REVIEW ARTICLE

Progresses in biological-targeted drug therapy for systemic lupus erythematosus

Qun Chen[1], Jie Wang[1], Shiyun Sun[2, *]

[1]School of Pharmacy, [2]Department of Intelligent Engineering, Bozhou Vocational and Technical College, Bozhou, Anhui, China.

Received: January 19, 2024; **accepted:** April 9, 2024.

Biological agents are those preparations made of carbon-based biological agents with medical research value using traditional processes or modern biotechnology, which have the functions of prevention (health care), treatment, and diagnosis of various physiological symptoms of human body. At present, biological agents used in systemic lupus erythematosus (SLE) management include inhibition of B cell activation and blocking of therapeutic autoantibodies, inhibition of T cell activation and induction of T cell tolerance, activation and regulation of cytokines, and synthetic peptide immunogens. Each biological agent has its specific indications. Biological therapy can relieve the disease quickly, which is a good adjuvant therapy for refractory and severe SLE. However, the long-term treatment needs to be combined with traditional treatments.

Keywords: systemic lupus erythematosus; biological agent; treatment; molecular biology; immunology

[*]**Corresponding author:** Shiyun Sun, Department of Intelligent Engineering, Bozhou Vocational and Technical College, Bozhou 236800, Anhui, China. Emails: 0430070098@bzy.edu.cn.

Introduction

Systemic lupus erythematosus (SLE) has a variety of autoantibodies, affecting many organs of the body. The pathogenesis of SLE has not been fully elucidated. The complex interaction of genetic, sex hormones, environment, viral infection, and other factors leads to the dysfunction of immune regulation, resulting in the occurrence and duration of SLE, making it difficult to relieve the disease (Table 1) [1]. The SLE incidence rate is about 0.7 per 1,000 people, and the lesions mostly involve the skin, joints, muscles, kidneys, and so on. Glucocorticoids (GC) and cyclophosphamide (CTX) are the main immunosuppressants for the treatment of SLE, but they have many side effects after long-term application. Generally, patients with SLE do not need surgical treatment. However, SLE can also be complicated by some conditions or coexisting diseases, which may require surgical treatment such as acute intestinal obstruction or aseptic necrosis of the femoral head that requires joint treatment. Replacement surgery, or due to kidney failure, kidney transplant surgery is required for treatment. SLE patients are extremely susceptible to infection during surgery and require highly intelligent and automated clean processing capabilities in the operating room. Therefore, people have been trying to develop new therapeutic drugs to improve the long-term prognosis and quality of the life of SLE patients [2].

Table 1. Incidence of major symptoms of systemic lupus erythematosus.

Symptoms	Incidence rate (%)
Joint pain	> 95
Respiratory lesions	> 90
Fever	> 85
Fatigue	> 80
Skin lesions	> 80
Central nervous symptoms	> 70
Thin	> 60
Renal lesions	> 50
Lymphatic system damage	> 50
Cardiovascular damage	> 46
Gastrointestinal disease	> 38

Table 2. Therapeutic targets of systemic lupus erythematosus biologics.

Biologics	Classification	Target
RCT-18	Fusion protein	APRIL, BAFF/BLyS
Geclosporin	Chemical drug	Unidentified
Forigerimod	Chemical drug	Unidentified
P140	Synthetic polypeptide	MHC molecule
Blisibimod	Fusion protein	BAFF/BLyS
Bortezomib	Chemical drug	Proteasome
Atacicept	Fusion protein	APRIL, BAFF/BLyS
Obexelimab	Antibody	FCGR2B, CD19
Tabalumab	Antibody	BAFF/BLyS
Ocrelizumab	Antibody	CD20
Epratuzumab	Antibody	CD22
pConsensus	Antibody	Anti-dsDNA antibody
Abatacept	CTLA-4 fuses with the Fc segment of human IgG1	CD28
Ajulemic acid	Chemical drug	CB2, IL1B
Anifrolumab	Antibody	IFNAR1
Sifalimumab	Antibody	IFN-α
AMG811	Antibody	IFN-γ
Toculizumab	Antibody	IL-6
Evobrutinib	Chemical drug	BTK

In recent years, with the development of molecular biology, modern immunology, and other disciplines, as well as in-depth studies on the pathogenesis of SLE, selective targeted therapy targeting a link in the pathogenesis of the key molecules that affect the pathogenesis and disease progression has become a new direction of treatment. The development and application of biologics based on biotechnology have become a hot spot in the treatment of autoimmune diseases [3]. Biological agents refer to drugs made directly or by modern biological technology or chemical methods using microorganisms, microbial metabolites, parasites, and animal toxins, human or animal blood or tissues, *etc*. for the prevention, treatment, and diagnosis of human diseases. Studies have shown that biological agents have good clinical efficacy and safety for SLE [4]. According to the mechanism of action, the current biologics for the treatment of SLE can be divided into five categories including (1)

biological agents targeting B cells such as anti-CD20 mAb, BLyS-related biological agents, *etc*., (2) biological agents that change the interaction of T and B cells such as CTLA4-Ig, anti-CD40L, *etc*., (3) biologics related to immune tolerance such as LJP394 (aberimus), *etc*., (4) cytokine-related biological agents such as anti-tumor necrosis factor (TNF)-α, anti-interleukin (IL)-10 mAb, *etc*., and (5) other biological agents such as complement inhibitors and T-cell vaccines (Table 2) [5].

Biological agents targeting B lymphocytes

The clinical manifestations of SLE are multi-system, multi-organ damage, and autoimmune diseases characterized by one or more autoantibodies in serum, especially anti-double-stranded DNA (anti-dsDNA) antibodies. Its pathogenesis involves immune intolerance, helper T cell hyperfunction, deficiency of B cell inhibition, and imbalance of cytokines caused by Th1 cell to Th2 cell transformation. Among them, B cells activate proliferation and hyperfunction, produce a large number of autoantibodies, form an immune complex, and lead to tissue damage, which is the main manifestation of SLE immune abnormality [6]. Therefore, targeted B cell therapy can prevent the occurrence and progression of SLE. B cells are therapeutic targets for many novel biological agents. Autoreactive B cells can produce autoantibodies and then form immune complexes deposited in tissues and organs, resulting in inflammation and injury. Anti-dsDNA antibodies are biomarkers of disease activity in SLE and have been implicated in the pathogenesis of lupus nephritis. In addition, B cells and their excreted fine cell factor play a role in the processing and presentation of autoantigen-induced autoreactive T cells activation and division [7].

1. Biological agents for the BAFF/APRIL system

The BAFF/APRIL system consists of two kinds of ligands including Bell Active Factor (BAFF) and a Probiotic Induced Ligand (APRIL), and three types of receptors including BAFF receptor (BAFF-R), transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI) receptor, and B cell maturation antigen (BCMA) receptor. Among them, BAFF and APRIL are both BCMA and TACI, while BAFF-R is a specific BAFF receptor. BAFF, also known as B-cell stimulatory factor (BLyS), belongs to the tumor necrosis factor superfamily (TNFSF). BAFF is a type II transmembrane protein, which can be broken down by Flin opal to form a dissoluble BAFF that can be combined with BAFF-R, BCMA, and TACI on the surface of B cells. BAFF plays an important role in B cell division, maturity, class conversion, and production. APRIL, a member of TNFSF, exists mainly in a dissolute form and binds to BCMA and TACI receptors, but not to BAFF-R [8]. The BAFF/APRIL system plays an important role in the mechanism of SLE. The results of dynamic experiments showed that BAFF overexpressed mice had multiple SLE-related autoantibodies, CIC, purpose-like changes in the liver, and opinuria. In contrast, anti-BAFF treatment in SLE mice delayed the course of the disease and reduced symptoms. Similar to mice, serum levels of BAFF and APRIL in SLE patients were higher than those in healthy subjects, and the extent of BAFF and APRIL may be related to the extent of SLE activity [9]. B lymphocyte stimulators (BLyS) work through their corresponding receptors including BCMA, BAFF-R, and TACI. Cyclophilin ligand interactor plays an important role in regulating B lymphocyte maturation, promoting immunoglobulin class conversion, assisting T cell activation, and participating in autoimmunity [10]. Overexpression of BLyS can promote excessive proliferation of B cells and secrete a large number of autoantibodies, resulting in immune imbalance of the body and inducing various autoimmune diseases. A lot of evidence has shown that overexpression of BLyS is one of the important mechanisms involved in the pathogenesis of SLE. Therefore, taking BLyS as the target, blocking its biological activity can inhibit the overactivation of B and T cells and promote the abnormal autoimmune tolerance to return to normal, which may provide a new method for the treatment of autoimmune diseases such as SLE. At present, the most widely

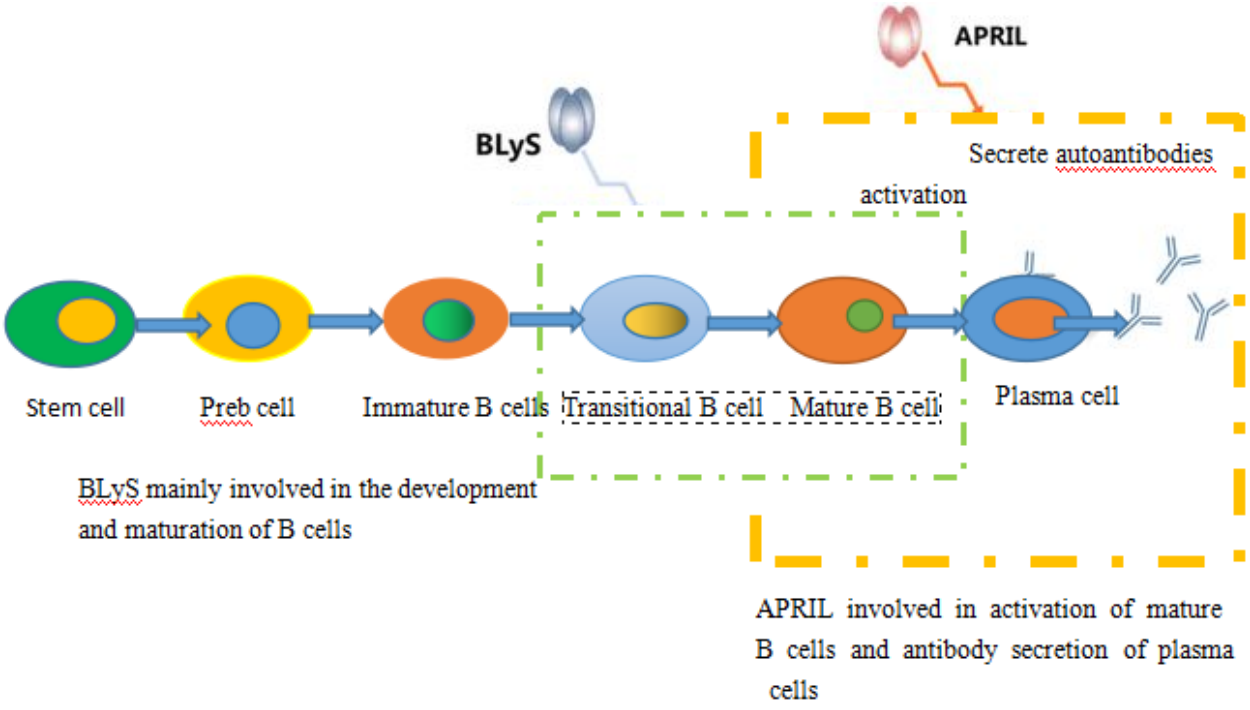

Figure 1. Therapeutic targets of BlyS/APRIL system biologics for SLE. (Cited and modified from the internet resource https://www.163.com/dy/article/FSSEB0N7051182D7.html)

studied antagonists of BLYS are monoclonal antibodies against BLyS and soluble receptors of BLyS (Figure 1) [11].

(1) Anti-BLyS monoclonal antibodies

Belimumab (Brand name: Benlysta) (GSK plc, London, United Kingdom) is a specific and the first inhibitor of BLyS, which is a humanized IgG1 lambda monoclonal antibody and can bind and neutralize soluble BLyS, block BLyS and B lymphocyte receptors on the cell membrane, restrain B cell survival, reduce B cells' reactivity, and inhibit the B cells' synthesis of immunoglobulin and plasma cell differentiation, thus, alleviate the symptoms of SLE [12]. The experimental results showed that belimumab reduced the number of activated B cells and anti-dsDNA antibodies, and patients had a significantly longer time to relapse. A total of 1,684 SLE patients were enrolled in the III clinical trial of belimumab. The results showed lower lupus activity index and British Isles Lupus Assessment Group (BILAG) score in the treatment group compared with the placebo group. However, belimumab is relatively expensive. The annual treatment cost reached $15,600 (USD) and has been resisted by the health care systems of European countries [13].

(2) BLyS receptor fusion protein (TACI-Ig)

Atacicept is a soluble, fully humanized, TACI-Fc fusion protein that binds to the ligands of BAFF and APRIL. Therefore, it should theoretically have a stronger effect than belimumab. A Phase II/III clinical trial examined the efficacy and safety of atacicept in preventing recurrence in patients with moderate to severe SLE. Lupus did not meet the primary endpoint based on the BILAG index and participants demonstrated adverse events of immunoglobulin reduction and severe infection [14]. Another phase II/III clinical trial for lupus nephritis was also prematurely terminated due to hypoimmunoglobulinemia and severe infection in the subject patients [15-17]. At present, the safety and efficacy of atacicept in the treatment of SLE remain to be verified.

2. Biologics that target B cell surface molecules

(1) Biologics targeting CD20

A. Rituximab (RTX)

CD20 is a specific marker on the surface of B cells and is a membrane-associated glycoprotein, which is highly expressed on the surface of pre-lymphocytes, resting phase, and activated mature B cells. Rituximab is a human/mouse chimeric anti-CD20 monoclonal antibody, which can block the action of CD20 positive B cells. However, plasma cells are CD20 negative cells, which will not be affected and can effectively clear abnormal proliferation of B cells *in vivo* [18]. Previous study reported 15 cases of refractory severe SLE patients including 6 neuropsychiatric lupus, 4 lupus nephritis, 5 immune thrombocytopenia treated with intravenous infusion of 500 mg rituximab for 1-4 times and combined with hormone and other immunosuppressants according to patients' conditions. The results showed that, in addition to four cases of severe infection that resulted in two deaths, rituximab treated refractory severe SLE in 33%, 40%, and 27% of cases with complete, partial, and no response, respectively. It was preliminarily suggested that rituximab was effective in treating some refractory severe SLE [19]. However, at present, anti-CD20 agent, rituximab, has been found to have an insignificant effect in treating kidney disease of SLE, and some patients experience relapses after discontinuing the drug [20, 21]. RTX is mostly used in combination with traditional therapeutic drugs, and most of them belong to small sample and prospective studies. The exact clinical effects of RTX need to be further confirmed by long-term systematic large sample studies.

B. Ocrelizumab

Ocrelizumab is another Fc segment modified humanized anti-CD20 monoclonal antibody. *In vitro* studies have demonstrated that ocrelizumab has higher antibody dependent cellular cytotoxicity (ADCC) and lower compliance-dependent cytotoxicity (CDC) compared to that of rituximab. A phase III clinical trial (BELONG) evaluating ocrelizumab for lupus nephritis was terminated early due to an increased probability of severe infection in patients in the ocrelizumab group. Trials have shown that ocrelizumab reduces urinary protein levels in patients with lupus nephritis and tended to be more effective than placebo. Anti-CD20 monoclonal antibodies can be used in SLE patients who do not respond to standard treatment, but the risk of serious infection when combined with immunosuppressants should be noted [22].

C. Ofatumumab

Ofatumumab specifically binds to the small cell and large extracellular loop of the CD20 molecule. The CD20 molecule is expressed on normal B lymphocytes (pre- to mature B lymphocytes) and B-cell chronic lymphocytic leukemia (CLL). The CD20 molecule does not fall off the cell surface and is not internalized after antibody binding. Research showed that the Fab domain of ofatumumab bound to the CD20 molecule, and the Fc domain mediated the immune effect function, resulting in B cell lysis *in vitro*. The data suggested that the possible mechanisms of cell lysis included complement-dependent cytotoxicity and antibody-dependent, cell-mediated cytotoxicity [23].

(2) Biologics targeting CD19

Mutations in CD19 are associated with severe immune deficiency syndrome, characterized by reduced antibody production. Studies have shown that CD19-deficient humans and mice are less responsive to transmembrane signals, while T cell-dependent humoral responses are weaker, resulting in an overall impaired humoral immune response. One hypothesis is that CD19 may play an important role in regulating the major histocompatibility complex (MHC) Class II expression and signaling *in vivo*. Therefore, CD19 can be used as a potential immunotherapeutic target for a variety of autoimmune diseases including rheumatoid arthritis and multiple sclerosis [24].

(3) Biologics targeting CD32

BI-1206 is a monoclonal antibody that recognizes FcgRIIB (CD32B) and the only inhibitory member of the FcgR family with high affinity and

selectivity. Overexpression of CD32B is associated with poor prognosis. By blocking CD32B, BI-1206 is expected to restore and enhance the activity of rituximab or other anti-CD20 monoclonal antibody drugs. Combining the two drugs promises to provide a new and important treatment option for patients with SLE and represents a huge commercial opportunity [25].

(4) Biologics targeting CD74

It was found that the levels of macrophage migration inhibitory factor (MIF) in kidneys and skin of MRL/lpr lupus mice were significantly higher than that of disease-free MRL/MpJ control mice. The MIF gene deficient MRL/lpr lupus mice had reduced glomerulonephritis and skin manifestations and survived longer than MRL/lpr mice. The levels of CD74 protein and mRNA in B cells of lupus mice were significantly higher than that of healthy control mice, and the levels of MIF and CD44 were also significantly higher. In the renal tissues of MRL/lpr lupus mice, the overall level of CD74 was higher than that of the normal control group, and the number of CD74* cells in the glomeruli and tubulointerstitial of the inflammatory infiltrating area was more than that of the control group, suggesting that CD74 might be a direct factor in the pathological manifestations and development of lupus nephritis [26].

Biologics (Abatacept, a CTLA4-Ig fusion protein) target T lymphocytes

A large number of T cells was found in joint synovium of SLE patients. The complete activation of T cells requires at least two kinds of signal transduction by antigen presenting cells, among which the interaction between CD28 on T cells and CD80 or CD86 between antigen presenting cells is a key step in costimulatory signal transduction. MHC II antigenic peptide-TCR leads to T cell activation, which is then enhanced by CD28-CD80/CD86 co-stimulatory signals. Abatacept is a fusion protein of cytotoxic T lymphocyte antigen-4 (CTLA-4) and the Fc segment of human IgG1 and is a selective T cell co-stimulatory modulator that blocks their interaction with CD28 on T cells by binding to CD80 and CD8 on antigen-presenting cells, thereby inhibiting T cell activation [27]. Based on the 3D structure stability analysis, the variant rs765515058 causing G167V in CD80 was found to reduce the protein's stability through changing the characters of constructed structure of complete CD80 *apo* form and stabilizing amino acid residues of CD80 *holo* form in a great degree. Furthermore, the interaction energy analysis results suggested that rs1022857991 causing C50F might reduce the binding energy of CTLA-4 with CD80. Along with the increasing of nonsynonymous single nucleotide variants (nsSNV), their effects on the interaction of CTLA-4 with CD80/CD86 would increase, and thus influence the CTLA-4-Ig treatment efficacy against lupus nephritis [28].

Biological agents against cytokine activation

1. Interferon (IFN)-α antagonist

IFN-α is the hallmark factor of SLE and plays a role in the beginning and progress of the disease. IFN-α is produced by plasmacytoid dendritic cells (pDC) that are activated by endogenous ligands to produce IFN-α, which then activates monocytoid dendritic cells with high antigen-presenting ability to promote autoantibody production by autoreactive B cells. Anifrolumab is an IgG1k monoclonal antibody that directly targets subunit 1 of type I interferon (IFN) alpha receptor 1 (IFNAR1). Type I IFNs such as IFN-α, IFN-β, and IFN-κ are cytokines involved in regulating inflammatory pathways in SLE and play a central role in the pathophysiology of SLE. Increased type I interferon signaling is associated with increased disease activity and severity. Anifrolumab can inhibit the binding of type I interferon and IFNAR1, thereby blocking the biological activity of type I IFN [29]. Anifrolumab is the only biologic approved by the U.S. Food and Drug Administration (FDA) for the treatment of SLE in more than 10 years and the first drug to target type 1 interferon channels [30]. Compared

with placebo, patients treated with Anifrolumab achieved more reductions in overall disease activity across organ systems including skin and joints, and sustained reductions in oral glucocorticoid doses [31].

2. Monoclonal antibodies against the IL-6 receptor

IL-6 is an important cytokine in the differentiation of plasma cells to mature plasma cells and T cells to effector cells. Serum IL-6 levels are elevated in SLE patients and are associated with disease activity and the presence of anti-dsDNA antibodies. Tocilizumab blocks IL-6 signaling. It has been reported that, in one phase III clinical trial, tocilizumab showed good safety in patients with SLE. Large amounts of *in situ* and/or circulating immune complexes in SLE patients can cause overactivation of complement components, which can directly or indirectly lead to inflammatory damage in multiple organs of the body. Both the classical and alternative pathways of complement form the C5a molecule and membrane attack complex through C5a. Therefore, inhibiting the interaction between C5a and its receptor can inhibit the formation of inflammatory mediators and reduce tissue damage. Anti-C5a monoclonal antibody (Eculizumab) can inhibit the activation of complement C5a and block the action of complement effectively [32]. Previous study reported that six SLE patients who were unsuitable or refused to receive immunosuppressive agents were treated with γ-ray-inactivated autoreactive T cell vaccine. 4 patients who received subcutaneous injections at 0, 2, 6, and 8 weeks resulted in a decrease in SLE Disease Activity Index (DAI) score. 4 out of 6 patients demonstrated the responses of peripheral blood T lymphocytes proliferation to T cell vaccine after immunization. There were no obvious adverse reactions during follow-up. It was suggested that T cell vaccine might be a safe and suitable new immunoagent for SLE patients who are refractory or unable to tolerate large dose of immunosuppressant [33].

3. Regulation of IL-21

It has shown that IL-21 and its co-stimulatory molecules (CD40L, ICOS-L) may become novel targeted therapeutic molecules for SLE. By targeting IL-21 to regulate the balance between immune proliferation and immunosuppression of B cells, the activation of B cells, the formation of plasma cells, the production of autoantibodies, apoptosis of B cells, and proliferation and differentiation of B10 cells, further optimization of B-cell targeted therapy strategies in SLE patients can be obtained. IL-21 regulates downstream signaling pathways through immune pathways. Its main role is to cause excessive activation of B cells, which plays a very important role in the mass production of autoantibodies and immune damage of target organs in SLE patients [34].

4. Reduction of cytokine tumor necrosis factor-like weak inducer of apoptosis (TWEAK)

The cytokine tumor necrosis factor-like weak inducer of apoptosis (TWEAK) is a new member of the TNF superfamily. TWEAK and its receptor fibroblast growth factor-induced 14 (Fn14) are expressed at low levels in healthy adult kidneys. The expression levels of TWEAK and Fn14 in kidney are upregulated when lupus nephritis occurs. In tubular epithelial cells, TWEAK binds to Fn14 and further activates NF-κB, thereby inducing the production of multiple cytokines and chemokines. TWEAK continuously activates NF-κB and promotes the proliferation of tubular epithelial cells, ultimately promoting inflammation and apoptosis. Animal models of kidney disease have demonstrated that neutralizing TWEAK in lupus nephritis reduces inflammation and damage in the kidney [35].

5. IL-12/23

The results of the Phase II clinical study showed that the anti-IL-12/23 monoclonal antibody, Ustekinumab (UST), used in active SLE patients had significantly higher SRI-4 compliance rate at 24 weeks, remission of musculoskeletal system and cutaneous mucosal system than the placebo group, while the incidence of adverse events was comparable between the two groups. The response of SLE patients to UST was not

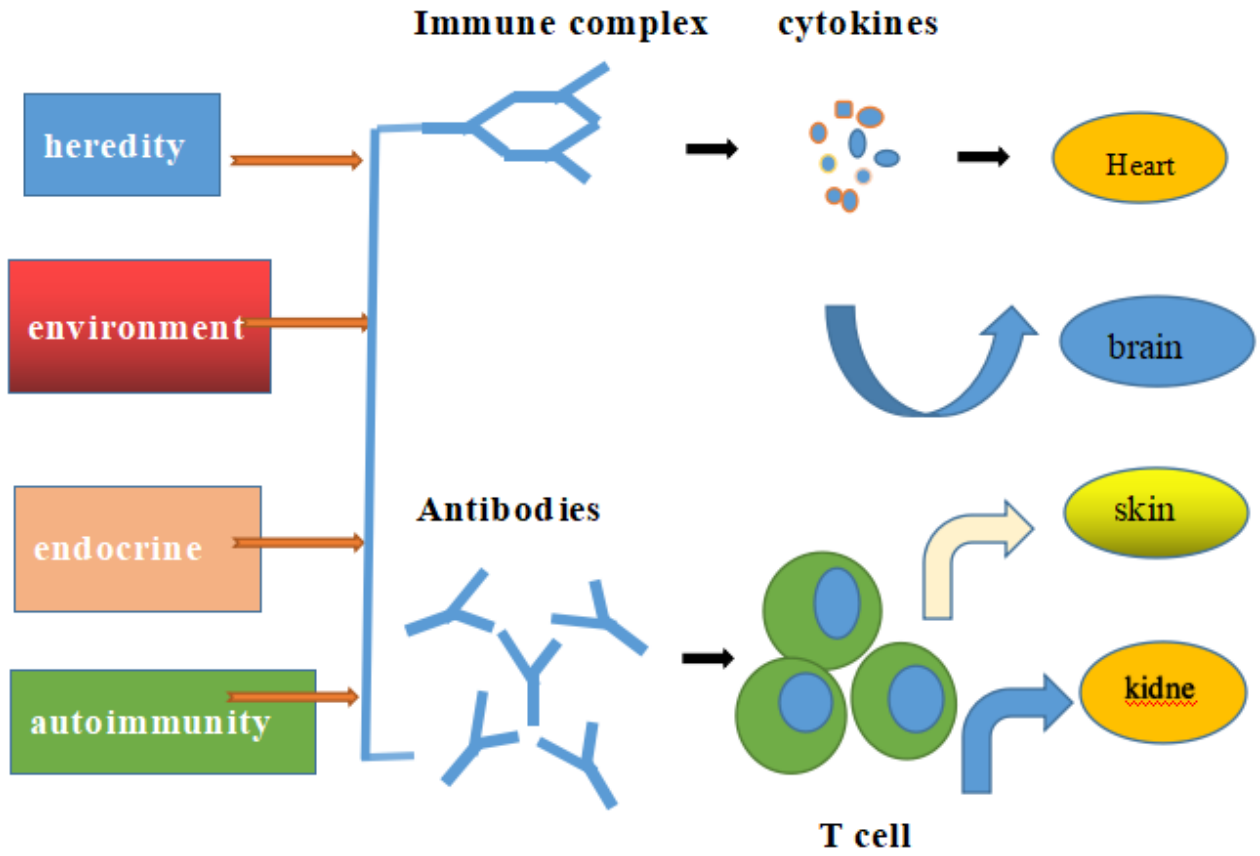

Figure 2. Pathogenesis of systemic lupus erythematosus.

correlated with the level of type I IFN. Therefore, UST exerts a biological effect by blocking IL-12/23, which is independent of the type I IFN signaling pathway [36].

Synthetic peptide immunogen (pConsensus)

pConsensus (pCons) is a 15-amino acid polypeptide derived from the complementary variable region of anti-dsDNA antibodies in BWF1 mice. Animal experiments have shown that pCons can regulate T cell subsets in lupus model mice and inhibit the production of various autoantibodies. In addition, the researchers also found that oral administration of pCons in lupus model mice could also significantly reduce the levels of urinary protein and serum anti-dsDNA antibodies and prolong the survival time of mice to achieve therapeutic effects [37]. At present, there are no clinical trials of pCons in SLE patients. However, inducing immune tolerance by oral administration may be the highlight of its treatment of SLE (Figure 2).

Conclusion

In recent years, the rapid development of biological agents has opened a new approach to the treatment of SLE, which brings hope to patients and provides health care providers with more options. The current biological agents used in SLE treatment are mainly divided into four categories including (1) changing cytokine activation and regulation, (2) inhibiting T cell activation, inducing T cell tolerance, and blocking T-B cell interaction, (3) acting on B cells to reduce cell production of anti-dsDNA antibodies, and (4) inhibiting complement activation. The applications of biologics especially provide treatment opportunities for SLE patients with

refractory recurrence to improve their treatment effects. However, at present, most biological agents are still in clinical trials, and only a small number of clinical trials have been successful. The exact efficacy and long-term adverse reactions of these drugs still need to be further confirmed through large-scale clinical trials and long-term follow-up. The current research mainly focuses on the development of specific targeted therapeutic drugs by using TH17 cells and TFH cells, which are closely related to SLE and other autoimmune diseases, and the screening of Traditional Chinese Medicine monomers. More effective and safer targeted biologics will be explored and become available in the near future.

Acknowledgements

This work was supported by 2021 Provincial Quality Engineering (Grant No. 2021xdxtz044), Key Province in 2020 (Grant No. KJ2020A1014), Anhui Provincial Education Department Annual Scientific Research Project in 2022 (Grant No. 2022AH052582), Research Project of Education Department of Anhui Province in 2022 (Grant No. 2022AH052583), Natural Science Research Project of Anhui (Grant No. 2023AH053211), Natural Science Research Project in Anhui Province (Grant No. 2023AH053221).

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