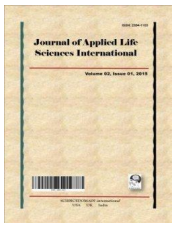

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Proposed Mechanisms of Suppression of B Cells by nTregs: B Cells as Targets for Suppressive Activity of nTregs

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Author's contribution

The sole author designed, analyzed and interpreted and prepared the manuscript.

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ABSTRACT

B cells have an important role in immune system due to their role in positive and negative regulation of immune response. As positive regulators, B cells can give rise to antibody-producing plasma cells, are critical cellular adjuvants that facilitate optimal CD4+ T-cell activation. B cells also contribute to immunoregulation through the production of cytokines including IL-4, IL-6, IL-10, interferon-gamma (IFN-gamma) and transforming growth factor-β (TGF-β). In addition, B cells are thought to have specific roles in stimulating Ag-specific CD4+ T-cell proliferation after activation by dendritic cells (DCs). While B cells can play negative regulatory roles during immune responses, particularly during inflammation, autoimmunity, cancer and infection. On the other hand, natural occurring regulatory T cells (nTregs) consider a body guard of immune system and play a pivotal role in the maintenance of homeostasis of immune system and tolerance to self-antigens and tissue graft. nTregs know all languages of the immune system cells and can chat successfully with any abnormal case that happen due to aberration of function of the immune cells. nTregs can use multiple mechanisms to exert their functions. In the current review we will focus on the mechanisms of suppression of B cells by nTregs.

Keywords: B cells; nTregs; mechanism of suppression; phenotype of B cells; autoimmune diseases.

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1. INTRODUCTION

In addition to antibodies secretion, B cells have many different functions in the body of mammals, such as introduce self and foreign antigen to T cells and do as antigen presenting cell (APC), activation of naive T cells, provide co-stimulatory signals for T cells, express anti-microbial activity by producing reactive oxygen intermediates and other inflammatory cytokines and isotype switch during humoral responses. B cells can provide co-stimulatory signals via their CD40 molecule to CD40L-expressing T cells. In addition to the CD40–CD40L co-stimulatory pathway, B cells can also interact with the CD28 and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) co-stimulatory molecules on T cells via CD80 or CD86. Furthermore, B cells respond to Toll-like receptor (TLR) ligands and present antigen in innate immune response.

The unique ability of B cells to produce antigen-specific antibodies makes them an important component of adaptive immunity. In secreted form, these antibodies can bind to specific molecules on invader pathogens, resulting in the immobilization and eradication of foreign pathogens through recruitment of effector cells and molecules. B cells also express membrane-bound antibodies (also called B cell antigen receptors BCRs), which act as stimulatory receptors upon encountering antigen. BCRs also facilitate internalization and processing of low abundance antigens onto MHC class II molecules, thereby enabling B cells to present antigen in a form recognized by the TCR of CD4+ T cells. Thus, B cells are responsible for maintenance of cellular and humoral memory, fulfilling a number of important functions.

In the majority of autoimmune diseases, B cells are generally considered to be pathogenic because of their capacity to secrete autoantibodies. However, it has known that specific subsets of B cells downregulate immune responses in mice and their absence or loss results in exacerbated autoimmune responses. Different B cell subsets have been described with regulatory function. Because B cells have an important role and function in immune system and aberrant in any of these functions resulting in harmful or sever disease, consequently putting B cells under disciplinary control especially under control of CD4+CD25+FoxP3+ regulatory T cells (which are naturally occurring and development within the thymus), these cells can control and regulate a wide spectrum of immune cells including CD4+ T cells, CD8+ T cells, DCs and B cells.

2. B CELLS IN THE DEVELOPMENT OF ADAPTIVE IMMUNITY

B cells develop from a small number of self-renewing haematopoietic stem cells (HSC) in the fetal liver throughout gestational period and from adult bone marrow (BM) throughout the life [1,2]. Differentiation of HSCs to B lymphocytes progress through multipotent progenitor (MPP), lymphoid-primed multipotent progenitor (LMPP) and common lymphoid progenitor (CLP) stages of development, accompanied by the sequential loss of megakaryocyte/erythroid (MEP) and myeloid potentials [3,4] (Fig. 1).

Stromal elements, soluble factors and surface IgM have all been recognized as playing distinct roles in the genesis and maturation of mature B lymphocytes [5]. After birth the maturation process of B cells takes place in the bone marrow. Lymphoid progenitor cells receive signals from stromal cells of bone marrow to start B cell development [6]. During the early stages of their development, B cells express one of the important receptor molecules called the pre-B-cell receptor (pre-BCR) which regulates B cell development. The pre-BCR is a heterodimer composed of an immunoglobulin (Ig) heavy chain molecule (H chain) covalently associated with an immunoglobulin light chain-like molecule usually called the surrogate light chain [7-9]. When B cells develop from their precursors they initiate a complex series of differentiation and selection program which leads to recombination of the H chain gene segments that occurs in pro-B stage [10]. A successful rearrangement of the heavy chain is a prerequisite for the recombination of the light chain genes that occurs in pre-B stage. After rearrangement of both heavy and light chains, if the two chains form a viable immunoglobulin, then this complex directs the cell to stop rearranging to ensure that only a single specificity is produced. Correspondingly, the developing B cells which fail to make a successful rearrangement undergo apoptosis [11,12]. Following successful antigen receptor rearrangement, signals from pre-BCRs signal the lymphocytes to promote the survival of the progenitors and induce their further differentiation [13]. However, the B cell receptor (BCR) is encoded by the same rearranged gene as encodes the immunoglobulin (Ig) that its later developmental offspring will secrete. This gene rearrangement is crucial to the diversity of the B cell repertoire—enabling a large number of

different specificities of Ig in order to improve chances of antigen recognition [14]. It may also be the case that a more diverse response is more effective than a high affinity oligoclonal response, since it has been shown that a human response to even a relatively simple antigen, such as tetanus toxoid, can comprise up to 100 different clones [15].

The process of BCR rearrangement can lead to the development of cells with autoreactive specificities, thus, there are also mechanisms for ensuring the destruction of any new B cell has antibody reacts high strongly with self-proteins on the surface of host cells [12]. One of these mechanisms is elimination; elimination of B-cell that bears receptors reactive with self antigen is initiated by the binding of self-antigens to surface Ig on immature B-cells within the bone marrow. The requirement for Ig engagement in triggering the elimination of autoreactive B lymphocytes has been largely established by the generation of mice in which the B-lymphocytes express a single, transgene-encoded rearranged Ig gene specific for an antigen such as hen egg lysozyme (HEL) or MHC antigens [16,17]. Interestingly, the elimination of autoreactive B-cells is not Fas-mediated deletion, when lpr mice (which lack Fas expression) were bred to mice expressing BCR that recognize membrane-bound autoantigen these autoreactive B-cells underwent elimination as efficiently as B-cells of wild-type(B cell bearing the Fas molecules) [18]. On the other hand, during B cell development, B-cell progenitors with self-reactive surface Ig BCR also face negative selection as a result of the antigen mediated signaling immature [19]. Immature B cells (also called T1 cells) export from the bone marrow to the periphery and migrate into the spleen for their final maturation step [20]. After this final maturation step, B cells become responsive to antigens and are able to produce antibodies. In the spleen, they have been categorized according to their size, micro-anatomical location, surface marker expression and functional activity [21].

The role of B cells is to interact with specific epitopes on foreign antigen via their BCRs and as a consequence of this interaction develop into plasma cells, which produce antibodies with the same specificity as the BCR. Plasma cells can be releasing large amounts of antibodies that enter the blood stream and bind the specific antigen on an invading organism. B cells can secrete antibodies to activate the cascade of complement proteins, phagocytic opsonization, NK cell cytotoxicity and mast cell degranulation [22-26], many such examples have been largely reviewed.

It has been reported that T cell-dependent humoral immune responses are preceded by cognate T cell–B cell interactions followed by activation of Ag-specific B cells, migration of the activated B cells to the follicles of secondary lymphoid organs and initiation of the germinal center (GC) reaction. Within the GC, B cells undergo rapid proliferation, mutation of Ig variable region genes and finally selection of B cells with high affinity BCR leading to formation of Ab-producing and memory compartments [5,27]. For example, The GC microenvironment provides a substructure that is critical for continuous Ag exposure to B cells through immune and complement receptor-mediated Ag capture [28].

As mentioned above, the activation of B cells and their differentiation to antibody-secreting plasma cells is triggered by antigen binding to the BCR. This process requires T helper (Th) cells cooperation via CD40-CD40L interaction and via stimulation by cytokines release from Th cells [29]. Although, it has reported that BCR engagement and activation of T helper cells is insufficient to promote antibody-producing B cells in mice [30]. It has known that the stimulation through BCRs affects in different ways related to different stages of B cells, for instance, immature B cells undergo apoptosis or clonal tolerance following BCR cross-linking, while this stimulus leads to a proliferative response in mature B cells [31]. Indeed, upon activation, some B cells remain in extra-follicular sites where they undergo limited proliferation and rapid differentiation into short-lived primary antibody-secreting cells, whereas other B cells enter the follicular dendritic network of germinal centers (GC) where they proliferation rapidly [32,33].

However, the number of B cells in the neonate of human is very high [34]; but the numbers of B cells in the periphery decrease in old humans [35] and appear to be in the same range in old mice [36], due to the maturation of plasma B cells is not yet completed at birth, leading to a defective antibody isotype switching. As a consequence of decreased generation of early progenitor B cells, the output of new naive B cells decreases in old mice [37] and consequently antigen-experienced B cells are expanded. This causes a reduced antigen-recognition repertoire of B cells in both old humans and old mice [38].

As a consequence of the relative T-cell and B-cell immaturity, neonates are capable of only rapid IgM and anti- IgM responses. Whereas, IgG and IgM are transferred from mother to her infant via breast milk. As for IgA, it is known that these antibodies protect the infant against infections passively [34]. Because attributed to both weaker innate and adaptive immune systems, the neonates suffer from different morbidity and mortality pathogens [39,40]. Neonatal B cells are efficient in their capacity to produce IgE if they are stimulated by exogenous IL-4. However, because of the minimal level of IL-4 produced by neonatal T cells, the level of IgE production by neonatal B cells is very low [41]. Furthermore, neonatal B cells were shown to effectively control the production of proinflammatory cytokines by neonatal dendritic cells that are present in higher percentage in neonatal mice than in adult mice. In the absence of B1 cell subset, neonatal mice developed stronger inflammatory responses than adult mice and became lethally susceptible to various TLR challenges, indicating that B1 cells might have a unique regulatory role in dampening the neonatal inflammatory response through regulation of dendritic cells [42]. Alteration in immunoglobulin generation (through class switch) in B cells is observed in old mice and humans [38], which may also contribute to the decline of the quality of humoral response in the elderly. A naive B cell expresses BCR of the IgM (monomeric) and IgD isotypes on its surface, while B cells which have previously encountered with antigen have undergone isotype switching. This means that the BCR on these cells include other isotypes like IgG, IgA or IgE. When these cells mature to plasma cells IgG, IgA or IgE antibodies are released. From biological insight, this is very useful for enhance immunity due to the different isotypes have different effector functions. It should be known that during the first tow years of life the switch to IgG1 and IgG3 is functional in the neonate, whereas the switch to IgG2 and IgG4 is inadequate in same period of age. Serum sIgA levels can reach adult levels within a few weeks when exposure to the pathogens in the highly levels [43].

Finally, a constant of circulating antibodies status with high range of specificity is very important in the maintenance of internal immunity and consider the first step in the defense system against different pathogens. It has been estimated that a healthy mouse has 16,000 different functional specificities [44]. Since antibodies have a limited life, a healthy population of plasma cells is required regardless of whether there are any specific pathogen challenges to generate new memory and plasma cells [14].

3. B CELL SUBSETS, CHARACTERISTICS AND BIOLOGICAL FUNCTION

The phenotypes of B cell subsets in both human and mouse are summarized in Table 1.

As mentioned above, B cell development takes place in fetal and neonatal liver and in adult bone marrow [1,2], by ordering B-lineage precursor cells progression through a series of genetically and phenotypically distinct stages of differentiation. These stages consist of (pre-pro-B, early pro-B, late pro-B, pre-B, immature B, and mature B cells) for mice [67] and the early-B, progenitor-B and precursor-B subsets that follow it, for humans [48], are each characterized by a determined surface phenotype and by the progressive status of Ig heavy and Ig light chain gene rearrangement and expression [10].

Generally, the earliest phase of B cells development from stem cell consists of two steps: The emergence of (CLP) cells and the subsequent differentiation of (CLP) to the earliest cells in the B-lineage pathway called progenitor B cells (pro-B) [68], identified these cells by expressing the B220 surface marker and give rise to B lineage (Table. 1) [69]. Pro-B can be divided into three stages called Fractions (Fr.) A, B and C [70]. Fr. A contains the earliest (germ-line) pro-B cells, in which the initial Ig rearrangement (D_HJ_H) has not yet been completed. While cells in Frs. B and C have completed this rearrangement and some cells, notably in Fr. C, have also completed $V_HD_HJ_H$ rearrangement.

In adult BM, the surface markers that discriminate pro-B cells from other subsets of B cell during developmental stage are B220 (CD45R) levels, CD4, CD19, CD24 (HAS), BP-1, CD43, IgM, IgD and MHC class II (Ia). It has found that only B220 and CD4 are expressed on germ-line pro-B cells. B220 is expressed at low or intermediate levels on all of mentioned cells, whereas CD4 is expressed on a major subset (which expresses B220 at intermediate levels). However, CD4+, B220 intermediate and Ia have all shown to express on germ-line pro-B cells in adults but not on neonates pro-B cells and the level of Ia that is expressed increases in stages as the B cell development proceeds [71].

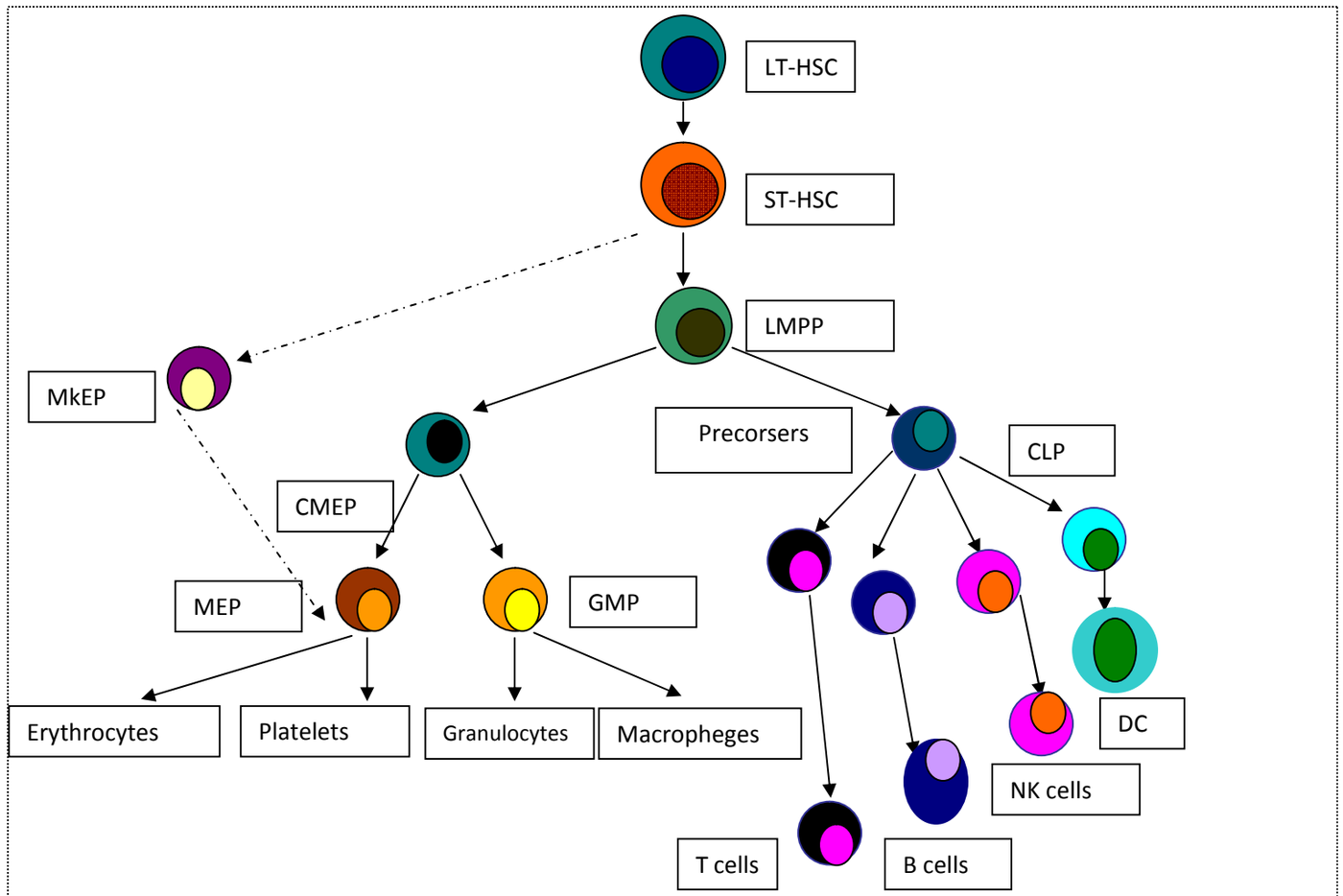

Fig. 1. Schematic view for progressing of haematopoietic stem cell (HSC) to different cell lines including B cells. long-term haematopoietic stem cell. (LT-HSC) , short-term haematopoietic stem cell (ST-HSC), lymphoid-primed multipotent progenitor (LMPP), megakaryocyte-erythrocyte progenitor (MkEP), common lymphoid progenitor (CLP), common myeloid-erythroid progenitor (CMEP), megakaryocyte-erythroid progenitor (MEP), granulocyte-macrophage progenitor (GMP), dendritic cell (DC) and natural killer cells (NK cells)

Table 1. The phenotype of B cell subsets in humans and mice. (h beside references indicate to human and m indicate to mouse)

B cell subsets	Phenotype identification		References
	Human	Mouse	
Pro-B	•CD34+CD10+CD19+	•IgM$^-$cμ$^-$AA4.1+CD43+B220+CD19+ •B220^{lo}CD43^{hi}BP-1^{lo}CD24^{int}	[45,46,47m] [48h] [49m]
Early Pre-B Late Pre-B	•CD34−CD10+CD19+	•IgM$^-$cμ+AA4.1+CD43+B220+CD19+ •IgM$^-$CD43$^-$B220+	[46m,48h] [46m]
Immature B	•CD19+Cd24^{hi}CD38^{hi} •CD24^{hi}CD38^{hi}CD5−CD20−IgD−IgM−CD10^{hi}	•AA4+CD23$^-$sIgM^{high} sIgD$^-$/^{low} CD24^{high} CD62L$^-$CD21/35$^-$/^{low} •IgM^{lo}IgD$^-$CD93^{hi}CD23$^-$CD21$^-$	[50m,51h] [52h, 49m]
T1B	Not clear	•CD23$^-$AA4+sIgM^{high} sIgD$^-$/^{low} CD24^{high} CD62L$^-$CD21/35$^-$/^{low} •IgM^{high}IgD^{low}CD23^{low}CD21/35^{low} •IgM^{hi}IgD^{lo}CD93^{int}CD23$^-$ CD21$^-$	[50m] [53m] [49m]
T2B	Not clear	•CD23+AA4+sIgM^{high}sIgD^{high} CD24^{high} CD62L+CD21/35^{low} •IgM^{high}IgD^{high}CD23+CD21/35$^{int/high}$ •IgM^{hi}IgD^{hi}CD93^{int}CD23^{hi}CD21^{int}	[50m] [53m] [49m]
B1a\mouse, B1\human	•CD20+CD27+CD43+ CD70$^-$CD5+ or CD5$^-$	•CD11b+IgM^{hi}IgD^{lo}B220+ CD23$^-$CD19+ CD5+ •B220^{int}IgM^{hi}IgD^{lo}CD5^{hi}CD23^{lo}CD21^{lo}	[54,55h,56, 57m] [49m]
Peritoneal B1b Splenic B1b	Not clear	•CD11b+ IgM^{hi} IgD^{lo} B220+ CD23$^-$CD19+CD5$^-$ •CD11b$^-$ IgM^{hi} IgD^{lo} B220+ CD23$^-$CD19+ CD5$^-$	[54,56,57,58m] [54m]
Bregs	•CD19+CD1d+CD5+IgD+ IgM+ CD38+ CD23+	Not clear	[59h]
MZ B	Not clear	•CD21^{hi}CD23$^-$IgM^{hi}CD1d^{hi} •CD24^{med}CD21^{hi}CD23^{lo} •CD23^{lo}CD21^{hi}CD1^{hi}IgM^{hi}IgD^{lo} •CD23$^-$ AA4$^-$ sIgM^{high} CD1d+ sIgD^{low} CD24+CD21/35^{high} •IgM^{hi}IgD^{low}CD23^{low}CD21/35^{hi}	[60,61m] [62m] [63,64m] [50m] [49,53m]
FO B	Not clear	•CD24^{lo}CD21^{med}CD23^{hi} •IgM^{low}IgD^{high}CD21^{int}CD23^{high} 1. CD23+AA4$^-$sIgM^{low} sIgD^{high} CD24^{low} CD62L+CD21/35$^{int.}$ 2. CD23+ AA4$^-$/^{low} sIgM^{high} sIgD^{high}CD24^{low}CD62L+CD21/35$^{int.}$ •IgM$^{int/low}$IgD^{hi}CD23+CD21/35^{int} •IgM^{lo}IgD^{hi}CD23^{hi}CD21^{int}	[62m] [64m] [50m] [50m] [53m] [49m]

B cell subsets	Phenotype identification		References
	Human	Mouse	
B10	•CD19+Cd24^{hi}CD38^{hi} •CD1d^{hi}CD5+CD24+CD27+ and/or CD38+	•CD19^{hi}CD1d^{hi} CD5+ •CD1d^{hi} CD5+ CD21+ and/or CD23+ •CD19+CD21^{hi}CD23^{hi}CD24^{hi}CD1d^{hi}	[65m,51h] [66m,h] [151m]
(T2)-MZ precursor B	Not clear	•CD21^{hi}CD23+IgM+CD1d^{hi} •CD23+AA4^{-}/^{low}sIgM^{high}CD1d+ sIgD^{high} CD24+CD21/35^{high}	[60,61m] [50m]

Generally, immature B cells that express IgM+B220^{lo} cell-surface Ag receptors (BCR) (that undergo positive and negative selection in bone marrow) leave the bone marrow to the periphery, where they undergo additional selection and develop and mature into other stage called (transitional) T1 B cells CD24^{hi}CD21^{-}B220^{+} and further into T2 B cells CD24^{hi}CD21^{+}B220^{+}, based on their phenotypes and ontogeny. T2 B cells can differentiate into Follicular (Fo) CD24^{lo}CD21^{med}CD23^{hi} B cells within spleen and follicles of lymph node or marginal zone (MZ) CD24^{med}CD21^{hi}CD23^{lo} B cells within the spleen [62], through intermediate MZ progenitor cells. T2–MZ precursor B cells have a CD21^{hi}CD23+CD1d^{hi} phenotype. BCR signal has been shown to play an essential role in the development of peripheral B cells [72]. It has been found that BC R specificities plus BCR signal strength are major determinants of the Fo versus MZ B cell differentiation in Ig transgenic mouse experiment. Thus, in V_H81X transgenic mice, B cells skewed to differentiate into the MZ B cell subset, while in anti-hen egg lysozyme (anti-HEL) transgenic mice, B cells skewed to differentiate into the Fo B cell subset [73]. Ag activation of mature B cells leads initially to the transient generation of extra-follicular foci that yield antibody-secreting plasmablasts and short-lived plasma cells that secrete Ag-specific antibodies [74]. Ag-specific B-cell proliferation also leads to B-cell entry into the germinal center microenvironment, where B cells diversify their Ag receptors and generate pools of long-lived memory B cells [75]. Germinal centers and restimulated memory B cells give rise to long-lived plasma cells within the bone marrow that are in charge of the maintenance of serum antibody in the stable levels [76]. Antibodies function both as a natural barrier to infection and as a humoral component of adaptive immune responses to pathogens.

B-1 lymphocytes represent a unique B-cell population distinguished from conventional B cells (B-2 cells within the peritoneum) by their surface phenotype, preferential anatomical localization, self-renewing capacity and production of natural circulating serum IgM [64,77]. Furthermore, B-1 cell development occurs primarily during fetal and neonatal periods, whereas B-2 cell production is most active after birth and continues throughout adult life [56]. B-1 cells contribute the bulk of natural serum IgM and IgA, which plays a key role in limiting microbial dissemination [78], for instance, these antibodies are essential for survival in a mouse model of influenza infection [78] and are also required for protection in a model of acute bacterial peritonitis [79] and because that, they have been participated in early innate resistance to infection [80] and autoimmunity [81]. Therefore, B-1 cells are commonly thought as a part of innate, T-cell-independent humoral immunity. Others have reported that B-1 cells, in contrast to B-2 cells, can respond to a limited range of T-independent antigens [82,83]. It has been indicated that B-1 cells also participate in T-cell-mediated immune reactions such as in the cases of immediate and delayed-type hypersensitivity (ITH, DTH) [84,85].

Mature B-1 cells also are distinguished from mature B-2 cells by the signals required for cell cycle progression, for instance, B-1 cells enter S phase of cell cycle and proliferating vigorously within 24 h in response to treatment with PMA [86,87], whereas B-2 cells are stimulated by the combination of a PMA and a calcium ionophore [86], but not by PMA alone [86,87]. It has shown that splenic B-2 cells responded strongly to anti-Ig by entering S-phase at 48 h, while peritoneal B-1 cells responded weakly [87]. Moreover, B-1 cells fail to respond to BCR crosslinking by anti-Ig, which induces the proliferation of B-2 cells.

B-1 cells are localized in the coelomic cavities (peritoneal and pleural), tonsils, Peyer's patches and spleen (approximately 5% of splenic B cells) and are absent in lymph nodes or circulation. B-

1b cells express CD11b (Mac-1), CD19, B220 and IgM surface markers. Moreover, CD11b is expressed on peritoneal but not splenic B-1 cells (Table 1). Whereas B-1a cells have expressed one additional molecule which is CD5 than B-1b. Based on the expression CD5 and CD11b, B-1 cells are further subdivided into the B-1a (CD5+CD11b+), B-1b($CD5^{-}CD11b+$) and B-1c ($CD5+CD11b^{-}$) subsets [87]. B-1b ($CD11b^{+}CD5^{-}$) cells give rise to adaptive humoral immune responses to T-cell-independent Ags [54]. It has largely demonstrated that B-1a cells responsible for innate and B-1b cells responsible for adaptive humoral immune responses during bacterial infection models. In experiment included three groups of mice, wild-type, Transgenic mice over-expressing CD19 (hCD19Tg) and CD19-deficient (CD19−/−), Haas and co-workers [54] have shown that B-1a cells from wild-type or hCD19 Tg mice were important for natural antibody production, while B-1b cells from wild-type or CD19−/− mice functioned independently to regulate protective anti-pneumococcal polysaccharide (anti-PPS) responses to *Streptococcus pneumoniae*. In addition, the B-1b subset was required for generating long-lasting protective responses to *S. pneumoniae*, concluded that there was equilibrium between B-1a and B-1b cell development in wild-type mice that balances innate and adaptive humoral immune responses during *S. pneumoniae* infection. Moreover, it seems that the expression of CD19 may implicate in the balance between innate and adaptive immune response. The same group has found that CD19 deficiency impaired B-1a development and furthers the production of protective natural antibody, while CD19 overexpression impaired B-1b development and adaptive responses to PPS-3 [54]. Other investigators have shown that animals lacking B-1b cells are susceptible to *Borrelia hermsii* infection and the adoptive transfer of this cell subtype obtained from convalescent mice confers protection against the bacteria [88]. On the other hand, B-1b cells have a possibility to link between innate and acquired immunity. This is emerged from observation that B-1b cells obtained from naive animals are capable of satisfactorily present antigen to and induce proliferation of T lymphocytes [89]. Taken together, the mentioned results indicate carefully that B-1a B cells represent the main source of natural antibodies that provide crucial protection during the early stages of infection by pathogens, whereas B1-b cells can provide antibodies that they are produced subsequently and are key to the fundamental clearance and long-term protection from invading pathogens [54,88]. Other effects of B-1 cells are to produce substantial amounts of autoreactive IgM, which may function as a restriction factor for parasite infections [90,91]. Furthermore, Natural antibodies can bind to self-antigens and this property could explain the role of B-1 B cells in autoimmune diseases [21]. The origins of B-1 cells and whether B-1a and B-1b cells are derived from the same or distinct progenitor cells are still controversial [64]. However, two models were suggested to explain the origin of B1 cells, the lineage model [92,93] and the selection model [77,94].

Peripheral mature B2 cells are comprised of, at least, two subsets including follicular (FO) B cells and marginal zone (MZ) B cells in the spleen of both mouse and human [95].These tow subsets are discriminated between each other by cell surface phenotype, manner of activation, anatomical localization and functions in innate and adaptive immune responses. Therefore, FO B cells have surface phenotype of IgM^{low} $CD23^{high}$ $CD21^{low}$, whereas, MZ B cells have surface phenotype of IgM^{high} $CD23^{low}$ $CD21^{high}$ [63]. Using the study of mutant mice deficient in negative or positive regulators of B cell signaling and the study of transgenic mice that express different levels of the Epstein-Barr virus protein LMP2A as a BCR surrogate have shown a role for BCR signaling in the direction to which subset of B cells could formation. These studies have demonstrated that the weak BCR signaling lead to the development of MZ B cells whereas higher BCR strength lead to the generation of FO B cells [73,96,97]. Moreover, MZ B cells are considered to be innate-like cells that can be induced to differentiate into short-lived plasma cells in the absence of BCR ligation [50]. While, FO B cells, which represent from the most of circulating B lymphocytes in the blood stream and normally locate in the central region of primary lymphoid follicles and are responsible mainly for T cell-dependent immune responses [98], following exposure to antigen and receive signals from T-helper cells, FO B cells can undergo Ig class switching, somatic hypermutation and differentiation into antibody-secreting plasma and memory B cells [99]. In addition, MZ B cells locate in the marginal sinus surrounding the periarterial lymphatic sheath and lymphoid follicles [63]. Moreover, MZ B cells are shown to position in MZ of the spleen, to initiate

a first-line defense against invading-pathogens, bacteria and microbes that found in the blood stream .Accordingly, these cells are also important for initiating-adaptive antibody responses involving FO B cells and could consider as a bridge between the innate and the adaptive immunity [82,100]. FO and MZ B cells also are difference between each other in the type of response to different stimuli. It has been found that MZ B cells express higher levels of co-stimulatory B7 molecules than FO B cells, accordingly, respond and proliferate more efficiently than FO B cells to a different of stimuli, including anti-CD40 and LPS [98]. Others have shown that CD1d is highly expressed by MZ B cells and is responsible for the interaction between MZ B and NK-T cell and leads to rapid secretion of IL-10 by B cells, resulting in optimal germinal center (GC) formation [101,102] and\or NK-T cell may activate MZ B within spleen through CD40-CD40L interactions and induce further rapid class switched and potentially somatically mutated antibody responses [103]. CD36 also has reported to express highly by MZ B compared with FO B cells, this molecule is known to have multiple functions such as lipid metabolism, needed for phagocytosis of *P. falciparum* infected erythrocytes and associated with CD9, integrin ß1 and the Src family protein tyrosine kinases Lyn in platelets and endothelial cells, suggested that these properties may be related with the role of MZ B cells in innate immunity in clearance of bacterial and other foreign antigens [104]. Also the high levels of CD21 expressed on MZ B cells presumably evolved to facilitate immune complex capture [50]. Other signaling pathways may important in the differentiation of peripheral B cells is Notch signaling pathway. Conditional knock-out of RBP-J, a key downstream transcription factor of Notch receptors, lead to decrease in MZ B cells with a concomitant increase of FO B cells, suggesting a cell-fate decision step in the differentiation of peripheral B cells into FO or MZ B cells [105]. Similar phenotypes have been observed in Notch 2 conditional knock-out mice [106]. However, the molecular mechanisms, as well as cross-talk between different pathways in regulating FO versus MZ B cell differentiation and function, are still ill-defined.

Despite of the largely highlight on the role of peripheral B cells in mediating innate and acquired humoral immune responses, indeed MZ B cells are highly expressing-MHC II molecules, can also produce and secrete cytokines and have the potential role in present antigen to and activation of naive T cells as a potential antigen-presenting cell (APC) than FO cells [107,108]. It has demonstrated that B cell with the capacity to present Ag is 10^3-fold to 10^4-fold more efficiently than other APCs [109]. However, B cell functions that are less well understood could summarize as following: The potential role of some B cell populations as regulatory cells in different inflammations, cancer and autoimmune diseases by mediate IL-10-secreting or by other manners [51,59,65,66,110], the putative role of activated cytokine-producing B cells in the activation of T cells that further can drive inflammation and the likely role of B cells in the induction of tertiary lymphoid organs at sites of disease-related inflammation [50].

Further analysis of B cells within GC of lymphoid follicles were involved some surface markers, in particular, IgD and CD38 have been used in discriminating of different stages of differentiation [111]. Thus, seven mature B cell subpopulation have been recognized, which were, naïve (IgD+ CD38–), once activated as (IgD+ CD38+), differentiate into GC founder (IgD+ CD38++), centroblasts and centrocytes (IgD–CD38++) and terminate as (IgD– CD38+), early and (IgD– CD38–) ultimate cells, i.e. memory B cells which express CD27 and plasma cells (PC) which do not. Furthermore, long-lived memory B cells subdivided into two types, one is resting and another is activated in BM [111]. But others have demonstrated that there is no marker for memory B cells in mice, because CD27 is a marker of recent activation, but not a marker for memory B cells in this species where most IgG+ splenic B cells are CD27– [112]. However, the investigation of memory B cells have been hampered in mouse by the fact that these cells represent only 5% of peripheral B cells, so that antigen-specific memory B cells may be no more than 10^4–10^5 cells per spleen [113,114]. [For more details related with memory B cells see ref. 115]. Functions of B cells, in addition to antibody production can summarized as following:

1. Shaping of the splenic architecture: Dendritic cells and T lymphocytes
2. Antigen presentations (in particular CD5-expressing and rheumatoid factor-making B cells)
3. Production of cytokines to trigger polarization of naive T lymphocytes into T helper (Th) 1 or Th2 [111].

4. B CELLS IN AUTOIMMUNE DISEASES

Normally, some immunoglobulin gene rearrangements produce B cells with receptors that bind to foreign molecules such as those associated with pathogenic invaders. Consequently, upon stimulation, B cells of this type produce antibodies that can prevent or, at least, limit infection. But gene rearrangement can also lead to the production of immunoglobulin that binds to self' molecules found within the healthy body. Activation of self-reactive antigen receptors results in the production of autoantibodies that might cause autoimmune disease. Autoimmune diseases can divide, generally, into two main categories: Organ-specific and nonorgan-specific settings. The former include Inflammatory bowel disease (such as Crohn's disease and ulcerative colitis), Experimental autoimmune encephalomyelitis (EAE), Autoimmune hepatitis, Hashimoto's thyroiditis, Graves' disease, type 1 diabetes, Addison's disease and Sjögren's syndrome. And the latter include rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), primary Sjögren's syndrome (pSS) and systemic sclerosis (SSc). These are associated with humoral and cellular abnormalities. Other categorization include two groups, one group of disorders in which disorder is driven by T cells and another group of conditions in which auto-antibodies play a pivotal role, either by binding to tissue antigens or by forming immune complexes. This approach segregating autoimmune disorders into T cell mediated and so-called B cell mediated diseases has recently been highlighted from many investigations. However, auto-antibody linked diseases, for instance SLE, likely involve a break in tolerance in antigen-specific B cells; an important role for T cells in this case of diseases has also long been studied. Most disease related autoantibodies are found to be IgGs that are somatically mutated suggesting that Th cells drive the autoimmune B cell response [116]. Moreover, it has also been found that B cells have important roles in inflammatory conditions such as in RA, multiple sclerosis (MS) and type I diabetes mellitus (DM), disorders that have long been considered to be mediated primarily by T cells. It is clear that in most autoimmune disorders cells of both lymphocyte lineages cooperate closely in disease pathogenesis.

Although studies on the role of B cells in autoimmunity have focused primarily on the mechanisms of B cell tolerance and how tolerance may be abrogated in autoantibody mediated diseases, it is possible that a loss of B cell tolerance might occur in almost all autoimmune disorders. In diseases in which specific autoimmune T cell clones drive the process of inflammation, auto-antibody production may represent a marker for the expansion of auto-antigen specific B cells that capture, endocytic, process and present self-antigen peptides to inflammatory T cells. In other disorders, T cell help appears to be a crucial component in driving self-reactive B cells to make pathogenic auto-antibodies [117]. However, in autoimmune diseases like SLE, myasthenia gravis (MG), Wegener's granulomatosis and Goodpasture's syndrome, a more direct role for antibodies has been appreciated. I will summarize positive and negative role of B cells in different autoimmune diseases as following:-

- There is accumulation evidence to indicate that B cells are involved in multiple aspects of the processes culminating in type I diabetes. 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 [118–120]. In contrast, B cells do not appear to be required as an important effector cell for beta cell destruction in the NOD-mice 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 [118]. 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 II restricted manner [121]. Constant with these evidences, B cells consider important players in diabetes pathogenesis and this is strongly supported from studies on the NOD mouse. In this model, B cells infiltrate the pancreas during the early stages of insulitis and, circulating autoantibodies, specific for beta cell auto-antigens are readily detected [121]. 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, Igμ^{null} mice, prevents diabetes [122]. In addition, treatment of NOD mice with anti-CD20 antibodies to mediate B cell elimination can also markedly reduce diabetes incidence [123]. 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.

- To investigate the role of B cells in the suppression of chronic colitis(CC), cell transfer experiments have been performed in TCRα−/−Igμ−/− mice using B cells from different strains of mice deficient in either CD80, CD86 or CD40 co-stimulatory molecules. While B cells from CD80−/− mice decrease the number of pathogenic CD4+ T cells like those from TCRα−/− mice, B cells from CD40−/− and CD86−/− mice do not affect the number of pathogenic T cells or the development of CC [124]. These experiments suggest that the suppressive effect in CC is due to mature activated B cells that directly interact with pathogenic CD4+ T cells through CD40 and CD86 co-stimulatory molecules. Consequently, colonic epithelial cell proliferation declines leading to a reduction in severity of disease [124]. Others have found that CD1d is clearly involved in the development of CC. Thus, TCRα−/−CD1d−/− double KO mice spontaneously develop the disease with an increased progression rate. Accordingly, mesenteric lymph node B cells from TCRα−/− mice present upregulation of CD1d molecule compared with wild type (WT) when intestinal inflammation appears [125]. Moreover, the transfer of B cells from TCRα−/−CD1d−/− mice in TCRα−/−Igμ−/− mice fails to inhibit the progression of intestinal inflammation.

- A model of SLE-prone mice illustrates the possible role of Breg cells in SLE. Decreased production of IL-12 is observed in the Palmerston North (PN) mice in response to LPS or CpG-ODN, compared with normal mice. On the same hand, inadequate immune response to infectious signals is associated with an increased secretion of IL-10 [126], leading to suggest that either macrophages or dendritic cells may display an inappropriate response to microbial antigens. However, these Ags may also stimulate B cells in some cases. Others have found that B cells from PN mice and also from NZB/W and MRL-*lpr/lpr* mice, raise the production of IL-10 in response to microbial danger signals that may contribute to the pathogenesis of SLE [127]. When B cells are depleted from SLE-prone PN mice, production of IL-12 by splenocytes is increased in response to CpG-ODN stimulation. In contrast, addition of purified B cells back to PN splenocytes results in an IL-10–mediated suppression of IL-12 in *In vitro* experiments. These data clearly indicate that in PN mice, Breg cells produce a high level of IL-10 that inhibits the production of IL-12 from macrophages or dendritic cells and consequently contributes to inappropriate infection responses.

  On the other hand, the higher sensitivity of SLE MZ B cells to CpG stimulation is not explained by an increased density of TLR9 expression, but rather might be due to a lower stimulation threshold than control B cells [128]. However, it has suggest that MZ B cells from control mice produce a low level of IL-10 when stimulated via TLR9; consequently allows macrophages and DCs to produce IL-12 that contributes to the development of an appropriate proinflammatory Th1 response. In contrast, MZ B cells from SLE-prone mice respond to TLR9 stimulation with a high level of IL-10 that restrains the production of IL-12 by macrophages and DCs and thus favors the development of a non-adapted immune response to infection. Moreover, increased sensitivity of TLR9 stimulation induces also the MZ Breg cells to differentiate into Ab-secreting cells that may be involved in the pathogenesis of SLE [128]. Also, signaling via TLRs uniquely stimulates memory B cells [129]. Collectively, the available data suggest the possibility that memory B cells in patients with SLE could easily be activated via TLR9 without T cell help, but in the presence of co-stimulation by TNFSF13A and/or B, which might account for the plasmacytosis [130].

- B cells have seemed to play protective roles as well in experimental autoimmune

encephalomyelitis (EAE) disease because both CD19-deficient ($Cd19^{-/-}$) and B cell-deficient mice develop a severe non-remitting form of EAE, a model of human multiple sclerosis [131,132]. B cell deficiency delays the emergence of regulatory T cells and IL-10 production in the central nervous system (CNS) during EAE [133]. It is known that the expansion of Treg cells depends on stimulation via CD28 by B7 [134]. In contrast to normal B cells, reconstitution of B 10. PLμMT mice with $B7^{-/-}$ B cells failed to up-regulate Foxp3 expression to increase the level of IL-10 and, consequently to recover from EAE [133]. The generation of regulatory B cells has been reported in mouse models of chronic inflammation, albeit their existence in normal mice remains unknown [135]. Moreover, it is unknown whether different populations of B cells or a distinct B cell subset implicates in inflammatory responses, whether regulatory B cells produce IL-10 or other cytokines directly, or whether regulatory B cells have used other activities *In vivo.* Thus, the importance of B cells during T cell-mediated inflammation was investigated with contact hyper sensitivity (CHS) responses as a model of inflammation in $Cd19^{-/-}$, human CD19 transgenic (hCD19 Tg) and in WT mice with intact immune systems that were depleted of B cells *In vivo* [136]. CHS was chosen as a model because a balance between B cells and dendritic cells regulates CD4+ T cell expansion (they do as APC) in response to antigens *In vivo* [137,138]. It has reported that B cell depletion inhibited antigen-specific CD4+ T cell expansion [139], however, skin Langerhans cells are the exclusive or main antigen-presenting cells during CHS [140]. These data demonstrate that B7 expression by Breg cells is required to trigger the development of Treg cells and to stimulate their production of IL-10 that important for EAE recovery. On the other hand, T cell clonal expansion was reduced and the differentiation of T cells, particularly Th2 cells, into cytokine-secreting effector cells, was impaired when the B cell compartment was deficient in MHC class II [141]. Furthermore, IL-10 produced by B cells could downregulate autoimmune disease in many types of diseases including EAE [131]. Also, IL-10 over-expression prevented the development of MOG-induced EAE [142]. Moreover, $IL\text{-}10^{-/-}$ knockout mice could not recover from EAE and displayed increased IFN-alpha production [143]. Others have recently suggested that regulatory B cells resolve EAE by biasing cytokine expression towards anti-inflammatory cytokines and transferred B cells also enhance production of BDNF in the afflicted brain and down-regulate the expression of chemokine receptors that are associated with trafficking of inflammatory cells into the CNS [144]. IL-10-deficient mice also have enhanced CHS responses [145]. Adoptive transfer of IL-10-producing regulatory B cells ($CD1d^{hi}CD5+$) has been demonstrated to reduce EAE pathogenesis [61]. Neutralizing IL-10 by monoclonal antibody (mAb) treatment also enhances CHS responses, whereas systemic IL-10 administration reduces CHS responses [146,147]. IL-10 is secreted by different types of cells such as B cells, T cells, macrophages, monocytes, mast cells and eosinophils and can suppress both Th1 and Th2 polarization, inhibit IL-12 production by macrophages and DCs and inhibit macrophage antigen presentation and proinflammatory cytokine production [148]. Thus, B cells and IL-10 both can play important inhibitory roles during T cell-mediated inflammatory responses.

- Another model of RA helps to understand the way by which B cells modulate the severity of the disease. In the DBA/1-TCRβ transgenic (Tg) mice, RA is induced by administration of collagen type II. The incidence of the disease is reduced by stimulation of the splenocytes with anti-CD40 antibody [149]. The authors have demonstrated that the anti-CD40–mediated protection is B cell-dependent. Thus, when B cells are depleted before CD40 stimulation, all of the mice develop arthritis. Moreover, CD40 stimulation results in a threefold increase in the number of IL-10–producing B cells while the number of B cells that produce IFN-γ decreased. Furthermore, using a wild type mouse model of autoimmune disease, Munroe and Bishop have observed increased numbers of CD40+ T cells in the

murine model of rheumatoid arthritis, collagen induced arthritis (CIA) [150].

To determine the role of IL-10 produced by CD40-stimulated B cells, DBA/1 mice were backcrossed with IL-10−/− mice and B cells from IL-10 KO or WT mice used in transfer studies after anti-CD 40 stimulation [149]. Unlike WT B cells, B cells from IL-10 KO mice were unable to protect WT recipient mice from developing arthritis following administration of collagen type II. Consistent with these data, injection of blocking anti-IL-10 or anti-IL-10 receptor Abs inhibited the protective effect of the WT B cells stimulated by anti-CD40. It is thus evident that, following stimulation of CD40, B cells regulate the induction of arthritis through secretion of IL-10.

Others have demonstrated that B cells at an immature stage of development subset protect mice from CIA. The protection from disease was paralleled by an inhibition of Th1 response as shown by the reduced amount of IFN-γ and an inhibition of the delayed-type hypersensitivity (DTH) response to bovine collagen type II (CII) in mice treated with T2-MZP compared with control group. Moreover, the transfer of unmanipulated naive T2-MZP B cells protected mice from developing arthritis and the results demonstrate that T2-MZP B cells exert their protective effect through the production of IL-10, suggesting that T2-MZP B cells have a regulatory capability in RA model of mice [151].

Moreover, it has found that the development of RA germinal centers is critically dependent on MHC class II positive cells and on the presence of B cells. Thus, when CD4+ T cell clones were transferred into SCID mice, the animals developed arthritis, but only in the presence of B cells, but when B cells were depleted, no disease occurred, suggesting a critical dependence of the arthritis pathophysiology on the presence of viable B cells, since all other compartments of the immune system remained intact [152].

5. MECHANISMS OF B CELL TOLERANCE AND HOMEOSTASIS

Immune tolerance represents a state of specific unresponsiveness either to self antigens (self-tolerance) or a specific foreign antigen (acquired immune tolerance as in the transplantation tolerance), in the absence of global immune system ablation. Self-tolerance is an inherent property of the immune system, whereas acquired immune tolerance is actively acquired and highly regulated. Induction and/or maintenance of acquired tolerance are a complex process involving multiple cellular components, which may change over time [153]. The concept continues to be refined, particularly with respect to the mechanisms underlying negative selection at the different stages of B cell differentiation [154-156]. However, the mechanisms of self-tolerance in the B-cell compartment can be divided into two main categories, primary and secondary mechanisms. It is now known that mechanisms ensuring tolerance to self antigens appear during the development of B cells, most notably at two check-points, first within the bone marrow where B cells are generated and the other in the periphery when these B cells migrate from the bone marrow to the periphery. Thus, most stages of B cell differentiation put under control of primary mechanism and contribute to shaping the repertoire, while secondary mechanism do not act on the repertoire but act in a fail-safe capacity in peripheral lymphoid organs by affecting the responsiveness of mature B cells. Many studies related with these mechanisms were performed in transgenic models involving self-antigens or neo-self-antigens [157]. For instance, three self tolerance mechanisms have been suggested to control developing autoreactive B cells in the bone marrow [17,158–162]. Strong BCR signals induce deletion by apoptosis through Fas\FasI, whereas intermediate signals promote secondary recombination events predominantly at the Ig light chain locus leading to edit cell`s BCR (a process through which antigen binding induces continued rearrangement of immunoglobulin gene segments) and decrease its self-reactivity. In contrast, self reactive B cells can become anergic or ignorant (a state of unresponsiveness to antigen) which allows the cells to leave the bone marrow [159,160,163]. It is indicated that more than half of all newly generated B cells have BCRs capable of binding autoantigen [164]. Other results have suggested that between 20–50% of all peripheral naive B cells have undergone receptor editing by Ig light chain replacement whereas deletion and anergy have a minor role in silencing of self-reactive B cells [165–168].

However, similar conclusions were appeared for acquired tolerance to different foreign antigens and to MHC or blood group antigens involved in prevention of graft rejection [169,170].

Microorganisms can affect B-cell responsiveness in different manners, either by direct infection of B-cells in the cases of EBV and HIV resulting in destruction of BCR signaling [171,172] or indirectly manner by inhibiting their function as antigen presenting cells in the case of *Helicobacter pylori* [173]. For more details see ref. [174].

On the other hand, there are two types of mechanisms for achieving immune tolerance and immune homeostasis as a secondary fail-safe mechanisms, namely “recessive” or cell-intrinsic mechanisms and “dominant” or cell-extrinsic mechanisms [175]. The former encompass microenvironmental niches wherein B-cell numbers can be regulated, interactions with the complement pathway, the effects of soluble molecules (such as cytokines) and negative T-cell influences (such as Tregs, lack of help, and/or direct killing by CD4+ and CD8+ T-cells) [176,177]. By contrast, the latter include various signalling manners and receptors that affect positively (such as CD19 and CD21/35) or negatively (such as CD22 and Fcg RIIB) influence in charge of regulating the threshold of BCR triggering and strength [157,178].

Many studies have been indicated that different molecules implicate to achieve tolerance. However, the role of each molecule in the achieving tolerance is still to be needs further elucidated. MHCII and B7 (CD80 and CD86) molecules were suggested to have an important role in the tolerance. The mechanistic studies have shown that transduced B cells must express MHC class II and B7.2 co-stimulatory molecules for successful tolerance induction [179,180]. It has well known that CD80 and CD86 are co stimulatory pairs with CD28 and CTLA-4 through interaction between APC and T cells to transduce co-stimulatory signals [181,182]. Prolonged allograft survival in rodent models is observed after transient blockade of B7\CD28 co-stimulation by monoclonal antibodies [183]. Other results have revealed that exposure to intra-nasal prototypic protein antigens was associated with rapid partial activation of the antigen-specific B cells, characterized by increased expression of MHCII and co-stimulatory molecules, whereas in the absence of B cells, respiratory tolerance could not be induced [184].

The usage of a-CD154 as a new strategy for elongating allograft tolerance has been investigated. However, allogeneic C57BL/6 hearts were rejected in 9 days when transplanted into untreated BALB/c recipients, while treatment with anti-CD154/DST (donor-specific transfusion) induced long-term allograft survival. Such studies revealed that the alloreactive-specific B cell responses are inhibited by regulatory T cells acting to constrain T cell help [185]. Or B cells were deleted in the periphery at the mature stage [186]. Whereas, other study argued that anti-CD154 treatment could suppress B cell responses, but not induce B cell tolerance [187]. Another allograft tolerant model induced by blockade of CD40/CD154 costimulation concluded that recruitment of Foxp3+ Treg cells to an allograft tissue was a vital factor, dependent in turn on the expression of the chemokine receptor, CCR4 [188]. Other results from transgenic mouse models have suggested that CD4+ T cells may play an important role in the elimination of peripheral auto-reactive B cells through MHC class II/T cell receptor, CD40/CD40L and Fas/FasL interactions [189,190]. By studying CD40L-deficient and MHC class II-deficient patients, the results revealed that antibody reactivity-new emigrant B cells was similar to those from healthy donors, suggesting that CD40/CD40L interactions and antigen presentation do not regulate central B cell tolerance. In contrast, mature naive B cells from CD40L-deficient and MHC class II-deficient patients expressed a high percentage of auto-reactive antibodies [191]. Therefore, CD40/CD40L interaction and antigen presentation are both essential for the establishment of peripheral naive B cell tolerance. The decreased numbers of Treg cells in both CD40L-deficient and MHC class II-deficient patients suggested that these cells may be involved in regulating peripheral human B cell tolerance through MHC class II/TCR and CD40/CD40L interactions [191]. However, the mechanism\s of how alloreactive B cells are regulated by such costimulation-targeted therapies is not clear.

6. MECHANISM OF SUPPRESSION OF B CELL FUNCTION BY NTREGS: DIRECT AND INDIRECT MECHANISMS

The suppressive activity of naturally occurring mouse $CD4^+CD25^+$ T (nTreg) cells on T-cell activation has been well studied. But the interaction between B cells and nTreg has more complications. However, it remains unclear whether that nTreg do as a direct inhibitor on B-

cell function or whether the effects are mediated indirectly by an inhibition of T-helper function, in the other words, it has been unknown whether Foxp3+ Tregs can directly suppress B cells to suppress, for instance, Ig production or whether they have to suppress Th cells to indirectly suppress the B cell response. On the other hand, few papers have established to investigate the suppressive role of nTregs against B cells. We will discuss all propose and putative aspects of mechanisms of nTreg that may use in the suppression of B cells functions.

6.1 Inhibition of Proliferation

B cells proliferate after activation through T-dependent and T-independent manners. Proliferated B cells must be under control to prevent further harmful effects. The most important regulator in the immune system is naturally-occurring regulatory T cells. Many studies have demonstrated that these regulatory cells exert their function through cell-cell contact manner. However, Zhao and co-workers reported that $CD4^+CD25^+$ T cells suppress B-cell proliferation in response to polyclonal B-cell activators by inducing death of the responding B cells. Most interestingly, B-cell death is not mediated by the Fas–FasL pathway, but instead is mediated by a granzyme-dependent, partially perforin-dependent pathway [176], whereas others have demonstrated that the suppression of B cells by cytotoxic CD4+ was lysed the target cell by Fas\FasL manner [192]. Because $CD4^+CD25^+$ T cells must be activated via their TCR to exert their inhibitory effects on responder T cells, it has found that inhibition of LPS-induced B-cell proliferation was not observed when freshly explanted $CD4^+CD25^+$ T cells were added in the absence of a TCR stimulus. However, addition of anti-CD3, soluble or plate-bound, to the co-cultures of fresh $CD4^+CD25^+$ T cells with B cells also did not affect B-cell proliferation [176]. Furthermore, this study has shown that no suppression of B-cell proliferation was observed in the absence of TCR re-stimulation, but potent suppression of B-cell proliferation was observed when the pre-activated $CD4^+CD25^+$ T cells were re-stimulated with anti-CD3. Similar results were obtained when B cells were activated with anti-IgM $F(ab')_2$ or anti-CD40 [176]. To test whether the presence of Treg cells altered the proliferative response of the transferred anti-chromatin B cells, Fields et al. [193] revealed that CFSE-labeled anti-chromatin B cells transferred without exogenous T cells or with only Treg cells underwent minimal proliferation. In contrast, in the presence of Th cells, many anti-chromatin B cells proliferated and this was not significantly diminished with the addition of Treg cells [193]. Collectively, these results indicated that nTreg could suppress B cell proliferation through Fas/FasL manner or it used other strategy to induce B cell lysis through granzyme-dependent manner. The contradictory between the results of different experiments may dependent on the different conditions of each experiment.

6.2 Down Regulation of Antigen-Presenting Function

The significance of the antigen presenting function of B cells has been described. B cells can internalize antigen via BCR in a receptor-mediated endocytosis manner. Also, they can act as antigen-presenting cell for protein antigens and can present self or non-self antigens to CD4+ T cells to activate these cells. Several factors have supported or diminished this function reviewed in ref. [194]. However, B cells can actively induce CD4+ T cells activation and then participate in the generation or regulation of immune responses. By contrast, CD4+ T cells produce ILs that important for activation and proliferation of B cells then facilitate their differentiation to antibody-secreting plasma cells or memory cells. However, if B cell interacts with nTreg instead of CD4+ T cell through MHC class II-antigen complex/TCR, the outcome of such interaction is absolutely different.

B cells have to encounter their specific antigen and CD40L on activated CD4+ T cells to activate their antigen presenting function. After this encounter, some co-stimulatory molecules up-regulate on activated B cells such as B7 (CD80 and CD86) molecules, facilitate further interaction with CD28 and CTLA-4 on CD4+ T cells. It has shown that a few remaining B cells displayed a small shift in activation markers (CD80 and CD86) when anti-chromatin B cells were transferred in the presence of Treg cells alone. While, in the presence of Th cells, the anti-chromatin B cells expressed higher levels of B220, CD80, CD86 and CXCR5 [193], concluding that anti-chromatin B cells transferred with Th cells have a more mature phenotype compared with anti-chromatin B cells transferred in the absence of exogenous Th cells. Furthermore, the co-administration of Treg cells did not alter the expression levels of these

markers [193]. Moreover, our results revealed that the percentage of Splenic and lymph node-B cells- expressing costimulatory molecules and also the expression of these molecules on the mentioned B cells increased after 24 h and was decreased after 48 h and 72 h upon activation by T-dependent and T-independent stimuli when whole population of these organs cultured separately (unpublished data), indicating that B cells characterize by maturation after 24 h of activation and start to loss the expression of costimulatory molecules negatively with the period of incubation.

Lymphocyte activation gene 3(LAG-3) is a CD4-related protein and is highly expressed on activated Treg. The reliable role of LAG-3 in the suppressive function of nTregs is not clear. However, LAG-3 binds to MHC class II molecules on APCs and thus reduces their ability to activate responder T cells. Antibodies to LAG-3 inhibit suppression by induced Treg both *In vitro* and *In vivo* [195].

6.3 Inhibition of Immunoglobulin Production

Immunoglobulin production considers one of the most important mechanisms against different pathogens. However, in some cases, such as in the autoimmune diseases, autoantibodies attack self organs or tissues and cause very harmful results. In such cases the control of autoantibodies decreasing the harmful effects and control of general aberrations. Lim et al. [196] have demonstrated that regulatory T cells can suppress B-cell–dependent immunoglobulin production and class switch recombination in the absence of T-helper cells. They have provided evidence that Foxp3+ Tregs are present in B cell areas (the majority of Foxp3+ T cells were localized in the T cell zone. It was notable that quite a few Foxp3+cells were found in T-B border areas including mantle zones) where T-B cell interaction and humoral immune responses are believed to occur and that they can directly suppress B cell Ig production and CSR without having to suppress Th cells. Also, small but significant numbers of Foxp3+ T cells were seen within the GCs. They have shown that Tregs can directly suppress B cells in addition to T cells [196]. Generally, Tregs need cell-cell contact with target cells to suppress them. When the Tregs were separated from B cells, B cell response was not suppressed, suggesting that the direct B cell suppression activity of Tregs requires cell-cell contact between B cells and Tregs. Although controversial, TGF-β1 and CTLA-4 are implicated in Treg suppression of non-Tregs, when used neutralizing Abs to block these molecules in culture. Abs to TGF-β1 and CTLA-4 had partial (~30%) blocking effects, suggesting possible involvement of these molecules as well as other unidentified molecules in Treg suppression of B cells [196].

Furthermore, the effect of Tregs suppression of immunoglobulin in some autoimmune diseases was studied. It has demonstrated that Tregs suppressed IgG production whereas Th cells did not, suggesting the ability of lupus Tregs to directly inhibit Ab production from B cells and it has found that the age of the mice did not affect the ability of Tregs to suppress B cells, suggesting that Treg-mediated suppression of B cells in SLE may not occur through Fas/FasL and TNF/TNFR pathways. However, as for nonautoimmune Tregs, NZB/W Tregs can use granule exocytosis pathways that involve perforin and granzyme to inhibit lupus B cells [197].

In model of third-party adoptive transfer to track the fates of Treg, Th and anti-chromatin B cells *In vivo*, Fields and his colleagues have shown that Anti-chromatin B cells produced significant amounts of autoantibodies 8 days after transfer of CD4+CD25− Th cells, but the coinjection of CD4+CD25+ Treg cells blocked the production of these antibodies [193]. Also they provided evidence that the presence of Treg cells during the initial stages of the Th/B cell interactions is required for full inhibition of autoantibody production. Moreover, in some induced models of autoantibody production, injection of Treg cells decreased or abolished autoantibody levels *In vivo* [198-200]. It has been proposed that CD4+CD25+ T cells which isolated from mouse spleen can suppress mitogen-induced Ig production by splenocytes [201]. Collectively, these results demonstrate clearly that Tregs play a pivotal or crucial role in the control or inhibition the production of antibodies that affect or interact with other immune functions and cause unwanted results.

6.4 Cytotoxic Effect

Targets of the cytotoxic effects encompass CD4+ T cells, CD8+ T cells, monocytes, antigen-presenting B cells and DCs. However, approximately all investigations have demonstrated that mechanisms which use by

nTregs to suppress other responder cells *In vitro* need cell-cell contact or direct interaction between two populations of cells [202]. Thus nTregs can induce or cause cytotoxic effect to kill target cells via perforin and\or granzyme manner [197] or via Fas\FasL manner [203]. Fas (CD95) is a type I membrane protein in the tumor necrosis factor receptor family [204]. FasL (CD95L) is a transmembrane protein and soluble FasL trimmers can be generated by a metalloprotease process [205]. However, the cytotoxic effect of nTregs have been well documented when effector T cells were the goal of suppression. Whereas the mechanism of nTreg-cytotoxic effect upon B cells was rare studied and need further investigations. The requirements for cell-to-cell contact of nTreg-mechanism of suppression have been investigated using transwell experiment model to segregate between nTregs and effector T cells. It has revealed that murine Treg cells can induce killing effect in responder T cells by granzyme and\or perforin-dependent mechanism [206]. The exclusive function of Fas is to transduce the apoptotic signals from cells that express FasL and the induction of apoptosis is believed to involve in self-tolerance by elimination unwanted cells such as auto-reactive T and B cells. The defection in this system lead to the breakdown of self-tolerance and cause different abnormal diseases. In addition to perforin\granzyme manner and Fas\FasL manner, nTregs use other factors with potential involvement in killing target cells. These molecules are Lag-3 [195], membrane-bound TGFβ [201], cytotoxic T-lymphocyte antigen 4 (CTLA-4) [207,208], galectin-1 [209] and programmed death-1 (PD-1) [210].

6.5 Indirect Effect via the Suppression of T helper Cells

Tregs can influence B cells indirectly by suppressing the T helper cells required for B cell activation and antibody production [193,196]. It has demonstrated that if nTregs suppress target cells by cell-cell contact, it is not known which target is under control, Th cells or APC cells [202]. In adoptive transfer model, Field et al. [193] have documented that presence of Tregs induce a dramatically reduction in the number of all group of Th cells (Th, Th1 and Th2) by day 8.

Collectively nTregs can suppress different faces of B cell functions and activity via direct interaction or to suppress Th and thereby prevent further interaction needed between Th and B cells for further activation and cytokine production.

7. CONCLUSION

B cells can influence immune system by two ways, positive and negative. As positive players, it has been found that B cells can take part in antigen presentation via MHCII molecules that express constitutively on their membrane and up-regulate rapidly upon activation. In addition to their function as APCs, B cells have multiple functions in adaptive immune system, for instance antibody secreting cells and eventually form a germinal center (GC) response, are critical cellular adjuvants that facilitate optimal CD4+ T-cell activation. B cells also contribute to immunoregulation through the production of cytokines including IL-4, IL-6, IL-10, interferon-gamma (IFN-gamma) and transforming growth factor-β (TGF-β). In addition, B cells are thought to have specific roles in stimulating Ag-specific CD4+ T-cell proliferation after activation by DCs. As negative players, B cells can play a crucial roles during immune responses, particularly during inflammation, autoimmunity, cancer and infection. Thus these type of cells have to put under control to avoid further harmful in the different tissues of the body. The most professional regulator in the immune system is Tregs and especially nTregs. nTregs can suppress\regulate wide spectrum of innate and adaptive immune cells. The question that still unresolved is how such small percentage of cells (about 1-2% of CD4+ in periphery) can regulate and control wide spectrum of cells? In current article we tried to resolve this question in addition to give some useful general knowledge with deep explanation to give a complete insight in the relationship between B and Treg cells.

COMPETING INTERESTS

Author has declared that no competing interests exist.

REFERENCES

1. Monson NL. The natural history of B cells. Curr Opin Neurol. 2008;21(Suppl 1):S3-8.
2. Ghia P, Ten Boekel E, Rolink AG, Melchers F. B-cell development: A comparison between mouse and man. Immunol Today. 1998;19:480–5.

3. Adolfsson J, Mansson R, Buza-Vidas N, Hultquist A, et al. Identification of Flt3 + lympho-myeloid stem cells lacking erythro-megakaryocytic potential a revised road map for adult blood lineage commitment. Cell. 2005;121:295-306.
4. Forsberg EC, Serwold T, Kogan S, Weissman IL, Passegue E. New evidence supporting megakaryocyte-erythrocyte potential of flk 2/flt 3+ multipotent hematopoietic progenitors. Cell. 2006;126:415-426.
5. Kalled SL. Impact of the BAFF/BR3 axis on B cell survival, germinal center maintenance and antibody production. Seminars in Immunol. 2006;18:290–296.
6. Messner HA. Human hemopoietic progenitors and their signals. Bone Marrow Transplant. 1991;7(Suppl 1):18-22.
7. Pillai S, Baltimore D. Formation of disulphide-linked mu 2 omega 2 tetramers in pre-B cells by the 18 K omega immunoglobulin light chain. Nature. 1987; 329:172-174.
8. Karasuyama H, Kudo A, Melchers F. The proteins encoded by the Vpre B and lambda 5 pre-B cell-specific genes can associate with each other and with mu heavy chain. J. Exp. Med. 1990;172:969-972.
9. Martensson IL, Ceredig R. Review article: role of the surrogate light chain and the pre-B-cell receptor in mouse B-cell development. Immunology. 2000;101:435-441.
10. Grawunder U, Haasner D, Melchers F, Rolink A. Rearrangement and expression of kappa light chain genes can occur without mu heavy chain expression during differentiation of pre-B cells. Int Immunol 1993;5:1609-1618.
11. Decker DJ, Kline GH, Hayden TA, Zaharevitz SN, Klinman NR. Heavy chain V gene-specific elimination of B cells during the pre-B cell to B cell transition. J Immunol. 1995;154:4924-4935.
12. Nemazee D, Kouskoff V, Hertz M, Lang J, Melamed D, Pape K, Retter M. B-cell-receptor-dependent positive and negative selection in immature B cells. Curr Top Microbiol Immunol. 2000;245:57-71.
13. Sebzda E, Mariathasan S, Ohteki T, Jones R, Bachmann MF, Ohashi PS. Selection of the T cell repertoire. Annu Rev Immunol. 1999;17:829–874.
14. Dunn-Walters DK, Ademokun AA. B cell repertoire and ageing. Current Opinion in Immunology. 2010;22:514–520.
15. Poulsen TR, Meijer PJ, Jensen A, Nielsen LS, Andersen PS. Kinetic, affinity and diversity limits of human polyclonal antibody responses against tetanus toxoid. J. Immunol. 2007;179:3841-50.
16. Hartley SB, Crosbie J, Brink R, Kantor AB, Basten A, Goodnow CC. Elimination from peripheral lymphoid tissues of self-reactive B lymphocytes recognizing membrane-bound antigens. Nature. 1991;353:765–769.
17. Tiegs SL, Russell DM, Nemazee D. Receptor editing in self-reactive bone marrow B cells. J. Exp. Med. 1993;177: 1009–1020.
18. Rathmell JC, Goodnow CC. Effects of the lpr mutation on elimination and inactivation of self-reactive B cells. J. Immunol. 1994; 153:2831–2842.
19. Melchers F, ten Boekel E, Seidl T, Kong XC, Yamagami T, Onishi K, et al. Repertoire selection by pre-B-cell receptors and B-cell receptors and genetic control of B-cell development from immature to mature B cells. Immunol Rev. 2000;175:33–46.
20. Allman DM, Ferguson SE, Lentz VM, Cancro MP. Peripheral B cell maturation. II. Heat-stable antigen (hi) splenic B cells are an immature developmental intermediate in the production of long-lived marrow-derived B cells. J. Immunol. 1993; 151:4431-4444.
21. Viau M, Zouali M. B-lymphocytes, innate immunity and autoimmunity. Clin Immunol. 2005;114:17– 26.
22. Cooper NR. The classical complement pathway: Activation and regulation of the first complement component. Adv Immunol. 1985;37:151–216.
23. Kalesnikoff J, Huber M, Lam V, Damen JE, Zhang J, Siraganian RP, et al. Monomeric IgE stimulates signaling pathways in mast cells that lead to cytokine production and cell survival. Immunity. 2001;14:801–11.
24. Leibson PJ. Signal transduction during natural killer cell activation: Inside the mind of a killer. Immunity. 1997;6:655–61.

25. Takai T, Ono M, Hikida M, Ohmori H, Ravetch JV. Augmented humoral and anaphylactic responses in Fc gamma RII-deficient mice. Nature. 1996;379:346–9.
26. Beaven MA, Metzger H. Signal transduction by Fc receptors: the Fc epsilon RI case. Immunol. Today. 1993; 14:222–226.
27. Allen CDC, Okada T, Cyster JG. Germinal-center organization and cellular dynamics. Immunity. 2007;27:190–202.
28. Tew JG, Wu J, Fakher M, Szakal AK, Qin D. Follicular dendritic cells: Beyond the necessity of T-cell help. Trends Immunol. 2001;22(7):361–7.
29. Male D, Brostoff J, Roth DB, Roitt I. Immunology, 7th edition, Mosby Elsevier; 2006.
30. Pasare C, Medzhitov R. Control of B-cell responses by Toll-like receptors. Nature. 2005;438:364–368.
31. Cooper MD, Kearney JF, Gathings WE, Lawton AR. Effects of anti-Ig antibodies on the development and differentiation of B cells. Immunol Rev. 1980;52:29-53.
32. Mac Lennan ICM. Germinal centers. Annu. Rev. Immunol. 1994;12:117-139.
33. Smith KC, Weiss U, Rajewski K, Nossal GJV, Tarlinton DM. BCL-2 increses memory B cell recruitment but does not perturb selection in germinal centers. Immunity. 1994;1:803-813.
34. Rabet LM, Paul Vos A, Boehm G, Garssen J. Breast-feeding and its role in early development of the immune system in infants: Consequences for Health later in life. J. Nutr. 2008;138:1782S–1790S.
35. Franceschi C, Cossarizza A. Introduction: The reshaping of the immune system with age. Int. Rev. Immunol. 1995;12:1–4.
36. Johnson SA, Cambier JC. Ageing, autoimmunity and arthritis: Senescence of the B cell compartment—implications for humoral immunity. Arthritis Res. Ther. 2004;6:131–139.
37. Allman D, Miller JP. B cell development and receptor diversity during aging. Curr. Opin. Immunol. 2005;17:463–467.
38. Frasca D, Riley RL, Blomberg BB. Humoral immune response and B-cell functions including immunoglobulin class switch are down regulated in aged mice and humans. Semin. Immunol. 2005;17:378–384.
39. Adkins B, et al. Neonatal adaptive immunity comes of age. Nat. Rev. Immunol. 2004;4:553–564.
40. Levy O. Innate immunity of the newborn: Basic mechanisms and clinical correlates. Nat. Rev. Immunol. 2007;7:379–390.
41. Pastorelli G, Rousset F, Pene J, Peronne C, Roncarolo MG, Tovo PA, de Vries JE. Cord blood B cells are mature in their capacity to switch to IgE-producing cells in response to interleukin-4 *In vitro*. Clin Exp. Immunol. 1990;82:114–9.
42. Zhao J, Yang X, Auh SL, Kim KD, Tang H, Fu Y. Do adaptive immune cells suppress or activate innate immunity? Immunol. 2008;30:8-12.
43. Mellander L, Carlsson B, Jalil F, Soderstrom T, Hanson LA. Secretory IgA antibody response against Escherichia coli antigens in infants in relation to exposure. J. Pediatr. 1985;107:430–3.
44. Brissac C, Nobrega A, Carneiro J, Stewart J. Functional diversity of natural IgM. Int Immunol. 1999;11:1501-07.
45. Miller J, Allman D. The decline in B lymphopoiesis in aged mice reflects loss of very early B-lineage precursors. J. Immunol. 2003;171:2326–2330.
46. Alter-Wolf S, Blomberg BB, Riley RL. Old mice retain bone marrow B1 progenitors, but lose B2 precursors and exhibit altered immature B cell phenotype and light chain usage. Mech. of Ageing and Dev. 2009;130:401–408.
47. Alter-Wolf S, Blomberg BB, Riley RL. Deviation of the B cell pathway in senescent mice is associated with reduced surrogate light chain expression and altered immature B cell generation, phenotype and light chain expression. J. Immunol. 2009;182:138–147.
48. Le Bien TW. Fates of human B-cell precursors. Blood. 2000;96:9–23.
49. Holl TM, Haynes BF, Kelsoe G. Stromal cell independent B cell development *in vitro*: Generation and recovery of autoreactive clones. J. of Immunol. Methods. 2010;354:53–67.
50. Allman D, Pillai S. Peripheral B cell subsets. Current Opinion in Immunology. 2008;20:149–157.

51. Ronet C, Hauyon-La Torre Y, Revaz-Breton, et al. Regulatory B cells shape the development of Th 2 immune responses in BALB/c mice infected with Leishmania major through IL-10 production. J. Immunol. 2010;184:886–894.
52. Wang X, Qi Z, Wei H, Tian Z, Sun R. Characterization of human B cells in umbilical cord blood-transplanted NOD/SCID mice. Trans. Immunol. 2012; 26:156–162.
53. Thomas MD, Srivastava B, Allman D. Regulation of peripheral B cell maturation. Cellular Immunology. 2006;239:92–102.
54. Haas KM, Poe JC, Steeber DA, Tedder TF. B-1a and B-1b cells exhibit distinct developmental requirements and have unique functional roles in innate and adaptive immunity to S. Pneumoniae. Immunity. 2005;23:7–18.
55. Griffin DO, Holodick NE, Rothstein TL. Human B 1 cells in umbilical cord and adult peripheral blood express the novel phenotype $CD20^{+}CD27^{+}CD43^{+}CD70$. J. Exp. Med. 2011;208(1):67–80.
56. Kantor AB, Herzenberg LA. Origin of murine B cell lineages. Annu. Rev. Immunol. 1993;11:501–538.
57. Tung JW, et al. Identification of B-cell subsets: An exposition of 11-color [Hi-D] FACS analysis. Methods Mol. Biol. 2004; 271:37–58.
58. Abrahao TB, Freymuller E, Mortara RA, Lopes JD, Mariano M. Morphological characterization of mouse B-1 cells. Immunobiol. 2003;208:401-411.
59. Zhang M, Zheng X, Zhang J, Zhu Y. CD19+CD1d+CD5+ B cell frequencies are increased in patients with tuberculosis and suppress Th 17 responses. Cellular Immunol. 2012;274:89–97.
60. Yanaba K, et al. A regulatory B cell subset with a unique $CD1d^{hi}CD5^{+}$ phenotype controls T cell dependent inflammatory responses. Immunity. 2008;28:639–650.
61. Matsushita T, et al. Regulatory B cells inhibit EAE initiation in mice while other B cells promote disease progression. J. Clin. Invest. 2008;118:3420–3430.
62. Wen L, Brill-Dashoff J, Shinton SA, Asano M, Hardy RR, Hayakawa K. Evidence of Marginal-Zone B Cell-Positive Selection in Spleen. Immunity. 2005;23:297–308.
63. Pillai S, Cariappa A, Moran ST. Marginal zone B cells. Annu. Rev. Immunol. 2005;23:161–196.
64. Hardy RR, Hayakawa K. B cell development pathways, Annu. Rev. Immunol. 2001;19:595–621.
65. Vitale G, Mion F, Pucillo C. Regulatory B cells: Evidence, developmental origin and population diversity. Mol. Immunol. 2010;48:1–8.
66. Hussaarts L, et al. Regulatory B-cell induction by helminths: Implications for allergic disease. J. Allergy clin. Immunol. 2011;128:733-39.
67. Hardy RR, Li YS, Allman D, Asano M, Gui M, Hayakawa K. B-cell commitment, development and selection Immunol. Rev. 2000;175:23–32.
68. Busslinger M, Nutt SL, Rolink AG. Lineage commitment in lymphopoiesis. Curr. Opin. Immunol. 2000;12:151–158.
69. Allman D, Li J, Hardy RR. Commitment to the B-lymphoid lineage occurs prior to DH-JH recombination J. Exp. Med. 1999; 189:735–740.
70. Hardy RR, Carmack CE, Shinton SA, Kemp JD, Hayakawa K. Resolution and characterization of Pro-B and pre-pro-B cell Stages in normal mouse bone marrow. J. Exp. Med. 1991;173:1213–1225.
71. Lu L, Tung J, Baumgarth N, Herman O, et al. Identification of a germ-line pro-B cell subset that distinguishes the fetal\neonatal from the adult B cell development pathway. PNAS. 2002;99(5):3007–3012.
72. Pillai S. The chosen few: Positive selection and the generation of naïve B lymphocytes. Immunity. 1999;10:493–502.
73. Martin F, Kearney JF. Positive selection from newly formed to marginal zone B cells depends on the rate of clonal production, CD19 and btk. Immunity. 2000;12:39–49.
74. Ho F, Lortan JE, MacLennan IC, Khan M. Distinct short-lived and long-lived antibody-producing cell populations. Eur J. Immunol. 1986;16:1297–1301.
75. Takahashi Y, Dutta PR, Cerasoli DM, Kelsoe G. In situ studies of the primary immune response to (4-hydroxy-3-nitrophenyl) acetyl. V. Affinity maturation develops in two stages of clonal selection. J. Exp Med. 1998;187:885–895.

76. DiLillo DJ, et al. Maintenance of long-lived plasma cells and serological memory despite mature and memory B cell depletion during CD20 immunotherapy in mice. J. Immunol. 2008;180:361–371.

77. Berland R, Wortis HH. Origins and functions of B-1 cells with notes on the role of CD5. Annu Rev Immunol. 2002;20:253–300.

78. Baumgarth N, Herman OC, Jager GC, Brown LE, Herzenberg LA, Chen J. B-1 and B-2 cell-derived immunoglobulin M antibodies are nonredundant components of the protective response to influenza virus infection. J. Exp. Med. 2000;192: 271–280.

79. Boes M, Prodeus AP, Schmidt T, Carroll MC, Chen J. A critical role of natural immunoglobulin M in immediate defense against systemic bacterial infection. J. Exp. Med. 1998;188:2381–6.

80. Baumgarth N, Tung JW, Herzenberg LA. Inherent specificities in natural antibodies: A key to immune defense against pathogen invasion. Springer Semin. Immunopathol. 2005;26:347–362.

81. Murakami M, Yoshioka H, Shirai T, Tsubata T, Honjo T. Prevention of autoimmune symptoms in auto-immune-prone mice by elimination of B-1 cells. Int. Immunol. 1995;7:877–882.

82. Martin F, Oliver AM, Kearney JF. Marginal zone and B1 B cells unite in the early response against T-independent blood-borne particulate antigens. Immunity. 2001;14:617–629.

83. Martin F, Kearney JF. B1 cells: Similarities and differences with other B cell subsets. Curr. Opin. Immunol. 2001;13:195–201.

84. DeLorenzo BH, Brito RR, Godoy LC, Lopes JD, Mariano M. Tolerogenic property of B-1b cells in a model of allergic reaction. Immunol. Lett. 2007;114:110–118.

85. Szczepanik M, Akahira-Azuma M, Bryniarski K, Tsuji RF, Kawikova I, Ptak W, Kiener C, Campos RA, Askenase PW. B-1 B cells mediate required early T cell recruitment to elicit protein-induced delayed-type hypersensitivity. J. Immunol. 2003;171:6225–6235.

86. Rothstein TL, Kolber DL. Peritoneal B cells respond to phorbol esters in the absence of co-mitogen. J. Immunol. 1988;140: 2880–2885.

87. Hastings WD, Gurdak SM, Tumang JR, Rothstein TL. CD5+/Mac-1− peritoneal B cells: A novel B cell subset that exhibits characteristics of B-1 cells. Immunology Letters. 2006;105:90–96.

88. Kelly-Welch AE, Melo ME, Smith E, Ford AQ, Haudenschild C, Noben-Trauth N, et al. Complex role of the IL-4 receptor alfa in a murine model of airway inflammation: expression of the IL-4 receptor alfa on non-lymphoid cells of bone marrow origin contributes to severity of inflammation. J Immunol. 2004;172:4545–55.

89. Vigna AF, Godoy LC, Rogeriod A, Mariano M, Lopes JD. Characterization of B-1b cells as antigen presenting cells in the immune response to gp43 from Paracoccidioides brasiliensis *In vitro*. Immunol Lett. 2002;83:61–6.

90. Alugupalli KR, Leong JM, Woodland RT, Muramatsu M, Honjo T, Gerstein RM. B 1b lymphocytes confer T cell-independent long-lasting immunity. Immunity. 2004;21: 379–90.

91. Al Qaoud KM, Fleischer B, Hoerauf A. The Xid defect imparts susceptibility to experimental murine filariosis-association with a lack of antibody and IL-10 production by B cells in response to phosphorylcholine. Int Immunol. 1998;10: 17–25.

92. Herzenberg LA. B-1 cells: The lineage question revisited. Immunol. Rev. 2000; 175:9–22.

93. Herzenberg LA, Tung JW. B cell lineages: Documented at last! Nat. Immunol. 2006;7:225–226.

94. Lam KP, Rajewsky K. B cell antigen receptor specificity and surface density together determine B-1 versus B-2 cell development. J. Exp. Med. 1999;190:471–477.

95. Rolink AG, Melchers F. B-cell development in the mouse. Immunol Lett. 1996;54:157–61.

96. Cariappa A, Tang M, Parng C, Nebelitskiy E, Carroll M, Georgopoulos K, Pillai S. The follicular versus marginal zone B lymphocyte cell fate decision is regulated by Aiolos, Btk and CD21, Immunity. 2001; 14:603-615.

97. Casola S, Otipoby KL, Alimzhanov M, Humme S, Uyttersprot N, Kutok JL, Carroll MC, Rajewsky K. B cell receptor signal strength determines B cell fate. Nat. Immunol. 2004;5:317-327.

98. Oliver AM, Martin F, Kearney JF: IgM^{high} $CD21^{high}$ lymphocytes enriched in the splenic marginal zone generate effector cells more rapidly than the bulk of follicular B cells. J. Immunol. 1999;162:7198-7207.

99. McHeyzer-Williams LJ, McHeyzer-Williams MG. Antigen-specific memory B cell development. Annu. Rev. Immunol. 2005; 23:487–513.

100. Martin F, Kearney JF. Marginal-zone B cells. Nat Rev Immunol. 2002;2:323–35.

101. Colgan SP, Hershberg RM, Furuta GT, Blumberg RS. Ligation of intestinal epithelial CD1d induces bioactive IL-10: Critical role of the cytoplasmic tail in autocrine signaling. Proc. Natl. Acad. Sci. U.S.A. 1999;96:13938–13943.

102. Sonoda KH, Stein-Streilein J. CD1d on antigen-transporting APC and splenic marginal zone B cells promotes NKT cell dependent tolerance. Eur. J. Immunol. 2002;32:848–857.

103. Leadbetter EA, Brigl M, Ilaironov P, Cohen N, Luteran MC, Pillai S, Besra GS, Brenner MB. NK T cells provide lipid antigen-specific cognate help for B cells. Proc. Natl. Acad. Sci. U.S.A. 2008;105:8339-44.

104. Zhang P, Li W, Wang Y, Houa L, Xing Y, et al. Identification of CD36 as a new surface marker of marginal zone B cells by transcriptomic analysis. Molecular Immunol. 2007;44:332–337.

105. Tanigaki K, Han H, Yamamoto N, Tashiro K, Ikegawa M, Kuroda K, Suzuki A, Nakano T, Honjo T. Notch-RBP-J signaling is involved in cell fate determination of marginal zone B cells. Nat. Immunol. 2002; 3:443–450.

106. Saito T, Chiba S, Ichikawa M, Kunisato A, Asai T, Shimizu K, et al. Notch 2 is preferentially expressed in mature B cells and indispensable for marginal zone B lineage development. Immunity. 2003;18: 675–685.

107. Song H, Cerny J. Functional heterogeneity of marginal zone B cells revealed by their ability to generate both early antibody-forming cells and germinal centers with hypermutation and memory in response to a T-dependent antigen. J. Exp. Med. 2003; 198:1923-1935.

108. Attanavanich K, Kearney JF. Marginal zone, but not follicular B cells, are potent activators of naive CD4 T cells. J. Immunol. 2004;172:803-811.

109. Liu Y, Wu Y, Ramarathinam L, Guo Y, Huszar D, Trounstine M, Zhao M. Gene-targeted B-deficient mice reveal a critical role for B cells in the CD4 T cell response. Int. Immunol. 1995;7:1353–1362.

110. DiLillo DJ, Matsushita T, Tedder TF. B10 cells and regulatory B cells balance immune responses during inflammation, autoimmunity and cancer. Ann. N. Y. Acad. Sci. 2010;1183:38–57.

111. Youinou P. B cell conducts the lymphocyte orchestra. J. of Autoimmunity. 2007;28: 143-151.

112. Xiao Y, Hendriks J, Langerak P, Jacobs H, Borst J. CD27 is acquired by primed B cells at the centroblast stage and promotes germinal center formation. J. Immunol. 2004;172:7432–7441.

113. Schittek B, Rajewsky K. Natural occurrence and origin of somatically mutated memory B cells in mice. J. Exp. Med. 1992;176:427–438.

114. Liu AH, Jena PK, Wysocki LJ. Tracing the development of single memory-lineage B cells in a highly defined immune response. J. Exp. Med. 1996;183:2053–2063.

115. Yoshida T, Mei H, Dorner T, Hiepe F, Radbruch A, Fillatreau S, Hoyer BF. Memory B and memory plasma cells. Immunol. Rev. 2010;237:117–139.

116. Shlomchik MJ, Marshak-Rothstein A, Wolfowicz CB, Rothstein TL, Weigert MG. The role of clonal selection and somatic mutation in autoimmunity. Nature. 1987; 328:805-811.

117. Pillai S, Mattoo H, Cariappa A. B cells and autoimmunity. Current Opinion in Immunology. 2011;23:721–731.

118. 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.

119. 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.

120. 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.
121. 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.
122. 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, Igμ^{null} mice. J. Exp Med. 1996;184:2049–53.
123. 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.
124. Mizoguchi E, Mizoguchi A, Preffer FI, Bhan AK. Regulatory role of mature B cells in a murine model of inflammatory bowel disease. Int. Immunol. 2000;12:597–605.
125. Mizoguchi A, Mizoguchi E, Takedatsu H, Blumberg RS, Bhan AK. Chronic intestinal inflammatory condition generates IL-10-producing regulatory B cell subset characterized by CD1d upregulation. Immunity. 2002;16:219–230.
126. Lenert P, Goeken A, Handwerger BS, et al. Innate immune responses in lupus-prone Palmerston North mice: Differential responses to LPS and bacterial DNA/CpG oligonucleotides. J. Clin. Immunol. 2003; 23:202–213.
127. Lenert P, Brummel R, Field EH, et al. TLR-9 activation of marginal zone B cells in lupus mice regulates immunity through increased IL-10 production. J. Clin. Immunol. 2005;25:29–40.
128. Brummel R, Lenert P. Activation of marginal zone B cells from lupus mice with type A(D) CpG-oligodeoxynucleotides. J. Immunol. 2005;174:2429–2434.
129. Bernasconi NL, Traggiai E, Lanzavecchia A. Maintenance of serological memory by polyclonal activation of human memory B cells. Science. 2002;298:2199–2202.
130. Dörner T, Jacobi AM, Lee J, Lipsky PE. Abnormalities of B cell subsets in patients with systemic lupus erythematosus. J. of Immunol. Met. 2011;363:187–197.
131. Fillatreau S, Sweenie CH, McGeachy MJ, Gray D, Anderton SM. B cells regulate autoimmunity by provision of IL-10. Nat. Immunol. 2002;3:944–950.
132. Matsushita T, Fujimoto M, Hasegawa M, Komura K, Takehara K, Tedder TF, Sato S. Inhibitory role of CD19 in the progression of experimental autoimmune encephalomyelitis by regulating cytokine response. Am. J. Pathol. 2006;168:812–821.
133. Mann MK, Maresz K, Shriver LP, Tan Y, Dittel BN. B cell regulation of CD4+CD25+ T regulatory cells and IL-10 via B7 is essential for recovery from experimental autoimmune encephalomyelitis. J. Immunol. 2007;178:3447–3456.
134. Salomon B, Lenschow DJ, Rhee L, et al. B7/CD28 costimulation is essential for the homeostasis of the CD4+CD25+ immunoregulatory T cells that control autoimmune diabetes. Immunity. 2000;12:431–440.
135. Mizoguchi A, Bhan AK. A case for regulatory B cells. J. Immunol. 2006;176: 705–710.
136. Uchida J, Hamaguchi Y, Oliver JA, Ravetch JV, Poe JC, Haas KM, Tedder TF. The innate mononuclear phagocyte network depletes B lymphocytes through Fc receptor-dependent mechanisms during anti-CD20 antibody immunotherapy. J. Exp. Med. 2004;199:1659–1669.
137. Bouaziz JD, Yanaba K, Venturi GM, Wang Y, Tisch RM, Poe JC, Tedder TF. Therapeutic B cell depletion impairs adaptive and autoreactive CD4+ T cell activation in mice. Proc. Natl. Acad. Sci. U.S.A. 2007;104:20882–20887.
138. Xiu Y, Wong CP, Hamaguchi Y, Wang Y, Pop S, Tisch RM, Tedder TF. B lymphocytes depletion by CD20 monoclonal antibody prevents diabetes in NOD mice despite isotype-specific differences in Fcg R effector functions. J. Immunol. 2008;180:2863–2875.

139. Bouaziz JD, Yanaba K, Tedder TF. Regulatory B cells as inhibitors of immune responses and inflammation. Immunol. Rev. 2008;224:201–214.

140. Bursch LS, Wang L, Igyarto B, Kissenpfennig A, Malissen B, Kaplan DH, Hogquist KA. Identification of a novel population of Langerin+dendritic cells. J. Exp. Med. 2007;204:3147–3156.

141. Crawford A, Macleod M, Schumacher T, Corlett L, Gray D. Primary T cell expansion and differentiation *In vivo* requires antigen presentation by B cells. J. Immunol. 2006;176:3498–3506.

142. Cua DJ, Groux H, Hinton DR, Stohlman SA, Coffman RL. Transgenic interleukin 10 prevents induction of experimental autoimmune encephalomyelitis. J. Exp. Med. 1999;189:1005–1010.

143. Bettelli E, Das MP, Howard ED, Weiner HL, Sobel RA, Kuchroo VK. IL-10 is critical in the regulation of autoimmune encephalomyelitis as demonstrated by studies of IL-10- and IL-4-deficient and transgenic mice. J. Immunol. 1998;161: 3299–3306.

144. Begum-Haque S, Christy M, Ochoa-Reparaz J, Nowak EC, Mielcarz D, Haque A, Kasper LH. Augmentation of regulatory B cell activity in experimental allergic encephalomyelitis by glatiramer acetate. J. of Neuroimmunol. 2011;232:136–144.

145. Berg DJ, Leach MW, Kuhn R, Rajewsky K, Muller W, Davidson NJ, Rennick D. Interleukin 10 but not interleukin 4 is a natural suppressant of cutaneous inflammatory responses. J. Exp. Med. 1995;182:99–108.

146. Ferguson TA, Dube P, Griffith TS. Regulation of contact hypersensitivity by interleukin 10. J. Exp. Med. 1994;179: 1597–1604.

147. Schwarz A, Grabbe S, Riemann H, Aragane Y, Simon M, Manon S, Andrade S, Luger TA, Zlotnik A, Schwarz T. *In vivo* effects of interleukin-10 on contact hypersensitivity and delayed-type hypersensitivity reactions. J. Invest. Dermatol. 1994;103:211–216.

148. Asadullah K, Sterry W, Volk HD. Interleukin-10 therapy-review of a new approach. Pharmacol. Rev. 2003;55:241–269.

149. Mauri C, Gray D, Mushtaq N, et al. Prevention of arthritis by interleukin 10-producing B cells. J. Exp. Med. 2003;197:489–501.

150. Munroe ME, Bishop GA. A costimulatory function for T cell CD40. J. Immunol. 2007;178:671–82.

151. Evans JG, Chavez-Rueda KA, Eddaoudi A, Meyer-Bahlburg A, Rawlings DJ, Ehrenstein MR, Claudia Mauri C. Novel suppressive function of transitional 2 B cells in experimental arthritis. J. Immunol 2007;178:7868-7878.

152. Takemura S, Klimiuk PA, Braun A, Goronzy JJ, Weyand CM. T cell activation in rheumatoid synovium is B cell dependent. J. Immunol. 2001;167:4710–18.

153. Hadeiba H, Sato T, Habtezion A, Oderup C, Pan J, Butcher EC. CCR9 expression defines tolerogenic plasmacytoid dendritic cells able to suppress acute graft-versus-host disease. Nat Immunol. 2008;9:1253-1260.

154. Keenan RA, De Riva A, Corleis B, Hepburn L, Licence S, Winkler TH, Martensson IL. Censoring of autoreactive B cell development by the pre-B cell receptor. Science. 2008;321:696-699.

155. Vinuesa CG, Sanz I, Cook MC. Dysregulation of germinal centres in autoimmune disease. Nat Rev Immunol. 2009;9:845-857.

156. Henderson RB, Grys K, Vehlow A, de Bettignies C, Zachacz A, Henley T, Turner M, Batista F, Tybulewicz VL. A novel Racdependent checkpoint in B cell development controls entry into the splenic white pulp and cell survival. J. Exp. Med. 2010;207:837-853.

157. Shlomchik MJ. Sites and stages of autoreactive B cell activation and regulation. Immunity. 2008;28:18-28.

158. Nemazee DA, Burki K. Clonal deletion of B lymphocytes in a transgenic mouse bearing anti-MHC class I antibody genes. Nature. 1989;337:562-566.

159. Goodnow CC, Crosbie J, Adelstein S, Lavoie TB, Smith-Gill SJ, Brink RA, Pritchard-Briscoe H, Wotherspoon JS, Loblay RH, Raphael K, et al. Altered immunoglobulin expression and functional silencing of self-reactive B lymphocytes in

transgenic mice. Nature. 1988;334:676-682.

160. Erikson J, Radic MZ, Camper SA, Hardy RR, Carmack C, Weigert M. Expression of anti-DNA immunoglobulin transgenes in non-autoimmune mice. Nature. 1991;349:331-334.
161. Radic MZ, Erickson J, Litwin S, Weigert M. B lymphocytes may escape tolerance by revising their antigen receptors. J. Exp. Med. 1993;177:1165-1173.
162. Gay D, Saunders T, Camper S, Weigert M. Receptor editing: An approach by autoreactive B cells to escape tolerance. J. Exp. Med. 1993;177:999-1008.
163. Hannum LG, Ni D, Haberman AM, Weigert MG, Shlomchik MJ. A disease-related rheumatoid factor autoantibody is not tolerized in a normal mouse: Implications for the origins of autoantibodies in autoimmune disease. J. Exp. Med. 1996;184:1269-1278.
164. Nemazee D. Does immunological tolerance explain the waste in the B-lymphocyte immune system? Experiment and theory. Ann. NY Acad. Sci. 1995;764:397–401.
165. Retter MW, Nemazee D. Receptor editing occurs frequently during normal B cell development. J. Exp. Med. 1998;188:1231-1238.
166. Casellas R, Shih TA, Kleinewietfeld M, Rakonjac J, Nemazee D, Rajewsky K, Nussenzweig MC. Contribution of receptor editing to the antibody repertoire. Science. 2001;291:1541-1544.
167. Oberdoerffer P, Novobrantseva TI, Rajewsky K. Expression of a targeted {lambda} 1 light chain gene is developmentally regulated and independent of Ig{kappa} rearrangements. J. Exp. Med. 2003;197:1165-1172.
168. Halverson R, Torres RM, Pelanda R. Receptor editing is the main mechanism of B cell tolerance toward membrane antigens. Nat Immunol. 2004;6:645-650.
169. Fan X, Ang A, Pollock-Barziv SM, Dipchand AI, Ruiz P, Wilson G, Platt JL, West LJ. Donor-specific B-cell tolerance after ABO-incompatible infant heart transplantation. Nat. Med. 2004;10:1227-1233.
170. Urschel S, Campbell PM, Meyer SR, Larsen IM, Nuebel J, Birnbaum J, Netz H, Tinckam K, Kauke T, Derkatz K, et al. Absence of donor-specific anti-HLA antibodies after ABO incompatible heart transplantation in infancy: Altered immunity or age? Am. J. Transplant. 2010;10:149-156.
171. Hasler P, Zouali M. Subversion of B lymphocyte signaling by infectious agents. Genes. Immun. 2003;4:95-103.
172. Rudnicka D, Schwartz O. Intrusive HIV-1-infected cells. Nat Immunol. 2009;10:933-934.
173. Baldari CT, Lanzavecchia A, Telford JL. Immune subversion by *Helicobacter pylori*. Trends Immunol. 2005;26:199-207.
174. Basten A, Silveira PA. B-cell tolerance: Mechanisms and implications. Current Opinion in Immunology. 2010;22:566–574.
175. Basten A, Brink R. Tolerance and autoimmunity: B cells. In The Autoimmune Diseases, fourth edn. Edited by Rose NR, Mackay IR. Academic Press. 2006;167-177.
176. Zhao DM, Thornton AM, DiPaolo RJ, Shevach EM. Activated CD4+CD25+ T cells selectively kill B lymphocytes. Blood. 2006;107:3925-3932.
177. Ludwig-Portugall I, Hamilton-Williams EE, Gottschalk C, Kurts C. Cutting edge: CD25+ regulatory T cells prevent expansion and induce apoptosis of B cells specific for tissue autoantigens. J. Immunol. 2008;181:4447-4451.
178. Healy JI, Goodnow CC. Positive versus negative signaling by lymphocyte antigen receptors. Annu. Rev. Immunol. 1998;16:645-670.
179. El-Amine M, Melo M, Kang Y, Nguyen H, Qian J, Scott DW. Mechanisms of tolerance induction by a gene-transferred peptide-IgG fusion protein expressed in B lineage cells. J. Immunol. 2000;165:5631-6.
180. Litzinger MT, Su Y, Lei TC, Soukhareva N, Scott DW. Mechanisms of gene therapy for tolerance: B7 signaling is required for peptide-IgG gene-transferred tolerance induction. J. Immunol. 2005;175:780-7.
181. Levings MK, Gregori S, Tresoldi E, Cazzaniga S, Bonini C, Roncarolo MG. Differentiation of Tr1 cells by immature

dendritic cells requires IL-10 but not CD25+CD4+ Tr cells. Blood. 2005;105:1162-1169.

182. Jordan MS, Boesteanu A, Reed AJ, Petrone AL, Holenbeck AE, Lerman MA, Naji A, Caton AJ. Thymic selection of CD4+CD25+ regulatory T cells induced by an agonist self-peptide. Nat Immunol. 2001;2:301-306.
183. Fowell D, Mason D. Evidence that the T cell repertoire of normal rats contains cells with the potential to cause diabetes. Characterization of the CD4+ T cell subset that inhibits this autoimmune potential. J. Exp. Med. 1993;177:627-636.
184. Tsitoura DC, Yeung VP, DeKruyff RH, Umetsu DT. Critical role of B cells in the development of T cell tolerance aeroallergens. The Japanese Soci. for Immunol. 2002;14:659-667.
185. Li Y, Ma L, Yin D, Shen J, Chong AS. Long-term control of alloreactive B cell responses by the suppression of T cell help. J. Immunol. 2008;180:6077–6084.
186. Li Y, Ma L, Shen J, Chong AS. Peripheral deletion of mature alloreactive B cells induced by costimulation blockade. PNAS. 2007;104:12093–12098.
187. Foy TM, Shepherd DM, Durie FH, Aruffo A, Ledbetter JA, Noelle RJ. *In vivo* CD40-gp39 interactions are essential for thymus-dependent humoral immunity. II. Prolonged suppression of the humoral immune response by an antibody to the ligand for CD40, gp39. J. Exp. Med. 1993;178:1567–75.
188. Lee I, Wang L, Wells AD, Dorf ME, Ozkaynak E, Hancock WW. Recruitment of Foxp3+ T regulatory cells mediating allograft tolerance depends on the CCR4 chemokine receptor. J. Exp. Med. 2005;201:1037-44.
189. Rathmell JC, Cooke MP, Ho WY, Grein J, Townsend SE, Davis MM, Goodnow CC. CD95 (Fas)-dependent elimination of self-reactive B cells upon interaction with CD4+ T cells. Nature. 1995;376:181-184.
190. Rathmell JC, Townsend SE, Xu JC, Flavell RA, Goodnow CC. Expansion or elimination of B cells *In vivo*: Dual roles for CD40-and Fas (CD95)-ligands modulated by the B cell antigen receptor. Cell. 1996;87:319-329.
191. Herve M, Isnardi I, Ng YS, Bussel JB, Ochs HD, Cunningham-Rundles C, Meffre E. CD40 ligand and MHC class II expression are essential for human peripheral B cell tolerance. J. Exp. Med. 2007;204:1583-93.
192. Janssens W, et al. CD4+CD25+ T cells lyse antigen-presenting B cells by Fas-Fas ligand interaction in an epitope-specific manner. J. Immunol. 2003;171:4604-4612.
193. Fields ML, Hondowicz BD, Metzgar MH, Nish SA, Wharton GN, Picca CC, Caton AJ, Erikson J. CD4+CD25+Regulatory T Cells Inhibit the Maturation but not the initiation of an autoantibody response. J. Immunol. 2005;175:4255-4264.
194. Rodríguez-Pinto D. B cells as antigen presenting cells. Cellular Immunology. 2005;238:67–75.
195. Huang CT, Workman CJ, Flies D, Pan X, Marson AL, Zhou G, Hipkiss EL, Ravi S, Kowalski J, Levitsky HI, Powell JD, Pardoll DM, Drake CG, Vignali DA. Role of LAG-3 in regulatory T cells. Immunity. 2004;21:503–513.
196. Lim HW, Hillsamer P, Banham AH, Kim CH. Cutting edge: Direct suppression of B cells by CD4+ CD25+ regulatory T cells. J. Immunol. 2005;175:4180-4183.
197. Likuni N, et al. Cutting Edge: Regulatory T cells directly suppress B cells in systemic lupus erythematosus. J. Immunol. 2009;183(3):1518–1522.
198. Zheng SG, Wang JH, Koss MN, Quismorio F. Jr, Gray JD, Horwitz DA. CD4+ and CD8+ regulatory T cells generated *Ex vivo* with IL-2 and TGF-β suppress a stimulatory graft-versus-host disease with a lupuslike syndrome. J. Immunol. 2004;172:1531–1539.
199. Seo Sj, Fields ML, Buckler JL, Reed AJ, Mandik-Nayak L, Nish SA, Noelle RJ, Turka LA, Finkelman FD, Caton AJ, Erikson J. The impact of T helper and T regulatory cells on the regulation of antidouble-stranded DNA B cells. Immunity. 2002;16:535–546.
200. Mqadmi A, Zheng X, Yazdanbakhsh K. CD4+CD25+ regulatory T cells control induction of autoimmune hemolytic anemia. Blood. 2005;105:3746–3748.
201. Nakamura K, Kitani A, Strober W. Cell contact-dependent immunosuppression by

CD4(+)CD25(+) regulatory T cells is mediated by cell surface-bound transforming growth factor beta. J. Exp. Med. 2001;194:629–644.

202. Shevach EM, McHugh RS, Piccirillo CA, Thornton AM. Control of T-cell activation by CD4+ CD25+ suppressor T cells. Immunol. Rev. 2001;182:58-67.
203. Hirohata S. The role of CD40–CD40 ligand interactions in suppression of human B cell responsiveness by CD4/ T cells. Cellular Immunology. 1997;182:20–28.
204. Nagata S, Golstein P. The Fas death factor. Science. 1995;267:1449-56.
205. Tanaka M, Itai T, Adachi M, Nagata S. Downregulation of Fas ligand by shedding. Nat. Med. 1998;4:31–36.
206. Gondek DC, Lu LF, Quezada SA, Sakaguchi S, Noelle RJ. Cutting edge: Contact-mediated suppression by CD4+CD25+ regulatory cells involves a granzyme B-dependent, perforin-independent mechanism. J. Immunol. 2005;174:1783–1786.
207. Tang Q, Boden EK, Henriksen KJ, Bour-Jordan H, Bi M, Bluestone JA. Distinct roles of CTLA-4 and TGF-beta in CD4+CD25+ regulatory T cell function. Eur. J. Immunol. 2004;34:2996–3005.
208. Read S, Greenwald R, Izcue A, Robinson N, Mandelbrot D, Francisco L, et al. Blockade of CTLA-4 on CD4+CD25+ regulatory T cells abrogates their function *in vivo.* J. Immunol. 2006;177:4376–83.
209. Garín MI, Chu CC, Golshayan D, Cernuda-Morollón E, Wait R, Lechler RI. Galectin 1: A key effector of regulation meditated by CD4+CD25+ T cells. Blood. 2007;109:2058–65.
210. Kornete M, Piccirillo CA. Critical co-stimulatory pathways in the stability of foxp3+treg cell homeostasis in type I diabetes. Autoimmun Rev. 2011;11:104–11.

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