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B cells biology in systemic lupus erythematosus—from bench to bedside

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Systemic lupus erythematosus (SLE) is a debilitating autoimmune disease that can involve multi-organs. B cells play a central role in the immunopathogenesis via antibody-dependent and antibody-independent ways. Excessive autoantibodies production, hyperresponsiveness and prolonged survival of autoreactive B cells are characteristics of SLE. In this article, mechanisms of self-tolerance loss of B cells and promising B cell-targeting therapies in lupus are reviewed and discussed.

systemic lupus erythematosus, B cell, pathogenesis, target therapy

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Systemic lupus erythematosus (SLE), the paradigm of autoimmune disease with the underlying mechanisms involving multiple immunological abnormalities, is a severely debilitating disease with multi-organ involvement and diverse autoantibodies spectrum [1]. Among the multiple elements in the pathogenesis, B cells play a central role in SLE through antibody dependent and independent manners [2]. Presence of pathogenic autoantibodies is not only the hallmark of SLE and the clue for diagnosis, but also associated with characteristic pathological injury and specific clinical manifestations [3–5]. In addition, the pathogenic role of B cells is also attributed to its antibody independent functions, including but not limited to antigen presentation, T cell crosstalk, dendritic cells (DCs) recruitment, pro-inflammatory cytokine secretion. Why and how auto-reactive B cells in lupus lose self-tolerance, escape from central and peripheral checkpoints, become over-activated and spontaneously produce autoantibodies, are always the focus of clinical and basic research. Therefore, it is important to summarize our current knowledge about the underlying mechanisms of self-tolerance breakdown and pathogenic functioning pathways of B cells in SLE. So we review here about B cell biology in SLE, including its differentiation and selection, functioning and signaling, surviving and apoptosis, and the resulting potential therapeutic targets both in mice and human lupus.

1 Role of B cells in the pathogenesis of SLE—antibody dependent and independent mechanisms

Naïve B cells undergo the process of heavy chain V region gene rearrangement, isotype switching, somatic hypermutation and affinity-based selection within germinal center (GC), then leave GC and develop into memory B cells , or alternatively, short lived or long lived plasma cells that are capable of producing antibodies including pathogenic autoantibodies [6], which is crucial for triggering and perpetuating disease in SLE. Various abnormality of the development, status and functions of B cells have been reported,

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including activation thresholds lowering, prolonged survival and inhibition of apoptotic processing [7,8].

Although the spectrum of lupus manifestations is diverse, indicating the heterogeneous nature of SLE, circulating autoantibodies is ubiquitous and is related to target organ injury and disease activity with diagnostic value [2,3]. For example, anti-Smith antibody is highly specific and pathognomonic for SLE [9,10]. Higher titers of anti-double strain DNA antibody (anti-dsDNA) correlates with lupus nephritis (LN) and disease activity [11,12]. The presence of anti-ribosomal P antibody predicts an increased risk of neuropsychiatric event [13,14]. Patients with antibody against Sjogren syndrome antigen A (anti-SSA or anti-Ro) are predisposed to photosensitivity, rash and haematological disorders [15,16]. Pregnant women with anti-SSA may give birth to babies with congenital heart block [17].

But the immunological role of B cell is not limited to the precursor of immunoglobulin (Ig) secreting cell, namely plasma cell. Mice with normal numbers of B cells but lacking of circulating antibodies (mIgM MRL/MP-Fas^{lpr} mice that expressmembrane-bound IgM but lack exons needed for secretion) still exhibit autoimmunity and accelerated mortality [18], whereas B cell-deficient MRL/lpr mice are resistant to development of lupus-like disease [19,20]. These data collectively indicate that B cells also play an autoantibody-independent role in SLE pathogenesis. Actually, B cells exert multipotent immunological functions such as presenting antigen, co-stimulating T cells, inducing immunogenic DCs, as well as producing cytokines and chemokines to promote inflammation, affect immune regulation and lymphogenesis (Figure 1) [2,21,22].

1.1 Autoreactive B cells and B_{REG} in SLE

SLE B cells can be divided into pathogenic autoreactive B cells that are involved in autoimmune response, protective B cells that are involved in immune defense against pathogenic microorganisms and regulatory B cells (B_{REG}) that help to keep self tolerance and immune homeostasis [23]. Abnormal proportional composition of B cell subgroups and accumulation of autoreactive B cells in murine and human SLE have been reported [24,25]. Autoreactive B cells exist in all human but with higher frequency in patients with SLE [26]. Moreover, defects of B_{REG} in numbers and/or functions may also contribute to inordinate immunological state in SLE [27,28]. Before entering peripheral circulation, B cells have to be checked for their autoreactivity, those with high affinity with autoantigens are deleted or anergized. Two major mechanisms in central and peripheral checkpoints are clonal deletion and receptor editing [29]. Additional censoring mechanisms may exist, as studies showed that 50%–75% immature B cells newly emerging into periphery can be autoreactive [30] and up to 20% of peripheral mature naïve B cells in normal individuals are reactive with self nuclear antigens [7,26].

1.1.1 Autoreactive B cell

Although pathogenic, lymphocytopenia other than lymphocytosis of B cells is often found in active SLE [6]. Disturbance of B cell homoeostasis with an abnormal shift of pre-immature B cell pool towards more immature subgroups independent of disease activity in peripheral blood has been noted, including expanded pre-naïve B cells and transitional B cells [31,32]. Marked reduction of naïve peripheral $CD19^+CD27^-$ B cells mainly account for B lymphocytopenia [6]. Whereas increased frequency of $CD27^{high}$ plasmablasts seems to correlate with active disease [6,25,33] and abates significantly after immunosuppressive therapy. Ig heavy chain variable (V_H) gene analysis has demonstrated extraordinary highly mutated and clonally

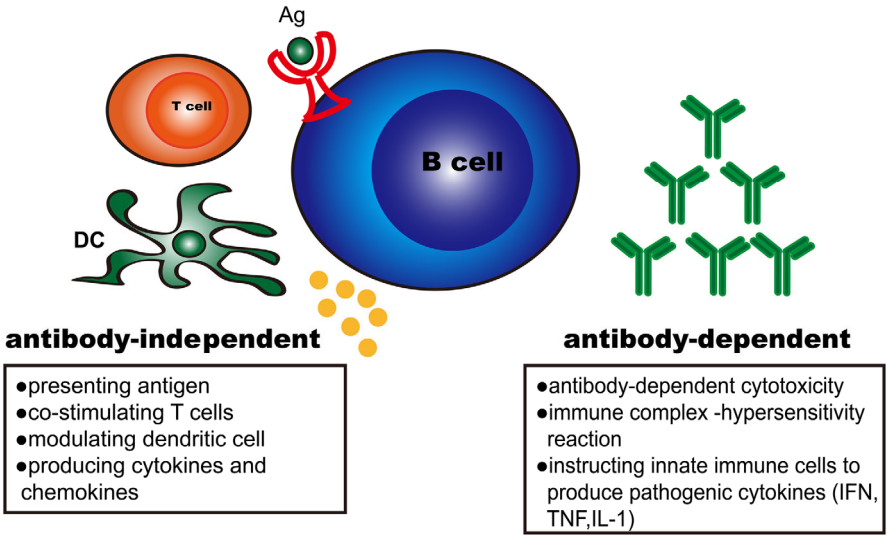

Figure 1 Antibody-dependent and -independent role of B cells in the pathogenesis of systemic lupus erythematosus. Ag, antigen; DC, dendritic cell; IFN, interferon; TNF, tumor necrosis factor.

related V_H gene rearrangements within $CD27^{high}$ plasmablasts, indicating autoreactive nature of this population. In addition, $CD27^{+}IgD^{-}$ antigen-experienced post-switched memory B cells are also expanded in SLE patients. These cells express less inhibitory IgG Fc receptor-FcγRIIB, are resistant to immunosuppressive drugs [34], and are easily and rapidly activated independent of antigen [35].

1.1.2 Abnormality of B_{REG}

B_{REG} are capable of secreting IL-10 and controlling T cell proliferation [36]. In mice, $CD19^{high}CD1d^{high}CD5^{+}$ B subset capable of producing IL-10 is deemed to be B_{REG} [37]. And in human, IL-10 secreting B cells with the phenotype of $CD19^{+}CD24^{high}CD38^{high}$ are thought to be B_{REG} [27,38]. B_{REG} could protect mice from development of lupus disease [39]. It has been also reported that B_{REG} in SLE patients produces less IL-10 and has compromised suppressive capacity [27,28]. The role of B_{REG} and IL-10 in SLE is controversial and paradoxical. For example, Yin et al. [40] reported that IL-10 deficient mice developed more severe lupus, whereas Llorente et al. [41] reported that blockade of IL-10 with antibodies reduced disease activity, indicating a double-side role of IL-10 in SLE.

1.2 Self-tolerance breakdown of SLE B cells

Multiple mechanisms to eliminate autoreactive B cells exist to keep self tolerance and ensure normal humoral response to exogenous pathogens. Self-tolerance breakdown contributes to differentiation and expansion, activation and survival of autoreactive B cells in SLE. But the precise mechanisms remain to be illuminated.

1.2.1 Gene associations with the loss of self-tolerance in B cells

Combination of gene loci constitutes the genetic background of lupus predisposition. Many of these loci are associated with abnormalities of B cells [42,43]. Genome-wide association studies identify a series of candidate lupus-susceptible genes including those encoding BANK (B-lymphocyte scaffold protein with ankyrin repeats), BLK (B-lymphoid tyrosine kinase), PTPN22 (protein tyrosine phosphatase non-receptor type 22), Blimp-1, Lyn, FcγIIRB, CD22 (cluster of differentiation 22), CD40L (cluster of differentiation 40 ligand) and AID (the activation-induced deaminase). These genes are associated with altered BCR (B cell receptor) signaling, B cell hyper-responsiveness and stimulative differentiation into plasma cells [44–46].

In murine lupus, *Sle1, Sle2, Sle3, Yaa* are found to be susceptibility genes and might impair BCR signaling and impede antigen-driven negative selection, thus contribute to breakdown of self-tolerance in B cells [47,48].

1.2.2 Surface molecules on B cells

CD40 in lipid raft is decreased on activated B cells from SLE [49], but functionally active CD154 (CD40L) expression on SLE B cells is increased [50,51]. CD154 transgenic mice have increased number and enhanced survival of B cells [52]. Spontaneous proliferation and Ig secretion of peripheral B cells from active lupus patients could be inhibited by blockade of CD154-CD40 interaction [50]. Ligation of CD40 with CD154 provides an important co-stimulation signal and plays an essential role in GC reaction. Studies show that CD40-CD154 interaction could not only induce T cell priming, promote Th2 type cytokines production and enhance T cell medicated immune effects, but also reciprocally function to promote B cell proliferation, isotype-switching, activation and antibody production [50,53–55].

CD5 expression on lupus B cells membrane is characteristically reduced [56]. $CD5^{+}$B cells are capable of producing IL-10 and possess regulatory potency [37]. Engagement of BCR and production of IL-6 down-regulate membrane CD5 expression through abnormally enhanced demethylation which can influence the balance of the transcripts of two CD5 isoforms (membrane CD5 and cytoplasmic CD5). As a negative regulator of BCR signaling, reduced membrane CD5 leads to activation and expansion of autoreactive B cells in SLE [56].

CD22 is a negative modulator of BCR signaling. Expressing on mature B cells, CD22 help to raise activation thresholds and regulate homeostasis and survival of B cells [57,58]. CD22-deficient mice are found to have hyper-responsive B cells, increased titers of serum autoantibodies, heightened calcium flux and increased proliferation of B cells [59,60]. Recently, studies *in vitro* show that epratuzumab, an anti-CD22 mono-clonal antibody, can reduce B cell count modestly and decrease the proinflammatory cytokines like tumor necrosis factor-α and IL-6 produced by activated B cells without influencing IL-10 level [61]. What's more, epratuzumab can substantially reduce the expression of multiple functional molecules like CD19, CD44, CD62L, then inhibit the hyperactivity and migration of B cells without depleting them [62,63]. Although epratuzumab could induce internalization of CD22, the functional consequence of modulating BCR signaling and reducing B cells results in negative regulation of immune reaction and applies to the treatment of autoimmune disease.

CD45 recruitment and retention in lipid raft with altered isoform have been observed increasing in lupus B cells [64]. CD45 negatively regulates Src family protein tyrosine kinase [65] and increased CD45 is associated with reduced Lyn expression (negative more than active BCR downstream signaling molecule) in lupus B cells [64]. CD45 also lowers BCR signaling threshold thus contributes to B cells hyperactivity [66].

FcγRIIB (CD32B) contains an ITIM (immunoreceptor

tyrosine based inhibition motif) domain and mediates inhibition of PIP3/PI3K (phosphatidylinositol 3,4,5-trisphosphate/Phosphoinositide 3-kinases) signaling by activation of SHIP (the Src Homology 2-containing inositol 5′-phosphatase) and dephosphorylation of CD19 [67,68]. Co-engagement of FcγRIIB and BCR by circulating immune complex could transmit negative regulatory signals to B cell activation and proliferation. Therefore FcγRIIB is an inhibitory Ig receptor, capable of down-regulating BCR complex signals. Defective FcγRIIB in SLE B cells contributes to increased calcium influx [69]. Polymorphisms of FcγRIIB with impaired expression and function has reported in SLE, especially on memory B cells [70]. Mice deficient of FcγRIIB on B cells are prone to develop SLE-like disease with increased susceptibility to autoimmune glomerulonephritis and autoantibodies production [71,72]. Restoration of proper FcγRIIB expression prevents the expansion and accumulation of autoantibody-producing plasma cells in lupus-prone mice [73]. Polymorphism of FcγRIIB is associated with SLE susceptibilities due to the failure of localization in membrane lipid rafts [74,75].

CD80/CD86 are constitutively expressed on B cells, and by interacting with CD28 on T cells, they could co-stimulate T cell activation. Up-regulation of CTLA4 (Cytotoxic T lymphocyte-associated antigen-4) on T cells upon activation can block CD80/CD86 binding to CD28 through competitive mechanism. A recombinant human IgG Fc fragment fusion protein, CTLA4-Ig, functioning like CTLA4, could dampen the crosstalk of T cell and B cell by binding to CD80/CD86. In murine lupus, CTLA4-Ig could reduce autoantibody levels and inhibit B cell class switch and ameliorate nephritis [76].

1.2.3 Intracellular signal transduction in B cells

Abnormal BCR down-stream signaling as indicated by augmented calcium influx and increased phosphorylation of protein tyrosine residues is observed in SLE patients, and may lead to disordered transcription and gene expression [42,77–79]. This may result in defective self-limitation of cell activation and breakdown of self tolerance. BCR comprises of Igα and Igβ heterodimer with intracellular ITAM (immunoreceptor tyrosine based activation motif) domain. After BCR linking with antigen, phosphorylation cascade of multiple downstream signaling molecules is initiated to tune B cell activation [80,81]. Firstly, ITAMs are phosphorylated by Src family kinases such as Lyn and Blk, and then Syk (spleen tyrosine kinase) with SH2 (Src homology 2) domain is recruited and phosphorylated, and it in turn activates multiple downstream signaling pathway such as Btk (Bruton's tyrosine kinase), PI3K, ERK (extracellular-signal regulated kinases), JNK (c-terminal Jun kinases), and PLCγ (phospholipase Cγ 2) [42,82]. These molecules are of critical importance in coordinating B cell growth, differentiation, survival, activation and apoptosis [83]. Altered BCR intracellular signaling affects calcium influx and leads to aberrant cellular activation status.

Among these key molecules, Lyn has dual role in B cell activation [84]. By phosphorylating Igα/Igβ ITAM domain of BCR complex and CD19, Lyn exerts positive regulation in BCR intracellular signal transduction. But Lyn is also capable of phosphorylating ITIM domain of inhibitory receptors including FcγRIIB and CD22, to attenuate BCR signal [85,86]. Transgenic mice deficient in Lyn developed severe nephritis and produced auto-antibodies reminiscent of SLE [87–89]. Mice with heterozygotic defect of Lyn ($Lyn^{+/-}$) also had similar manifestations, indicating the pivotal role of Lyn in negative-regulation of BCR signaling [90]. Lyn deficiency in B cells has been found in two thirds of SLE patients, and is associated with heightened spontaneous proliferation, anti-dsDNA antibody and IL-10 production [91,92]. Studies have also suggested that the reduction of Lyn expression on B cells is disease pathognomonic but not related to disease activity [92]. Mechanism of Lyn down-regulation is not clear although altered ubiquitination modification and post-transcription inhibition by elevated microRNA-30a have been suggested [91,93]. On the other hand, mice with constitutively activated Lyn in B cells ($Lyn^{up/up}$ mice) also develop circulating autoantibodies and lethal autoimmune glomerulonephritis [94]. Therefore Lyn seems not an ideal therapeutic target because of its dual role in immune-regulation which makes the net effect of intervention on Lyn hardly predicted.

Our group together with other groups has demonstrated that increased PI3K/Akt activation in SLE patients, both in T cells and B cells [95,96]. And PI3Kδ (p110δ containing PI3K complex) plays an important role in B cell differentiation and function, regulating class switch recombination and AID [97,98]. PI3K is also involved in downstream signal transduction of BCR, BR3 (B lymphocyte stimulator receptor 3), CD40 and TLRs (Toll like receptors) [99,100]. Inactivation of PI3Kδ could lead to significantly decreased autoantibody production and amelioration of autoimmune glomerulonephritis with improved survival in mice model of SLE [101,102].

1.2.4 B cell tolerance checkpoints

Peripheral B cell repertoire in SLE is shaped by abnormal selection, exaggerated somatic hypermutation and increased receptor editing. Abnormalities of these checkpoints contribute to defective autoreactive B cells selection [26,103]. During B cell differentiation, central and peripheral tolerance checkpoints serve to eliminate most of the harmful autoreactive B cells (Figure 2) [103]. The stage from immature pre-B to naive B in bone marrow is an important central checkpoint and the mechanisms include receptor

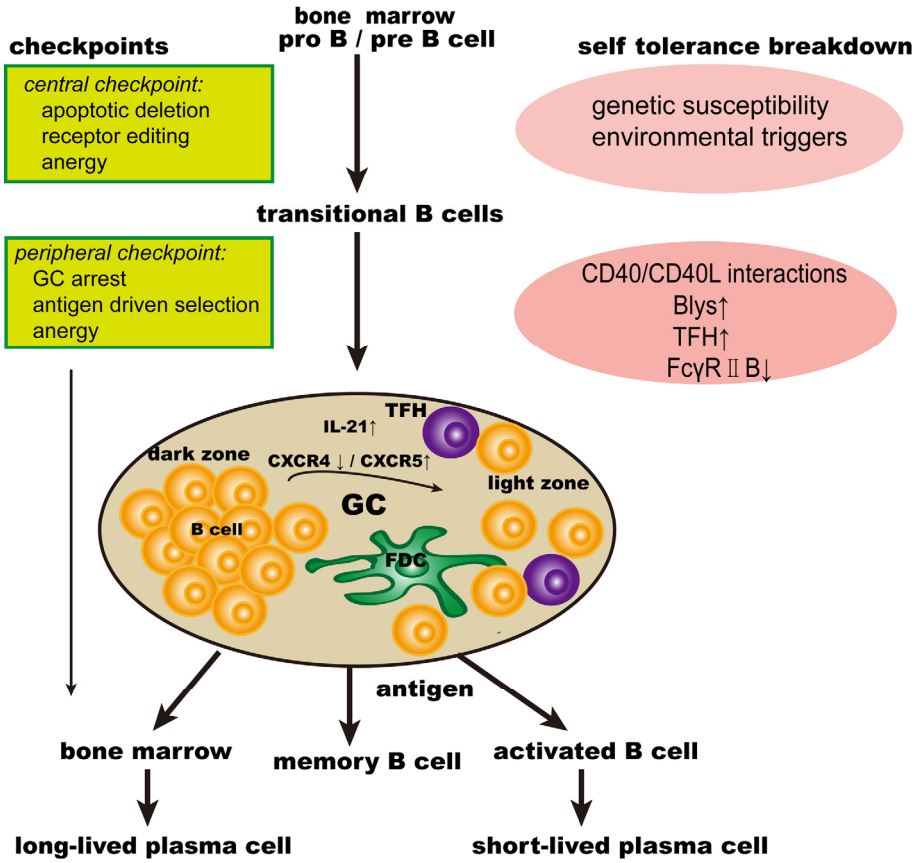

Figure 2 Central and peripheral checkpoints during B cell development. GC, germinal center; TFH, follicular helper T cell; FDC, follicular dendritic cell; Blys, B lymphocyte stimulator; CD40L, CD40 ligand.

editing by V(D)J recombination, clonal deletion by induction of apoptosis and anergy [104,105]. At the stage of pre-BCR, surrogate light chain pairs with Ig heavy chain to form pre-BCR, and multiple mediators may be involved in this checkpoint [106]. Surrogate light chain-deficient mice produce antinuclear antibodies in serum [107]. Decreased RAG-2 transcription may contribute to prolonged survival and decrease apoptosis of pre-B, leading to accumulation of this stage of B cells in lupus mice [108]. Failure of central tolerance checkpoints in human remains largely unknown. Up to 20% of new emigrant naïve B cells are self-reactive, so peripheral tolerance checkpoint is also important by inhibiting activation and preventing affinity maturation of these self-reactive B cells [30]. In GC, naïve B cells migrate from dark zone where they experience fast proliferation and somatic hypermutation, to light zone where they receive antigen-driven selection under the assistance of follicular helper T cells (TFH) [109]. Self-reactive B cells escaping from GC checkpoints due to migration failure in SLE patients have been reported [110]. Chemokines expressing on B cells guide the migration and the most important ones are CXCR4 and CXCR5 [111,112]. Abnormal expression of CXCR4 and its ligand in SLE has been reported in several studies and its role in SLE is recognized [113,114]. Considering the important role of TFH in B cells selection, functional status of TFH would contribute to autoreactive B cells escaping into circulation [113,115,116]. Increased numbers of TFH and its association with autoantibody production have been reported in SLE patients and mice [117–119]. IL-21, as one of the signature molecules of TFH, is up-regulated in SLE and leads to expansion of TFH [120–122]. But the precise mechanism that expanded TFH leading to release of autoreactive B cells is not clear. Deficiency of MyD88, IRAK4 (interleukin-1 receptor-associated kinase 4) and UNC-93B contribute to abnormal selection of B cells in central and peripheral checkpoints [123,124]. Defective receptor editing and accumulation of autoreactive B cells in peripheral blood can be observed in patients with MyD88, IRAK4 or UNC-93B deficiency. These molecules are regulators of TLRs signaling. TLRs signaling especially TLR7, TLR8 and TLR9 are associated with B cell tolerance breakdown [103,125,126]. What's more, MyD88, IRAK4 or UNC-93B deficient patients have altered function of regulatory T cells and DCs, which could also contribute to self tolerance breakdown of B cells [124].

1.2.5 Cytokines involved in self-tolerance loss of B cells

Blys (B lymphocyte stimulator, B cell activator of the TNF family): Blys could promote B cell development and sur-

vival via binding to its receptors: BR3, transmembrane activator-1 and calcium modulator and cyclophillin ligand-interactor (TACI), and B-cell maturation antigen (BCMA) [127–131]. APRIL (a proliferation-inducing ligand) is homology to Blys and shares some biological functions with Blys [132]. TACI and BCMA can bind to both Blys and APRIL [127]. Excessive Blys could rescue autoreactive B cells from deletion and anergy [133,134]. Transgenic mice with over-expression of Blys develop a lupus-like phenotype with excessive numbers of mature B cells and plasma cells, spontaneous GC formation and presence of abundant auto-antibodies [135,136]. In lupus-prone mice with elevated circulating Blys levels, blockade of Blys with soluble Blys receptor ameliorates disease progression [137]. Increased Blys levels in serum and occupancy of BR3 on B cells have been demonstrated to be related to disease activity in SLE patients [138–141]. Raised APRIL levels have also been found in SLE patients although they do not correlate with disease activity [142,143]. Excessive Blys and APRIL contribute at least partly to the prolonged survival of auto-reactive B cells [144].

1.2.6 Other cytokines

IL-21 is an essential cytokine to co-stimulate B cells differentiating into plasma cells [122,145]. IL-21 is mainly produced by TFH in GC and TFH is essential for GC B cells selection [146,147]. Excessive IL-21 in mice can promote autoantibodies production and lupus-like disease [148–150]. Increased IL-21 has also been reported in SLE patients and it correlates with disease activity [121,151,152]. Type I IFN (interferon) could promote the differentiation of activated B cells into plasmablasts and trigger B cells expansion in conjunction with TLR7 [153,154]. IFNα/β can also lower activation threshold for autoreactive B cells, enhance B cell resistance to Fas-mediated apoptosis and prolong its survival [155]. Harigai et al. [156] also found IFNγ could induce more Blys production and release from lupus monocytes to promote B cells activation. IL-6 is critical for the differentiation of B cells and promotes the survival of plasmablasts/plasma cells. Excessive IL-6 is reported to correlate closely with lupus disease activity [157]. Anti-IL-6 receptor antibody is shown to be capable of restoring B cell homeostasis by reducing the frequency of abnormally expanded $CD27^{high}CD38^{high}IgD^{-}$ plasmablasts/plasma cells and $CD27^{+}IgD^{-}$ post-switched memory B cells, whereas increasing the frequency of reduced $CD27^{-}IgD^{+}$ naïve B cells [34].

2 B-cell targeted therapy in SLE

Given the pathogenetic role of B cells in SLE, suppressing the production of autoantibodies by depletion of B cells, inhibition of B cells proliferation or modulation of B cells function is a plausible approach in treating SLE [158]. Of course, due to the complicated mechanisms and heterogeneous nature of SLE, no individual approach would be efficacious for all patients. So far the main approach of B cell targeted therapy can be divided into B cell depletion, B cell inactivation and B cell survival blockade. The molecular target and related biologics are summarized in Figure 3.

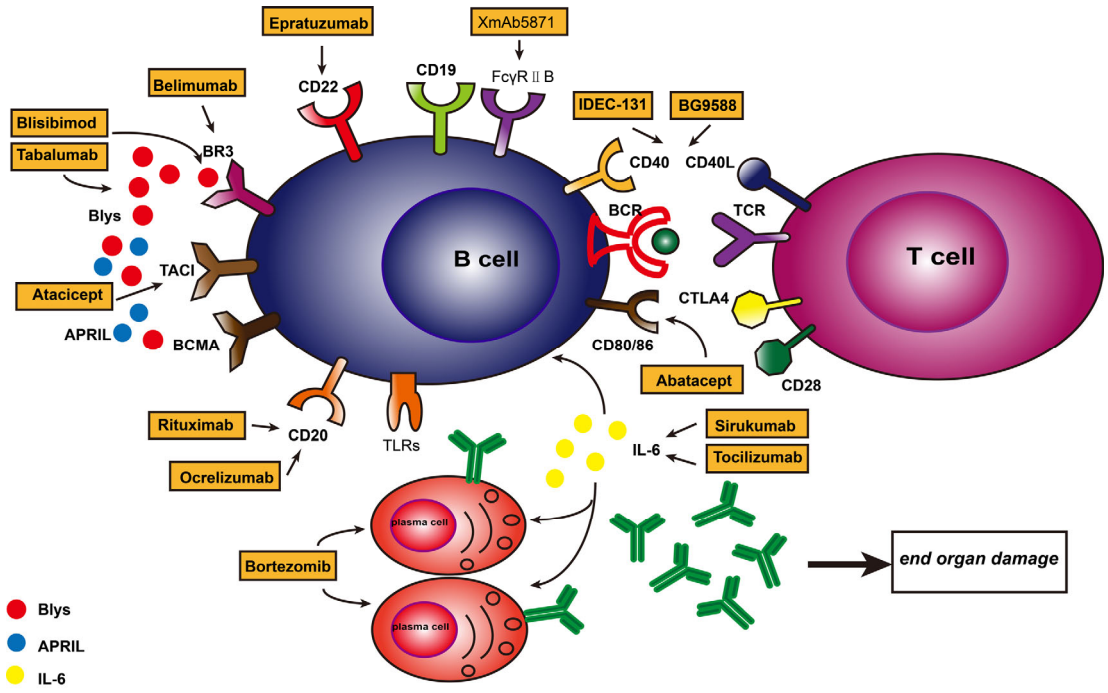

Figure 3 Biologics targeting B cell surface molecules. BLys, B lymphocyte stimulator; APRIL, a proliferation-inducing ligand; TACI, transmembrane activator-1 and calcium modulator and cyclophillin ligand-interactor; BCMA, B-cell maturation antigen; CTLA-4, cytotoxic T-lymphocyte- associated protein 4; CD40L, CD40 ligand; BCR, B cell receptor; TCR, T cell receptor.

2.1 B cell depletion

Depletion of B cells protects lupus-prone mice (MRL.*lpr* or NZM 2328) from developing disease [159,160]. B-cell depletion is promising to induce disease amelioration by inhibiting autoantibody production and/or by interfering with other B-cell pathogenic functions. Ideal B cell target used for B cell depletion should be those molecules highly and exclusively expressed on B cell surface, not be sheared off into circulation, and expressed on both mature B cells and plasma cells so that could be targeted quickly and effectively.

2.1.1 CD20-targeted therapy

CD20 is a B cell lineage specific surface marker, expressed from early preB stage to mature B cells before differentiation into plasma cells. Antibodies binding to surface CD20 could deplete B cells in circulation by mechanisms including antibody-dependent cell-mediated cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and direct induction of apoptosis [23]. Plasma cells don't express CD20 thus being insusceptible to anti-CD20 antibody. Although disease remission is always after ultimate elimination of autoantibodies, clinical improvement can be observed early before autoantibodies elimination. This is attributed to the abolishment of antibody-independent function of B cells. Current available CD20-targeted biologics include Rituximab (chimeric anti-CD20 with mouse derived variable regions and human IgG1 derived constant regions), Ocrelizumab and Ofatumumab (both are fully humanized anti-CD20).

Two major classic RCT (random controlled trial) studies of Rituximab in treating SLE, the exploratory phase II/III SLE evaluation of rituximab (EXPLORER) and the lupus nephritis assessment with rituximab (LUNAR) trial have not achieved their primary endpoints but certain beneficial effects can be observed in a proportion of the enrolled patients [161,162]. Among other small sample open clinical trials, encouraging results of Rituximab, such as steroid-sparing effects and histological improvement in treating LN, were reported [163–165]. The negative results of EXPLORER and LUNAR trials may mainly due to the imperfect study design such as the enrollment criteria of baseline severity, evaluation tools and endpoints settings, instead of inefficiency. What's more,the use of background mycophenolate mofetil (MMF) and high-dose steroids in these trials may have overwhelmed and masked the beneficial effect of Rituximab. Both guidelines from American College of Rheumatology (ACR) and European League against Rheumatism (EULAR) still suggest Rituximab be used in patients with active nephritis that fail to respond to conventional therapies based on real-life experience reports and open label studies that justify the efficacy of Rituximab [166,167].

A phase III clinical trial examining Ocrelizumab in treating patients with active LN also gained negative results, with no statistically significant superiority of both 400 and 1,000 mg dosage versus placebo, although the overall response rates are numerically higher. The increased rate of serious infections in group of Ocrelizumab which may partly due to combined MMF has caused early termination [168].

Another humanized anti-CD20 mAb—Ofatumumab now is in clinical trial for B cell hematological malignancy and rheumatoid arthritis.

2.2 Inactivating B cells

2.2.1 CD22-targeted therapy

Epratuzumab is a humanized anti-CD22 antibody. An open-label study show Epratuzumab could reduce the circulating B cells by about 35%–40% and inhibit lupus disease activity, though serum levels of Ig and autoantibodies have not been significantly affected [169]. Recently published data from a phase I/II RCT study in Japanese show Epraruzumab could down-regulate CD22 expression as well as decrease total B cell count to a mild-to-moderate extent [170]. Two other RCT studies have been launched previously to evaluate the efficacy of Epratuzumab in SLE: ALLEVIATE-1 and ALLEVIATE-2. The results showed Epratuzumab could reduce British Isles Lupus Assessment Group (BILAG) scores and improve health-related quality of life (HRQOL) with reduced corticosteroid exposure. But premature termination due to cessation of drug supply led to a small sample of study population (only enrolled 90 patients), which maybe the cause of failure to achieve primary endpoint [171,172]. EMBLEM was a phase IIb RCT study targeting moderate to severe SLE patients and the results showed 2,400 mg (cumulative dose in four weeks) Epratuzumab was well tolerated with considerable clinical improvements. A higher proportion of responders than placebo group was observed [173], whereas both of the two phase III trials (EMBODY^{TM}-1 and -2)have not meet their primary clinical efficacy endpoints, announced on 28 July, 2015. (http://www.ucb.com/ presscenter/News/article/UCB-announces-Phase-3-clinical-trial-program-for-epratuzumab-in-Systemic-Lupus-Erythematosus-did-not-meet-primary-endpoint-nbsp).

2.2.2 FcγRIIB-targeted therapy

XmAb5871 is a genetically modified anti-CD19 mAb binding FcγRIIB with high affinity, which could promote coengagement of FcγRIIB with BCR complex and amplify FcγRIIB mediated inhibitory signal in activated B cells without depletion of B cells physically. *In vitro* study showed that XmAb5871 could reduce calcium influx and expression of CD80/CD86, and improve survival of lupus mice [174]. SM101, a soluble, recombinant non-glycosylated FcγIIB receptor, functions to inhibit the binding of immune complexes to cell surface Fcγ receptors and in turn

prevent FcR signaling. Preliminary result from a phase IIa RCT is promising and encouraging. It seems prolonged SM101 treatment may lead to higher SLE response rate and patients with LN may benefit even more. (http://acrabstracts.org/abstract/sm101-a-novel-recombinant-soluble-human-fcγiib-receptor-in-the-treatment-of-systemic-lupus-erythematosus-results-of-a-double-blind-placebo-controlled-multicenter-study/).

2.2.3 Sirukumab/Olokizumab/Tocilizumab

Both Sirukumab and Olokizumab are human anti-IL-6 monoclonal antibody, and Tocilizumab is a humanised anti-IL-6 receptor monoclonal antibody. All these three biologics could block IL-6 mediated effects. In patients with rheumatoid arthritis, significant improvement of disease activity by blocking IL-6 signaling has been reported [175–177]. But till now no concrete data about efficacy in patients with SLE have been obtained and phase I studies indicate that adverse effects such as neutropenia and infection are worthy of attention [178,179].

2.3 Blocking crosstalk between B cells and T cells

2.3.1 Abatacept

Abatacept is a fusion protein of CTLA4 (cytotoxic T-lymphocyte- associated protein 4) and IgG Fc that could block the interaction of CD28 and CD80/CD87 (B7), which is the co-stimulation signal for T/B activation. The abatacept and cyclophosphamide combination: efficacy and safety study (ACCESS) trial did not demonstrate extra benefit of Abatacept on the basis of pulse cyclophosphamide followed by azathioprine [180]. Another phase II/III study enrolled patients with class III/IV LN, and showed improvement in serum immunological abnormalities and urine protein, although these studies did not meet primary endpoint of complete remission of LN [181].

2.3.2 IDEC-131/BG9588

Data from a phaseII RCT demonstrated no superiority in efficacy of IDEC-131 (a humanized anti-CD40L antibody) versus placebo in active SLE patients [182]. BG9588 is another humanized anti-CD40L antibody that blocks the interaction of CD40 and CD40L. In an open-label study on patients with proliferative LN, BG9588 therapy decreased anti-dsDNA antibodies by 50% two months after last treatment, increased serum complement 3 (C3) levels and eliminated hematuria. But serious thromboembolic events caused premature discontinuation [183].

2.4 Affecting B cells growth and survival by blocking Blys

2.4.1 Belimumab

Belimumab is a fully humanized monoclonal antibody against Blys. By blocking the binding of Blys to its receptors (mainly but not limited to BR3), Belimumab could resettle the apoptosis and maturation of B cells. It has received marketing approval for lupus treatment by the European Medicines Agency and USA, and it is the first biological medication officially approved for refractory SLE. Evidence comes primarily from two clinical trials, BLISS (the study of Belimumab in Subjects with SLE) 52 and BLISS 76, both enrolled lupus patients with mild or moderate disease from different ethnic origins, excluding those with active nephritis or neuropsychiatric involvement, and both have met their endpoints [184–186]. Combined results show Belimumab is effective in treating musculoskeletal and mucocutaneous manifestations and slows down the worsening of the BILAG haematological and renal domains than placebo [186]. Post Hoc analysis suggests that patients with renal involvement especially those with serological activity or receiving MMF at baseline might also benefit from Belimumab [187]. In addition, Belimumab treatment helps to normalize complement levels and reduce anti-dsDNA antibodies and decrease certain B cells populations [188]. Responses more likely occurr in patients with higher disease activity [189].

2.4.2 Atacicept

Atacicept is a fusion protein of extracellular domain of TACI conjugated with human IgG Fc. Atacicept could block Blys and APRIL binding to TACI. Phase Ib placebo-controlled trial displayed biological activity of Atacicept in abating Ig levels and reducing total B cell numbers, in a dose-dependent manner [190]. Two phase II RCT of Atacicept in treating refractory rheumatoid arthritis displayed a rapid and profound decline of Ig and rheumatoid factor levels as well as circulating mature B cells and plasma cells in Atacicept group, although the primary endpoint of ACR20 was not met [191,192]. The biologic effects justify clinical trials in SLE. But a clinical trial aiming at LN patients was terminated prematurely because of serious infections associated with hypogammaglobulineamia which might be due to simultaneous MMF therapy [193]. In another SLE randomized trial, 150 mg but not 75 mg Atacicept showed benefits in reducing flare rates and prolonging prior-relapsing time compared to placebo, although both dosages have improved serological index [194]. Notably, 150 mg arm was discontinued early because of two deaths.

2.4.3 Blisibimod/Tabalumab

Blisibimod (AMG 623) is a human IgG-Fc fused protein with high affinity to soluble and membrane-bound Blys. As for NZB/NZW F1 lupus mice, Blisibimod led to decreased B cell number and improvement of disease activity [195]. In PEARL-SC study, a phase II/III trial of Blisibimod which enrolled moderate to severe SLE patients, reduced proteinuria and decreased B cell number, as well as restoration

of serum C3 levels and lowering of anti-dsDNA antibodies have been observed with a favorable outcome on cumulative severe flare in Blisibimod therapeutic group [196]. Tabalumab is another human neutralizing monoclonal antibody targeting both membrane and soluble Blys [197]. Although in rheumatoid arthritis, phase II clinical trials of Tabalumab show inconsistent results [198–200] and phase III RCT is terminated due to lack of efficacy [201,202], recently published data from two multicentre phase III RCT of Tabalumab in treating moderate to severe SLE (ILLUMINATE-1 and -2) (NCT00111306 and NCT00383214) seems promising. Both trials show significantly improvement in serum biomarkers of disease activity like anti-dsDNA and C3. But the primary endpoint of SLE responder index 5 has been only met in ILLUMINATE-2 at the dose of 120 mg Q2w, but not met at the dose of 120 mg Q4w and in ILLUMINATE-1 study. These trials suggest that the dosing strategy and the demographic characteristics have important influence on the therapeutic effects, and regime for different patients should be optimized [203,204].

2.5 Proteasome inhibitor

Long-lived plasma cells, being capable of continuing producing autoantibodies and resistant to conventional treatments and anti-CD20 biologics, are responsible for refractory disease and flare. Bortezomib, a proteasome inhibitor that has been approved for multiple myeloma treatment, shows effects in efficiently depleting long-lived plasma cells, ameliorating nephritis, reducing disease activity and prolonging survival in lupus mice [205,206]. The mechanism is explored and inhibition of IFNα production by suppressing TLR-activated plasmacytoid DC is proposed, probably through interrupting the translocation and intracellular trafficking of TLR [207,208]. Data from non-controlled small sample clinical trial indicates Bortezomib could significantly reduce anti-dsDNA titers and plasma cell numbers as well as disease activity [209]. But these effects could not perpetuate, and the adverse effects occur frequently, leading to discontinuation in more than half of the patients. Further randomized controlled well-designed studies are needed for evaluation of its application in SLE.

3 Perspective of SLE targeted therapy focusing on B cells

B cell-targeting therapy seems to be a promising approach in the treatment of SLE, but more effective agent and appropriate enrollment criteria and further elucidation of B cells pathogenesis in SLE are needed. Strictly speaking, all these so far developed targeting therapy do not accurately "target" pathogenic B cells without affecting "good" B cell populations. Thus we should be always vigilant about the increased risks of infection and other adverse effects. Moreover, due to the complicated mechanisms and various components involved in the pathogenesis of SLE, no single drug will be appropriate for all SLE patients at each stage of disease course. More precise targeting therapy and rationally combined medications should be explored in the future.

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