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B cells as effectors and regulators of autoimmunity

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Abstract
A classic understanding of the interplay between B and T cell components of the immune system that drive autoimmunity, where B cells provide an effector function, is represented by systemic lupus erythematosus (SLE), an autoimmune condition characterised by the production of auto-antibodies. In SLE, CD4 + T cells provide cognate help to self-reactive B cells, which in turn produce pathogenic auto-antibodies (1). Thus, B cells act as effectors by producing auto-antibody aided by T cell help such that B and T cell interactions are unidirectional. However, this paradigm of B and T cell interactions is challenged by new clinical data demonstrating that B cell depletion is effective for T cell mediated autoimmune diseases including type I diabetes mellitus (T1D) (2), rheumatoid arthritis (3), and multiple sclerosis (4). These clinical data indicate a model whereby B cells can influence the developing autoimmune T cell response, and therefore act as effectors, in ways that extend beyond the production of autoantibody (5). In this review by largely focusing on type I diabetes we will develop a hypothesis that bi-directional B and T interactions control the course of autoimmunity.

Keywords: *B cells, autoimmune, type 1 diabetes, NOD mouse, T cells*

Abbreviations: *APRIL, a proliferation-inducing ligand; BAFF, B cell activating factor; BCMA, B cell maturation antigen; GAD, glutamic acid decarboxylase; MAdCAM, mucosal addressing cell adhesion molecule; MHC, Major Histocompatibility Complex molecules; NOD, non-obese diabetic mouse; NOD.μMT, B cell deficient NOD mice; SLE, systemic lupus erythematosus; T1D, type 1 diabetes; TNF, tumor necrosis factor*

Introduction

A classic understanding of the interplay between B and T cell components of the immune system that drive autoimmunity, where B cells provide an effector function, is represented by systemic lupus erythematosus (SLE), an autoimmune condition characterized by the production of auto-antibodies. In SLE, CD4 + T cells provide cognate help to self-reactive B cells, which in turn produce pathogenic auto-antibodies [1]. Thus, B cells act as effectors by producing auto-antibodies aided by T cell help such that B and T cell interactions are unidirectional.

However, this paradigm of B and T cell interactions is challenged by new clinical data demonstrating that B cell depletion is effective for T cell mediated autoimmune diseases including type I diabetes mellitus (T1D) [2], rheumatoid arthritis [3], and multiple sclerosis [4]. These clinical data indicate a model whereby B cells can influence the developing autoimmune T cell response, and therefore act as effectors, in ways that extend beyond the production of auto-antibody [5]. In this review by largely focusing on T1D we will develop a hypothesis that bi-directional B and T interactions control the course of autoimmunity.

Type I diabetes mellitus

T1D is an autoimmune disease marked by insulin deficiency and hyperglycemia [6]. The target of the autoimmune attack is the insulin producing pancreatic beta cell residing within the islet of Langerhans.

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Disease development indicates a failure of the immune system to maintain self-tolerance. Many lines of evidence support the concept that T cells play an important role in beta cell destruction in T1D. Lymphocytes including both CD4 + and CD8 + T cells that recognize tissue specific antigens are found within the lesions of T1D subjects [7–12] as indeed they are in animal models of T1D [10, 13, 14] such as the non-obese diabetic (NOD) mouse [15]. In man, progression to T1D is associated with certain MHC alleles [16], disease can be transferred by bone marrow transplantation [17, 18], and conversely, diabetes development can be slowed by treatment with immunosuppressive drugs that target T cells [19] [20]. Thus our current understanding of T1D is that T cells specific for beta cell antigens comprise an important class of effectors and are essential for diabetes pathogenesis.

B cell depletion and type I diabetes mellitus

Given the notion that T1D is considered a T cell dependent disease, it was of great interest that human subjects with T1D showed improved metabolic control when treated with a B cell depleting agent [2, 21]. The B cell depleting agent utilized, rituximab, targets the CD20 antigen on the cell surface of naïve and memory B cells resulting in B cell depletion through mechanisms including complement-mediated cytotoxicty [22]. In the T1D trial, newly diagnosed T1D subjects received infusions of rituximab on days 1, 8, 15, and 22 of the study. Patients treated with rituximab showed partially preserved beta-cell function at one year post treatment as evidenced by decrease in loss of C-peptide and less insulin requirements [2]. These data might support the notion that B cells are essential for diabetes to develop. However this conclusion needs to be tempered somewhat by the single report of a subject with hereditary B cell deficiency presenting with T1D [23], suggesting that diabetes can under some circumstances progress without B cells.

In trials separate to the T1D study, B cell depletion with Rituximab was shown to be effective for other T cell mediated diseases [5] including multiple sclerosis [4] and rheumatoid arthritis [3]. That human subjects with T1D showed improvement with B cell depletion demonstrates, and supports, the concept that B cells make salient contributions to the pathogenic process leading to T1D [24]. Given the important contribution of T cells as effectors of beta cell destruction in T1D [6], the clinical data also reveals the possibility that bi-directional B and T interactions play important roles in the course of autoimmune diseases characteristically considered to be T cell mediated in their aetiology.

Clinical evidence that B cells play a role in type I diabetes mellitus

Prior to the clinical trials with Rituximab, earlier data was suggestive of a role for B cells in the pathogenesis of T1D. B cells contribute to the mononuclear cell lesions [25] long known to be associated with T1D [7, 9]. Further to this, a well-characterized feature of T1D is the production of auto-antibodies [25, 26]. In T1D subjects auto-antibodies can be found that target islet proteins including insulin, glutamic acid decarboxylase (GAD) and the tyrosine phosphatase-like molecules IA-2/IA-2β [27]. Further, the presence of anti-islet autoantibodies can be utilized to predict risk [28, 29], which suggests that B cell activation is a component of diabetes pathogenesis.

Animal models reveal a role for B cells in type I diabetes mellitus

Studies in the NOD mouse, an important animal model of diabetes [15], support a role for B cells in diabetes pathogenesis. As has been found in human cases of T1D [25], B cells infiltrate the NOD pancreas during the early stages of insulitis, where they can comprise as much as 60% of the mononuclear infiltrate [30–32]. NOD B cells remain a constant component of the pancreatic infiltrate once formed [33,34], providing evidence that B cells could be contributing to the autoimmune phenotype at multiple stages in the disease process.

Serreze and colleagues, as well as Akashi *et al.*, introduced the μMT mutation onto the NOD background [35,36]. μMT mice have no mature B cells in the periphery due to the introduction of a functionally inactivated immunoglobulin μ heavy chain gene, deleting IgM and resulting in B cell developmental arrest in the bone marrow [37]. The B cell deficient NOD (NOD.μMT) mice strains are resistant to the development of diabetes [35,36]. Of interest, NOD.μMT mice still exhibited an early insulitic lesion [36,38,39]. These observations indicate that B cells are more important for the progression to hyperglycemia, though it was originally suggested that B cells were required for the initiation of the primary autoimmune response [35]. Subsequently, it was demonstrated that reconstitution of NOD.μMT mice with B cells from NOD donors could recapitulate diabetes development [40]. In separate studies, two groups demonstrated that inhibition of B cell development by either administration of anti-mouse Ig [41] or anti-IgM antibody [42] abrogated disease development in NOD mice.

Effect of manipulating B cells in adult NOD mice

More recently, a series of studies to target B cells in otherwise B cell sufficient adult NOD mice has

demonstrated a key role for B cells in diabetes development [21]. B cell reduction was achieved via monoclonal antibodies that directly target the B cell surface proteins CD20 [43,44] or CD22 [45]; or, by preventing B cell access to trophic support provided by the B cell activating factor (BAFF) system via monoclonal antibody mediated blockade of BAFF [46] or administration of a B cell maturation protein (BCMA)-receptor fusion protein (BCMA-Fc) [47], that is capable of blocking both BAFF and a proliferation-inducing ligand (APRIL) [48]. These studies all found that diabetes was prevented when B cell depletion was provided prior to the onset of clinical disease, and in some cases disease progression could be reversed when B cell depletion was provided after clinical disease onset.

Collectively, these studies demonstrate a necessary role for B cells in diabetes pathogenesis in the NOD model. It is worthwhile to note that the very definitive results from the above-mentioned mouse studies contrast with the human data, where B cell depletion showed efficacy but did not provide complete protection [2], and indeed some human data suggests B cells are redundant [23], if even under rare circumstances. These differences may indicate the inability of the NOD mouse model to reflect the true heterogeneity of the human disease.

B cells as effectors: production of autoantibody

The presence of circulating auto-antibodies in human subjects with T1D specific for islet-derived antigens raises the possibility of a pathogenic role. This is supported somewhat by the observation that in human T1D, pancreatic islets exhibit antibody deposits *in situ* [25]. To date, and in contrast to human T1D, only insulin has been identified as a specific target of auto-antibodies in the NOD model, although auto-antibodies that nonspecifically bind to GAD and IA-2 are present [49]. Auto-antibodies could play a number of different roles in diabetes pathogenesis, such as inducing beta cell destruction by stimulating antibody-dependent cell-mediated lysis (ADCC) of target cells [25] or aid antigen capture and uptake by antigen presenting cells [50–52].

Infusion of immunoglobulin from diabetic NOD mice into B cell deficient NOD.μMT mice did not recapitulate diabetes nor cause islet damage suggesting that antibodies may not be a dominant effector of beta cell destruction [39,40]. Other studies examining the role of auto-antibodies in diabetes pathogenesis found that maternally transmitted auto-antibodies were required for T1D susceptibility in the progeny of female NOD mice [53], though insulin-specific auto-antibodies did not mediate this effect [54].

This suggested that auto-antibodies that cross the placental boundary or auto-antibodies transferred during lactation could play a role in priming diabetes development. However, in human studies examining whether fetal exposure to islet auto-antibodies modified the risk of T1D did not support these NOD mouse data [55]. Thus despite their predictive value [28,29], and some anecdotal evidence to suggest a pathogenic role [25] the significance of auto-antibodies in human T1D remain uncertain. These data contrast T1D with autoimmune conditions like multiple sclerosis, where a direct pathogenic role for auto-antibodies has been more clearly demonstrated [56,57].

B cells as effectors: an antibody independent role

In an effort to tease out the role of auto-antibody in autoimmune diabetes, Wong and colleagues generated transgenic mIg.NOD mice in which all B cells express a non-secreted form of IgM on the cell surface [39]. Compared to B cell deficient NOD mice, these mIg.NOD mice developed insulitis and diabetes suggesting that auto-antibody production is not the essential contribution of B cells to diabetes development [39]. Another relevant model that illuminates the role of B cells, beyond auto-antibody production, is the TNFα-transgenic NOD mouse [58,59]. TNFα-transgenic NOD mice develop an accelerated form of diabetes, but when introgressed onto the B cell deficient NOD.μMT background, results in significantly delayed diabetes [60], similar to NOD B cell deficient mice [35]. Reintroduction of B cells incapable of secreting immunoglobulin into TNFα-transgenic NOD mice was sufficient to restore diabetes development [60]. Taken together, these findings indicate that the antibody-secreting function of B cells is unlikely to be the dominant role by which B cells contribute to the development of diabetes in NOD mice.

B cells are required to generate productive CD4 + T cell responses

The animal studies highlighted here all point to an antibody-independent mechanism by which B cells modulate diabetes development. One possible mechanism by which B cells can modulate diabetes development is by providing cognate help or trophic support to the nascent self-reactive T cell immune response. Indeed, in the NOD model a number of studies point to B cells as important antigen presenting cells. Falcone and colleagues showed that T cells from B cell deficient NOD.μMT mice did not proliferate in response to the self-peptide GAD65 as compared to T cells from B cell sufficient NOD mice [61]. In parallel studies, it was demonstrated that T cells from NOD mice showed stronger proliferative responses *in vitro* to B cells rather than to B cell deficient antigen presenting cells [40]. Moreover,

T cells from diabetes-resistant NOD.μMT mice failed to respond to GAD65, whether it was presented by B cells or non-B cell antigen presenting cells [40].

Later studies demonstrated an absolute requirement for B and T cell cognate interactions for the activation of self-reactive CD4 + T cells [62]. When B cell deficient NOD.μMT mice were reconstituted with splenic B cells carrying the NOD susceptibility MHC class II haplotype, IA^{g7}, diabetes developed [62]. However, when NOD.μMT mice were reconstituted with MHC class II deficient B cells, diabetes did not develop [62]. Thus, despite the presence of MHC class II on all non-B cell antigen presenting cells, the singular absence of B cell surface MHC class II prevented diabetes development. Indeed, self-reactive CD4 + T cells are particularly attuned to B cell surface MHC class II as T cells transferred into NOD mice reconstituted with MHC class II deficient B cells do not proliferate [62].

Further, the proliferation of BDC2.5 CD4 + T cells, a self-reactive CD4 + T cell line cloned from NOD mice [63], was severely impaired when transferred into B cell deficient NOD mice, as compared to the proliferative response observed for B cell sufficient NOD mice [38]. Importantly, purified B cells were shown to be able to internalize, process and present intact insulin, a prominent islet autoantigen [64], to self-reactive NOD T cells [34,65]. This capacity to present insulin peptides to self-reactive CD4 + T cells resides in both the follicular and marginal zone B cell compartments [34], the two mature splenic B cell subsets [66]. These animal studies demonstrate that B cells can dictate the CD4 + T cell autoimmune response, indicating the importance of bi-directional B and T cell interactions in the development of autoimmunity.

B cells and epitope spreading

B cell-derived signals may be particularly important for epitope spreading and the subsequent maturation of the self-reactive CD4 + T cell immune response. Insulin and GAD proteins, produced by the pancreatic beta cell, are significant auto-antigens [10,67] and a target of the self-reactive T cell repertoire [13,61]. It is possible that insulin, amongst others, constitutes a primary antigenic determinant [68,69] driving the initial T cell attack, which subsequently spreads to other epitopes and antigens as disease progresses [68–71]. The process of epitope spreading may be particularly sensitive to loss of B cell derived signals [61]. In other studies mapping T cell responses to defined auto-antigens in the NOD model, GAD was identified as one primary T cell target [72,73]. The anti-GAD response subsequently spreads to other antigens including insulin [73]. In the absence of B cells, the anti-GAD T cell response did not spread to additional antigens correlating with a failure to progress to fulminate diabetes [71].

Anatomical locations for B-T cell interactions in type I diabetes mellitus

The pancreatic lymph node is one potential cellular location where the spreading of the self-reactive T cell response can occur. Self-reactive CD4 + T cells engage antigen presenting cells in the pancreatic lymph node [74,75]. B cells expressing a high density of co-stimulatory molecules accumulate in the pancreatic lymph node of NOD mice with time [34], and this B cell presence correlates with an increased pool of activated self-reactive CD4 + T cells [34].

Depletion of B cells in NOD mice prior to the onset of clinical disease, but after the initial priming of the self-reactive T cell response and the advent of insulitis, prevents the onset of diabetes [43–47]. B cell depletion mediated by blocking BAFF with the BCMA-Fc fusion protein [47], or with monocloncal antibodies targeting CD20 [76], reduced the frequency of self-reactive CD4 + T cells within the pancreatic lymph node exhibiting an activated phenotype [47,76]. These data highlight the pancreatic lymph node as an important site for B and T cell interactions; further studies could focus on this anatomical location with regards to epitope spreading.

B cells as the preferred antigen presenting cell for self-reactive CD4 + T cells

It is interesting that self-reactive CD4 + T cells appear to be particularly dependent upon cognate interactions with B cells in the context of autoimmunity, given that antigen presentation is characteristically considered to be a function dominated by dendritic cells [77]. Analysis of T cell responses in the context of B cell depletion showed that T cells are able to respond normally to TCR ligation *in vitro* and proliferate in response to a nominal antigen *in vivo* [76]. Further, T cells are able to mount some effector responses including allograft rejection in B cell deficient environments [78,79]. Analysis of T cell populations after B cell depletion shows that B cells do not control the homeostatic maintenance of CD4 + T cells in the periphery [47;76]. Rather, CD4 + T cells appear particularly dependent for B cell help in the context of autoimmune responses [47,76]. This dependency may relate to defective antigen presenting activity present in other cellular compartments including the macrophages and dendritic cell subsets of NOD mice [80–82] a characteristic also noted for antigen presenting cells isolated from human subjects with T1D [83–85].

By contrast, self-reactive CD4 + T cells are particularly responsive to co-stimulation by NOD B cells [38,86] which are enriched for the expression of

MHC class II, CD80 and CD86 [34;65,87]. The NOD B cell pool also harbours an increased frequency of self-reactive clonotypes [24] stemming from defects in B cell tolerance and negative selection [88–91]. In addition, B cells isolated from human subjects with T1D show evidence of reduced receptor editing, an important mechanism for tolerizing autoreactive B cells [92]. These features, perhaps coupled with the given capacity of B cells to provoke effector T cell responses when antigen supply is limiting [76; 93; 94] may result in B cells functionally dominating as a preferred antigen presenting cell in the context of T1D.

B cells and self-reactive CD8 + T cells

In addition to aiding the self-reactive CD4 + T cell response via presenting auto-antigen, there is the possibility that B cells may be necessary for the full activation of self-reactive CD8 + T cells [95]. When TNFα-transgenic NOD mice [60] were crossed to B cell deficient NOD.μMT mice diabetes was significantly delayed compared to their B cell sufficient counterparts [60].

Of note, diabetes development in TNFα-transgenic NOD mice is CD8 + T cell dependent. The requirement for B cell help was shown to be antibody independent as re-introduction of B cells incapable of secreting immunoglobulin restored diabetes development [60]. B cell deficiency resulted in apoptosis of intra-islet self-reactive CD8 + T cells [60]. One possibility is that B cells provided trophic support for the maturation and expansion of self-reactive CD8 + T cells [96] via the production of cytokines [97].

In another study, NOD mice were B cell depleted by administration of BCMA-Fc to block the action of BAFF and APRIL [47]. The BCMA-Fc treated mice showed complete protection from diabetes [47]. Protection was associated with a decrease in the circulating levels of the cytokine IL-15, required for CD8 + T cell maturation and effector function, as well as IL-7 and IL-17 [47]. Further, BCMA-Fc-treated mice exhibited a reduced frequency of CD8 + T cells expressing CD40L in the pancreatic lymph node [47]; CD40L has been suggested to be a marker of activated self-reactive effector T cells [98]. These data suggest that B cell depletion prevented the access to critical cytokines needed for development of the effector CD8 + T cell response. One possibility is that by preventing B-CD4 + T cell interactions, elaboration of cytokines by CD4 + T cells is reduced.

B cell production of cytokines that regulate auto-immunity

As well as cognate B-T cell interactions, B cells can secrete soluble factors to support the autoimmune response. Some data suggests that B cells can be functionally sub-divided on the basis of their profile of secreted cytokines [97]. As one example, B cells primed by T cells and antigen in the presence of Th1-type cytokines will produce IFN-gamma, the p40 subunit of IL-12 but also TNF [97]. In the NOD model the entry of self-reactive T cells into the pancreas is a critical development in the progression of autoimmune diabetes. A role for B cell secreted cytokines in T1D has been demonstrated in mice co-expressing the OVA-specific TCR transgene, DO11.10, and the RIP-mOVA transgene [99]. These mice develop diabetes, however in DO11.10 RIP-mOVA mice lacking B cells T cells are primed in the pancreatic lymph node but fail to enter the pancreas and diabetes does not develop [99]. However, when the B cell deficient DO11.10-RIP-mOVA mice were reconstituted with B1 cells, T cells regained entry into the pancreas [99].

The mechanism by which B1 cells facilitated T cell migration was to localise to the pancreas and elaborate TNF, which in turn induced expression of adhesion molecules on the pancreatic vasculature, specifically, VCAM-1 and MAdCAM-1 [99]. In another study administration of antibodies to MAdCAM-1 inhibited $> 90\%$ of B cell migration into the pancreatic lymph node [100], the site of T cell activation. Further, depleting B1 cells prevents diabetes in NOD mice [101]. Thus B1 cells are emerging as a new player in the pathogenesis of T1D through their ability to elaborate cytokines.

B cells as effectors that dampen auto-immunity

Much of the evidence we have reviewed so far supports the concept that B cells can act as drivers of the self-reactive T cell response. However, there are some data that suggests B cells can act as negative regulators, and suppress the auto-immune response in T1D.

In support of this possibility, one study showed that transfer of LPS-activated NOD B cells to NOD mice reduced diabetes incidence from 90% in control groups to $< 20\%$ [102]. The LPS-activated B cells expressed Fas ligand and secreted TGF-beta [102], two immunoregulatory molecules with known protective effects in diabetes models [103,104]. The LPS-activated B cells were able to induce apoptosis of diabetogenic T cells as well as mononuclear cells and impaired the activity of antigen presenting cells [102]. These data support the concept B-T interactions can have a regulatory impact upon autoimmunity.

In another study it was found that BCR-stimulated NOD B cells delayed and prevented diabetes when transferred into pre-diabetic young NOD mice, whereas treatment after the insulitis phase delayed the onset, but did not reduce, T1D [105]. The protective effect was dependent upon production of

IL-10, as transfer of BCR-stimulated NOD B cells from NOD.IL-$10^{-/-}$ mice did not confer protection from T1D [105]. The transferred B cells directly reduced T cell activation, decreased islet inflammation, and caused the production of cytokines more typical of Th2 immunity exemplified by increased IL-4 and IL-10 production.

B cell regulatory populations in NOD mice?

These data indicate that B cells can express soluble factors to mitigate, or alter the ongoing diabetes pathogenesis. Emerging data from other models indicate that B cells that can directly suppress inflammation and dampen T cell immune responses can be engendered under conditions of chronic inflammation, such as colitis [106]. In some cases these so named regulatory B cells [107] have been identified as B cells expressing high levels of CD1d and producing IL-10 [108].

As well as playing a role in the regulation of gut inflammation, these B regulatory cells can modulate autoimmunity through the production of IL-10 as shown in experimental autoimmune encephalomyelitis, a mouse model of multiple sclerosis [109,110]. It is of interest that these cells are engendered under conditions of chronic inflammation, and express CD1d [107]. NOD mice exhibit prolonged pancreatic insulitis and also harbour an expanded population of splenic marginal zone B cells [34,111–113]. A feature of marginal zone B cells is their unique location, positioned at the marginal sinus, but also their high surface expression of CD1d [114].

Of interest, NOD mice also exhibit an accumulation of CD1d high expressing cells in the pancreas and pancreatic lymph node [34]. The surface phenotype of these CD1d B cells is reminiscent of splenic marginal zone B cells [34]; however, it would be of interest to explore further whether the pancreatic NOD CD1d high B cells [34] express features of regulatory B cells and are acting to suppress or drive autoimmune diabetes.

B cells and antigen specific tolerance

The suppressive activity of B cells can be harnessed to generate antigen specific tolerance in autoimmunity. In an effort to achieve antigen specific regulation, a retroviral mediated gene expression approach was utilised to express GAD in B cells [115]. Administration of GAD-IgG retrovirally transduced B cells stopped diabetes development in NOD mice [115]. Fas ligand was found to be important for generating this protective effect as when donor B cells were derived from Fas ligand-negative *gld* mice protection from diabetes was not achieved [115]. Taking a different route to generate antigen specific responses, B cells were transduced with a TAT-fusion protein containing insulin called TAT-B9-23 [116].

The insulin specific TAT-B9-23-B cells also delayed the onset of diabetes when transferred into NOD mice [116]. These results show that B-T cell interactions can be harnessed to generate antigen specific tolerance. In man, T1D can be ameliorated by the administration of systemic immunosuppression [20], agents more often used in the context of organ transplantation. However, these approaches are marred by the problems associated with a compromised immune system and increased risk of organ damage [117]. Thus, the development of antigen specific therapies targeting autoimmune activity while sparing normal immune function is desirable.

B cells can engender Foxp3 + regulatory T cells to dampen autoimmunity

One of the mechanisms by which B cells can restore immune tolerance is by engendering Foxp3 + regulatory T cells. In a follow-up study to earlier work described above [115], it was shown that the diabetes protective effect of GAD-IgG retrovirally transduced B cells was dependent upon the induction of CD4 + Foxp3 + Treg cells [118]. The generation of CD4 + Foxp3 + Treg cells required both TGF-beta or IFN-gamma, as blocking these factors prevented the conversion of CD4 + T cell precursors into CD4 + Foxp3 + Treg cells [118].

It is interesting to consider the role of inflammation in framing the environment for inducing B cells that suppress autoimmune diabetes by engendering Foxp3 + regulatory T cells. In mice over expressing the B cell survival factor BAFF, a chronic inflammation ensues with the mice developing autoimmune like conditions [48,119]. Autoimmunity in BAFF-transgenic mice is dependent upon B cell hyperactivation and signals provided through the Toll like receptors [120]. Within this inflammatory environment BAFF-transgenic mice exhibit a ~3-fold increase in Foxp3 + regulatory T cells that suppress T cell mediated rejection of an islet allograft [78]. In the absence of B cells, the expansion of Foxp3 + regulatory T cells does not occur [78], suggestive of a link between autoimmunity and B cell dependent expansion of Foxp3 + regulatory T cells.

Chronic inflammation is also a critical environmental determinant necessary for the generation of IL-10 producing regulatory B cells [107]. It is possible that inflammatory activation of B cells is a key trigger for promoting a B cell phenotype that can engender regulatory T cells and suppress diabetes. In the case of antigen-specific tolerance induction driven by infusion of TAT-B9-23 expressing B cells [116] or GAD-IgG retrovirally transduced B cells [118] LPS was utilised to activate the B cells prior to their genetic manipulation. Whether Foxp3 + regulatory T cells

also play a role in the protective effect when B cells were stimulated with LPS was not determined [102,116,118].

The ability to engender regulatory T cells may be a B cell function not necessarily restricted to inflammatory activated B cells. In some studies it was shown that unstimulated B cells can interact with T cells to engender Foxp3 + T cells that show suppressive activity [121,122]. Of interest, these approaches can be used to generate human antigen specific regulatory T cells, furthermore antigen specificity was dictated by the interacting B cell [123] supporting the proof-of-concept approaches where auto-antigen-expressing NOD B cells showed efficacy against diabetes in the NOD model [115,116,118].

Concluding remarks

B cells play an essential role in immunity and in the pathophysiology of auto-immune disease through the production of immunoglobulin. T cell dependent B cell responses necessitate T cell help to support formation of productive antibody producing plasma cells [124]. This unilateral relationship of B and T cell interactions could be presumed to be most important for the development of autoimmunity. However it is clear from the many examples provided in human T1D, and from animal models of diabetes, that complex bi-directional cross talk stemming from the B to the T cell are also at play. Thus, B cells form a central nexus in the development of T1D, marking them as a highly desirable therapeutic target for T1D [21] but also other T cell-dependent autoimmune diseases [5].

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