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B lymphocytes — chief players and therapeutic targets in autoimmune diseases

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1. ABSTRACT

For some time, B cells have been considered as passive actors, exclusively depending on T cell conductors that provide them with instructions to engage in antibody secretion. With further investigation, however, it became evident that B cells can exert a number of antibody-independent functions, capturing and concentrating antigen for presentation, producing cytokines, influencing T cell and dendritic cell responses, contributing distinct functions during the immune response, affecting lymphoid tissue structures, and, even participating in tissue repair. Because of their multiples functions, B cells are currently recognized to play a key role in a variety of antibody-, and T cell-mediated autoimmune diseases, including lupus, rheumatoid arthritis, type-1 diabetes and multiple sclerosis. This recent insight led to novel immuno-intervention strategies that target B cells, with beneficial effects in patients. While such novel therapeutic bio-drugs are being introduced into the clinical arena, research intensifies in order to identify novel targets and strategies whose ultimate goal is to knock out specifically pathogenic B cells, and to amplify the numbers and the activity of cells endowed with regulatory functions.

2. INTRODUCTION

Autoimmune diseases continue to cause significant morbidity in affected persons. In the past few years, important progress was made in understanding their pathogenesis and the underlying molecular mechanisms. In addition, a number of emerging findings support the view that B cells play a chief role in their expression. As a result, new exciting therapeutic options have become available, and novel therapeutic targets are emerging.

3. MECHANISMS THAT CONTROL B CELL FATE

Mammalian B cell development originates primarily in the fetal liver, and continues in neonatal and, then, adult bone marrow (BM) throughout life. A number of investigations have led to a fair description of the patterns of gene expression during successive stages of B cell development. Targeted disruption of genes encoding transcription factors, immunoglobulin (Ig) heavy (H)- and light (L)-chains, and a variety of B cell receptor (BcR)-associated signaling molecules have revealed the importance of several pathways in B cell development

nodes. In addition, the extracellular matrix and stromal cell components of the BM microenvironment, together with interleukins, chemokines, interferons, and colony-stimulating factors, play a crucial role in regulating survival, proliferation, differentiation and death in the B cell lineage (1).

In order to prevent aggressive autoreactivity, B cells must undergo negative selection at multiple stages. In the BM, clonal deletion, clonal anergy and receptor editing prevent the emergence and/or the persistence of potentially threatening autoreactive B cells. Whereas deletion consists in physical elimination of the cells, anergy leads to a state of functional silencing. Anergic B cells are characterized by down-modulation of surface IgM, decreased responsiveness to BcR stimulation, and a shortened lifespan (2-5). Their BcR signaling is partially uncoupled and the quality of the transmitted signal is altered, with impairment of NF-κB and c-Jun N-terminal kinase activation, and continued extracellular signal-regulated kinase signaling (6). When they interact with activated T cells, anergic B cells are sensitive to Fas-mediated killing (7). Receptor editing, by contrast, is a mechanism that does not lead to cell death. It enables autoreactive B cells to modify their BcR specificity and to extinguish their autoreactivity (8, 9).

In the periphery, B cell development leads to two distinct mature subsets that differ significantly in their localization, cell surface phenotype, and functional properties. In the splenic marginal zone, reside B cells —called MZ— that are IgM^{high}, IgD^{low}, $CD21/35^{high}$, $CD23^{low}$, and express high levels of the non-classical MHC molecule CD1d. In contrast, the primary follicle is populated with B cells —called FO— that are $IgM^{low\text{-}high}$, IgD^{high}, $CD21/35^{int}$, $CD23^{high}$, and that express lower levels of CD1d (1) MZ B cells are also larger than FO B cells and display higher levels of class II MHC and the co-stimulatory molecules B7.1. (CD80) and B7.2 (CD86). The *in vitro* responses of MZ B cells to BcR ligation, T cell-independent (LPS), and T cell-derived (CD40L + IL-4) stimuli are greater than those of FO B cells. Furthermore, MZ B cells activated either *in vitro* or *in vivo* are more effective than equivalently activated FO B cells at co-stimulating naive $CD4^+$ T cells (10). Several pieces of evidence indicate that MZ B cells play a particularly important role in mediating responses to thymus-independent type 2 Ags *in vivo* and that FO B cells have evolved to specialize in T cell-dependent responses. Consistently, the MZ and FO B cell subsets show distinctive sensitivities to molecules produced by infectious agents to subvert immune functions (11, 12).

In order to participate in the humoral branch of the immune response, B cells differentiate in the peripheral lymphoid system, upon antigen (Ag) exposure, to memory B cells and highly proliferating, short-lived antibody (Ab) secreting plasma blasts. After systemic infection or vaccination, plasma blasts appear in the blood, secreting large mounts of specific antibodies and migrating from the lymphoid organs to the BM to become fully mature, non-dividing, long-lived Ab-secreting plasma cells (13). Their survival in the BM for several months to years is supported by specific survival niches, such as the BM or inflamed tissues. By continuously releasing Abs, long-lived plasma cells impart humoral immunity. In autoimmune disease, they also represent a potential source of autoAbs (14, 15).

A number of studies disclosed that the affinity of Ag-experienced B cells within GCs influences their differentiation fate. For example, the overall intrinsic affinity of the BcR controls B cell fate and survival of an Ag-specific polyclonal population by determining the differentiation program that provides the host with persistent Ab protection (16). Additionally, the intrinsic BcR affinity of naive B cells regulates GC B cell differentiation and the subsequent development of short- or long-lived plasma cells. Such findings point towards the existence of a continuum of responses controlled, at least partially, by BcR affinity (16). At one end of the spectrum, low-affinity BcR engagement results in GC formation, somatic mutation, and the generation of B cell memory and long-lived plasma cells. At the other, high-affinity interactions terminate GC formation and the generation of B cell memory and long-lived plasma cells. However, the molecular details of how BcR affinity controls B cell fate decisions are not completely understood. Among the specific transcriptional regulators involved in the differentiation of GC B cells to plasma cells, two genes, *Blimp-1* and *XBP-1*, play a critical role in PC differentiation by repressing genes required for GC function, including *Bcl-6* and *Pax5*.

4. B CELLS CONTRIBUTE MULTIPLE FUNCTIONS DURING THE ADAPTIVE IMMUNE RESPONSE

For some time, B cells have been considered as passive actors, exclusively depending on T cell conductors that provide them with instructions to engage in Ig secretion. However, in recent years, a number of studies have demonstrated that B cells can exert a number of Ab-independent functions. For example, B cells have Ag-specific receptors, allowing them to concentrate Ag and to present it much more efficiently to T cells than other Ag-presenting cells (APCs) (17). In particular, they preferentially capture polyvalent Ags that can aggregate the BcR, initiate signaling cascades, and elicit a coordinated series of cellular responses to even low-affinity Ags (18). Since only B cells with Ag-specific BcRs efficiently take up Ag, and because the frequency of Ag-specific B cells is too low for them to take part significantly in T cell priming, it is generally accepted that naive $CD4^+$ T cells are primed in association with dendritic cells (DC) and only interact subsequently with B cells. However, B cells were demonstrated to act as Ag presenters to the very early stages of the response (19). Thus, B cells can provide an essential Ag presentation capacity over that provided by DC, and their role may be crucial when Ag levels are very low.

Besides capturing and concentrating Ag for presentation, B cells can alter DC function and homeostasis (20) and influence T cells in a number of other ways. Activated B cells express high levels of class II MHC

molecules, B7, CD40, and other second signal-associated molecules (17). One consequence of CD40 ligation on B cells is the up-regulation of OX40L, a critical regulator of $CD4^+$ T cell responses during and after the *in vivo* expansion phase (21, 22).

In addition to providing co-stimulatory signals, B cells promote naïve $CD4^+$ T cell differentiation into Th1 or Th2 subsets, may influence regulatory T cell numbers and functions (23), and secrete effector cytokines, such as IL-10, thus potently contributing to the immune response. In humans, the mode of stimulation critically determines the profile of cytokine secretion by B cells, suggesting that, depending on the context of their activation, these cells have the potential to contribute distinct functions during the immune response *in vivo*. For example, newly developing naive B cells mainly produce the anti-inflammatory cytokine IL-10, and mature memory B cells essentially secrete the pro-inflammatory cytokines lymphotoxin and TNF-α (24). From these polarized cytokine productions one might conclude that memory B cells actively contribute to the efficiency of a memory immune response by elaborating TNF- and lymphotoxin —promoters of local follicular dendritic cell activation, GC formation, and lymphoneogenesis; and naive B cells produce IL-10 to sense potentially threatening immune responses, and perhaps to maintain tolerance to self.

5. B CELLS AND INNATE IMMUNITY

It is generally thought that the B cell compartment is solely a contributor to the adaptive branch of immune defense, with mature re-circulating FO B cells having evolved to generate a huge repertoire able to mount T cell-dependent B cell responses with high-affinity and long-term memory. However, accumulating evidence indicates that B cells play an important role in linking the innate and adaptive branches of immunity (25). B cells express Toll-like receptors, whose expression is augmented following engagement of the BcR or the co-stimulatory molecule CD40, or by stimulation with *S. aureus* Cowan I bacteria or unmethylated CpG DNA. They also produce low-affinity polyreactive Igs that can bind various ligands, a possible consequence of positive selection by self-Ags. Two B cell subpopulations, B-1 and MZ, with innate-like functions are present in the peripheral lymphocyte compartment. Because of their anatomical location, they are the first cell subsets to encounter Ags acquired through the gut/peritoneum and the blood stream. Secreting natural antibodies, and responding rapidly and vigorously to stimulation, these two B cell subsets have evolved to provide a first line of defense against pathogens. With their additional properties to produce factors that can directly mediate microbial destruction and to express Toll-like receptors, B cells provide an important link between the innate and adaptive branches of the immune system.

Strikingly, studies of mice rendered deficient in B cells uncovered functions that could not be predicted. It was, for example, demonstrated that B lymphocytes can affect lymphoid tissue structure (26) and can even participate in tissue repair in the liver (27).

6. B CELLS, CHIEF PLAYERS IN AUTOANTIBODY-MEDIATED DISEASES

Because of their multiples functions within the immune system, B cells play a key role in a variety of autoAb-mediated diseases. They can process and present self-Ags to naive T cells (28), and, under certain conditions, they can activate memory T cells (29). For example, the expansion of activated and memory T cells in MRL-*lpr/lpr* mice is highly dependent on B cells (30). Importantly, B cells can mediate disease in an Ig-independent manner. For example, MRL-*lpr/lpr* mice with B cells expressing surface Ig, but no circulating Abs, developed nephritis characterized by cellular infiltration within the kidney (31). This indicates that, in the absence of serum autoAbs, B cells can exert a pathogenic role, probably because they serve as APC for autoreactive T cells and promote the breakdown of peripheral T cell tolerance (32), and/or because they can contribute directly to local inflammation. There is therefore an Ab-independent mechanism for tissue injury, and it is likely that there is a concerted action of B and T cells to mediate a variety of pathogenic outcomes in autoimmune disease.

Even within the thymus, B cells may play an important role in the elimination of autoreactive thymocytes (33). In MRL-*lpr/lpr* mice lacking B cells, activated and memory T cells are markedly reduced, and nephritis is attenuated, indicating that B cells are essential in promoting systemic autoimmunity in this mouse model (31, 34). In the absence of B cells, activated and memory T cells accumulation, nephritis and vasculitis are inhibited. Studies of SLE susceptibility loci suggest that expression of the *Sle1* gene in B cells is essential for the development of autoimmunity in mice (35).

In addition to their potential contribution to T cell expansion, B cells also promote CD4 T cell differentiation (22). For example, Ag-specific B cells can drive IL-4 production *in vitro* and *in vivo* (36), indicating that B cells promote Th2 responses. That B cells are key players in T cell development is further supported by a study of mice with B cell-specific Fas deficiency (37). The mice developed marked splenomegaly and lymphadenopathy, as well as elevated anti-nuclear Abs, and the cells expanded in these mice were mainly T cells, suggesting that Fas on B cells is somehow necessary for restraining the accumulation of Fas-intact T cells. However, Fas deficiency in T cell or DC lineages is also sufficient to break self-tolerance (37). Nevertheless, these results extend earlier findings in which B cells were found to be required for the accumulation of memory T cells in the context of global Fas deficiency (30).

It has been proposed that sequestration of autoreactive B cells in the marginal zone and in the peritoneal cavity is essential for the maintenance of self-tolerance (38). Since B-1 cells are able to home to ectopic target organs in aged (NZB x NZW)F_1 (39), it is possible that the location and function of the MZ and B-1 cell subpopulations are key determinants in the emergence of autoreactivity. Their expansion in pre-clinical young

autoimmune mice suggests that they may participate in tissue damage.

Another line of evidence in support of the key role of B cells is that tertiary lymphoid structures develop in the inflammatory tissues of both patients and experimental animals with autoimmune diseases, including rheumatoid arthritis (RA), multiple sclerosis (MS), myasthenia gravis, Sjörgen's syndrome, autoimmune thyroiditis, and autoimmune gastritis (40-45). In type-1 diabetes (T1D), for example, ectopic lymphoid structures form in inflamed islets of prediabetic NOD mice, with a microarchitecture consisting of B cell follicles surrounding T cell zones (46, 47). These tertiary structures likely provide a site where somatic evolution of selected B lymphocytes diversifies the autoimmune attack and promotes disease progression, suggesting a unique function for these ectopic lymphoid tissues in autoimmune disease.

7. THE ROLE OF B CELLS IN T CELL-MEDIATED AUTOIMMUNE DISEASES

T1D in humans and experimental animals results from T cell-mediated autoimmune destruction of insulin-secreting pancreatic β cells. In the NOD mouse model, the central role of T cells was demonstrated by the ability of T cells to transfer disease and the protection afforded by immunotherapies targeting T cells (48). B lymphocytes are among the earliest cells to infiltrate the pancreatic islets (49), and their maternal transmission appears to have an early diabetogenic role in NOD mice (50). Yet, even though autoAbs are useful predictors of diabetes development in prediabetic individuals, the presence of B lymphocytes initially was thought to be secondary to T cell activation. With further study, an important role for B cells in T1D development was discovered in NOD mice rendered deficient in this lymphocyte subset (51, 52). Currently, it is recognized that B cells are required for disease induction and that they are likely to exert a number of roles in pathogenesis (52, 53). During T1D development, B lymphocytes migrate to the pancreatic islets, but their exact role remains poorly understood. At present, few studies have analyzed the nature of B cells that infiltrate the islets. In NOD mice, it appears that BcR-stimulated B cells that infiltrate pancreatic islets are not $CD5^+$ B-1 cells (54), lymphocytes that may accumulate in sites of inflammation and exacerbate disease in lupus-prone mice (55). Although often divergent, the results obtained in NOD mice suggest that islet-infiltrating B lymphocytes play a crucial role in T1D (56, 57) The importance of B cells is further supported by the dramatic reduction in insulitis and diabetes incidence following B cell depletion from birth using Abs or in NOD mice genetically deficient in B cells.

Naturally, B cells can play multiple roles in T1D. In NOD mice, they act as APC, with a preferential ability to expand autoreactive $CD4^+$ T cell responses (2, 3). Specifically, they are endowed with the ability to specifically capture, through their BcR, β islet cell autoAgs for subsequent MHC class II-mediated presentation (4). Although the production of autoAbs is not absolutely necessary for diabetes to occur, they may facilitate or enhance T1D development. In two experimental models, B cells, but not other APCs, were found to be essential for the spreading of spontaneous Th1 autoimmunity as well as induced Th2 responses to β islet cell Ags (5).

Reminiscent of intrinsic B cell defects seen in SLE (58-60), several B cell alterations were reported in T1D. Compared with non-autoimmune mouse strains, B cells from NOD mice respond more robustly to several types of stimuli (56). Following BcR stimulation, they proliferate strongly with a relative resistance to activation-induced cell death, and exhibit a unique pattern of B7 expression, features that could contribute to pro-inflammatory responses in the islets (61, 62). This B cell hyper-responsiveness could be due to deregulations of signaling pathways, *e.g.* increased activation of the pro-inflammatory transcription factor NF-κB, or to increased expression of co-stimulatory molecules (56), differences that may lower the activation threshold of NOD B cells and enhance their capacity to respond to encounters with self-Ags in pro-inflammatory contexts.

In a transgenic model, immature B cells expressing a BcR specific for hen egg lysozyme (HEL) from NOD mice were found to have a significantly lower ability than those of B6 origin to be deleted or anergized following low-avidity Ig engagement of soluble HEL (63). Additionally, mechanisms that normally enable B cells to become anergic following low-avidity Ig engagement of soluble self-Ag are impaired in NOD mice by the activity of susceptibility genes within the *IDD5* and *IDD9/11* loci (64), further supporting the important role of pathogenic B cells in NOD mice. The impaired ability of immature NOD B cells to undergo tolerance upon Ig cross-linking is likely to result in increased numbers of self-reactive clones that could mature and act as APC for diabetogenic $CD4^+$ T cells.

Even in MS, a disease initially though to be exclusively T cell-mediated, several lines of evidence suggest that B cells play a pathogenic role. First, administration of autoAbs enhances disease severity in mice with experimental autoimmune encephalomyelitis (EAE), a model of MS (65). Second, severe MS relapses respond to plasmapheresis, suggesting that the humoral immune response contributes to central nervous system (CNS) damage (66). Third, oligoclonal Ig bands present within the cerebrospinal fluid (CSF) represent a hallmark of the disease, and intrathecal anti-myelin IgG and IgM responses seem to be associated with a more progressive disease course in MS patients (67-69). Fourth, clonally expanded populations of B cells carrying somatic mutations of Ig variable region genes have been detected in chronic lesions and in the CSF from MS patients, suggesting that a process of B cell affinity-maturation with ensuing production of potentially pathogenic autoAbs may occur inside the CNS. Sixth, several studies suggested that the CNS itself can provide a "germinal center like" environment. In mice, follicular B cell structures were identified in meninges of animals affected by EAE (70). In patients with secondary progressive MS, the CNS harbors

GC structures in the meninges of brain samples that contain severely demyelinated lesions (41, 70). Importantly, $CD38^{high}$, $CD77^{+}$, $Ki67^{+}$, $Bcl\text{-}2^{-}$ centroblasts, that reside specifically in GCs, are present in the CSF of MS patients, but not in their peripheral blood (71), and high levels of chemokines and cytokines known to support GC formation and function (CXCR3, lymphotoxin-α, CXCL12, and CXCL13) are also present in the CSF of MS patients, indicating that these molecules play a role in the organization of the immune response in the CNS (71). Furthermore, $CD27^{+}$ memory B cells were significantly enriched in the CSF versus peripheral blood from all patients investigated (71). In addition to this lymphoid neogenesis, there is an expansion of short-lived plasmablasts —that maintain CD19 expression— in the CSF of MS patients, and this expansion correlates with inflammation (72), identifying plasma blats as the main B cell effector in MS. Consistently, a study of post-mortem brain tissue samples from 29 secondary progressive MS cases found that the presence of follicles correlated with younger age of onset, irreversible disability and death, more pronounced demyelination, microglia activation, and loss of neurites in the cerebral cortex (73).

8. B CELLS THAT REGULATE AUTOIMMUNITY DEVELOPMENT

In addition to playing a pathogenic role in MS, a subset of B cells seem to convey a protective role, at least in experimental models of the disease. In EAE, B10.PL mice rendered deficient in B cells become unable to resolve disease symptoms, and exhibit a chronic disease course and a more severe form of EAE (74). In C57BL/6 mice receiving myelin oligodendrocyte glycoprotein, B cell production of IL-10 and expression of CD40 are required for recovery from EAE (75). In this MS model, BM chimeras, in which B cells —but not T cells or professional APCs— are deficient in IL-10 production, develop a severe non-remitting form of disease (75). That IL-10 produced by B cells plays a role in remission from EAE is supported by the demonstration that transfer of B cells from normal mice that had recovered from EAE could rescue the defect. Investigating the mechanisms of how B cells regulate the recovery from clinical disease in the B10.PL acute EAE model, a recent study demonstrated that mice lacking B cells, or those with B7-deficient B cells, were not only unable to recover from EAE, but also had a delay in the expression of IL-10 and the emergence of $Foxp3^{+}$ regulatory T cells (Treg) in the CNS during EAE (76). The requirement for B7 expression by B cells shows that this cell subset is an active participant in the immune regulatory mechanisms required for the resolution of inflammation in the CNS. The data also suggest that B cells regulate EAE clinical recovery by interacting with $CD4^{+}CD25^{+}$ Treg cells through a B7-dependent mechanism that causes the cells to migrate into the CNS, resulting in IL-10-mediated disease resolution.

This regulatory potential of B cells is not unique to this MS model. In NOD mice, transfusion of BcR-stimulated B cells can maintain long-term tolerance and protect the recipients (54). The transfused B cells can polarize T cell responses toward a Th2-like phenotype, with an increased secretion of IL-4 and IL-10 by $CD4^{+}$ spleen T cells (54), suggesting that IL-10 produced by B cells is important in the generation of a Th2 response by increasing IL-4 production by $CD4^{+}$ T cells.

These observations are reminiscent of reports of a regulatory role of B cells in other models of Th1-mediated autoimmune diseases. In collagen-induced arthritis, a model of RA, transfer of CD40-activated B cells obtained from arthritic mice to collagen-immunized mice inhibits disease development (77, 78), and the inhibitory effect was also attributed to increased IL-10 production by these B cells. Importantly, the subset of regulatory B cells that produce IL-10 and protect from EAE (75) and arthritis (77) is dependent on T cell help for IL-10 production.

Overall, the converging studies support the notion that IL-10 produced by B cells is important for the inhibition of Th1-mediated autoimmune diseases (54, 75, 77, 78). However, given that IL-10 is produced by several cell types, including IL-10-producing Tregs that can also protect autoimmune mice, polarization toward a Th2 response may be a necessary, but not sufficient, requirement for B cell-mediated protection from autoimmunity. Yet, other observations indicate that B cells can be engineered to down-regulate T cells via cell to cell contact and to confer protection against diabetes (79). In as much as B cells activated by either LPS or BcR stimulation produce IL-10 and survive in the host for 2-3 weeks after transfusion (56, 80), this recent insight may provide a novel potential avenue for disrupting the autoimmune process at the site of attack. One intriguing possibility is that administration of autologous IL-10-producing BcR-stimulated B cells to human subjects at high risk for autoimmunity may represent a novel therapeutic approach in Th1-mediated autoimmune diseases (54, 79). Further support to this view comes from the demonstration that activated B cells also express a membrane-bound form of TGF-β that can enhance tolerance induction (81).

9. B CELLS ENTERING THE CLINICAL ARENA

The observations summarized above indicate that B cells play a key role in several autoimmune diseases. They suggest that their elimination may be a highly beneficial therapeutic goal in a variety of disorders. This prediction is supported by the encouraging results of B cell depletion therapies in a variety of disorders. For example, rituximab, a humanized anti-CD20 monoclonal Ab that induces B cell depletion and is approved for B cell lymphoma therapy, has shown efficacy in treating autoimmune diseases such as RA, SLE, and immune-mediated thrombocytopenia (82). It is currently being assessed in T1D and in MS (83-85). Importantly, randomized controlled trials have shown clear benefits of rituximab in RA and in ongoing MS trials, two autoimmune diseases in which T and B cells are involved (82, 86). Efficacy in RA is of particular interest because of the prominent role T cells are thought to play in the pathogenesis.

An important feature of B cell depletion therapy is that it can be sustained for four years following a single cycle of treatment (82, 86). To understand how B cell depletion ameliorates autoimmune disease, a NOD mouse model expressing transgenic human CD20 was recently developed, allowing B cell depletion with anti-human CD20 Ab (87). Remarkably, a single round of B cell depletion could prevent or delay full-blown diabetes. B cells returned to pre-depletion levels within three months of the initiation of the treatment and were present at substantial levels within weeks, but the disease incidence lagged behind controls for months. The repopulated splenic B cells were enriched in type-2 transitional B cells, but MZ B cells were decreased. Importantly, even temporary removal of B cells after disease onset could reverse diabetes in over one-third of mice (87), and the resulting B cell depletion could also be detected long after B cells had returned. The reversal of hyperglycemia, together with the long-term effect could result from the combination of a short-term anti-inflammatory effect in the β islets, and a later emergence of regulatory cell population (s) that could convey long-term tolerance.

In the course of these studies (87), anti-CD20 treatment was found to induce a state of transferable immune tolerance, with generation of Treg and regulatory B cell populations that can control diabetes in an adoptive transfer model. Thus, cells from NOD mice expressing human CD20 that had received anti-CD20 treatment six to seven months earlier and that remained nondiabetic after full B cell reconstitution significantly delayed the induction of diabetes by spleen cells from NOD mice upon transfer into NOD/SCID recipients. In addition to Tregs, B cells could also mediate dominant suppression upon co-transfer with diabetogenic T cells.

While the studies suggest that B cells from anti-CD20-treated mice impart regulatory functions in B cell–T cell interactions (87), the mechanisms underlying their emergence remain to be resolved. One possibility is that T and B cells with regulatory functions influence their mutual activities (76). Alternatively, B cells that emerge following anti-CD20 treatment home to a non-inflammatory niche that favors acquisition of regulatory functions. Consistent with this view, studies of experimental arthritis identified regulatory B cells among immature B cell subsets (78), and SLE patients undergoing B cell depletion therapy show an expansion of transitional B cells during the B cell reconstitution phase (88). The observation that rituximab may favor the development of regulatory B cells in autoimmune diseases would imply that the activity of regulatory B cells should be monitored during anti-CD20 therapy. Reversibly, their elimination may represent an undesirable side effect in B cell depletion therapy. In line with this view, a complete depletion of CD20-positive mucosal B cells associated with a suppression of local IL-10 production were reported with disease exacerbation in a recent case report of human active long-standing ulcerative colitis (89).

In addition to B cell depletion therapy, other approaches targeting B cell longevity may be of significant therapeutic value in the treatment of autoimmune disease (90, 91). In a mouse model of MS, myelin oligodendrocyte glycoprotein (MOG)-induced EAE, a BAFF/APRIL antagonist (soluble BCMA-Fc) inhibited central nervous system inflammation and demyelination, such that it suppressed the onset and progression of clinical symptoms of EAE (92).

The observations that B cells with innate-like functions are important in autoimmunity suggest novel approaches in manipulating autoimmune diseases (25). It is tempting to suggest that targeting B-1 and MZ B cells in systemic autoimmune disorders would represent an efficient means of treatment. In (NZBxNZW) F_1 mice, for example, experimental reduction of B-1 cells delayed disease onset and reduced disease severity (93). It is of related interest that bacterial proteins were found to deplete the B-1 and MZ B cell subpopulations, potentially providing a novel immunointervention strategy in autoimmunity (11, 12). In the (NZW x NZB) F_1 mouse model, weekly intraperitoneal injections of the B cell superantigen protein A from *Staphylococcus aureus* delayed the progression of serum anti-DNA IgG and reduced proteinuria early in young female (NZB x NZW) F_1 mice (55). It also induced a specific depression in the numbers of peritoneal B-1 cells, as compared to mice treated with a control protein.

As novel therapeutic bio-drugs are being introduced into the clinical arena, research is intensifying in order to identify novel immunointervention targets and strategies whose ultimate goal is to knock out pathogenic B cells, and to amplify the numbers and the activity of cells endowed with regulatory functions.

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