing beta cells through the release of cytolytic granules containing perforin and granzyme, or through Fas and Fas ligand dependent interactions [22]. Concordantly, both perforin and Fas knockout NOD mice show delayed onset and reduced incidence of diabetes [23,24]. These data suggest that CD8+ T cell-mediated beta cell killing is a major mechanism of beta cell destruction underlying the pathogenesis of type I diabetes. CD8+ T cell dependent killing pathways could be activated following the engagement of the self-reactive TCR expressed by theses pathogenic CD8+ T cells with MHC class I molecules expressed on the surface of beta cells. Beta cells express MHC class I and, significantly, beta cell restricted MHC class I deficiency is sufficient to arrest diabetes development and prevent beta cell destruction [25]. One interpretation of these studies is the absolute requirement for CD8+ T cells in the process of final beta cell destruction. This concept might be further articulated to indicate that CD8+ T cells are a late requirement in the pathogenesis of type I diabetes.

5. Are B cells required late in the development of diabetes?

A major pathologic feature of the aetiology of type I diabetes mellitus in the NOD model is that diabetes proceeds in distinct stages or check-points. The earliest evidence of diabetes is clearly apparent by 4–6 weeks of age when NOD mice exhibit a pancreatic mononuclear cell infiltrate, or insulitis. Despite the persistence of this mononuclear infiltrate and the presence of self-reactive T cells, overt diabetes, evidenced by the onset of hyperglycaemia, does not begin to manifest until 12–16 weeks of age. Thus, one could infer that qualitative or quantitative changes in the autoimmune response must occur over this later period to facilitate the transition to overt diabetes.

One intriguing result to come out of a recent study exploring the effect of anti-CD20 monoclonal antibody-mediated B cell depletion on diabetes incidence [11], was the demonstration that treatment was most effective when provided from ∼9–15 weeks of age. That is, treatment was most effective when B cell depletion was achieved during the transition to overt diabetes in NOD mice. Using a conceptually similar approach, we have also examined the effect of B cell elimination on diabetes incidence and penetrance in female

NOD mice (EM and STG, unpublished data). In contrast to anti-CD20 treatment, we achieved B cell depletion by administering a soluble BCMA-Fc fusion protein to NOD mice. BCMA-Fc binds the cytokine BAFF, leading to a block in B cell development at the transitional stage in the spleen, preventing the emergence of mature B cells [26]. Similar approaches designed to target BAFF have been utilized to delineate the role of B cells in experimental models of lupus. Surprisingly, we also found that eliminating B cells from 9–15 weeks of age was the most effective strategy in protecting NOD mice from diabetes. Collectively, these studies indicate a distinct role for B cells at a later phase in diabetes pathogenesis.

These data raise the question as to whether B cells, acting as antigen presenting cells, are necessary for the transition from insulitis to frank diabetes that occurs from ∼12 weeks of age in NOD mice. If this presumption was correct, one would predict that B cells should exhibit features and characteristics consistent with an enhanced capacity to provide support for T cell activation over this time period. With respect to the presentation of auto-antigen to self-reactive T cells, the pancreatic lymph node is recognized as a critical site [27]. Interestingly, B cells specifically accumulate at this location in increasing numbers in an age-dependent manner [28], suggesting that this is not a random event, but rather is closely linked to the conversion to overt diabetes in the NOD model. Moreover, NOD B cells undergo a marked numerical expansion and exhibit an increased activation status from ∼12 weeks of age. This enhanced activation status is evidenced by an increase in the expression of MHC class I and II molecules, as well as the co-stimulatory molecules CD80 and CD86 on the surface of B cells colonizing the pancreatic lymph nodes and the pancreas [28]. Interestingly, B cells have been postulated to be critical for the epitope spreading and the subsequent maturation of the CD4+ T cell anti-beta cell immune response [13]. Collectively, these data correlate the transition to overt diabetes with the phenomena of heightened B cell activation, indicating an increased and specific involvement of B cells in the late evolution of the autoimmune assault on the pancreatic islets.

6. The late expansion and affinity maturation of pathogenic CD8+ T cells is a critical step in diabetes development

If B cells do indeed play a particular role in the late stages of diabetes, first, what is the nature of that function and, second, who is the recipient of that help? Clearly, one possibility lies in the ability of B cells to activate diabetogenic CD4+ T cells. However, we propose that new insights into the particular dynamics of CD8+ T cell activation raise the intriguing possibility that B cells are also required for the expansion of pathogenic CD8+ T cells. These data relate to the study of CD8+ T cells reactive to the islet-specific glucose-6-phosphatase catalytic subunit-related protein (IGRP). IGRP-reactive CD8+ T cells were initially isolated from the pancreatic lesion of NOD mice. This clone represents a major proportion of the self-reactive CD8+ T cell repertoire infiltrating the pancreas, moreover, this T cell clone is sufficient to mediate beta cell killing and precipitate diabetes when transferred to NOD recipients [29]. Of interest in NOD mice, IGRP-specific CD8+ T cells undergo a marked clonal expansion and affinity maturation from ∼10–16 weeks of age, a period overlapping with the onset of overt hyperglycaemia in female NOD mice [30]. Further, the expansion of IGRP-specific CD8+ T cells is predictive of diabetes onset in NOD mice [31]. Importantly, consistent with studies demonstrating that removal of MHC class I from beta cells can prevent diabetes, interventions that thwart IGRP-specific CD8+ T cell activation can prevent diabetes onset in NOD mice [25,32]. Thus, IGRP-reactive CD8+ T cells expand late in the pathogenesis of diabetes, overlapping with the period of transition from benign insulitis to overt diabetes and, perhaps provocatively, these events coincide with the period when B cell elimination is the most efficacious at preventing diabetes.

7. Evidence for interactions between B cells and pathogenic CD8+ T cells

We observed that B cell elimination mediated by BCMA-Fc-treatment protected NOD mice from diabetes when administered over the time period during which IGRP-reactive CD8+ T cells underwent a marked expansion. Similarly, anti-CD20-mediated B cell elimination also reduced diabetes incidence in NOD mice when administered over this same time period. These results suggested a potential relationship between B cells and CD8+ T cell activation, and so prompted us to explore the kinetics of IGRP-reactive CD8+ T cell expansion in our BCMA-Fc model system. Intriguingly, we found that NOD mice treated from 9 to 15 weeks of age with BCMA-Fc lacked the characteristic expansion of IGRP-specific CD8+ T cells typical of un-manipulated NOD mice (E.M. and S.T.G., unpublished observation). Thus, in the absence of B cells, no expansion of IGRP-specific CD8+ T cells was observed in NOD mice. These data indicate the existence of a tight relationship between the presence of B cells, IGRP-specific CD8+ T cell expansion and diabetes onset.

8. Are B cells necessary for the optimal expansion of CD8+ T cells?

These data provide the first hints that B cells may be linked to the activation of a diabetogenic CD8+ T cell clone in the spontaneous NOD model of diabetes. A major question arising from these observations is what is the nature of this B cell dependent help? B cells are able to capture, process and present autoantigen to self-reactive CD4+ T cells. These B cell-activated CD4+ T cells could in turn provide help to CD8+ T cells by way of cytokines to facilitate their proliferation, survival and or their acquisition of effector function. The cytokine interleukin (IL)-21 represents one candidate molecule that could provide this function. IL-21 is produced by antigen-activated CD4+ T cells and following the engagement of its cognate receptor expressed by CD8+ T cells, it potently induces CD8+ T cell expansion and enhances CD8+ T cell effector function [33]. Of further interest, IL-21 expression is dysregulated in NOD mice [34], such that IL-21 is expressed at high levels by NOD CD4+ T cells over the 10–16-week time period. Thus, B cell-mediated presentation of autoantigen to CD4+ T cells could lead to the elaboration of CD4+ T cell-dependent help, which by way of providing critical cytokines, could enable the activation of autoreactive CD8+ T cells.

A very recent report [35], utilizing a TNF-transgenic accelerated model of diabetes crossed onto the B cell deficient NOD background, provided further evidence that B cells may be important for the activation of CD8+ T cells. In that report, B cell deficiency correlated with a decrease in intra-islet CD8+ T cell survival and a delay in diabetes onset. The decreased CD8+ T cell survival may be consistent with a requirement for the provision of CD4+ T cell-dependent cytokines in the maintenance of the self-reactive CD8+ T cells' assault on the beta cells. Indeed, the lack of CD8+ T cell expansion found in our study may also be consistent with a failure of CD8+ T cell survival. Together, these studies predict that without B cells to support their clonal expansion, self-reactive CD8+ T cells cannot reach the threshold necessary to achieve fulminant beta cell destruction.

9. Can B cells provide pathogenic CD8+ T cells with MHC class I restricted help?

If CD8+ T cells are required to engage their cognate beta cell targets to mediate the final killing blow, it would be important to

elucidate whether this beta cell CD8+ T cell interaction was also sufficient to mediate the initial activation of CD8+ T cells. Perhaps surprisingly, expression of MHC class I on beta cells alone is not sufficient to incite diabetes [36], pointing to the existence of another cellular player necessary for the initial activation of CD8+ T cells. Though this function is classically relegated to dendritic cells, we speculate that one of the cell types involved may also be the B cell, so that B cells may be important antigen presenting cells for the activation of pathogenic CD8+ T cells. B cells express high levels of MHC class I and are thus theoretically capable of acting as antigen presenting cells for CD8+ T cells. However, there is debate as to the *in vivo* significance of this potential. For instance, whilst *in vitro* B cells can activate CD8+ T cells, *in vivo* B cells do not appear to be absolutely required for CD8+ T cell activation, but rather turn off naive T cells. Moreover, studies utilizing a model antigen system indicated that the normal outcome of antigen presentation by B cells is the induction of CD8+ T cell tolerance [37]. Though, if the tolerizing capacity of B cells relates to the lack of expression of the appropriate co-stimulatory molecules by resting, *versus* activated B cells, then under the inflammatory conditions observed during the development of diabetes, the balance might be shifted from one of tolerance induction to activation. Indeed, we have found that B cells invading the islets and pancreatic lymph nodes do express MHC class I, as well as appropriate co-stimulatory molecules, including CD80 and CD86, necessary for CD8+ T cell activation.

As mentioned above, studies in which reconstitution of B cell deficient NOD mice with MHC class II deficient B cells prevented diabetes have been interpreted to indicate a critical role for MHC class II-mediated presentation by B cell in the pathogenesis of type I diabetes. However, this strategy would also alter the MHC class I alleles present in NOD mice. Indeed, in the light of this discussion it is interesting to speculate that the protection observed in those particular experiments may also indicate a requirement for MHC class I mediated B cell dependent antigen presentation for diabetes pathogenesis.

10. Which B cell subtype provides the T cell help necessary for diabetes development: is there a marginal zone B cell requirement?

B cell development proceeds in the spleen to give rise to two mature subsets: follicular B cells and marginal zone B cells, respectively [38]. Despite this fact, there has been little investigation into the relative roles of these two splenic B cell subsets in type I diabetes. Indeed, there may be a presumption in the field that follicular B cells, which mediate the germinal centre reaction and produce high affinity antigen and memory cells, are perhaps the most likely B cell candidates to be involved in the pathogenesis of type I diabetes. This is unwarranted, as B cell deficient NOD mice, as well as anti-CD20 and BCMA-Fc treated NOD mice, all exhibit reduced levels of both follicular B cells and marginal zone B cells. Thus these current studies do not preferentially rule out a role for one or other B cell subtype.

In particular, marginal zone B cells exhibit a number of features that might mark them as candidate players in type I diabetes. Their location within the marginal sinus of the spleen enables them to sample blood borne antigens, such as those potentially released from dying beta cells [38]. Moreover, marginal zone B cells exhibit an activated 'effector' phenotype, as indicated by their ability to generate rapid antibody responses to antigens and blood borne pathogens. These features, coupled with their propensity to harbour a self-reactive repertoire, indicate a potential for involvement in autoimmunity. Significantly, mice transgenic for BAFF, as well as NZB/W F1 mice, exhibit an increased frequency of marginal zone B cells, harbour high titres of circulating antibodies directed against self-constituents and develop autoimmune conditions reminiscent of lupus and sialadenitis [26]. Of relevance to the provision of T cell help, marginal zone B cells are able to act as efficient antigen presenting cells and can provide cognate help to naive CD4+ T cells [39]; indeed, marginal zone B cells have been shown to be as capable as dendritic cells in driving antigen-specific T cell proliferation and IL-2 production.

Emerging studies in the NOD model indicate that marginal zone B cells may make an important contribution to diabetes pathogenesis. NOD mice exhibit significantly increased numbers of marginal zone B cells compared to non-autoimmune prone strains, and the expansion of marginal zone B cells is linked to a major region on chromosome 4 co-localizing with the diabetes susceptibility locus *Idd*9/11 [28,40]. Moreover, elimination of marginal zone B cells by way of a depleting anti-CD21/35 (CR1/2) mAb reduced disease incidence in one experimental model of diabetes [41]. More recent evidence shows that both marginal zone and follicular B cells are able to capture, process and present the autoantigen insulin to self-reactive T cells from NOD mice [28]. In addition, activated marginal zone B cells accumulated in the pancreatic lymph node of NOD mice with an increasing frequency over the ~10–16 week period when overt diabetes manifests. These are the first data to indicate marginal zone B cells can present an important autoantigen to T cells and drive their proliferation. Further studies to determine whether both marginal zone and follicular B cells are equally capable of acting as antigen presenting cells for CD4+ or CD8+ T cells will provide further insights into their respective roles in the pathogenesis of type I diabetes.

11. Concluding remarks

Type I diabetes is an autoimmune disease caused by the immune-mediated destruction of the pancreatic beta cells. The realization that T cells play a critical role in the process of beta cell destruction, based on studies from human subjects with type I diabetes and the NOD model, has subsequently led to investigations into the mechanisms by which these self-reactive T cells are activated. One possible model indicates that naive, self-reactive CD4+ and CD8+ T cells are initially activated by dendritic cells within the pancreatic lymph nodes, during the inductive phase of type I diabetes. However, the clone size of these self-reactive T cells does not reach the threshold necessary to precipitate the onset of clinical hyperglycaemia. A late event triggers the activation and expansion of self-reactive B cells, which capture antigen and present this to self-reactive CD4+ T cells, which in turn mediate beta cell destruction and activate CD8+ T cells through the elaboration of cytokines. Additional mechanisms of B cell help may include the presentation of autoantigen to MHC class I restricted CD8+ T cells, facilitating their late expansion, activation and precipitating the onset of diabetes. Future challenges remain to directly test these propositions and determine the exact role of differing B cell subsets in the aetiology of type I diabetes.

Acknowledgements

EM is supported by a NH&MRC Dora Lush Fellowship. This work has been supported by grants from the Juvenile Diabetes Foundation (5-2005-1132) and from the NSW BioFirst Program to STG.

References

[1] Nejentsev S, Howson JM, Walker NM, Szeszko J, Field SF, Stevens HE, et al. Localization of type 1 diabetes susceptibility to the MHC class I genes HLA-B and HLA-A. Nature 2007;450:887–92.
[2] Park Y, Eisenbarth GS. Genetic susceptibility factors of Type 1 diabetes in Asians. Diabetes Metab Res Rev 2001;17:2–11.

[3] Exner BG, Groninger JH, Ildstad ST. Bone marrow transplantation for therapy in autoimmune disease. Stem Cells 1997;15(Suppl 1):171–5 (discussion 175-6).
[4] Herold KC, Hagopian W, Auger JA, Poumian-Ruiz E, Taylor L, Donaldson D, et al. Anti-CD3 monoclonal antibody in new-onset type 1 diabetes mellitus. N Engl J Med 2002;346:1692–8.
[5] Roep BO, Atkinson M, von Herrath M. Satisfaction (not) guaranteed: re-evaluating the use of animal models of type 1 diabetes. Nat Rev Immunol 2004;4: 989–97.
[6] Silveira PA, Grey ST. B cells in the spotlight: innocent bystanders or major players in the pathogenesis of type 1 diabetes. Trends Endocrinol Metab 2006; 17:128–35.
[7] Yu L, Eisenbarth GS. Chapter 10: Humoral Autoimmunity. In: Eisenbarth GS, editor. Type I Diabetes: Molecular, Cellular and Clinical Immunology. Springer; 2005.
[8] Nakayama M, Abiru N, Moriyama H, Babaya N, Liu E, Miao D, et al. Prime role for an insulin epitope in the development of type 1 diabetes in NOD mice. Nature 2005;435:220–3.
[9] Martin S, Wolf-Eichbaum D, Duinkerken G, Scherbaum WA, Kolb H, Noordzij JG, et al. Development of type 1 diabetes despite severe hereditary B-lymphocyte deficiency. N Engl J Med 2001;345:1036–40.
[10] Serreze DV, Chapman HD, Varnum DS, Hanson MS, Reifsnyder PC, Richard SD, et al. B lymphocytes are essential for the initiation of T cell-mediated autoimmune diabetes: analysis of a new ''speed congenic'' stock of NOD.Ig mu null mice. J Exp Med 1996;184:2049–53.
[11] Hu CY, Rodriguez-Pinto D, Du W, Ahuja A, Henegariu O, Wong FS, et al. Treatment with CD20-specific antibody prevents and reverses autoimmune diabetes in mice. J Clin Invest 2007;117:3857–67.
[12] Serreze DV, Fleming SA, Chapman HD, Richard SD, Leiter EH, Tisch RM. B lymphocytes are critical antigen-presenting cells for the initiation of T cell-mediated autoimmune diabetes in nonobese diabetic mice. J Immunol 1998; 161:3912–8.
[13] Tian J, Zekzer D, Lu Y, Dang H, Kaufman DL. B cells are crucial for determinant spreading of T cell autoimmunity among beta cell antigens in diabetes-prone nonobese diabetic mice. J Immunol 2006;176:2654–61.
[14] Falcone M, Lee J, Patstone G, Yeung B, Sarvetnick N. B lymphocytes are crucial antigen-presenting cells in the pathogenic autoimmune response to GAD65 antigen in nonobese diabetic mice. J Immunol 1998;161:1163–8.
[15] Greeley SA, Katsumata M, Yu L, Eisenbarth GS, Moore DJ, Goodarzi H, et al. Elimination of maternally transmitted autoantibodies prevents diabetes in nonobese diabetic mice. Nat Med 2002;8:399–402.
[16] Harbers SO, Crocker A, Catalano G, D'Agati V, Jung S, Desai DD, et al. Antibody-enhanced cross-presentation of self antigen breaks T cell tolerance. J Clin Invest 2007;117:1361–9.
[17] Hulbert C, Riseili B, Rojas M, Thomas JW. B cell specificity contributes to the outcome of diabetes in nonobese diabetic mice. J Immunol 2001;167: 5535–8.
[18] Wong FS, Wen L, Tang M, Ramanathan M, Visintin I, Daugherty J, et al. Investigation of the role of B-cells in type 1 diabetes in the NOD mouse. Diabetes 2004;53:2581–7.
[19] Noorchashm H, Lieu YK, Noorchashm N, Rostami SY, Greeley SA, Schlachterman A, et al. I-Ag7-mediated antigen presentation by B lymphocytes is critical in overcoming a checkpoint in T cell tolerance to islet beta cells of nonobese diabetic mice. J Immunol 1999;163:743–50.
[20] Serreze DV, Chapman HD, Varnum DS, Gerling I, Leiter EH, Shultz LD. Initiation of autoimmune diabetes in NOD/Lt mice is MHC class I-dependent. J Immunol 1997;158:3978–86.
[21] Katz JD, Wang B, Haskins K, Benoist C, Mathis D. Following a diabetogenic T cell from genesis through pathogenesis. Cell 1993;74:1089–100.
[22] Benoist C, Mathis D. Cell death mediators in autoimmune diabetes – no shortage of suspects. Cell 1997;89:1–3.
[23] Kagi D, Odermatt B, Seiler P, Zinkernagel RM, Mak TW, Hengartner H. Reduced incidence and delayed onset of diabetes in perforin-deficient nonobese diabetic mice. J Exp Med 1997;186:989–97.
[24] Itoh N, Imagawa A, Hanafusa T, Waguri M, Yamamoto K, Iwahashi H, et al. Requirement of Fas for the development of autoimmune diabetes in nonobese diabetic mice. J Exp Med 1997;186:613–8.
[25] Hamilton-Williams EE, Palmer SE, Charlton B, Slattery RM. Beta cell MHC class I is a late requirement for diabetes. Proc Natl Acad Sci U S A 2003;100: 6688–93.
[26] Mackay F, Sierro F, Grey ST, Gordon TP. The BAFF/APRIL system: an important player in systemic rheumatic diseases. Curr Dir Autoimmun 2005;8:243–65.
[27] Hoglund P, Mintern J, Waltzinger C, Heath W, Benoist C, Mathis D. Initiation of autoimmune diabetes by developmentally regulated presentation of islet cell antigens in the pancreatic lymph nodes. J Exp Med 1999;189:331–9.
[28] Mariño E, Batten M, Groom J, Walters S, Liuwantara D, Mackay F, et al. Marginal-zone B-cells of nonobese diabetic mice expand with diabetes onset, invade the pancreatic lymph nodes, and present autoantigen to diabetogenic T-cells. Diabetes 2008;57:395–404.
[29] Amrani A, Verdaguer J, Anderson B, Utsugi T, Bou S, Santamaria P. Perforin-independent beta-cell destruction by diabetogenic CD8(+) T lymphocytes in transgenic nonobese diabetic mice. J Clin Invest 1999;103:1201–9.
[30] Amrani A, Verdaguer J, Serra P, Tafuro S, Tan R, Santamaria P. Progression of autoimmune diabetes driven by avidity maturation of a T-cell population. Nature 2000;406:739–42.
[31] Trudeau JD, Kelly-Smith C, Verchere CB, Elliott JF, Dutz JP, Finegood DT, et al. Prediction of spontaneous autoimmune diabetes in NOD mice by quantification of autoreactive T cells in peripheral blood. J Clin Invest 2003;111:217–23.
[32] Han B, Serra P, Amrani A, Yamanouchi J, Maree AF, Edelstein-Keshet L, et al. Prevention of diabetes by manipulation of anti-IGRP autoimmunity: high efficiency of a low-affinity peptide. Nat Med 2005;11:645–52.
[33] Zeng R, Spolski R, Finkelstein SE, Oh S, Kovanen PE, Hinrichs CS, et al. Synergy of IL-21 and IL-15 in regulating CD8+ T cell expansion and function. J Exp Med 2005;201:139–48.
[34] King C, Ilic A, Koelsch K, Sarvetnick N. Homeostatic expansion of T cells during immune insufficiency generates autoimmunity. Cell 2004;117:265–77.
[35] Brodie GM, Wallberg M, Santamaria P, Wong FS, Green EA. B cells promote intra-islet CD8+ cytotoxic T lymphocyte survival to enhance type 1 diabetes. Diabetes 2008;57:909–17.
[36] de Jersey J, Snelgrove SL, Palmer SE, Teteris SA, Mullbacher A, Miller JF, et al. Beta cells cannot directly prime diabetogenic CD8 T cells in nonobese diabetic mice. Proc Natl Acad Sci U S A 2007;104:1295–300.
[37] Bennett SR, Carbone FR, Toy T, Miller JF, Heath WR. B cells directly tolerize CD8(+) T cells. J Exp Med 1998;188:1977–83.
[38] Martin F, Kearney JF. Marginal-zone B cells. Nat Rev Immunol 2002;2:323–35.
[39] Attanavanich K, Kearney JF. Marginal zone, but not follicular B cells, are potent activators of naive CD4 T cells. J Immunol 2004;172:803–11.
[40] Rolf J, Motta V, Duarte N, Lundholm M, Berntman E, Bergman ML, et al. The enlarged population of marginal zone/CD1d(high) B lymphocytes in nonobese diabetic mice maps to diabetes susceptibility region Idd11. J Immunol 2005; 174:4821–7.
[41] Noorchashm H, Moore DJ, Lieu YK, Noorchashm N, Schlachterman A, Song HK, et al. Contribution of the innate immune system to autoimmune diabetes: a role for the CR1/CR2 complement receptors. Cell Immunol 1999;195:75–9.