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Aberrant B-Cell Activation in Systemic Lupus Erythematosus

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Keywords
B-cell activation · Systemic lupus erythematosus · B-cell receptor pathway · Toll-like receptor pathway · B-cell activating factor receptor pathway

Abstract
Background: B lymphocytes (B cells) are essential in humoral response, and their activation is an important first step for the production of antibodies. However, aberrant B-cell activation is common in the development and progression of autoimmune diseases including systemic lupus erythematosus (SLE), which is characterized by the generation of superfluous autoantibodies. SLE exhibits clinical manifestation such as excessive inflammation and tissue damage. This review aims to summarize the recent emerging studies on aberrant B-cell activation and the associated concurrent therapeutic targets in SLE. ***Summary:*** Aberrant B-cell activation is closely associated with the pathogenesis of SLE. Among a variety of mechanisms, dysregulations of B-cell receptor (BCR), toll-like receptor (TLR), and B-cell activating factor receptor (BAFF-R) pathways are the common and dominating factors involved in aberrant B-cell activation. These aberrant signaling transductions play diverse and integrated roles in the development and the pathogenesis of SLE. Therapies targeting aberrant B-cell activation have shown promising efficacy in achieving the clinical alleviation of SLE, suggesting the discovery of new drug targets from these aberrant signaling pathways is imminent. Here, an integrated survey or review of published high-throughput sequencing database covering RNAs of B cells from SLE versus criteria-matched healthy controls highlights that reported signaling molecules in BCR pathway (*VAV2*, *PLC-γ2*), TLR pathway (*TLR9*, *P105*, *IRF7*, *TAB1*), and BAFF-R pathway (*SDF-1α*) are attitudinally upregulated in SLE patients. This review thus suggests the concurrent and future therapeutic targets and potential biomarkers in both basic and clinical studies of SLE. ***Key Messages:*** This review focuses on core B-cell signaling pathways, discussing the progress in the role of aberrant B-cell activation during the pathogenesis of SLE. This review also highlights the signaling molecules from published studies and database for the possible prevention and treatment targets serving the future clinical treatments of SLE.

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Introduction

B lymphocytes (B cells) in the adaptive immune system aim to produce antibodies, which are critical for the protection against infectious diseases as well as for the development of the majority of the current commercial vaccines. B cells are usually maintained in quiescent status in the peripheral lymphoid organs, and thus their activation is an essential first step for proliferation and differentiation to professional antibody-secreting plasma cells. B-cell activation is typically triggered by the surface-expressed receptors including but not limited to B-cell receptors (BCRs), toll-like receptors (TLRs), and B-cell activating factor receptors (BAFF-Rs), mediating the cell fate decisions upon ligand recognition. Abnormalities in B-cell activation interrupt immune homeostasis and become a catalyst of multiple pathological conditions. Among all these, an indispensable link in the pathogenesis of systemic lupus erythematosus (SLE) is the aberrant activation of auto-reactive B cells [1, 2]. SLE is characterized as an autoimmune disease showing multiple organ involvement and complex clinical manifestations. The disease onset of SLE is related to heredity, infection, and ultraviolet radiation, etc. Numerous studies reported that B cells in SLE patients are aberrantly activated in response to self-antigens, producing a large number of auto-reactive antibodies (autoantibodies), potentially triggering an inflammatory cascade response and is closely related to the occurrence of SLE [1, 2]. In SLE patients, B cells are aberrantly differentiated into plasma cells producing pathological autoantibodies, which form immune complexes and are deposited in various tissues/organs, including kidneys, rendering systemic tissue/organ damage [3]. Lupus nephritis (LN) is the prime cause of morbidity and mortality in SLE patients. LN develops when patients lose immune tolerance and deposit autoantibodies in the kidneys [4]. Therapies targeting aberrant B-cell activation have become the clinical treatment options for SLE and LN.

Over the past few decades, the complex signaling pathways involved in B-cell activation have been extensively studied using traditional biochemical and genetic methods. Recently, as high-throughput sequencing technology developed rapidly, the transcriptional landscapes of B cells in SLE patients have been intensively characterized. Here, we review the canonical pathways, molecular mechanisms, and targeted medications of B-cell activation. We further incorporate correlation review for target SLE-associated molecules obtained by high-throughput sequencing experiments in the literature. All these messages hopefully can improve targeted therapeutic interventions and the development of precision medicine against SLE.

Signaling Pathway for B-Cell Activation

B-Cell Receptor

In quiescent B cells, BCR exists on the surface of the plasma membrane in a randomly distributed state. In response to antigen recognition, the BCR initiates signaling cascade events by oligomerizing BCRs and recruiting membrane proximal signaling molecules to the cytoplasmic domain. In the next step, a signaling complex initiates and triggers a series of cascade reactions and conspicuously completes signal transmission, all of which must be well-organized and precisely regulated [5–7]. As a brief description of BCR signaling pathway, antigen stimulation leads to the cross-linking and oligomerization of BCRs, which are then deposited in the lipid raft area of the cell membrane. Src family tyrosine kinases (such as LYN) typically reside in the lipid raft, which can efficiently phosphorylate the oligomerized BCRs on their ITAM tyrosine residues within the cytoplasmic domain of Igα/Igβ [8, 9]. Consequently, phosphorylated Igα/Igβ signaling subunits further recruit and activate a wide range of downstream proximal signaling molecules to intensify the immune cascade events. For instance, activated Bruton's tyrosine kinase (BTK) and spleen tyrosine kinase (SYK) recruit and activate phospholipase Cγ2 (PLC-γ2), which in turn catalyzes the decomposition of 4,5-bisphosphate acyl inositol into two intracellular second messengers: inositol triphosphate and diacylglycerol [10, 11]. Upon binding to inositol triphosphate receptors on the endoplasmic reticulum, calcium ions are released from the endoplasmic reticulum, and extracellular calcium ions influx into the cytosol [12–15]. Diacylglycerol and elevated intracellular calcium result in the recruitment and activation of PKC, mitogen-activated protein kinase, and other pathways to generate transcription factors such as transcription factor nuclear factor-kappa B (NF-κB) and NFAT, all of which potently promote gene transcription changes important for B-cell proliferation and differentiation [16–18]. In addition, scaffolding proteins also play a pivotal role in BCR signaling. For example, B cells cannot recruit PLC-γ2 and influx calcium, when lack the scaffolding protein BLNK [19–22] (shown in Fig. 1b).

Once the BCR signal transduction process is abnormally regulated, pathological immune responses such as

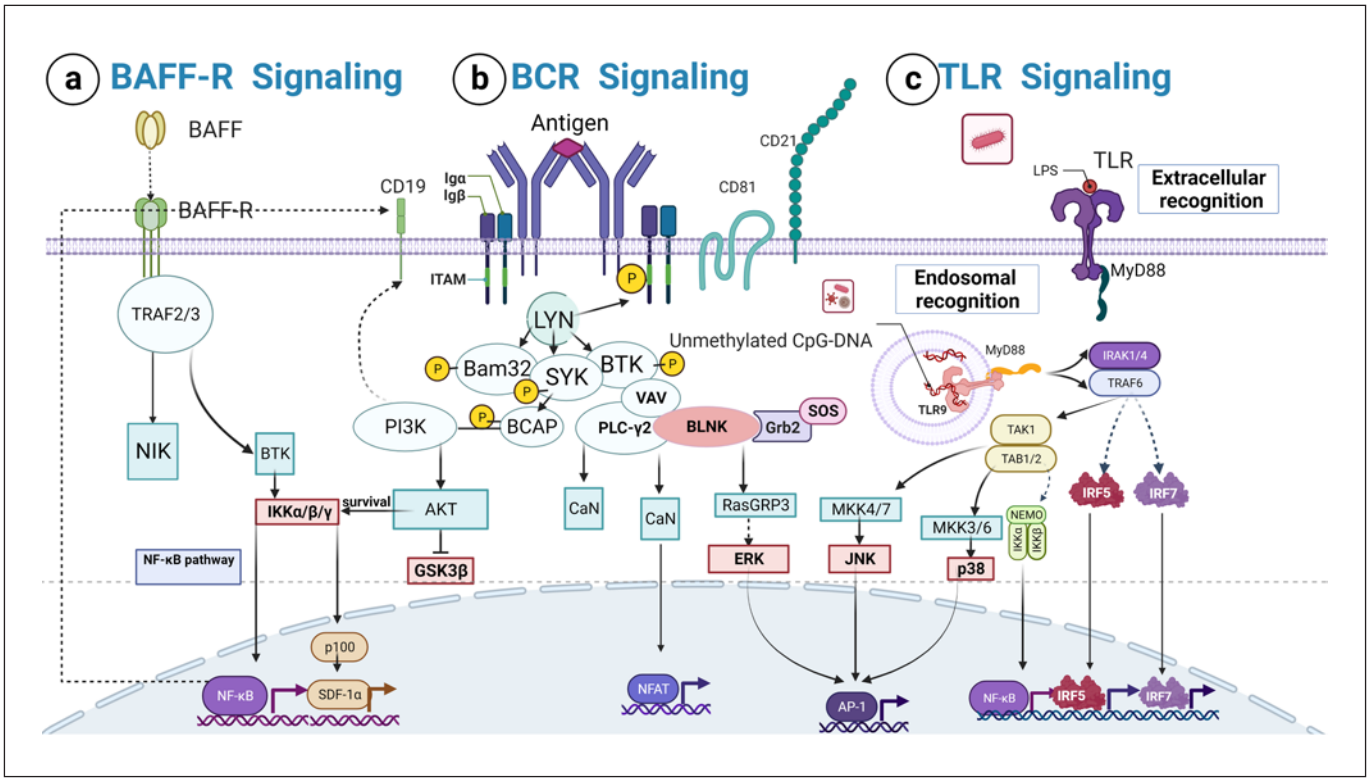

Fig. 1. Signal transduction pathways from BAFF-R, BCR, and TLR. **a** BAFF-R increases CD19 expression via the NF-κB pathway, enhancing BCR signaling and p100 production. BAFF-R survival signal can be transduced by SYK molecules through the ERK and PI3K pathways in addition to NF-κB activation through IKKα. **b** Antigen stimulation leads to the cross-linking and oligomerization of BCR; then Src family tyrosine kinases are activated and phosphorylate a tyrosine residue of ITAM in the cytoplasmic region of Igα/Igβ to form an unfolded conformation. Subsequently, phosphorylated Igα/Igβ recruits and activates various signaling molecules, including BTK, SYK, and PLC-γ2, then catalyzes the decomposition of PIP2 into IP3 and DAG. **c** TLRs recognize PAMPs or signals depending on MyD88. Then MyD88 attracts IRAK4 to TLRs and activates IRAK1. IRAK4 recruits TRAF6 to activate TAK1, which phosphorylates IKKα/β/γ leading to MAP kinase (JNK, p38 MAPK) and NF-κB activation.

immunodeficiency, hypersensitivity, autoimmune diseases, and tumor growth occur. There are intensive next-generation sequencing studies investigating the mRNA levels in purified B cells from SLE patients and matched healthy controls (HCs) (GSE4588, GSE30153, GSE92387, GSE149050, GSE156751, and GSE10325 datasets) [23–27]. Here, we reviewed these sequence data and found that the transcription of *VAV2* and *PLC-γ2* in the BCR signaling pathway were significantly upregulated in SLE B cells in comparison to that from HCs. VAV2 and PLC-γ2 act essentially in triggering calcium influx and cytoskeleton remodeling. In murine SLE disease model studies, there are reports showing elevated PLC-γ2, Rho-family GTP-GDP exchange factor VAV, and Ca^{2+} mobilization in mice harboring B-cell-specific ablation of Cbl, manifesting SLE-like autoimmune disease [28]. However, the underlying molecular mechanism behind such bifurcation is not fully understood. Interestingly, the upregulated transcriptions of *VAV2* and *PLC-γ2* in SLE patients were also mirrored by a published study toward SLE T cells showing the higher levels of PLC-γ1 than that in HCs [29]. It is worth noting that VAV1, VAV2, and VAV3 belong to the VAV family proteins, while the expression of VAV2 shows the opposite trend with VAV1 and VAV3 in SLE. Based on an integrative Bayesian network approach to highlight key drivers in SLE patients, the expression levels of VAV1 and VAV3 in SLE patients were downregulated, while the levels of VAV2 were enriched in B cells of SLE patients [4]. Furthermore, the transient interaction between the T and B cells was typically reported to be in line with the enhanced PKC activation in T cells and diminished VAV1 recruitment at the interface [30].

Table 1. Differentially expressed genes in B cell between the SLE and HC

DGEs in B cell between the SLE and HC	Tendency	Reported in SLE
BCR pathway		
VAV2	Increased	[4, 28]
PLC-γ2	Increased	[28, 29]
IGH	Decreased	[31]
VAV1	Decreased	[4]
VAV3	Decreased	[4]
NFAT	Decreased	[32, 33]
RAC	Decreased	No reports
AKT1	Decreased	[37]
AKT3	Decreased	[37]
GSK3β	Decreased	[34–36]
TLR pathway		
TLR9	Increased	[52, 53]
P105	Increased	[54–56]
IRF7	Increased	[57, 58]
TAB1	Increased	[63–65]
IRF5	Decreased	[59–62]
TAK1	Decreased	[63–65]
IKKβ	Decreased	[66]
MKK3/6	Decreased	No reports
BAFF-R pathway		
SDF-1α	Increased	[86–88]
TRAF3	Decreased	[89]
IKKβ	Decreased	[66]

The other six genes (*IGH*, *NFAT*, *RAC*, *AKT1*, *AKT3*, and *GSK3β*) were found to be downregulated in SLE. Single-sequence analysis indicates that *IGHV3-23* was the most abundant V gene in BCR IGH repertoire from HCs, whereas *IGHV3-21* was the most abundant V gene in SLE patients [31]. NFAT1 showed its involvement in the clinical heterogeneity of SLE. Similarly, aberrant activation of the AKT-GSK3β signaling pathway was observed in SLE T cells. Hydrogen sulfide and mesenchymal stem cells are known to downregulate B-cell proliferation and activation by inhibiting PI3K/AKT/GSK3β pathways in SLE patients [32–36]. Although the transcription of AKT is downregulated in SLE patients, kinome profiling reveals that AKT phosphorylation could be increased in SLE patients (shown in Table 1) [37].

Besides the BCR pathway, SLE is also characterized by the presence of large numbers of IgG subtypes of autoantibodies, in which IgG-B-cell receptor potently enhances memory IgG antibody responses through the conserved cytoplasmic tail of membrane-bound IgG (mIgG-tail) [38]. The mIgG-tail amplifies BCR signaling via its phospho-immunoglobulin tail tyrosine (ITT) motif, which recruits the adaptor protein Grb2 to enhance Ca^{2+} mobilization, synergistically with the transduction of BTK and PLC-γ2 signaling cascade [39, 40]. Recently, it has been reported that a single-nucleotide polymorphism rs117518546, which is common in the East Asian population, results in a glycine-to-arginine substitution at codon 396 in the mIgG-tail portion of human IgG1-BCR (hIgG1-G396R, G396R) [40]. This G396R variant is located near the ITT motif and can modulate B-cell activation and differentiation. It enhances the ITT motif phosphorylation by LYN and promotes the recruitment of downstream BCR signaling molecules GRB2 and BTK to the immunological synapse. GRB2 is an essential adaptor protein of the mIgG-BCR signalosome, which transmits signals from phosphorylated ITT by recruiting BTK to amplify BCR-induced calcium mobilization [41]. Consequently, the G390R ITT motif can bind LYN kinase more effectively than the wild-type ITT motif, promoting GRB2's longer dwell time at the immunological synapses. This results in a more pronounced BCR signaling and lowering of the threshold for BCR activation when GRB2 is released and recaptured rather than released and escaped after its recruitment to the phospho-ITT motif. Individuals carrying this variant showed elevated G390R variant IgG1+ B-cell activation and differentiation to plasma cells producing IgG1 antibodies in autoimmunity, anti-tumor immunity, and vaccination-induced humoral response [40, 42].

A study in three independent case-control cohorts in China (1,786 HCs vs. 1838 SLE patients) showed that the G396R variant frequency was significantly higher in SLE patients and was associated with a more severe disease phenotype including early disease onset, increased LN development, and autoantibody production [40] (unpublished data by Sun et al.). In patients with LN, G396R presence is associated with an elevated risk of early disease development, skin and mucosal involvement, hematological involvement, and an increase of several autoantibodies (unpublished data by Sun et al.). The association of the G396R variant with LN might be due to the increased deposition of IgG1+ immune complexes in glomeruli, which was observed in the SLE model induced in mice with this variant [40].

Toll-Like Receptors

TLRs can recognize molecules with conserved structures from microorganisms, promoting activation of both innate and adaptive immunity [43–45]. TLR9 belongs to the TLR family and is a type I transmembrane protein that recognizes pathogen-associated molecular

patterns or signals depending on myeloid differentiation factor 88 (MyD88). For TLR signal transduction to occur, the toll/interleukin-1 receptor domain conspicuously needs to interact with MyD88, an adaptor protein found in the toll/interleukin-1 receptor domain [46]. MyD88 then attracts IRAK4 to TLRs, activating its death domain [47]. In addition, tumor necrosis factor receptor-associated factor 6 (TRAF6) recruits IRAK4, which further activates TAK1. TAK1 phosphorylates IKKα/β/γ, thereby activating MAP kinases (JNK, p38 MAPK) and NF-κB [47]. To this end, AP-1 and NF-κB perpetually regulate the transcriptional activity of inflammatory factors [48]. IRAK4, IRAK1, TRAF6, and IRF7 are composed of the IRF7 signaling complexes, which induce type I interferons (IFNs) [49]. Similarly, the MyD88-IRF5-TRAF6 complex can activate IRF5 and promote the transcription of tumor necrosis factor-α and IL-6 [50, 51] (shown in Fig. 1c). It would be interesting to investigate whether or not the recognition strength of RNA- or DNA-based ligands by TLR7 or TLR9 would be differently regulated in SLE versus HCs [52]. The answer is likely yes as there are reports showing that the enhanced expression of TLR9 is highly associated with the risk of developing SLE in murine models [52]. Moreover, TLR9 expression is higher in the B cells of SLE patients than in HCs, and IL-6 and ds-DNA antibodies were also more elevated in the serum of SLE patients, which had a positive correlation with TLR9 expression, suggesting that the TLR pathway plays a crucial role in this disease [53].

According to high-throughput sequencing studies, P105, IRF7, and TAB1 are also upregulated in SLE patients, while IRF5, TAK1, IKKβ, and MKK3/6 were downregulated in SLE patients in contrast with HCs [54–56]. In B cells, IRF7 is constitutively expressed as a lymphoid-specific factor that is strongly stimulated by IFNs and viral components [57]. Experimental inculcations also elucidated that patients with SLE expressed significantly more IRF7 mRNA than those with HCs, which is positively correlated with serum levels of IFN-α and lupus disease activity, exerting a crucial effect on its pathogenesis [58]. In addition to IRF7, genetic variations within IRF5 are associated with the increased risk of developing SLE, and mice lacking IRF5 experience reduced symptoms and onset of SLE [59–62]. It is also reported that TAK1 interacts with TAB1 to counterbalance NF-κB, AP-1, and JNK signals, which is essential for the activation and survival of B cells [63–65]. In addition, IKKβ was also found to be downregulated in SLE patients in comparison to HCs [66] (shown in Table 1).

B-Cell Activating Factor Receptor

The ligands of B-cell activating factor of the TNF family (BAFF family) are directly involved in B-cell homeostasis, proliferation, maturation, and survival [67–70]. BAFF is a type II transmembrane protein that is capable of binding to three different distinct types of receptor entities including the BAFF-R, transmembrane activator and calcium modulator, and B-cell maturation antigen [71, 72]. BAFF overexpression is frequently detected and is thus thought to play a significant role in the pathogenesis of SLE and other rheumatic diseases [52]. BAFF acts via its receptor, the BAFF-R, which is expressed in almost all human B-cell subsets and is essential for their survival [73]. Mechanistically, it has been reported that BAFF-R signaling does so by enhancing the phosphorylation of SYK and BCR-coupled Ig molecules, and this phosphorylation requires both BCR and BAFF-R to maintain B-cell trophoblast signaling in a coordinated manner [74, 75]. BAFF-R activates classical and alternative NF-κB pathways, both of which are significant survival signals for B cells. Several studies have elucidated that BAFF-R typically enhances the CD19 expression profile by enhancing NF-κB activity, which in turn further regulates BCRs transmitted downstream signaling, and p100 production [76–80]. Additionally, BAFF-R-mediated survival signals can be transduced by SYK molecules through both ERK and PI3K pathways [81, 82]. Moreover, BAFF-R can also provide the survival signal via the interaction with BTK through a mechanism involving TRAF2 and cIAP2 [83, 84] (shown in Fig. 1a).

Due largely to all these essential functions of BAFF-R in B cells, there is evidence showing that excessive BAFF promotes autoantibodies during autoimmune disease progression. As a result, recent clinical studies have demonstrated BAFF as a potential therapeutic target in various autoimmune disorders. Despite the apparent roles of BAFF's involvement in renal damage and autoimmune disease progression, the relationship between BAFF expression levels, disease severity activity, and damaging roles in SLE devastation is still controversial [85]. As BAFF and BAFF-R pathway products, there are also studies showing that the blood SDF-1α level was significantly higher in SLE patients. The receptor for SDF-1 is CXCR4, and thus the impact of targeting the CXCR4/CXCL12 axis on SLE patients is rather significant [86–88]. It has been recently reported that another signaling molecule TRAF3 was also highly expressed in the kidney in the LN mouse model [89] (shown in Table 1). An additional high-affinity BAFF receptor, known as the Nogo-66 receptor (NgR), was recently identified. Through its effect on NgR, BAFF

inhibits the formation of central nervous system axonal growth, suggesting a role for BAFF in aggravating the multiple sclerosis pathogenesis [90].

Representative Therapies Targeting B Cells for SLE

There has been significant interest in developing drugs that target B-cell surface receptors for the treatment of SLE, several of which have gained approval for clinical use, showing promising results in improving therapeutic outcomes in SLE. Due to space limitations, here we review some representatives of these B-cell targeting drugs which have been approved/recommended for clinical treatment.

Rituximab: Anti-CD20 Monoclonal Antibody

CD20 is expressed on the surface of B cells at different stages of development and differentiation but not on plasma cells. CD20 plays a crucial function in regulating B-cell proliferation and differentiation, both of which are downstream cellular effects upon BCR and TLR signaling. Rituximab (RTX) is a human chimeric monoclonal antibody that binds specifically to CD20, which mediates the lysis of B cells through mechanisms of complement-dependent cytotoxicity and antibody-dependent cytotoxicity [91]. As a result, RTX eliminates B cells, reducing autoantibody production, thereby partly weakening cellular immunity and alleviating antibody-mediated pathogenic consequences. Several clinical trials have demonstrated that RTX can significantly reduce SLE Disease Activity Index (SLEDAI) and British Isles Lupus Assessment Group (BILAG) scores and prednisone doses in patients with SLE, showing promising efficacy and safety in refractory SLE and LN [92]. The results of a second retrospective study of 45 SLE patients also confirmed the benefit of RTX; 89% of these patients achieved either complete or partial remission after treatment with RTX despite a history of inadequate response or nonresponsiveness to conventional therapy [93]. Furthermore, it has been elucidated that RTX was initially approved and developed to treat non-Hodgkin's lymphoma but has subsequently become an established treatment for rheumatoid arthritis and ANCA-associated vasculitis [94, 95]. The glomerular filtration rate improved significantly after RTX treatment, and the improvement of clinical symptoms was associated with the decrease of anti-dsDNA and other autoantibodies in LN patients [93]. The most common side effects of RTX are infection and infusion-related reactions.

Belimumab: Anti-BAFF Monoclonal Antibody

As a member of the TNF family of cytokines crucial for the survival of mature B cells, the blood levels of BAFF are elevated in SLE patients, and patients with higher levels of BAFF are more prone to develop organ damage [96]. Belimumab, a humanized monoclonal antibody, is promising to treat a variety of diseases. By inhibiting the binding of soluble BAFF to its receptor, belimumab perpetually inhibits B-cell proliferation and antibody production, which in turn induces the apoptosis of autoreactive B cells in the serum and reduces serum autoantibodies [97]. Belimumab coupled with standard care has been approved by FDA since 2011 for SLE patients with active, autoantibody-positive disease [98]. A multicenter double-blinded clinical trial for SLE showed that belimumab treatment exhibited higher efficacy (53.8%) than the placebo group (40.1%) [99]. In addition, the treatment group reduced the risk of disease relapse in SLE patients by 50%. For SLE patients taking >7.5 mg/day of prednisone at baseline, belimumab significantly reduced their dependence on glucocorticoids. The adverse effects of the belimumab treatment and control groups are comparable. In a phase III randomized, double-blind, controlled clinical trial (BLISS-LN) for patients with active LN, belimumab reached the primary and all secondary endpoints of the trial, and 43% of patients treated with belimumab in combination with standard therapy achieved significantly higher positive effect than the patients treated with standard therapy plus placebo (32%, $p = 0.0311$) [100].

Telitacicept: A BAFF and APRIL Dual Inhibitor

Telitacicept is a BAFF and APRIL (ligand for B-cell maturation antigen and NgR) dual inhibitor. BAFF and APRIL have been reported as key regulatory cytokines in B-cell maintenance and humoral immunity. BAFF promotes immature B-cell differentiation and maturation events, while APRIL modulates the function and survival of long-lived plasma cells [101]. Blocking both of these factors may be a more effective way of inhibiting B-cell-mediated pathogenic response than blocking either of them. A recent clinical trial of telitacicept supported this rationale in active SLE treatment [102]. This multicenter, randomized, placebo-controlled phase-II clinical trial carried out an in-depth evaluation of the safety and efficacy of telitacicept versus placebo in combination with standard therapy. 249 patients received either telitacicept (80, 160, 240 mg) or placebo (an equal number of each). This study showed a greater SLE Response Index (SRI) in the telitacicept 240 mg group compared with the placebo group (79.2 vs. 32.0%); thus, the primary endpoint was

met. The use of telitacicept decreases the levels of both B cells and blood Ig, increases complement synthesis, and reduces the recurrence of severe SLE [102]. Currently, telitacicept is being studied in several other diseases, including multiple sclerosis, IgA nephropathy, myasthenia gravis, neurological disorders, rheumatoid arthritis, and Sjögren's syndrome [103].

Conclusion

An increasing pool of evidence suggests that aberrant B-cell activation plays an essential role in SLE. Therefore, therapies targeting B-cell functionality are considered a promising new strategy. As of today, there have been several drugs designed to target B cells; however, most of them regulate B-cell survival, not activation. As a result, extensive research and target-oriented drug development are needed based on the effect of B-cell activation on SLE disease. Given the complex pathogenesis of SLE, a drug inhibiting more than one pathway would offer a significant therapeutic benefit. High-throughput sequencing from the purified B cells reveals that *VAV2*, *PLC-γ2*, *TLR9*, *P105*, *IRF7*, *TAB1*, and *SDF-1α* were highly accumulated in SLE patients. However, the exact molecular mechanisms involved are still unclear. Here, we point out the possibilities of these promising targets, while there is still a long way to go before their application for curing SLE.

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Conflict of Interest Statement

The authors declare no competing financial interests.

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Author Contributions

All the authors have contributed to this review. Na Kang and Xujie You drafted the manuscript. Xiaohang Liu analyzed the data. Na Kang and Xiaohang Liu drawn the figures and tables. Wenbo Sun and Kabeer Haneef revised the manuscript. Xiaolin Sun and Wanli Liu designed, revised, and approved the final manuscript.

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