Nephro-Urol Mon. 2012;4(1):336-339. DOI: 10.5812/kowsar.22517006.1486
Nephro-Urology Monthly
Journal home page: www.NUmonthly.com

Role of B Cells in Immune Tolerance

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ARTICLE INFO

Article type:
Review Article

Article history:
Received: 28 May 2011
Revised: 17 Jun 2011
Accepted: 29 Jun 2011

Keywords:
B-lymphocytes
Immune Tolerance
Transplantation

ABSTRACT

B cells are well known for their roles in antibody production, antigen presentation, modeling of the spleen architecture, and Th1/Th2 polarization of T cells. There is increasing evidence that some specific strains of B cells can also act as negative regulators and affect the development of graft tolerance. In certain experimental and clinical models, B-cell depletion has produced a time-dependent negative effect on the course of graft tolerance. In this article, we have discussed the implications of recent research on B-cell depletion therapy in transplantation.

Implication for health policy/practice/research/medical education:
The daul nature of B cells in either promoting or impairing the tolerance should be considered when using B- Cell -depleting immunsuppressive regimens.

Please cite this paper as:
Ardalan M. Role of B Cells in Immune Tolerance. *Nephro-Urol Mon.* 2012;**4**(1);336-9. DOI: 10.5812/kowsar. 22517006.1486

1. Introduction

B cells in their premature state exit the bone marrow and continue their maturation in the periphery. At their transitional stage, they home to the marginal zone of the spleen (marginal zone B cells). However, the majority of these cells continue to patrol the marginal areas of the spleen and lymph node until they encounter antigens. On encountering antigens, the B cells form germinal centers and undergo affinity maturation to produce antibodies specific to the encountered antigen. Autoreactive B cells are eliminated by clonal deletion and receptor editing. B cell clonal selection in the germinal center produces antibodies with higher antigen affinity and helps prevent antibody cross-reactivity with self-antigens (1). B cells are well known for their roles in antibody production and antigen presentation. Additional processes in which B cells have been reported to participate include T cell Th1/Th2 polarization and modeling of the spleen architecture. There is mounting evidence that specific strains of B cells can also act as negative regulators/modulators and can affect the development of graft tolerance (2).

2. Negative Roles of B Cells in the Development of Graft Tolerance

Antibodies against non-self human leukocyte antigens (HLAs), known as donor-specific antibodies (DSA), are a recognized major barrier for transplantation. DSAs directly contribute to endothelial damage either with or without complement activation (C4d deposition) and T-cell activation (3, 4). B-cell-mediated antigen presentation is a primary event in acute cardiac allograft rejection and B-cell depletion eliminates alloantibody production and CD4 T-cell activation in experimental heart transplantation (5).

B cells also promote alloreactive T-cell differentiation into memory T cells; increasing numbers of memory T cells is a major barrier to the induction of tolerance (5,

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DOI: 10.5812/kowsar.22517006.1486

6). These lines of evidence were sufficient for B cells to be pharmaceutically targeted as a potential block to successful organ transplantation. Rituximab (anti-CD20), a drug which first appeared in the fields of oncology and then rheumatology, was next trialed in the field of transplantation (7). However, antibody-producing plasma B cells do not normally express CD20 and are mostly unaffected by rituximab (8), with the caveat that recent evidence suggests that a group of "short-lived plasma cells" exist that express CD20 and are sensitive to rituximab (9).

3. Positive Roles of B Cells in the Development of Graft Tolerance

Rituximab uncovered the dual immunologic contributions of B cells. B-cell depletion has been reported to have opposing effects on the course of some conditions that are very similar. It seems that this is related to opposing B-cell activities at the time of B-cell depletion (7). In support of B-cell depletion, it has been shown that the elimination of B cells augments the antitumor activity of T cells (9-11). Antibodies may help to clear apoptotic cells from the mesenteric lymph nodes of the colon, and interestingly B-cell-depleting therapies have been reported to negatively correlate with the occurrence of ulcerative colitis (11, 12). B-cell depletion in mice before the induction of experimental autoimmune encephalomyelitis (EAE), a model of human multiple sclerosis (13), exacerbated the clinical course of the disease, while B-cell depletion after EAE induction alleviated the disease course. Interestingly, the addition of IL-10-producing CD-$1d^{high}CD5^{+}$ B cells (regulatory B10 cells) after the first step of the experiment prevented the exacerbation of EAE (12, 13). A single course of rituximab in patients with relapsing–remitting multiple sclerosis reduced inflammatory brain lesions and clinical relapses for 48 weeks (13, 14). It seems that it is resemble to condition that we start Rituximab after disease induction in EAE model. In a study comparing rituximab with anti-CD25 (daclizumab) as induction therapy in renal transplantation revealed that 5/6 patients in the rituximab group had an episode of biopsy-confirmed acute rejection as compared with 1/7 in the daclizumab group. These rejection events suggest that B-cell depletion should be considered with caution, and the precise role of B cells remains to be fully elucidated (14, 15).

Interleukin-10-producing B cells, in collagen-induced arthritis (16), are found within the immature transitional two-marginal zone B-cell subset (T2-MZP) and display a CD19 + CD21 + ^{high} CD23 + ^{high} CD24 + ^{high} CD1d + ^{high} phenotype. Adoptive transfer of T2-MZP B cells from naive or convalescent mice prevented syngenic recipient mice from developing arthritis (15-17). In humans, IL-10-producing B cells are mainly contained within the CD19 + CD24 + ^{high} CD38 + ^{high} B cells population. They also express high levels of CD1 and CD5 markers (B10 markers) (17, 18). In patients with rheumatoid arthritis and systemic lupus erythamatosus treated with rituximab, long-term clinical remission was shown to be positively correlated with a high ratio of transitional B cells to memory B cells (18, 19). Regulatory B-cell function is not dependent on regulatory T cells (T_{reg} cells). The mechanisms of regulatory B-cell function are proposed to include the induction of apoptosis in targeted cells, signal transduction via CD80/CD86, and the induction of TGF-β (18, 19). Interestingly, B regulatory cells and IL-10 production are exploited by parasitic infections and malignant cells to subvert host CD4/CD8 protective responses (18, 20).

Passage through transitional B cell state to mature follicular B cells requires the presence of B lymphocyte survival factors (BLyS) receptors and ligands, which belong to the tumor necrosis factor (TNF) family. Transmembrane activator 1 (TMA1) and B-cell maturation antigen (BCMA) are the 2 BLyS receptors that were initially identified. BLys receptor 3 (BR3), also known as BAFF receptor (BAFF-R), is now known to be another important BLyS receptor. More BLyS binding is observed in CD23+ immature B cells. APRIL (another TNF family ligand) also binds to BCMA and TMA1 receptor on B cells. BLyS receptor binding promotes nuclear factor-κB activation and the upregulation of antiapoptotic proteins. BLyS deficiency produces the condition of common variable immunodeficiency, a paucity of mature B cells and low antibody levels. Conversely, when BLyS is highly expressed, autoreactive B cells may be spared from elimination. Rituximab therapy has been reported to cause a significant elevation of BLyS levels at 3 months post-transplantation (21). B-cell depletion could also increase BLyS expression by B cells and create autoreactive B cells despite B cell lymphopenia (22).

A second line of evidence against B-cell depletion emerged from the nature of nodular B-cell infiltrates in the transplant organs. The presence of nodular B-cell infiltrates with structures similar to secondary lymphoid organs has recently been noticed in renal allografts (23). These nodules consisted of B-cell aggregations forming germinal centers, surrounded by immature double-positive IgM and IgD/B cells and mature single-positive IgM/B lymphocytes (24). What is the purpose of the immune system in building such a complex structure outside the secondary lymphoid organs? The simple answer is: to improve spatial conditioning and reduce the distance between effectors and responders to increase the efficacy of immune responses (25). Further observation showed that diffuse B-cell infiltrates are more commonly found in indication biopsies taken from patients with allograft dysfunction, and nodular infiltrations are frequently found in protocol biopsies taken from clinically stable renal allografts. Nodular infiltrations are not correlated with acute humoral rejection. Diffuse infiltrations are dominated by histiocytes, cytotoxic T lymphocytes and plasma cells, whereas nodular infiltrations are dominated by CD20-positive B cells (26, 27). Recently, it has been shown that these B-cell clusters contain a dominant clone and each patient utilizes a particular set of dominant germ line genes as well as a dominant com-

plementarity-determining region. It seems that a B-cell clone that produces antibodies with greater affinity to the specific antigen is selected over time (28).

A third line of evidence against B-cell depletion, this time concerning the regulatory functions of B cells, came from animal models of allograft tolerance. In a rat model of long-term cardiac-allograft tolerance, the presence of nodular B-cell infiltrations in the allograft was associated with a good prognosis. There was also a deviation toward a Th2-alloantibody response and IgG1 deposits on endothelial cells without complement activation (in mice IgG2b is a Th1-related isotype and is involved in complement fixing) (29).

They also showed that in tolerant animals, alloantibodies increase the expression of protective molecules by endothelial cells, including heme oxygenase 1 (HO-1), NOTCH-4, and C-type lectin-like receptor CLEC-1. It seems that not only are DSAs in tolerant recipients not harmful, but that DSAs could even be protective in tolerant recipients (29, 30). Treatment with low-dose antidonor antibodies upregulates the expression of complement regulatory proteins by the graft endothelium: decay accelerating factor (DAF), complement receptor-related protein (CRRY), and CD59 (31). In nonhuman primates, long-term allogeneic pancreatic islet survival was associated with an enrichment of non-isotype-switched immature transitional CD19 +/CD27 -/CD38 +/+ IgM + B cells (32). Increased number of IL-10-producing CD19 + CD24 + CD38 + cells has been reported in renal transplant patients with operational tolerance (33).

B cells may contribute to the maintenance of long-term graft function in humans. Some patients, named operational tolerance patients (TLOs), have stable kidney graft function despite discontinuation of their immunosuppressive medicines. TLOs show an upregulation of the costimulatory/migratory molecules B7-2/CD80, CD40, and CD62L by B cells and memory (CD19 + IgD - CD38 +/- CD27 +) B cells. The ratio of activatory FcγRIIA (CD32a) signals to inhibitory FcγRIIB (CD32b) signals is decreased in B cells from TLOs. The CD32a/CD32b ratio is a relevant index of B-cell activation/inhibition, and compared with TLOs, patients with chronic rejection have an increased CD32a/CD32b ratio. B-cell scaffold protein with ankyrin repeats 1 (BANK1) is a negative modulator of CD40-mediated AKT activation preventing hyperactive B-cell responses. There is an accumulation of BANK1 transcripts in the blood of TLOs. Increased numbers of B cells expressing CD1d and CD5 have also been reported in TLOs. Despite these changes, TLO B cells are not hyporesponsive to polyclonal stimuli (34).

While DSAs are considered important players in both acute and chronic rejection, recent advances expand our understanding about B-cell hemostasis. The dual nature of B cells in potentially either promoting or impairing graft tolerance should be recognized when considering the use of B-cell-depleting therapies.

Acknowledgments

The author is thankful to Federica Casiraghi for her encouregment and assistance in prepration of this paper.

Financial Disclosure

None declared.

Funding/Support

None declared.

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