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Advances of Immune Cells in the Pathogenesis and Targeted Therapy of Systemic Lupus Erythematosus

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Abstract

Systemic lupus erythematosus (SLE) is a heterogeneous autoimmune disease reflecting an imbalance between regulatory and effector immune responses. With the rapid development of molecular biology and multi-omics, the pathogenesis of SLE has been gradually elucidated. In particular, imbalances and abnormalities in immune cell function have been shown to play an important role in the development of SLE. Understanding the specific pathogenesis of SLE is the basis for targeted therapy against specific targets. In this review, we describe the latest research progress on the involvement of immune cells in the pathogenesis of SLE and the potential of targeting different immune cells for therapeutic purposes. Then the importance of precision medicine for SLE disease management is also discussed. Finally, we emphasize recent advances in nanoparticle (NPs)-mediated drug delivery systems for targeted therapy of SLE.

Keywords: Systemic lupus erythematosus, Pathogenesis, Immune cells, Target therapy, Nanoparticles

Introduction

Systemic lupus erythematosus (SLE) is a classic chronic autoimmune disease characterized by formation of nuclear auto-antibodies and autoimmune complexes, which may affect every organ and tissue [1,2]. The pathogenesis of SLE is very complex, involving both innate and adaptive immunity, and is the result of the interaction of complex factors such as molecular genetics, epigenetics, immune regulation, race, and environment (drugs, infection, and ultraviolet radiation) [3]. In recent years, with the promotion and application of fine typing of immune cells, genome-wide association research and multi-omics technology, people have gained a deeper understanding of the pathogenesis of SLE. Simultaneously, it has also promoted the development and clinical research of various monoclonal antibodies or small molecule drugs targeting immune cells, co stimulatory molecules, cytokines/signal transduction pathways, and chimeric antigen receptor

T (CAR-T) cell immunotherapy [4]. Due to the involvement of multiple immune cells in the pathophysiology of SLE, for example, the main pathogenic factor of SLE - abnormal IFN pathway, is the common stimulation result of abnormal immune cells in SLE [5]. At present, clinical scholars still focus more on different immune cells (*e.g.*, T cells, B cells, NK cells, dendritic cells, neutrophils, macrophages) in SLE to explore better targeted therapeutic strategies.

Currently, the main therapeutic drugs for SLE include glucocorticoids, antimalarial drugs, immunosuppressants [6]. For example, first-line treatment for skin involvement in SLE includes local medication (glucocorticoids, calcineurin inhibitors), antimalarial drugs (hydroxychloroquine), and/or systemic steroid therapy [7]. Although these conventional therapies have achieved remarkable efficacy in the treatment of SLE, there are still some critical unresolved issues, especially their low bioavailability, toxicity, and side effects, which result in poor therapeutic efficacy. Thus, there is an urgent need to explore new modalities and strategies for the treatment of SLE. The emergence of targeted therapies has opened a new path for SLE treatment, and SLE researchers have embraced this targeted therapies principle [8]. Notably, there has been unprecedented clinical trial activity in SLE, and novel therapies including biologics and small molecule drugs targeting different immune cells have yielded encouraging results [8].

Nanoparticles (NPs)-mediated drug delivery has begun to play a greater role in the biomedical field due to their unique benefits, which achieve precise targeted delivery to achieve better therapeutic effects and can significantly reduce side effects for patients. Targeted therapy for SLE combined with NPs-mediated drug delivery system is a promising therapeutic strategy. Up to now, researchers and scholars have been actively trying and exploring the treatment of SLE by utilizing this novel delivery kit to encapsulate different drug components [9-11]. With the help of novel engineering technologies such as nanomedicine delivery, SLE may be truly individualized in the future. In this review, we review the latest advances in the involvement of different immune cells in the pathogenesis of SLE and focus on the possibility of different immune cells as therapeutic targets for SLE, discussed the importance of the SLE precision treatment concept and emphasize the potential of NPs-mediated targeted drug delivery systems in the treatment of SLE.

Different Immune Cells Involved in the Pathogenesis of SLE

Various immune cells in the immune system play crucial roles in immune defense, immune monitoring, and immune homeostasis. More and more studies have shown that the pathogenic mechanism of SLE is related to the dysfunction of various immune cells [12-16]. Immune cells include innate immune cells and adaptive immune cells, The innate immune cells involved in the pathogenesis of SLE are mainly DCs, macrophages, natural killer (NK) cells, and neutrophils, while adaptive immune cells are mainly T cells and B cells. Meanwhile, as one of the most important inflammatory factors in SLE, the interaction between immune complex and type I interferons formation with innate immune cells and adaptive immune cells contributes to organ damage in the pathophysiologic cycle of SLE (**Figure 1**). Next, we will review the latest advances of impact of different immune cells on the pathogenesis of SLE.

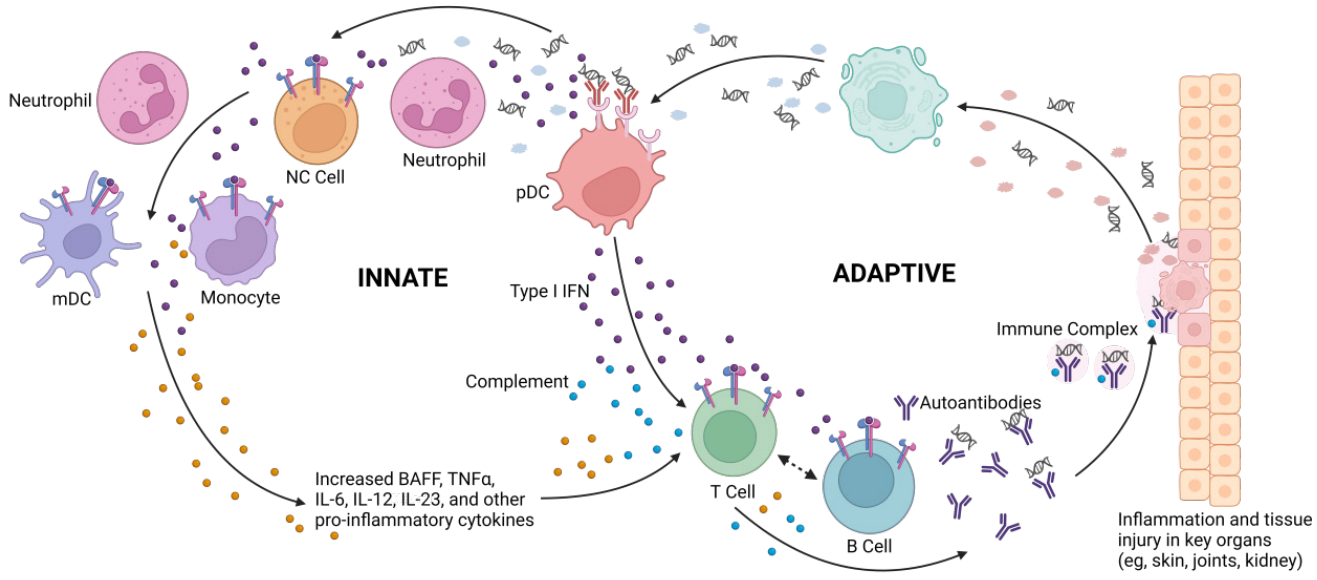

Figure 1. The formation of type I IFN, immune complex, and multiple immune cell function imbalances thereby creating a ring of innate and adaptive immune cell imbalances are collectively involved in the pathogenesis of SLE.

T cells

T cells play a central role in the inflammatory response, with $CD4^+$ T helper cells or $CD8^+$ cytotoxic T cells being the most common subgroup of T cells [17]. A recent study combining information from Hi-C, RNA-seq, ATAC-seq motif enrichment analysis and histone modifications (H3K27ac, H3K4me1, H3K4me3) deciphered the three-dimensional chromosome structure of T cells from patients with SLE, which was found to be significantly different from that of healthy controls and to be closely associated with the disease activity of SLE [18]. Furthermore, a recent report also found that T-cell pathway was most strongly associated with SLE by cluster association analysis and polygenic risk scoring of sequencing results of immune pathway-related genes from 958 SLE patients and 1,026 healthy individuals [19]. $CD4^+$ T cells regulate the immune response by providing costimulatory signals and cytokines and are key drivers of the autoantibody response in SLE, and the cytolytic activity of $CD8^+$ T cells can lead to functional impairment in SLE patients [12]. Imbalances in pathogenic T helper cells such as uncontrolled expansion of Tfh (follicular helper) cells, reduction and functional deficits of $CD4^+$ and $CD8^+$ T cells are associated with SLE pathogenesis [20,21]. The impact of cytokines released by T cells on the pathogenesis of SLE cannot be ignored. With the exception of IL-17, IFN-γ, and IL-21, their pathogenic role in organ damage and inflammation has been widely accepted [22-24]. Elevated inflammatory cytokines, including IL-23, IL-6, and type I have been proved in SLE [25,26]. Additionally, Treg cells, a subset of T cells, have attracted more attention from research scholars. Notably, Treg cells can control the activation of the immune system and are ideal cells for adoptive cell transfer. The only clinical report on Treg cell adoptive cell transfer therapy for SLE shows significant improvement in skin symptoms in active skin type SLE patients receiving treatment. Simultaneously, biopsy results showed an increase in Treg cells and CD41 and CD81 cells producing IL-17, secreting IFN- γ T cells decrease [27]. Despite limited experience in the treatment of SLE, overall data suggest that Treg cells on adoptive cell transfer is safe and effective (moderate efficacy) in autoimmunity [27]. The advent of gene editing technology, which allows for the massive expansion of antigen-specific Treg cells, has greatly facilitated the development of this field.

B cells

B cells are also undoubtedly a very important part of the pathogenesis of SLE, which has been confirmed from basic research to clinical medication [28-30]. Autoreactive B cells escape from the immune tolerance checkpoint at the early stage of SLE pathogenesis and mature with the help of T cells, which secrete autoantibodies targeting autoantigens to form immune complexes, and further recruit DCs, phagocytes, and pDCs, which produce a large number of cytokines and chemokines and mediate inflammatory responses in organs/systems [31]. At the same time, these inflammatory mediators feedback stimulate the activation of self-reactive T and B cells, forming a vicious circle [31]. Bregs, a subpopulation of B cells with cytokine-secreting properties, have a crucial role in suppressing effector T cell responses. Among them, IL-10 and IL-35 secreting Bregs subtypes have the most prominent regulatory role in maintaining immune homeostasis, but such Bregs subpopulations are numerically and functionally defective in SLE [32]. Autologous Bregs adoptive cell transfer and Bregs *in vitro* expansion may be promising to restore the Bregs defects in SLE [33]. Notably, anergic autoreactive B cells (B_{ND} cells), a population of autoreactive B lymphocytes deposited in the peripheral circulatory system to achieve a state of immune tolerance through clonally incompetent mechanisms, has recently been found to play a key role in the pathogenesis of SLE [34]. IL-4 disrupts the internalization of sIgM and promotes its protein stability through the STAT6 signaling pathway, thereby upregulating sIgM and ultimately reversing the function of B_{ND} cells, promoting the pathogenesis of SLE [34].

Natural killer (NK) cells

NK cells are different from T cells and B cells and belong to innate immune cells. Over the past few years, the role of NK cells in shaping the immune response has been emphasized, and abnormal numbers and function of NK cells have been reported in several different autoimmune diseases [16]. Most current studies suggest that NK cells have abnormal numbers in SLE, but the mechanisms remain unclear [35]. Some studies also have shown the presence of IgG-type anti-KIR antibodies in SLE patients, which can attenuate the killing ability of NK cells against K562 cells *in vitro* [36]. Anti-CD94-NKG2A antibodies and anti-CD94-NKG2C antibodies are present in the peripheral blood of some patients with active SLE, and these antibodies can reduce the number and killing function of NK cells [37]. A recent study found an autoantibody (anti Pp150) in patients with autoimmune diseases, which can recognize the single channel membrane protein CIP2A and induce CD56 (bright) NK cells death [38]. In patients with several autoimmune diseases, the proportion of circulating CD56 (bright) NK cells is reduced and negatively correlated with anti Pp150 concentration [38]. The above results suggest that the imbalance of NK cells plays a crucial role in autoimmune diseases such as SLE. More and more data suggest that NK cells play a dual role in autoimmune diseases, and their roles and mechanisms between intrinsic and adaptive immunity still need to be further investigated. More in-depth studies of NK cells in the pathogenesis of SLE may lead to new therapeutic strategies for SLE.

Dendritic cells

Dendritic cells (DCs), as the most important antigen-presenting cells, play a crucial role in triggering pathogenic autoimmune responses and maintaining immune tolerance [39]. Different DC subpopulations [*e.g.*, conventional dendritic cells (cDCs), monocyte-derived DCs (MoDCs) plasmacytoid DCs

(pDCs), and tolerogenic DCs (tolDCs)] have diverse phenotypic and functional characteristics and play different roles in shaping immunity and tolerance during SLE development [14]. cDCs are primarily responsible for identifying broad signals from invading pathogens and causing tissue damage through toll like receptors (TLRs), nucleotide oligomerization domain (NOD)-like receptors (NLRs), and retinoic acid induced gene I (RIG-I) like receptors (RLRs). The cDCs of SLE patients exhibit dysregulated expression of immune regulatory factors. Compared to healthy cDCs, they can induce more allogeneic T cell proliferation [40]. pDCs, as the main producers of type I IFNs in response to TLR7 and TLR9 signaling, have been a focus of SLE research. Type I IFNs are considered an important pathogenic marker of SLE, and the most crucial biological or pathological function of pDCs is their ability to stimulate viruses or their own ssRNA or dsDNA to produce a large amount of IFN-I [41]. tolDCs, also called regulatory DC (DCreg), play an essential role in the maintenance of immune prevention and tolerance of SLE autoimmunity [42]. Mechanistically, tolDCs express inhibitory-interacting surface molecules and inhibitory mediators (*e.g.*, transforming growth factor beta, IL-10 and indoleamine 2, 3-dioxygenase) to maintain self-tolerance in SLE by inducing T-cell deletion and anergy [43]. Notably, DCs also produce B cell activating factor (BAFF, a B cell factor with a specific role in autoimmunity) and activate T cells through their powerful antigen presentation function [44]. DCs show critical roles in the pathogenies of SLE. With the rapid development of multi-omics analyses, it will contribute to a better understanding of DCs biology and pathology and suggest new therapeutic strategies for treating SLE.

Macrophage

Macrophages are important participants in innate immunity, which identify and effectively respond to invading pathogens, providing early defense against external attacks. In addition, macrophages can participate in T cell proliferation and antigen presentation of CD86 cells through surface co expressed molecules MHCII and CD1, indicating that macrophages play a vital role in the occurrence of viral infections, autoimmune diseases and even cancer [45,46]. The polarization imbalance and abnormal activation of macrophages are closely related to the occurrence and development of SLE [47]. Changes in the immune microenvironment of SLE patients promote metabolic reprogramming of macrophages, resulting in changes in their glucose metabolism, lipid metabolism, and amino acid metabolism, leading to the accumulation of intermediate metabolites that act as inflammatory signaling molecules to exacerbate the inflammatory response and cause a series of complications [48-50]. Especially M1 macrophages play a pro-inflammatory role in the pathogenesis of SLE. Gene expression profiles of myeloid cells from active SLE patients express more M1-related genes and tend to pro-inflammation. In contrast, myeloid cells from patients with inactive SLE expressed more M2-related genes and were involved in immune repair [51]. A recent study isolated macrophages and IgG Fc from inflammatory tissues of immune complex related diseases (such as SLE and rheumatoid arthritis), revealed the molecular mechanism of FcγR-mediated metabolic reprogramming in macrophages and proposed a therapeutic strategy for autoantibody induced inflammation [52]. Notably, another recent study reveals that a lupus pathogenic variant (NCF1-H90) can reduce macrophage excretion function, enhance Tfh2 response, promote autoantibody production, and cause kidney damage in both mice and patients with SLE [53]. In addition, macrophages can form an inflammatory phenotype through interferon signal transduction, thereby expanding the immune response and ultimately leading to self-inflammation [54]. These immune adaptations place the role of macrophages at the center of the interferon system. A better understanding of the role of macrophages in the pathogenic mechanism of SLE will help elucidate new targets that can be used for SLE clinical treatment in the future.

Neutrophils

Neutrophils, the most abundant immune cells in the human body, serve as the first line of defense against a large number of microorganisms mediated by cells and playing a core role in immune defense. In recent years, neutrophil extracellular traps (NETs) have been proposed as a novel immune defense mechanism for neutrophils. NETs are involved in the pathogenesis of various diseases, especially inflammatory diseases. Abnormal increase or decrease of neutrophils can affect the pathological processes of various acute and chronic inflammatory diseases with a bidirectional regulatory effect [55]. Neutrophil dysfunction or death provides dangerous molecules and autoantigens, promoting the production of inflammatory cytokines and activation of autoreactive lymphocytes, thus playing an essential role in the pathogenesis of SLE [56]. Individuals with genetic tendencies, decreased neutrophil phagocytosis leads to decreased clearance of apoptotic cells, impaired generation of reactive oxygen species and excessive formation of NETs. NETs are deposited in the skin and renal tissues inducing dendritic cells to produce large quantities of type I IFNs via the TLR [3]. Neutrophils have been confirmed to be involved in the pathogenesis of SLE. In addition, multi-omics and other functional analysis indicate that LDGs (a pathogenic neutrophil subpopulation called low-density granulocytes) are a unique subgroup of pro-inflammatory neutrophils associated with the pathogenesis of SLE [57,58]. A recent study identified 23 ferroptosis-related genes that are aberrantly expressed in SLE patients by transcriptome sequencing of neutrophils. Among them, GPX4 was significantly reduced, and the degree of reduction correlated with lupus disease activity and recovered after treatment [59]. Notably, the crosstalk between neutrophils and other immune cells can promote the pathogenesis of SLE (**Figure 2**). Another recent study has shown that immune complexes can induce neutrophils to release BAFF during the formation of NETs [60]. In addition, neutrophils directly promote the activation and differentiation of B cells [60].

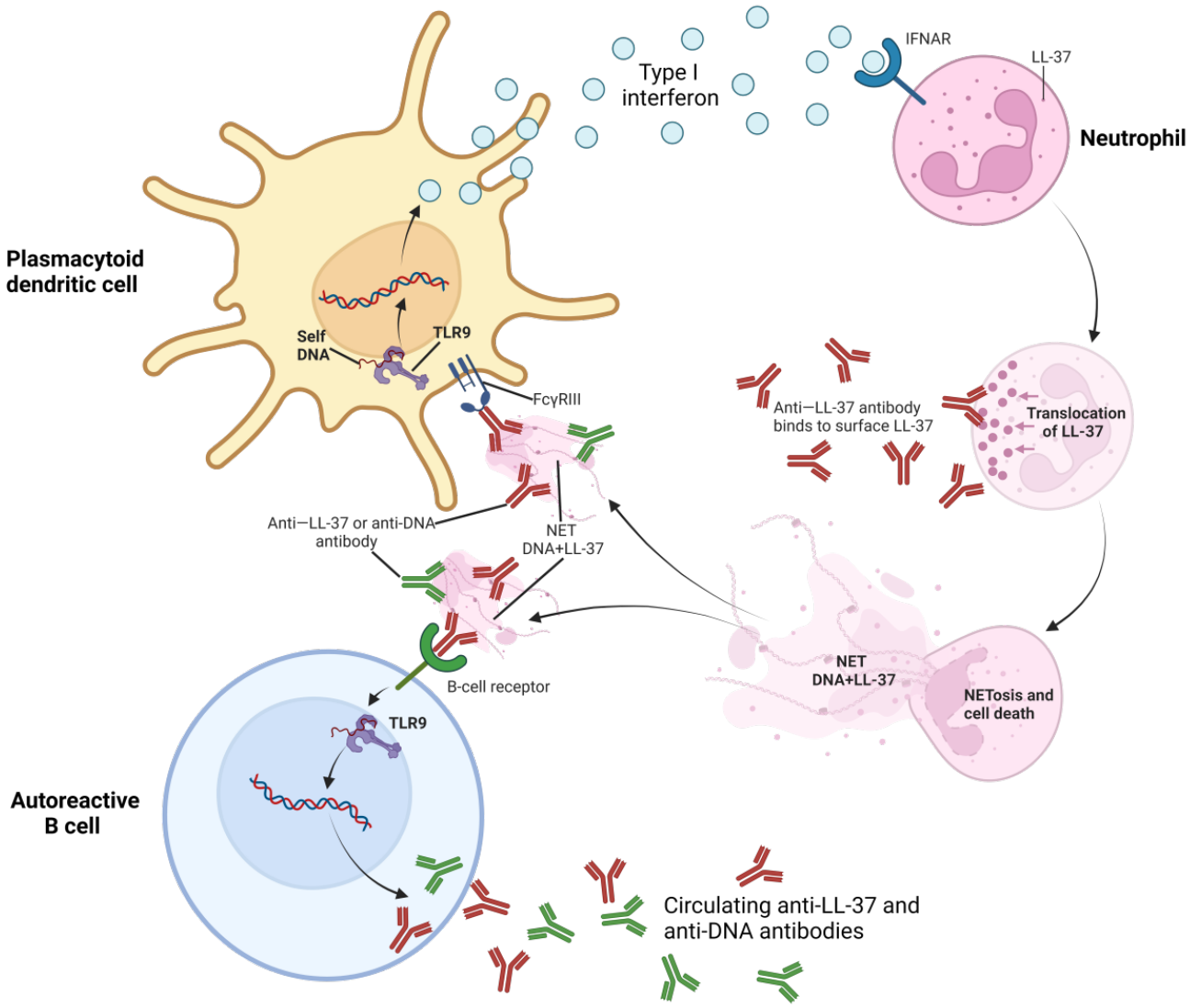

Figure 2. The activation of NETs released by neutrophils and pDCs guides the production of type I IFN observed in SLE. Type I IFN provides energy for the NETs of neutrophils and translocates LL-37 to the surface. After the binding of anti LL-37 autoantibodies to surface LL-37, NETs begin to occur. The NETs released by dying neutrophils, along with anti LL-37 or anti DNA autoantibodies, are absorbed by plasma dendritic cells as NET-related LL-37 DNA immune complexes. In addition, the LL-37-DNA complex stimulates the synthesis of IFN by pDCs, which may also promote the stimulation of B cells and the development of antibodies against antimicrobial peptides such as LL-37.

In summary, the involvement in SLE pathogenesis is not caused by a single category of immune cell imbalance, but by the mutual influence and joint action of different immune cells, forming an immune cell imbalance loop. Targeting the various nodes of the closed loop of immune cell imbalance is a key potential target for the treatment of SLE.

Current Management of SLE

At present, there are three main modes of immunomodulatory therapy for SLE: glucocorticoids, which act quickly but are prone to serious side effects; hydroxychloroquinone takes effect slowly, but is safety and can prevent SLE flares; immunosuppressive drugs can be used for a wider range of systemic symptoms, such as conventional therapies (including cyclophosphamide, azathioprine, mycophenolate mofetil, cyclosporine a, methotrexate, and tacrolimus) and biologics (rituximab and belimumab) [61]. Early identification and targeted therapy have gradually become a new management model for SLE. Due to changes in both the adaptive and innate immune arms of the SLE immune system, almost every immune cell exhibits significant dysregulation. Therefore, SLE therapy targeting immune cells seems to have enormous potential (**Figure 3**).

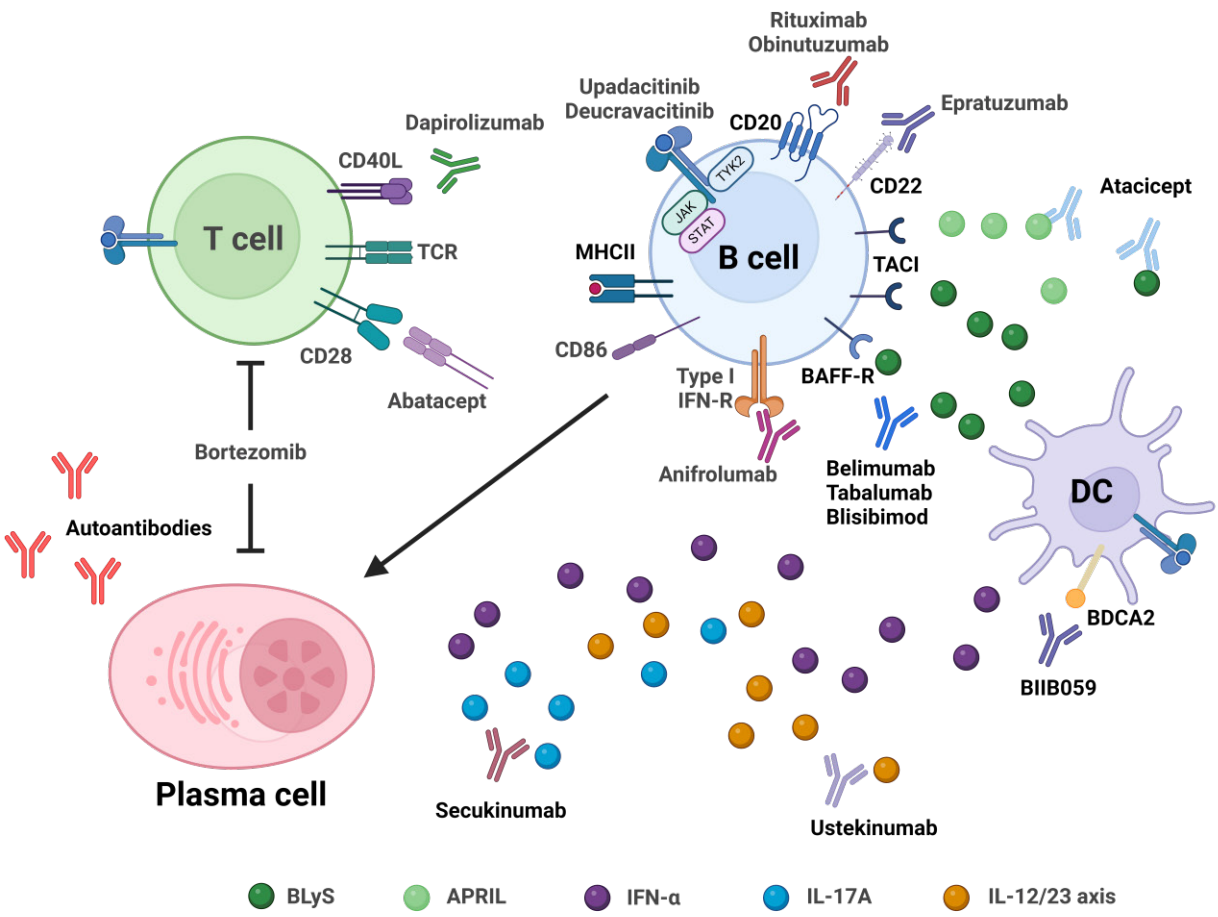

Figure 3. Schematic diagram of current use of targeted immune cells for SLE.

Targeted T cell therapy for SLE

Although it has been confirmed that T cell abnormalities such as phenotype and functional changes are closely related to the pathogenesis of SLE, the therapeutic options targeting T cells are limited. Abnormal T cell receptor signaling in SLE can lead to abnormal increase in calcium influx and activation of calcineurin, thereby enhancing the dephosphorylation effect of nuclear factor (NFAT) that activates T cells [62]. A recent study has shown that the application of tacrolimus (a calcineurin inhibitor that can organize NFAT dephosphorylation) can significantly improve the complete remission rate of a mouse lupus model compared to intravenous cyclophosphamide [63]. Notably, Voclosporin, a novel calcineurin inhibitor, was approved by the FDA for the treatment of lupus nephritis in 2021 [64]. In addition, co stimulatory signals targeting and promoting Tfh-B cell interactions have shown therapeutic effects in lupus animal models [65]. However, the efficacy of biologics targeting a single co stimulatory molecule in SLE is not satisfactory. For example, the phase II clinical trial of dabirolizumab targeting CD40L and polyethylene glycol did not reach the main endpoint, and the phase III clinical trial is still ongoing [66]. More and more evidences suggest that metabolic reprogramming plays an important role in T cell differentiation and is a crucial mechanism for Th17/Treg imbalance. Some targeted metabolic sensors, such as mammalian target of rapamycin (mTOR), AMP activated protein kinases, small molecule compounds of some nuclear receptors, and low-dose IL-2, can improve Th17/Treg imbalance and have good therapeutic prospects for SLE [67,68].

Targeted B cell therapy for SLE

One tenth of registered lupus clinical trials are focused on B cells. Specifically, new B-cell therapy drugs for SLE include: obexelimab and CAR-T, which are resistant to CD19; Rituximab and Otuzumab against CD20; Belizumab, tabalumab, etc. against B cell activating factor (BAFF); Anti-BAFF/APRIL drugs such as Taetaxel; BTK inhibitors and proteasome inhibitors, etc. Rituximab is the best representative of anti-CD20 monoclonal antibodies, and it is a typical biological preparation that has been approved for the treatment of rheumatoid arthritis [69]. There are reports indicating that the efficacy of rituximab in treating active lupus nephritis is comparable to that of non-specific immunosuppressants [70]. In a trial of 54 patients with lupus nephritis, rituximab was compared with MMF

and CYC, and the results showed that it was equally effective as other drugs [71]. BAFF is an important B cell activating factor that is crucial for the survival and maturation of B cells. Belimumab is a highly specific whole human IgG targeting BAFF- λ monoclonal antibodies were officially approved in March 2011 for the treatment of active adult SLE patients with autoantibody positivity receiving standard therapy. This is the first biological preparation approved by the FDA for the treatment of SLE in over 50 years. The therapeutic mechanism of belimumab mainly involves regulating the binding of BAFF and its receptors, inhibiting the maturation and survival of B cells, reducing the number of plasma cells, and ultimately reducing the production of autoantibodies. At present, multiple large-scale phase III clinical studies on the treatment of SLE with belimumab have fully confirmed its tolerability and safety [72,73]. Daratumumab, a human monoclonal antibody targeting CD38, which can consume plasma cells and has been approved for the treatment of multiple myeloma. Longevity plasma cells are associated with the pathogenesis of systemic lupus erythematosus, as they secrete autoantibodies but are ineffective against standard immunosuppression. The use of daratumumab significantly reduces long-lived plasma cells and type I interferon activity. A case study described the substantial clinical response induced by daratumumab in two life-threatening lupus patients and maintained the clinical response through maintenance therapy with belimumab [74].

Another treatment related to B cells, CAR-T therapy, has attracted more and more attention from clinical researchers. CAR-T therapy, also known as chimeric antigen receptor T cell therapy, is a genetic engineering method that modifies human T cells *in vitro* and then reinforces them into the patient's body for the treatment of diseases. The clinical results indicate that CAR-T therapy has great advantages in the treatment of hematological malignancies [75]. In recent years, some clinical studies have shown that CD19 targeted CAR-T cell therapy has produced good therapeutic effects on patients with SLE, which brings a new, safe, and effective treatment option for patients with SLE [76]. Recently, five other patients with refractory systemic lupus erythematosus were reported to have improved their condition after CAR-T cell therapy, with no recurrence observed during a 17 months follow-up period, and all achieved drug-free remission [77].

Target other immune cells therapy of SLE

At present, the indications for cell therapy are gradually expanding from tumors to autoimmune diseases with a huge market, and SLE has become the preferred target for many cell therapies. The research on NK cell therapy in the treatment of SLE is also showing a growing trend. In August of 2023, the US FDA approved its IND application for allogeneic NK cell therapy AB-101 (AlloNK) (a candidate drug for enhanced NK cell therapy) in combination with rituximab for SLE (www.artivabio.com), marking the first-time allogeneic NK cell therapy has been used to treat autoimmune diseases.

Macrophages have strong plasticity and can differentiate into M1 like macrophages with pro-inflammatory effects and M2 like macrophages with anti-inflammatory activity. Considering the prominent role of monocytes and macrophages in SLE, there is potential for strategies to inhibit monocytes and macrophages, limit their tissue infiltration, polarize their phenotype to reduce disease activity. For example, by inhibiting chemokines CSF-1, CCL2, CXCL-12, or TNF α etc. to inhibit the function of macrophages to achieve relief of symptoms in the lupus model [78-80]. Other strategies to improve SLE include monocyte depletion [81], inhibition of Beclin-1 to prevent cell apoptosis [82] and in vitro M2a polarized cells [83]. Unfortunately, there are currently no relevant clinical trials on targeted macrophage therapy for SLE.

Blood dendritic cell antigen 2 (BDCA2) is only expressed on pDC. BDCA2 is a pDC-specific receptor that inhibits IFN-I production in human pDC. Thus, the involvement of BDCA2 is an attractive therapeutic target for inhibiting IFN-I production by pDC and may be an effective therapy for the treatment of SLE [84]. Litifilimab (a humanized monoclonal antibody against BDCA2, also known as BIIB05) is a subcutaneous administered humanized IgG1 monoclonal antibody that can bind to BDCA2, thereby downregulating the production of type I interferon, cytokines, and chemokines. Recently, in a phase II trial involving patients with SLE, litifilimab was found to significantly reduce the number of joint swelling and tenderness from baseline within 24 weeks compared to placebo (NCT02847598) [85]. Similarly, this trial randomized 132 CLE patients aged 18-75 to receive treatment. The results indicate that litifilimab can improve skin disease activity in patients with cutaneous lupus erythematosus (CLE), and its therapeutic effect on CLE is higher than placebo treatment [86].

The New Trend of SLE Treatment: Precision Medicine

At present, the treatment of various diseases mostly adopts the "average treatment" method, but this method cannot benefit some patients. Precision medicine is a tailor-made approach to healthcare and clinical decision-making for patients based on their intrinsic biological information, clinical symptoms, and signs. The concept of precision medicine often appears in the field of oncology, and SLE also has the possibility of precision medicine. Although stratified treatment and precision medicine for SLE pose significant challenges, studies have found that an increasing number of genes and phenotype related loci (STAT4, IRF5, PDGF genes, HAS2, ITGAM, and SLC5A11) are associated with the clinical heterogeneity of SLE, and epigenetic variations (DNA methylation, histone modifications, and microRNAs) also play an essential role in the strong heterogeneity of SLE [87]. Due to the high heterogeneity of SLE, it is difficult to achieve similar therapeutic effects in all patients by removing B cells through

targeted therapy. However, it is worth noting that significant differences in treatment responsiveness were observed in the overall IIb phase trial of nifrolumab through analysis based on IFN characteristic gene expression levels [88]. This experiment may mark the first step in precise treatment of SLE.

With the continuous follow-up of multi-omics technology and bioinformatics methods, the more specific applications of SLE precision medicine are gradually becoming more abundant. In 2021, the FDA approved the use of anifrorumab (an anti-interferon receptor antibody) for the treatment of non-nephrotic SLE and approved the use of the novel calcineurin inhibitor voclosporin for the treatment of lupus nephritis [64]. Prior to this, the FDA also approved belimumab (an antibody against B cell activating factor), which enriches the arsenal of SLE treatment. However, precise medical assistance is needed to stratify patients based on their immune phenotype.

Although our understanding of the pathogenesis of SLE at the genetic level has improved, the heterogeneity of SLE has not yet been fully elucidated. Future treatments are expected to be based on information obtained from multi-omics analysis, including immune phenotypes and disease subgroups at the cellular and molecular levels. We believe that SLE precision medicine will improve SLE care and increase opportunities for SLE drug approval, which is crucial in future.

Exploration of New Methods for SLE Treatment: NPs-Mediated Targeted Therapy for SLE

Nanocarrier drug delivery systems are beginning to play a greater role in the biomedical field due to their unique benefits, which achieve precise targeted delivery to achieve better therapeutic effects and can significantly reduce side effects for patients. In the past two decades, the rapid development of nanotechnology combined with biomedicine has opened up a new era of nano-based carrier therapy for diseases. Whether encapsulating conventional drugs, nucleic acid drugs, vaccines, or aptamers, the potential of nano-delivery drug systems in different diseases, especially in cancer therapy, has attracted the attention of a growing number of scholars [89-91]. Moreover, selective delivery of drugs to inflammatory tissues or specific cells has the potential to improve drug delivery. Targeted delivery of nanomedicines has been extensively attempted in the treatment of autoimmune diseases (such as psoriasis and rheumatoid arthritis) and has shown promising therapeutic effects [92,93]. Compared with conventional drugs, nanomaterials have the advantages of high drug loading capacity, long blood circulation time, improved pharmacokinetic profile of cytotoxic drugs, as well as the ability to target targeting of target cells, tissues, and organs, modulation of overactive immune responses, and the ability to reduce toxicity and other adverse effects of drugs. Similarly, given the unique advantages of NPs, NPs-mediated targeted therapy for SLE seems to be a promising strategy.

NPs-mediated delivery of conventional drugs for the treatment of SLE

Corticosteroids have been used for many years in the treatment of autoimmune diseases (e.g., psoriasis, rheumatoid arthritis, and SLE). However, the pharmacokinetics and biological distribution of corticosteroids are poor and are limited by high doses. There have been many successful attempts to use nano encapsulated hormone drugs in autoimmune diseases. Recent studies have shown that encapsulating glucocorticoids into NPs can significantly improve their bioavailability [94]. For example, researchers have developed a pH and reactive oxygen species dual response, loaded with methylprednisolone and arginine glycine aspartic acid modified NPs. *In vivo* experiments can reduce the release of pro-inflammatory cytokines and alleviate joint swelling and cartilage damage [95]. Similarly, a new type of liposome steroid (methylprednisolone succinate) nanomedicine has been developed, which can specifically accumulate in inflammatory tissues and has better efficacy than free glucocorticoids in SLE mouse models [96]. Another recent study prepared a steroid-loaded recombinant high-density lipoprotein (PLP-CaP-rHDL), a nanoparticle that significantly reduced inflammatory cytokine levels in macrophages *in vitro* and was effective in alleviating lupus nephritis in MRL/lpr mice [97]. Cyclosporine A (CSA) is an immunosuppressive agent which has a good therapeutic effect on SLE. In order to improve the bioavailability of CSA and reduce nephrotoxicity, a recent study have synthesized biodegradable ligand conjugated NPs targeting CD71 and encapsulated CSA, which can enhance targeting of lymphatic tissue and greatly improve the therapeutic effect of SLE model [9].

NPs-mediated targeted immune cells therapy for SLE

As we mentioned earlier, the disorder and dysfunction of immune cells play a crucial role in the pathogenesis of SLE. Therefore, targeted immune cell therapy, especially the introduction of nano delivery systems, is a highly imaginative strategy in the treatment of SLE. Recently, researchers have developed a new nano delivery system (PEALmiR-125a) to deliver miRNA to T cells, reshaping effector T cells and Tregs balance therapy for SLE [98]. The experimental results showed that PEALmiR-125a NPs can be preferentially enriched in the spleen and effectively transfected into T cells of MRL/lpr mice, and PEALmiR-125a NPs can alleviate the development of SLE by restoring effector/regulatory T cell balance. In addition, compared to non-specific immunosuppressive glucocorticoids reagents, PEALmiR-125a NPs exhibit excellent safety [98]. Targeting the SLE-specific upregulated costimulatory molecules (CD40L or ICOS) on T-helper cell can block T-helper cell and B reciprocal activation. A recent study has developed rapamycin encapsulated ICOS/CD40L bispecific NPs that can selectively target SLE T-helper cell and effectively inhibit the mutual activation of T-helper

cell and B cells through targeting the dual costimulatory pathway, thereby significantly alleviating the progression of SLE in both induced and spontaneous lupus models without significant toxicity [99]. During the progression of SLE, PD-1 and TIGIT in pathogenic $CD4^+$T cells are upregulated, while their ligands PD-L1 and CD155 are downregulated. Therefore, dexamethasone (DXM)-loaded IFN-γ-treated MHC class I-deficient cancer membrane-encapsulated nanoparticles (IM-MNPs/DXM) have been developed, which specifically target SLE $CD4^+$ T cells and agonist PD-1/TIGIT signaling to inhibit the function of effector T cells and enhancing the immune-suppressing function of Tregs. IM-MNPs/DXM showed significant efficacy in ameliorating lupus nephritis and reducing side effects *in vivo* [100]. In addition, a novel biocompatible polyhydroxyalkanoic acid (PHA) ternary copolymer poly (3-hydroxybutyrate-3-hydroxyvalerate-3-hydroxyhexanoic acid) (PHBVHHx) based nanoparticle simultaneously encapsulates the immunosuppressive agent azathioprine (AZA) (AZA-PHA) for the treatment of SLE. AZA-PHA NPs have better therapeutic effects than AZA and AZA-polylactic acid NPs, and there is no significant toxicity [101]. This delivery system can provide a new universal platform for the development of nanomedicines with stronger efficacy and lower side effects in the treatment of SLE. Notably, a recent study reported that PLGA NPs loaded with IL-2 and targeting T cells inhibit the development of lupus like disease in BDF1 mice by inducing functional Tregs [102].

In addition to T cells, NPs- mediated delivery systems have also made potential attempts to target other immune cells. MiR-7 specifically targets PTEN mRNA in B cells. AntagoMir-7 treatment reduced the high reactivity of B cells and prevented the onset of lupus. Recently, a newly developed SA (sialic acid) poly (D, L-lactide co glycolide) (SA-PLGA) nanocarrier system has been developed to deliver anti miR-7 to spleen B cells. Meanwhile, antagomir-7 NPs exhibit excellent therapeutic efficiency and high biosafety, which may lead to more effective treatment of SLE [103]. For NPs-mediated targeting of macrophages for the treatment of SLE, two recent studies are noteworthy.

A study rationalized the design and generation of an apoptotic cell-mimicking gold nanocage (AuNC)-based nanomedicine carrier (PS-lipos-AuNC) that corrects the impaired clearance of apoptotic cells in patients with SLE by conjugating phosphatidylserine (PS) to the surface of liposome-encapsulated gold nanocages (AuNC) for liver X receptor (LXR) agonist T0901317 delivery. Notably, PS-lipos-AuNC@T0901317 could effectively enhance apoptotic cell clearance by increasing the expression of Mer, one of the key phagocytosis-associated receptors on macrophages, thereby reducing the production of anti-dsDNA autoantibodies, decreasing inflammatory responses and alleviating kidney injury in lupus model mice [104]. Another study prepared mycophenolate nanoparticles of dextran (MPA@Dex-MPA NPs), which promoted local M2-like macrophage polarization and alleviated SLE symptoms in the MRL/Lpr mouse model [105]. The NETs are a reticular chromatin structure, and targeted ablation of neutrophil extracellular traps is critical for the treatment of NETs-related diseases (e.g., SLE). Recently, a study has utilized the specific interaction between CCDC25 and NETs to prepare mimetic CCDC25 overexpressing cell membrane hybrid liposomes capable of targeting NETs in NETs-associated diseases. After encapsulating DNase I in the liposomes, the nanopreparations effectively abrogated NETs and significantly inhibited neutrophil recruitment. This may be a promising therapeutic approach for the treatment of NET-related diseases such as SLE [106].

NPs-mediated targeted siRNA therapy for SLE

In recent years, nucleic acid drugs, especially small interfering RNA (siRNA), have been one of the hotspots in the therapeutic research and development of refractory diseases due to their ability to inhibit the expression of disease-promoting target genes or up-regulate the target genes that inhibit the disease. The world's first siRNA drug, patisiran (trade name: onpattro®), was approved by the FDA in 2018 for the treatment of hereditary thyroxine mediated amyloidosis in multiple neuropathies. siRNA therapy has great potential in the treatment of autoimmune diseases and even cancers. For example, a study using cationic lipid NPs to encapsulate both TNF-a siRNA (siTNF-a) and STAT3 siRNA (siSTAT3) demonstrated that these NPs synergistically alleviated the symptoms of psoriatic skin lesions by inhibiting the expression of STAT3, TNF-a, and IL-23TLR4 [107]. Signal transduction is a target of anti SLE drugs. High mobility group box 1 (HMGB1) is a nuclear protein with pro-inflammatory cytokine activity that can specifically bind to TLR4 and induce inflammation. Recently, research has developed PEG functionalized TAT peptide cationic liposomes (TAT-CLs) to deliver anti HMGB1 siRNA and dihydroartemisinin (DHA), which can significantly downregulate the expression of HMGB1. This may be one of the potential strategies for treating inflammatory diseases such as SLE mediated by the TLR4 signaling pathway [108]. B-lymphocyte-induced maturation protein-1 (Blimp-1), an important transcription factor that maintains antigen-specific immune responses, plays a crucial role in the pathogenesis of SLE. Researchers constructed lentivirus-mediated Blimp-1 siRNA and injected into MRL-Fas (lpr) lupus mice. The results showed that Blimp-1 expression and anti-dsDNA levels in the peripheral blood of the model mice were reduced by 78% and 28%, respectively, and the lupus mice with SLE-induced renal disease were alleviated, with a significant decrease in urinary protein level [109].

The above studies suggest that NPs-mediated drug delivery system for SLE targeted therapy may be a very promising strategy. The latest research progress on the application of NPs-mediated drug delivery systems in SLE was summarized in **Table 1**.

Table1. The latest research progress on application of NPs-mediated target immune cells in SLE.

Reference	Nano vehicle	Drugs	Target	Immune regulatory mechanisms
[97]	Liposome	Glucocorticoids	Macrophage	Significantly reduced TNF-α, IL-1β and IL-6 in macrophages in vitro and was effective in alleviating lupus nephritis in MRL/lpr mice.
[9]	PLA-PEG-NPs	CSA	T cells	Improved lymphatic bioavailability of CsA was paralleled by normalization of anti-ssDNA immunoglobulin G titer, plasma cytokines, and glomerulonephritis.
[98]	PLGA	Micro RNA-125a	T cells	Alleviated SLE disease progression by reversing the imbalance of effector/regulatory T cells.
[99]	Micelle	Rapamycin, ICOS/CD40L inhibitor	T-helper cells	Selectively target SLE Th cells and potently inhibit Th-B-cell reciprocal activation by targeting dual costimulatory pathways.
[100]	Micelle	Dexamethasone, agonist PD-1/TIGIT	T cells	Targeted pathogenic CD4+ T cells and activated coinhibitory receptors to modulate the effector CD4 T cell/Treg balance via ligation to PD-1 and TIGIT.
[101]	PLGA	Azathioprine	T cells	Reduce urinary protein as well as the serum titers of IgG, anti-dsDNA and ANA.
[102]	PLGA	IL-2	Tregs, T follicular helper	Inhibit T follicular helper cell in lupus mice and decrease production of autoantibodies and reduces lupus nephritis.
[103]	PLGA	AntagoMir-7	B cells	Decrease immunological abnormalities, normalizes splenic B cell subtypes, and suppresses B cell activation.
[104]	Liposome	Liver X receptor (LXR) agonist T0901317	Macrophage	Enhance apoptotic cell clearance by elevating the expression of Mer, decreased production of anti-dsDNA autoantibodies, reduced inflammatory response, and alleviation of kidney damage in lupus model mice.
[105]	Nanostructured NPs	Mycophenolic acid	Macrophage	Macrophages polarized towards a CD206+M2-like phenotype, with a downregulation of surface CD80 and CD40, and reduced TNF-α production in the spleen and kidney.
[106]	Liposome	DNase I	Neutrophils (NETs)	Eliminated NETs and significantly suppressed the recruitment of neutrophils.
[108]	Liposome	Anti HMGB1 siRNA and dihydroartemisinin	Macrophage	Downregulated expression of HMGB1 mRNA and protein, and diminished Toll-like receptor 4 (TLR4) expression and subsequent activation of MyD88, IRAK4, and NF-κB.

Conclusion and Outlook

The pathogenesis of SLE is complex and extremely heterogeneous, and imbalances and abnormalities in immune cell function have been widely recognized as important factors regulating the development of SLE. Current therapeutic advances in SLE are also mainly aimed at biological agents such as T cells, B cells, IFN, or small molecule targeted drugs. However, given the complexity of immune cell interactions in human SLE patients, as well as the variability of disease manifestations and responses to therapy, they may not be adequately represented in preclinical models. In an era when targeted therapy for complex refractory diseases is gradually taking over, the proposal of precision

medicine has undoubtedly provided the strongest solution for personalized treatment of SLE. Although these drugs have achieved great clinical success, more efforts are needed to address their shortcomings, especially toxicity and side effects. NPs-mediated drug delivery systems bring another promising attempt for targeted therapy of SLE. However, the application of nanotools still faces many difficulties and challenges. Translating these findings into clinical applications, for example, will be one of the key issues to be addressed in the future. With the rapid development of more advanced technologies, the pathogenesis of SLE will be better understood, and we believe that more and more therapeutic approaches can be better utilized in the treatment of SLE.

Conflict of Interest

The authors declare no conflict of interest.

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