Review

B cell abnormalities in systemic lupus erythematosus

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Received: 9 Sep 2003 Accepted: 22 Oct 2003 Published: 2 Dec 2003

Arthritis Res Ther 2003, **5(Suppl 4)**:S22-S27 (DOI 10.1186/ar1009)

Abstract

Systemic lupus erythematosus (SLE) is a chronic, multisystem autoimmune disease characterized by the differentiation of short- and long-lived immunoglobulin secreting plasma cells that secrete pathogenic autoantibodies. Ectopic germinal centers and plasma cells secreting autoantibodies have been observed in lupus nephritis kidneys. Candidate genetic susceptibility loci for SLE include genes that affect differentiation and survival of plasma cells, such as those that influence activation, proliferation, cytokine and chemokine secretion/responsiveness, and apoptosis of the T and B cells that are involved in humoral immunity generated in germinal centers, as well as genes that are involved in presentation and clearance of apoptotic material and autoantigens by antigen presenting cells and other phagocytes. Emerging data have demonstrated that B lymphocytes are active participants in humoral immune responses that lead to T-dependent and T-independent differentiation of immunoglobulin-secreting plasma cells by homotypic CD154–CD40 interactions as well as continued stimulation by B cell activating factor through B cell maturation antigen, B cell activating factor receptor and transmembrane activater.

Keywords: B cells, germinal centers, immunoglobulin-secreting cells, plasma cells, systemic lupus erythematosus

Introduction

Systemic lupus erythematosus (SLE) is the prototypic systemic autoimmune disease. It is a chronic, multisystem disease that is characterized by abnormal B cell activation and differentiation to memory or plasma effector cells. Abnormal memory effector cells in SLE have specificity for autoantigen with surface immunoglobulin that is usually of high avidity because of somatic hypermutation of immunoglobulin variable regions and possible switching to the IgG isotype. Abnormal plasma effector cells in SLE secrete pathogenic autoantibodies including those that are specific for double stranded (ds)DNA and are involved in glomerulonephritis, those that are specific for phospholipid-β_2 glycoprotein I or cardiolipin and are involved in thrombosis, those directed to Ro SSA or La SSB and are involved in the etiology of congenital heart block, and those specific for Sm/RNP whose mechanism of action is unclear [1–3].

The precise cause of SLE is unclear, but the initial presentation of disease appears to depend on a multitude of genetic susceptibility and environmental factors that initiate and/or contribute to pathogenic autoimmunity. Candidate initiating factors include female sex hormones, ultraviolet light from sun exposure, cigarette smoking, and infections with bacteria and/or viruses that polyclonally activate B cells. More frequent or aggressive disease is associated with African-American or African-Caribbean origin, but SLE also emerges in Asian and Caucasian populations. Genetic susceptibility loci include genes that affect differentiation and survival of immunoglobulin secreting cells (ISCs), such as those that influence activation, proliferation, cytokine and chemokine secretion/responsiveness, and apoptosis of the T and B cells that are involved in humoral immunity generated in germinal centers (GCs), as well as genes that are involved in presentation and clearance of apoptotic material and

BAFF = B cell activating factor; BCMA = B cell maturation antigen; ds = double stranded; GC = germinal center; ISC = immunoglobulin secreting cell; SLE = systemic lupus erythematosus; TACI = transmembrane activater and CAML interacter; TD = T dependent; TI = T independent.

autoantigens by antigen presenting cells and other phagocytes [4].

The role of B cells in systemic lupus erythematosus

Emerging data have demonstrated that B lymphocytes are active participants in humoral immune responses that lead to differentiation of ISCs. For example, activated B cells in secondary lymphoid tissues and in the blood of patients with active SLE express CD154/TNFSF5/CD40 ligand, and homotypic CD154–CD40/TNFRSF5 interactions between B cells from these sources are crucial for differentiation to ISCs [5–8]. Moreover, differentiation of ISCs is affected by continued stimulation by B cell activating factor (BAFF/BlyS/TNFSF13B) through two of its receptors – B cell maturation antigen (BCMA) and BAFF receptor (BAFF-R) – in a T dependent (TD) manner [9], and through its third receptor – transmembrane activater and CAML interacter (TACI) – in a T independent (TI) manner [10–13]. Of note, BAFF is located in an SLE susceptibility locus (13q32-34) [14–17] and has been found to be elevated in the serum of patients with active SLE [18,19].

Simultaneous emergence of the idea that B cells play a role in autoregulating humoral immune responses, and data suggesting that B cells from active SLE patients and lupus prone mice have an intrinsic tendency to overreact to immunologic stimulation during antigenic challenge have set the stage for novel hypotheses regarding therapeutic approaches to interfere with the emergence and progression of SLE. The profound B cell abnormalities observed in SLE patients may either reflect the impact of multiple genetic factors that affect intrinsic B cell function and/or they may be secondary to other primary immunologic abnormalities [1]. For example, abnormalities during B cell differentiation in secondary lymphoid tissues may permit the generation and survival of ISCs that secrete pathogenic autoantibodies. Alternatively, an intrinsic tendency to respond excessively to immunologic stimulation may provide the drive for the emergence of pathogenic ISCs, even though B cell maturation, somatic hypermutation of immunoglobulin, and subsequent selection are not mechanistically abnormal. Because the mature B cell repertoire has tremendous cellular turnover every day, even minor abnormalities may lead to active SLE over time [20]. Importantly, the emergence of active SLE does not usually occur until the second or third decade of life. Development of SLE during childhood may reflect a greater total load of genetic and environmental influences.

Immunoglobulin secreting cells

ISCs are defined by very high expression of CD38 and the presence of intracellular immunoglobulin [21,22]. In addition, all ISCs have a high ratio of secreted to membrane forms of immunoglobulin heavy chain mRNA, a high cytoplasmic to nuclear ratio with prominent endoplasmic reticulum, expanded Golgi apparatus and secretory vacuoles, and expression of J chain – a molecule that is involved in polymerization of IgM and IgA. In normal individuals the ISC B cell pool secretes immunoglobulin that protects the host from infection. In SLE patients the ISC B cell pool secretes pathogenic autoantibodies that contribute to disease activity.

There are two subsets of ISCs, long-lived plasma cells and short-lived plasmablasts/plasmacytes, which are generated in normal immune responses and that are found to secrete autoantibodies in SLE [23]. Long-lived plasma cells are generated during TD humoral immune responses, arise in GC reactions, and home to the bone marrow where they produce antibodies for protracted periods of time in the absence of T cells and antigenic stimulation. In contrast, plasmablasts/plasmacytes often arise during TI humoral responses, and under normal circumstances they remain in the lymphoid tissue in which they are generated.

Long-lived plasma cells are generated in response to TD stimulation in GCs and home to the bone marrow, where they survive for long periods of time. They secrete antibodies constitutively, which accounts for the majority of serum immunoglobulin and long-lived immunity to many antigens [23]. The lifespan of long-lived plasma cells has been observed to be months to years. In addition, long-lived plasma cells are nondividing cells in the G_0/G_1 phase of the cell cycle that have downregulated many mature B cell markers including CD40, CD19, surface immunoglobulin, and CD20 [23]. As a result, they are not responsive to either T cells or antigens. Moreover, they are not affected by therapy with rituximab, which deletes $CD20^+$ B cells. Moreover, when cultured *in vitro*, long-lived plasma cells have the capacity to secrete immunoglobulin in the presence of antiproliferative agents such as hydroxyurea [24–26]. Finally, long-lived plasma cells largely derive from conventional (B2) B cells, are the products of TD GC reactions, and their immunoglobulin genes bear the impact of somatic hypermutation and selection [22]. Of interest, the ISCs that secrete immunoglobulin specific for cardiolipin, antinuclear antibodies, Ro, La, and Sm that are found in SLE patients are likely to be long-lived plasma cells because treatment with antiproliferative reagents has minimal effect on plasma levels of these autoantibodies [27,28]. In addition, autologous stem cell transplantation may not eliminate long-lived plasma cells producing these particular autoantibodies because plasma titers are not diminished [29].

The second group of ISCs is termed the short-lived plasmablasts or plasmacytes. Plasmablasts are generated as products of the TI humoral immune response. Alternatively, plasmablasts can be derived from TD responses and are the GC derived precursors of the long-lived plasma cells that undergo a round of cell division before

final differentiation [23]. Plasmablasts can be generated from either the B1 subset of B cells or from conventional (B2) B cells. TI immune responses occur in extrafollicular regions of secondary lymphoid tissues. These include specialized regions of a number of tissues, including the subepithelial region of the tonsil, the medullary cords of lymph nodes, and the marginal zone in the spleen. TI antigens are subdivided into two subsets. TI-1 antigens are polyclonal B cell activators such as bacterial lipopolysaccharide that bind Toll-like receptors. TI-2 antigens have repeating antigenic epitopes and cross-link surface immunoglobulin to initiate the immune response. Plasmablasts have lifespans of days to weeks, and in normal individuals they remain in the tissue in which they were generated. In contrast to the situation in normal individuals, plasmablasts are found in the bloodstream of SLE patients [8] and in kidneys of lupus prone mice [30].

Plasmablasts can be found in all phases of the cell cycle and still express the mature B cell markers CD19, CD20, and CD40 [8,23]. As a result, their functional activity can be regulated by exogenous influences. Moreover, when cultured *in vitro*, plasmablasts are not able to secrete immunoglobulin in the presence of antiproliferative agents such as hydroxyurea [24–26]. Of interest, the ISCs that secrete immunoglobulin specific for dsDNA that are found in SLE patients are likely to be plasmablasts because treatment with antiproliferative reagents decreases plasma levels of anti-dsDNA antibodies [31].

The role of BAFF and its receptors in immunoglobulin secreting cell generation

As stated above, BAFF (BlyS/TNFSF13B) stimulation of B cells generates ISCs through two of its receptors – BCMA and BAFF-R – in a TD manner [9], and through its third receptor – TACI – in a TI manner [10–13]. Interestingly, mice that over-express BAFF [32–34] exhibit an autoantibody mediated, lupus like disease, and BAFF (13q32-34) is encoded in human genetic regions [14–17] that contain SLE susceptibility loci. Moreover, soluble, biologically active BAFF has been found to be elevated in the serum of a fraction of patients with active SLE [18,19].

BAFF interactions with two of its receptors, BCMA (TNFRSF17) and BAFF-R (TNFRSF13C), enhance CD40-mediated TD GC reactions [19]. Moreover, mice genetically deficient for BAFF-R [11] are not able to generate long-lived plasma cells following immunization. Furthermore, although mice genetically deficient for BAFF-R [35] are not able to generate GC derived long-lived plasma cells, these mice exhibit no defect in generating IgM secreting plasmablasts. These findings are particularly notable because mice deficient in BAFF-R exhibit reduced numbers of cells at a particular stage of conventional B cell maturation, namely transitional B2 cells [10,36]. Therefore, the majority of IgM plasmablasts may be derived from the B1 subset in BAFF-R deficient mice. In humans, BAFF stimulation of splenic $CD38^{-}CD27^{+}$ memory B cells that express very high levels of BAFF-R, but little or no BCMA or TACI, increases survival of this memory B cell population and induces differentiation of plasmablasts and plasma cells [11]. Whereas BAFF increased the survival and amount of immunoglobulin secreted from human plasmablasts, BAFF has no direct effect on immunoglobulin secretion from fully differentiated nondividing human $CD20^{-}$ plasma cells.

Mice genetically deficient for an alternative BAFF receptor, TACI (TNFRSF13B), are not able to generate plasmablasts in response to TI antigens [37,38]. Moreover, mice transgenic for APRIL/TALL2/TNFSF13, the TACI and BCMA ligand, had an exaggerated serum IgM response to TI antigens [39]. In mice transgenic for phosphorylcholine specific immunoglobulin, soluble BAFF derived from *Streptococcus pneumoniae* loaded splenic dendritic cells or peritoneal macrophages, respectively, drove antigen induced survival and IgM plasmablast differentiation from marginal zone or B1 B cells in a TACI dependent manner. Forced expression of bcl-2 in this system rescued antigen induced B cell apoptosis that resulted with the TACI Ig fusion protein [12]. Of note, BAFF stimulation of B cells has been shown to induce expression of antiapoptotic molecules in the bcl-2 family. Using dense human tonsillar B cells containing the subepithelial marginal zone-like $CD5^{-}$ memory subset, soluble BAFF derived from peripheral blood derived dendritic cells or macrophages co-stimulated B cell proliferation induced by anti-IgM, but not by recombinant CD154/CD40 ligand, in a manner that did not require APRIL [13].

The role of CD154–CD40 interactions in generation of immunoglobulin secreting cells

Examination of children or mice with defective expression of CD40 or CD154 [5,40] has demonstrated that CD154–CD40 interactions are essential for formation of GCs and the differentiation of memory and plasma cell effector populations. GCs have been shown to be initiated when CD154 expressing T cells engage CD40 expressing B cells in the extrafollicular regions of secondary lymphoid tissues, thereby inducing them to express CD154 [7] and to proliferate rapidly to form the dark zone of GC reactions. Homotypic B cell interactions involving CD154 and CD40 have been shown to be essential for differentiation of GC B cells to memory B cells, and for the formation of secondary GC structures that allow reactivated memory B cells to differentiate into plasma cells secreting high affinity antibodies [7]. The presence of blocking anti-CD154 antibody inhibits the initiation of GC reactions and causes ongoing GC reactions to disassemble in immunized [41] and lupus prone mice [42]. Moreover, the presence of GC and GC derived memory and immunoglobulin secreting plasma effector populations in the periphery of

patients with active SLE is greatly diminished following treatment with blocking anti-CD154 antibody (BG9588, 5c8) [8,43,44]. Importantly, CD154 has been found to be hyper-expressed on lymphocytes in secondary lymphoid tissues from lupus prone mice and from active SLE patients [45,46], and mice transgenic for CD154 on all cells [47], T cells alone [48], or B cells alone [49] spontaneously developed GC reactions that resulted in anti-dsDNA secreting plasmablasts.

Ectopic germinal centers

Normally, in non-autoimmune situations, GC reactions and GC generated effector cells are observed in secondary lymphoid tissues (lymph nodes, spleen, and mucosal tissues such as tonsil and Peyer's patches). Recent studies have observed that inflammation occurring in many autoimmune/inflammatory conditions drives GC/follicle formation in many ectopic sites, including the kidney in lupus nephritis [50–52]. Ectopic GCs/follicle development in autoimmune tissues with a large amount of autoantigen, such as dsDNA in lupus nephritis kidneys, may create an environment in which autoreactive B cells undergo somatic hypermutation, IgH class switching, and positive selection mediated by the autoantigen to the functional memory and plasma cell effector pools.

Germinal centers in systemic lupus erythematosus

The dysregulation of mechanisms controlling normal or ectopic TD GC reactions to exogenous or endogenous antigens may contribute to the emergence of SLE. Normally, immature polyreactive and mature B cells with specificity for endogenous autoantigens are excluded from follicular GC reactions that generate memory and immunoglobulin secreting plasma effector cells. The elements that may contribute to these events in humans have not been fully characterized, but recruitment of autoreactive B cells into TD GC reactions has been examined in lupus prone *lpr/lpr* [53,54] and NZB/W [55] mice. Autoreactive B cells were able to form/enter splenic follicles in lupus prone mice, but were retained outside follicles in the T cell zone of non-autoimmune control mice. Furthermore, B cells from autoimmune mice that produced pathogenic rheumatoid factor and anti-dsDNA antibodies were localized in follicles [56]. Similar to autoreactive B cells in non-autoimmune mice, anergic autoreactive B cells that were generated in the classic HEL/anti-HEL double transgenic murine system, in which the mouse expresses both the autoantigen (HEL) and the surface immunoglobulin specific for the HEL autoantigen, were excluded from follicles until challenge with class II directed allogeneic T cell help or stimulation with CD154 itself [57]. Notably, however, intense CD154 stimulation, as is present in active SLE patients, could induce anergic, autoreactive B cells to enter follicles where they could differentiate to long-lived plasma cells secreting high affinity autoantibodies [58,59]. Thus, CD40 stimulation could be pivotal in redirecting autoantibody producing B cells into a differentiation pathway leading to the production of long-lived plasma cells.

In this regard, exposure of anergic, nonresponsive, autoreactive B cells to exogenous CD154 resulted in proliferation, antigen presentation, and immunoglobulin secretion at levels comparable to that of normal B cells. This finding indicates that ligation of CD40 on anergic B cells is a sufficiently strong signal to reactivate them and redirect them into the mature B cell pool that can differentiate to memory or immunoglobulin secreting plasma effector cells.

Conclusion

SLE is a complex, polygenic, chronic multisystem disease characterized by abnormal B cell activation and differentiation to plasma cells or plasmablasts/plasmacytes. Current research has begun to define the receptor–ligand interactions and signals that are involved in activation and differentiation of human B cells to plasma cells and plasmablasts/plasmacytes. Many of these genes are located within SLE susceptibility loci and their encoded molecules may be effective targets of biologic therapies in SLE patients. The exact cause of SLE is unclear but emergence of active disease may depend upon environmental factors that initiate and/or contribute to the development of this systemic autoimmune disease in genetically prone individuals. Notably, recent research has highlighted the central and active role that B cells play in regulating many aspects of the humoral immune response leading to differentiation of autoreactive effector B cell populations. Therefore, the possibility that ongoing B cell hyperreactivity in SLE, mediated by a number of defined receptor–ligand interactions, including signaling through CD40 or BAFF receptors, could be specifically targeted and should be considered as a novel approach to treat this systemic autoimmune disease.

Competing interests

None declared.

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