

The Role of B Cells in Autoimmunity: Insights on B Lymphocyte Stimulation (BlyS) as a Target for Biologics in Systemic Lupus Erythematosus

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Abstract

Systemic lupus erythematosus (SLE) is a heterogeneous condition with significant impact on morbidity and mortality among affected individuals, usually young females during their most productive stage in life. The production of pathogenic autoantibodies has been the classical hallmark for the disease. B cells, the precursor of the antibody producing plasma cells, are believed to play a central role in SLE disease activity. It has long been considered a difficult disease to manage and diagnose due to its wide ranging manifestations and severity. This systemic autoimmune condition has attracted many clinicians and researchers for decades in the hope of fully unraveling the disease pathogenesis in order to come up with more effective treatments. Treatment strategies have been broadly directed at dampening the immune response with consequential adverse effects in the long term care of diseased patients. An improved understanding of the role B cells play in lupus pathology has led to the development of belimumab, a monoclonal antibody which became the first successful treatment for SLE introduced after more than half a century. The drug is among the class of targeted biologic therapies now evolving in the field of rheumatology and clinical immunology. It is directed to inhibit the survival of autoreactive B cells that are implicated in SLE disease activity. This review article discusses the stages in B cell ontogeny predisposing SLE development and reports the critical role of B lymphocyte stimulator in the occurrence of SLE disease flares.

Keywords: Belimumab; Systemic lupus erythematosus; B lymphocyte stimulator

Introduction

Lupus and its varied systemic manifestations came to be an important medical condition in the twentieth century due to its complexity; it is a chronic illness affecting mostly females during their reproductive years that often requires a physician's considerable time and effort. Systemic lupus erythematosus (SLE) is not easy to diagnose or manage. It is a disease of still unknown etiology that is sometimes over diagnosed and in certain instances diagnosed after great delay. Patients who develop SLE are postulated to have inherited or acquired defects in B-cell tolerance either through the presence of susceptible genes or by an environmental trigger such as exposure to infectious antigens. The development of autoantibodies against chromatin components contributes to its main pathology.

A dynamic growth in interest for SLE, the prototype autoimmune disease, has been spun by the much awaited landmark approval of the biologic drug belimumab by the United States Food and Drug Administration during the first quarter of 2012. This was preceded by the publication of the groundbreaking phase III study primarily authored by Filipino collaborator Sandra Navarra. This multi-center international trial heralded the first approved drug developed specifically for SLE. Belimumab, a human monoclonal antibody that inhibits the B lymphocyte stimulator (BlyS), is the first SLE drug treatment successfully developed after more than half a century. The increased awareness for SLE has been supplanted by the enhanced survival of a rising number of persons being diagnosed with this

multisystemic disease [1]. The improving prognosis among SLE patients also entails a protracted course of the disease that is not free from complications brought about by its waxing and waning character and its concomitant medications. Hence, the enhanced understanding of its molecular pathomechanisms, genetic susceptibility and racial epidemiology today have warranted an introduction to improved targeted therapies that decreases SLE morbidity.

Several decades have passed since the advent of corticosteroids, the conventional treatment modality for SLE; only a number of drugs that generally suppress the human immune system have been approved as part of the treatment armamentarium for SLE. The treatment goal for SLE is to achieve long standing clinical remission [2] but the present medications used for SLE act in a nonspecific manner given in long term cycles and tapering dosages, none of which were devoid of inherent toxicities. SLE manifests clinically after chronic immune dysregulation and the hallmark of the disease is immunogenic autoantibody production, a consequence of the loss of tolerance to self antigens. The pathomechanistic role of B cells, the precursor of the antibody producing plasma cells, has been implicated as a central feature in SLE disease activity. Once tolerance is broken, autoreactive B cells promotes overactive humoral and cell mediated immune response through multiple effector functions acting simultaneously; aside from autoantibody production and immune complex deposition, production of cytokines, antigen presentation to T cells, induction of epitope spreading, and amplification of tissue specific autoimmune responses are brought about by uncontrolled B cell stimulation [3]. This current level of understanding in clinical immunology paved the way for the advancement of biologic targets of therapy to include SLE (Table 1).

S.no	Biologics for SLE
1	Belimumab
2	Rituximab
3	Epratuzumab
4	Abatacept
5	Infliximab
6	Etanercept
7	Sifalimumab
8	Rontalizumab
9	Tabalumab
10	Bortezomib

Table 1: Biologics currently being developed and marketed for SLE.

B Cell Ontogeny and SLE

The capacity of the immune system to educate or eliminate autoreactive cells is important for the prevention of SLE autoimmunity [4,5]. Immune responses are tightly regulated complex interaction of cells and mediators, all of which provides mechanisms to maintain a specific unresponsive state induced by exposure to antigenic epitopes. This state of immune tolerance is initiated during embryonic life and employs B cells that require both T cell dependent and independent mechanisms [6].

The origins of B cells were derived from hematopoietic stem cells. The process of B cell differentiation begins in the fetal embryonic liver and bone marrow via a systematic manner of gene rearrangement ultimately producing an immunoglobulin receptor, the functional segment utilized in antigen recognition (Figure 1). Mechanisms of B cell tolerance could be broadly categorized into central and peripheral tolerance. Central tolerance in the B lineage includes pre B Cell Receptor (BCR) censoring, receptor editing, clonal deletion, and anergy of which, the latter two occurs as well in the peripheral tissues along with inactivation by inhibitory receptors, and the elimination via the FasL/Fas pathway.

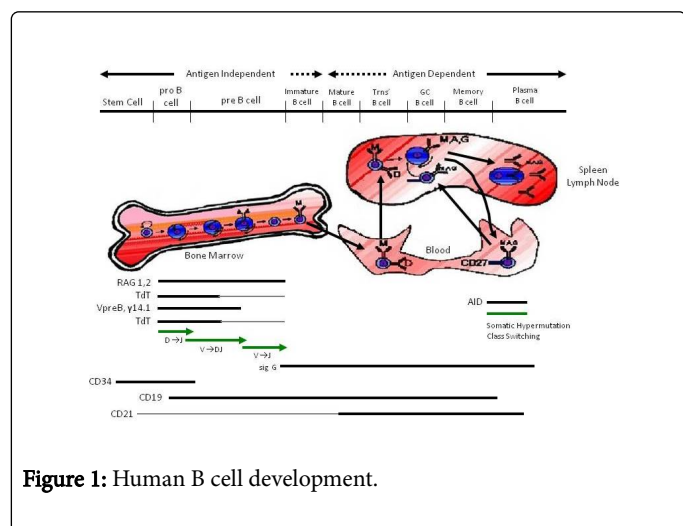


Figure 1: Human B cell development.

During the initial stages, B cell developmental checkpoints are present to test immunoglobulin function. The first step is to undergo either a positive or negative selection of B cells. In positive selection, the BCR signals detects and selects B cells with low levels of self-reactivity while cells with strong autoreactive potentials are negatively selected. B cells undergoing negative selection will either develop anergy or become eliminated by apoptosis. Immature B cells exposed to antigens usually die while some negatively selected cells could be rescued by receptor editing of the gene segments [7]. A defect in the process of receptor editing has been implicated among patients with SLE [8]. Experimental analysis revealed that up to 75% of B-cells in the bone marrow are autoreactive and this level of autoreactivity is reduced to 7%, presumably largely because of receptor editing [9]. Both receptor editing and deletion depend on effective BCR signaling; defective BCR signaling results in defective receptor editing [10].

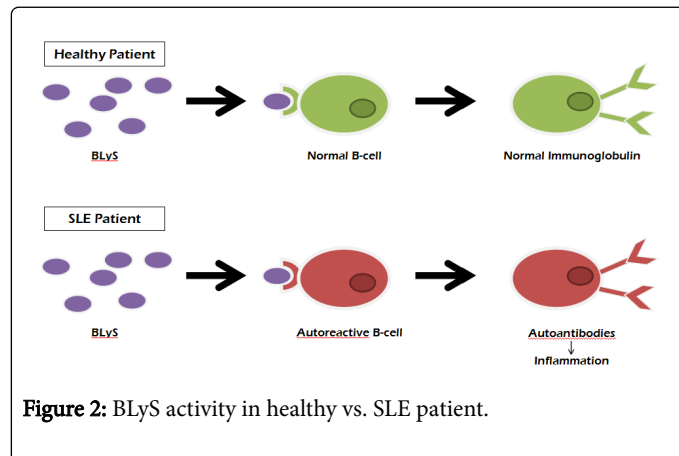
In the periphery, the B cell remains in the primary follicle of the lymphoid tissues. Naïve B cells compete for space with new B cells produced by the bone marrow as well as mature B cells, it can only remain for a certain period of time. The dendritic cells (DCs) inside the lymphoid follicles release signals that promote B cell survival which includes BlyS. These B cells exist in a resting inactivated state until it comes into contact with an antigen it can recognize. B cells that are repeatedly triggered by an antigen that is not membrane bound and is not intrinsically multivalent become unresponsive. Constant stimulation makes these B cells extremely dependent on BlyS for survival but they are unable to compete with normal follicular B cells for the BlyS that are available in B cell follicles [11]. Among mature B cells, the marginal zone B cells of the spleen exists in a transiently activated state enabling immediate response to antigen presence composed of polysaccharides while the conventional B cells typically responds to protein antigens that requires T cell co-stimulation.

In the late stages of B cell development, antigen exposure in the peripheral tissues results in B cell activation, class switching and affinity maturation. Several B cells are selected for receptor specificity and affinity maturation. The final stages consist of B cell differentiation into plasma or memory B cells. Overactive T cell dependent germinal center (GC)-like reactions produces expanded and largely unregulated numbers of memory B cells and plasma cells among SLE patients. One major reason for the breakdown in peripheral B cell tolerance via the absence of the Fas pathway appears to be the failure to eliminate autoreactive B cells generated during T dependent immune responses [12,13]. While receptor editing, deletion and anergy tolerate B cells that recognize self-structures with high avidity, weakly autoreactive B cells mature and migrate to the peripheral lymphoid tissue. It is therefore necessary to prevent these weakly autoreactive B cells from inadvertently causing T cell co-stimulation. In essence, defects in central and peripheral B cell tolerance provides immature transitional cells, memory cells, and plasma cells to expand in the periphery while autoreactive cells are also incompletely deleted in the bone marrow of SLE patients [14].

SLE and BlyS Homeostasis

High BlyS levels have been reported among SLE patients among different racial groups [15-17] and the serum BlyS levels generally correlated with anti-dsDNA titers [18]. In murine models with overexpression of BlyS, development of SLE like features such as antinuclear antibodies and immune complex deposition in the kidneys was demonstrated [19,20] (Figure 2). Patients with SLE with an expanded autoantibody profile and raised BlyS levels at baseline have

failed to achieve sustained remission from disease activity upon B cell depletion [21], a delay in the recovery of B cell memory in the peripheral blood and lymphoid tissue were also seen [22]; this implies a disease nature of SLE requiring therapies that would regulate B cells beyond cell elimination.



BlyS, also known as B cell activation factor of the Tumor Necrosis Family (BAFF), aside from providing a homeostatic signal for B cell survival, it also acts in B cell differentiation and activation, serving as a bridge between the innate and adaptive immune response in conditions of chronic immune stimulation [23]. High serum expression levels of soluble BlyS, and its homolog APRIL (a proliferation inducing ligand) are seen among monocytes, DCs, neutrophils, basophils, stromal cells, activated T cells, activated and malignant B cells, and epithelial cells particularly among SLE patients [24]. Elevated BlyS expression supports expansion of the late transitional B cells thus contributing to SLE autoimmune response [25]. Among SLE patients, BlyS levels rose significantly during B-cell depletion therapy and declined close to pre-treatment levels upon B-cell repopulation; on the contrary, APRIL levels declined significantly upon B cell depletion indicating differences in the regulation of autoimmune response [26]. The inverse correlation observed between APRIL and BlyS suggests that APRIL acts as a protective factor [27].

BlyS receptor expression have been shown to be reduced on peripheral B cells of patients with SLE [28]. BlyS interacts with three different receptors: BR3 (BAFF receptor 3), TACI (transmembrane activator and calcium modulator and cyclophilin ligand interactor), and BCMA (B-cell maturation antigen) [29-32]. BR3 binds solely to BlyS, whereas TACI and BCMA ligate both BlyS and APRIL, all of which activates the nuclear factor- κ B (NF- κ B) pathway [33]. BR3 expression progressively increases throughout B cell development and is universal in mature B cells. Among the other receptors, TACI is an inducible receptor expressed by all peripheral B cells while BCMA expression is restricted to antibody producing cells [34]. The occupancy of BlyS receptors on blood B cells is likely to contribute to disease mechanisms in SLE and targeting BlyS as a therapeutic strategy will require overcoming the persistent binding of BlyS to these receptors [35]. Among lupus mouse models, selective blockade of BlyS reduces transitional type 2 follicular and marginal-zone B-cells, and significantly attenuates immune activation [36] and in SLE patients, treatment with belimumab has been demonstrated to lower levels of activated B cells (CD69⁺ B cells) [37].

Major Key Points

- Unusually high amounts of BlyS seen among SLE patients allows overactive immune cells to resist their body's innate defenses and into the circulation.
- Therapeutic agents targeting B cells such as Belimumab acts by blocking BlyS and thereby allow B cells to undergo regular programmed cell death.
- The argument as to whether BlyS elevation is a consequence of ongoing inflammation or whether high BlyS levels contribute to the onset of disease is beginning to be fully elucidated.

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