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Revolutionizing Autoimmune Kidney Disease Treatment with Chimeric Antigen Receptor-T Cell Therapy

Rui Gu[1†], Jiayi Shen[1†], Jiayu Zhang[1†], Jianhua Mao[1*], and Qing Ye[2*]

[1]Department of Nephrology, Children's Hospital, Zhejiang University School of Medicine, Hangzhou 310052, China. [2]Department of Laboratory Medicine, Children's Hospital, Zhejiang University School of Medicine, Hangzhou 310052, China.

*Address correspondence to: qingye@zju.edu.cn (Q.Y.); maojh88@zju.edu.cn (J.M.)
†These authors contributed equally to this work.

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Autoimmune kidney diseases (AIKDs) depict a range of disorders involving immune-mediated damage to the kidneys, where conventional biologic therapies involving monoclonal antibodies often prove insufficient because of persistent autoreactive B cell reservoirs in lymphoid organs and inflammatory tissues. The appearance of chimeric antigen receptor (CAR)-T cell therapies targeting B cells has shown transformative potential, with recent clinical trials showing the remarkable efficacy of anti-CD19 CAR-T cells in achieving profound B cell depletion, reducing immune complex deposition, and ameliorating renal inflammation in AIKDs. While these results highlight the potential of CAR-T cell therapy in facilitating immune reset and overcoming treatment resistance, further clinical investigations are imperative to establish its long-term safety and sustained therapeutic benefits. This review synthesizes current evidence on CAR-T cell applications in AIKDs, discusses critical considerations for clinical translation, identifies existing limitations and challenges, and proposes strategic directions for therapeutic optimization and advancement.

Introduction

Autoimmune kidney diseases (AIKDs) are driven by disruption of immune tolerance and aberrant autoimmune responses, leading to renal inflammation and tissue damage. They encompass systemic autoimmune disease-related nephritis [e.g., lupus nephritis (LN) and anti-neutrophil cytoplasmic autoantibody-associated glomerulonephritis (AAGN)], organ-specific autoantibody-mediated conditions (e.g., anti-glomerular basement membrane disease), and some primary kidney diseases closely related to the autoimmune mechanism [e.g., membranous nephropathy (MN), idiopathic nephrotic syndrome (INS), and immunoglobulin A nephropathy (IgAN)] [1,2]. B cell-driven humoral immune dysregulation plays a central role in their pathogenesis, as evidenced by the clinical success of B cell-targeted monoclonal antibody therapies [3,4]. However, a substantial proportion of patients exhibit persistent or relapsing disease activity, likely due to incomplete depletion of pathogenic B cell subsets.

Targeted antigen-specific chimeric antigen receptor (CAR)-T cells represent an innovative category of genetically modified T cells, with the unique ability to identify and target specific antigens precisely. Their remarkable success in treating hematologic cancers has ushered in a novel era of immunotherapy. Notably, the regulatory approval of CAR-T cell therapies that target CD19, a marker stated on the surface of B cells, has catalyzed advancements in applying CAR technology beyond oncology, fostering pioneering translational research in areas such as autoimmune disorders, with systemic lupus erythematosus (SLE) being a prime example [4–6], myasthenia gravis [7], rheumatoid arthritis [8], and multiple sclerosis [9], and has demonstrated the durable efficacy of high specificity for the removal of B cells and the preservation of remission. This finding offers a new therapeutic option for other systemic autoimmune diseases, including those of the kidney. Although the inflamed kidney may act as a tertiary lymphoid structure with high in situ infiltration of B cells [10–12], currently available preclinical models and case reports continue to demonstrate the powerful ability of CAR-T cell therapy to achieve deep B cell clearance and immune reset.

In this review, we outline the critical function of B cells in the pathogenesis of AIKDs and focus on the therapeutic potential of CAR-T cell therapy. We summarize the available evidence, including findings from preclinical studies and ongoing and planned CAR-T cell clinical trials. Furthermore, we discuss key considerations of CAR-T cell therapy prior to large-scale clinical rollout, summarize potential limitations and challenges, and suggest future directions for optimization and improvement.

Targeting B Cell Therapy for AIKDs

The pathogenic mechanisms of B cells in AIKDs involve multiple levels of aberrant activation and dysregulated immune regulation (Fig. 1). The most critical aspect is the escape of autoreactive B cells from immune tolerance checkpoints, resulting in their abnormal activation as well as subsequent secretion of pathogenic

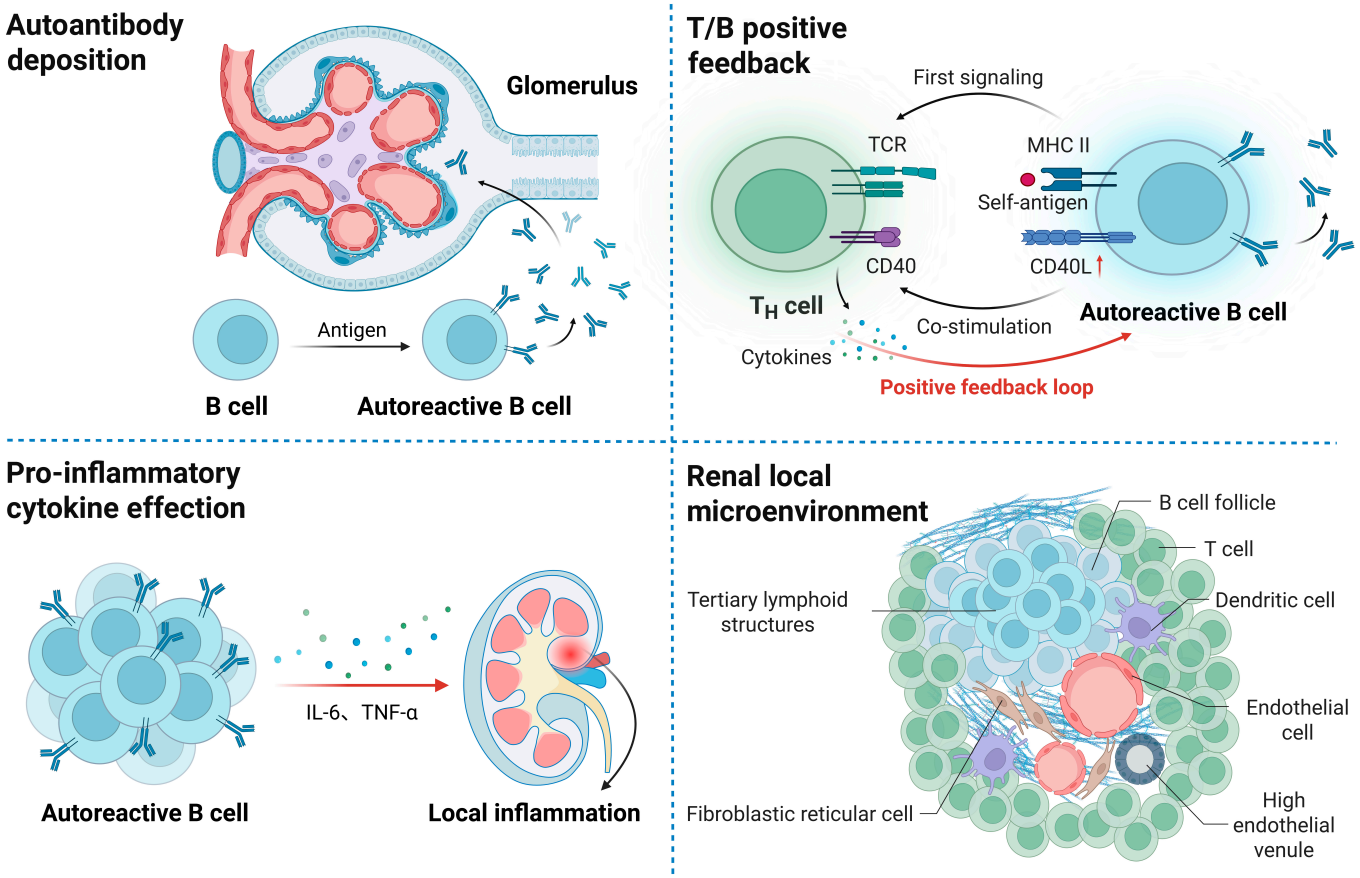

Fig. 1. Pathogenic mechanisms of B cells in autoimmune kidney diseases (AIKDs). T_H cell, T helper cell; TCR, T cell receptor; MHC, major histocompatibility complex; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α.

autoantibodies against specific self-antigens, such as DNA, nuclear proteins, glomerular basement membrane proteins, and podocyte surface antigens [13–16]. Second, B cells present self-antigens via major histocompatibility complex (MHC) class II molecules and provide costimulatory signals to activate autoreactive $CD4^+$ T cells. The activated T cells subsequently secrete pro-inflammatory cytokines, further enhancing B cell function and up-regulating costimulatory pathways, establishing a bidirectional positive feedback loop that is progressively amplified under conditions of immune tolerance breakdown and chronic inflammation, ultimately driving disease progression [17]. Moreover, autoreactive B cells produce cytokines like interleukin-6 (IL-6), further amplifying local inflammation [3,18]. Finally, chronic inflammation may reshape the renal immune microenvironment, with high endothelial vein aberrant expression of chemokines recruiting circulating lymphocytes (T/B cells, macrophages) to infiltrate the kidneys, inducing the formation of ectopic tertiary lymphoid structures, and exacerbating immune attacks on renal target tissues. Abnormal interactions between infiltrating immune cells and tissue-resident cells (fibroblasts, endothelial cells) lead to a vicious cycle of chronic inflammation-promoting fibrosis, which ultimately results in irreversible glomerular and interstitial injury [19,20]. B cell depletion therapies act by targeting aberrant B cell functions, thereby helping to halt or slow the progression of AIKDs.

A deeper understanding of B cell development, differentiation, immune responses (Fig. 2A), and membrane-specific markers (Fig. 2B) is essential for designing precise therapeutic strategies targeting specific B cell subsets. B cell responses can manifest as either germinal center or extrafollicular responses. The extrafollicular response generates plasmablasts and short-lived plasma cells (PCs) that secrete low-affinity antibodies, a phenomenon frequently observed in infections and autoimmune diseases [21,22]. Increased circulating short-lived PCs have been reported in patients with SLE [23], and in INS, autoreactive extrafollicular B cell clones may serve as a primary source of podocyte autoantibodies [24]. In contrast, the germinal center response primarily involves long-lived PCs (LLPCs) and memory B cells [25]. In autoimmune diseases, inflammatory tissues, including the kidney, can sustain LLPCs, leading to the continuous generation of high-affinity pathogenic autoantibodies and the localized inflammation [26–30].

B cell-targeted biologics have been approved for the treatment of LN, MN, AAGN, and refractory INS. Rituximab (RTX) induces rapid depletion of circulating $CD20^+$ B cells, whereas belimumab achieves a relatively mild reduction in B cells by blocking survival signal transduction mediated by B cell activating factor. However, in certain patients, the therapeutic efficacy of these agents remains suboptimal, with frequent relapses observed. A major limitation is the widespread distribution of B cell reservoirs within mucosal immune tissues, while monoclonal antibodies are largely confined to the bloodstream and exhibit limited tissue penetration. This poses a challenge for the complete eradication of tissue-resident B cells, including B cell maturation antigen (BCMA)-positive LLPCs. Studies indicate that residual B cells remain in the lymphoid tissues and

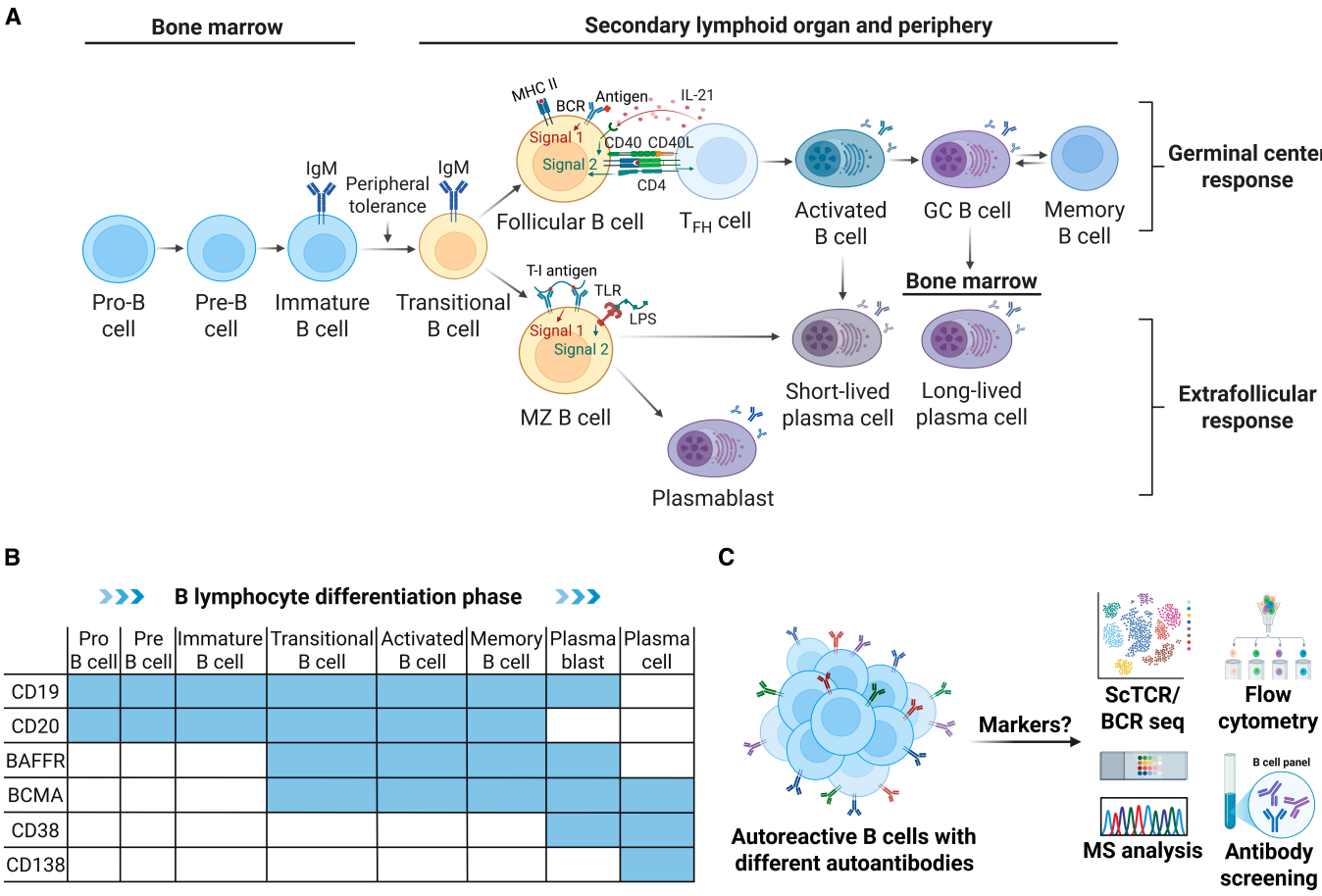

Fig. 2. (A) B cell differentiation and development process. (B) B cell surface antigen markers at different phases. (C) Technical methods for the precise characterization of surface markers of pathogenic B cell clones. MZ, marginal zone; GC, germinal center; BAFFR, B cell activating factor receptor; BCMA, B cell maturation antigen; BCR, B cell receptor; MS, mass spectrometry; Ab, antibody; T_{FH}, T follicular helper.

renal interstitium of LN patients after RTX treatment [31]. Notably, a study on myasthenia gravis demonstrated that during B cell reconstitution after RTX therapy, newly emerging B cell clones still included autoreactive populations [32]. In addition, memory B cells and PCs are not dependent on B cell activating factor for survival, which may lead to resistance to belimumab in SLE patients [33]. These findings suggest that RTX fails to completely eliminate pathogenic autoreactive B cells, which is akin to merely trimming visible weeds while retaining their roots. In contrast, CAR-T cell therapy can uproot these pathogenic B cell clones, achieving true immune reset. As living drugs, CAR-T cells can proliferate and migrate to various lymphoid tissues and organs, sustaining B cell depletion and inducing long-time remission. In patients receiving anti-CD19 CAR-T cell therapy for autoimmune diseases, B cells are completely depleted in secondary lymphoid organs [34]. A systematic comparison of CAR-T cell therapy and conventional biologics is summarized in Table 1.

Compared with CD20, CD19 covers a broader spectrum of the B cell lineage and remains the most extensively utilized CAR-T cell therapy target to date [35,36]. In contrast, BCMA exhibits a highly restricted expression pattern within the antibody-secreting lineage, specifically in plasmablasts and PCs. CAR-T cell therapies aimed at BCMA have shown significant effectiveness in treating relapsed or refractory multiple myeloma, and recent translational efforts have extended BCMA-targeted strategies to autoimmune diseases characterized by pathogenic PC activity [37,38]. Dual-targeting approaches combining BCMA and CD19 leverage the synergistic effects of PC depletion and precursor B cell targeting, potentially enhancing therapeutic durability and preventing antigen escape.

However, most current CAR-T cell therapies rely on fixed antigen targets for global B cell depletion, an indiscriminate approach that may result in the loss of nonpathogenic B cell populations, resulting in humoral immunodeficiency and prolonged immunosuppression. Thus, next-generation CAR-T cell therapies must focus on "just pulling weeds"—precisely identifying and selectively removing pathogenic B cell clones while maximizing immune homeostasis (Fig. 2C). To achieve this goal, advanced technologies like single-cell immune repertoire sequencing and flow cytometry can be employed to delineate the phenotypic characteristics and specific molecular markers of autoreactive B cell clones. This information can inform the design of personalized CAR constructs, ultimately enabling precision immune intervention for autoimmune diseases.

Fundamentals and Overview of CAR-T Cell Therapy

CAR is a genetically engineered fusion protein, and the typical CAR structure contains 5 key functional domains (Fig. 3A): an extracellular single-chain fragment variable that targets antigens,

Table 1. Comparison between CAR-T cell therapy and conventional biologics in AIKDs

Indicators	CAR-T cell	Conventional biologics
Mechanism	Genetically engineered modified T cells directly recognize and kill specific target cells (e.g., $CD19^+$ B cells and $BCMA^+$ plasma cells)	Recognition of specific molecular antigens on the surface of B cells (e.g., CD20 and BAFF) and targeted clearance through cytotoxicity and other effects
Therapeutic features	High response rate, deep remission	Moderate-high response rate, predominantly partial remission
Durability	Long-term remission, potential curability	Requires repeat infusion therapy, high relapse rate, potential for drug resistance
Side effects	CRS, ICANS, hematologic toxicity, increased risk of infection, nephrotoxicity	Infusion-related reactions, hematologic toxicity, increased risk of infection
Treatment cost	High cost of single infusion treatment, reduced treatment costs when long-term remission is achieved	Higher cumulative cost of repeated infusions
Individualized treatment	Target-specific customization and personalized optimization for patient's B cell phenotype, pathological clonal expansion, antigenic mutations	Often the target is fixed and the "one drug fits all" model is difficult to optimize for the individual

CAR, chimeric antigen receptor; BCMA, B cell maturation antigen; BAFF, B cell activating factor; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome

a hinge region that enhances receptor flexibility, a transmembrane structural domain, a costimulatory molecule (e.g., CD28 or 4-1BB), and a T cell activation signaling domain (CD3ζ) [39,40]. CAR-T cells kill target cells independently of MHC recognition and trigger the death receptor pathway mainly by targeting B cell surface antigens (Fig. 3B): The release of tumor necrosis factor (TNF)-related apoptosis inducing ligand with Fas ligand induces caspase-3-dependent apoptosis in target cells, whereas the perforin granule enzyme system directly disrupts the target cell membrane structure by forming transmembrane pores [41]. In addition, proinflammatory cytokines (e.g., IL-2, interferon-γ, and TNF-α) secreted by CAR-T cells can further activate macrophage-mediated antibody-dependent cellular phagocytosis, resulting in a cascade effect that synergistically removes pathologic B cells [42].

Current production strategies for CAR-T cell therapies have undergone a significant shift (Fig. 4A), expanding from traditional autologous infusion to allogeneic universal CAR (UCAR)-T cells and introducing an in situ engineering platform that uses lipid nanoparticle (LNP) delivery of messenger RNA (mRNA) encoding CARs to directly reprogram T cells in vivo [43–45]. The innovative methods have significantly decreased patient waiting times, simplified manufacturing processes, and lowered the costs of treatments. To transform T cells from donors into UCAR-T cells, CRISPR gene editing technology is frequently used to disable endogenous T cell receptors and MHC-like genes. This step is crucial for preventing allogeneic rejection [46,47]. The initial clinical trial utilizing UCAR-T cell therapy in 3 patients with systemic sclerosis and necrotizing myositis demonstrated promising efficacy and safety [48]. Nonetheless, there remains a need for further data regarding long-term efficacy and safety. Particularly in patients with autoimmune diseases, the prevalent immune dysregulation still has the risk of leading to immune rejection. This may significantly increase additional healthcare expenditures, including prolonged hospitalization, intensified use of immunosuppressants, and management of associated complications, thus partially offsetting the original cost advantage of UCAR-T products. The development of CAR-T therapies is in a transitional stage of seeking an optimal solution between "cost efficiency" and "safety and control", and the balance between efficacy and affordability will be the key to their clinical translation. In terms of gene delivery systems, retroviral vectors are still predominant, and although long-lasting and stable expression of CARs can be achieved, the auto-immunogenicity and randomized integration of viral vectors increase the risk of insertional mutagenesis. To overcome this shortcoming, multiple advanced nonviral approaches such as LNP delivery vectors not only avoid the risk of genome integration but also enable transient expression with controlled regulation [49,50]. CRISPR-based targeted integration technology precisely inserts CAR genes into predefined "safe harbor" sites, improving safety while enhancing the functional durability and phenotypic stability of CAR-T cells [51,52] (Fig. 4B).

Moreover, the development of innovative vectors for CAR-T cell therapy aims to address the limitations of traditional T cells, thereby enhancing the applicability and safety of this therapeutic approach (Fig. 4C). In parallel, CAR- natural killer cells have emerged as promising alternatives. These cells significantly lower the risk of graft-versus-host disease and cytokine release syndrome (CRS) because of their MHC-unrestricted recognition mechanism and inherent immune characteristics [53–55]. CAR-macrophages possess naturally efficient tissue permeability and phagocytic antigen presentation dual functional functions, which may have potential advantages in targeting local inflammation modulation and removing aberrant immune complexes in the kidney [56]. γδ T cells [57] and regulatory T (T_{reg}) cells [58], on the other hand, utilize their pan-specific recognition pattern and immunomodulatory properties to expand their targeting scope while enhancing safety. In addition to dual-target CAR structural designs, which are already quite widely used in autoimmune

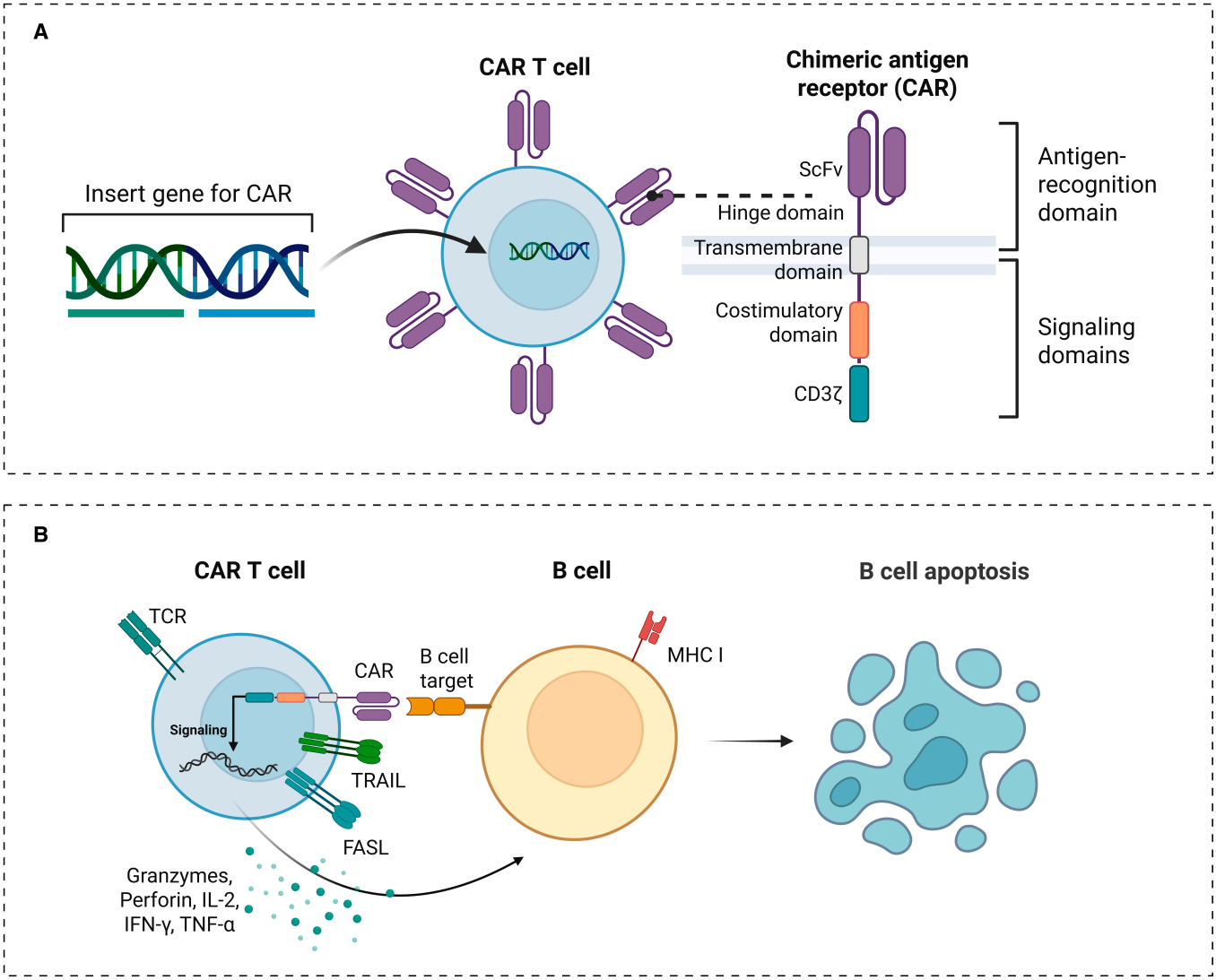

Fig. 3. (A) Typical structural design of chimeric antigen receptor (CAR) constructs. (B) Mechanism of action of CAR-T cells targeted to kill B cells. TRAIL, TNF-related apoptosis-inducing ligand; FASL, Fas ligand; IFN-γ, interferon-γ.

diseases, other advanced and innovative CAR technologies are being continuously developed (Fig. 4D). Chimeric autoantibody receptor (CAAR)-T cells, also referred to as "trans-CAR T" cells, are designed to eliminate autoreactive B cells with high precision by expressing disease-specific autoantigens as their extracellular domains. This antigen-directed approach enables the selective targeting of pathogenic B cell clones while sparing nonpathogenic B cell populations, thereby minimizing systemic immunosuppression [59–61]. Recent studies have demonstrated the therapeutic potential of CAAR-T cells in experimental models of MN [62] and LN [63], highlighting the critical importance of precise antigen identification for optimizing treatment efficacy. Enhanced CAR-T cell therapies demonstrate improved persistence and survival in inflammatory microenvironments, largely due to optimized costimulatory signals such as 4-1BB or OX40 replacing traditional CD28. CRISPR-based reprogramming of T cell metabolism and cytokine secretion has also been shown to enhance efficacy while reducing the required dose [64–68]. The suicide CAR, on the other hand, realizes spatiotemporally specific regulation. By implanting suicide-inducible genes (e.g., Caspase9), suicide CARs can activate suicide signaling with specific small-molecule drugs when severe adverse effects are detected, leading to rapid programmed apoptosis of CAR-T cells [69,70]. These innovations provide multidimensional solutions to overcome the bottlenecks of CAR-T cell therapies in terms of insufficient durability, off-target toxicity, and immune microenvironment resistance. However, these emerging technologies for CAR in AIKDs are still in the early exploratory stage, and more studies are needed to validate their safety and efficacy before large-scale clinical accessibility.

Clinical Progress and Prospects of CAR-T Cell Therapy in AIKD Patients

CAR-T cell therapy has shown significant effectiveness in treating hematologic malignancies and autoimmune diseases. This success has driven further research into CAR-based therapies for AIKDs, with ongoing clinical trials aiming to evaluate the potential of CAR-T cells in modulating immune responses, alleviating renal injury, and improving patient outcomes (Table 2).

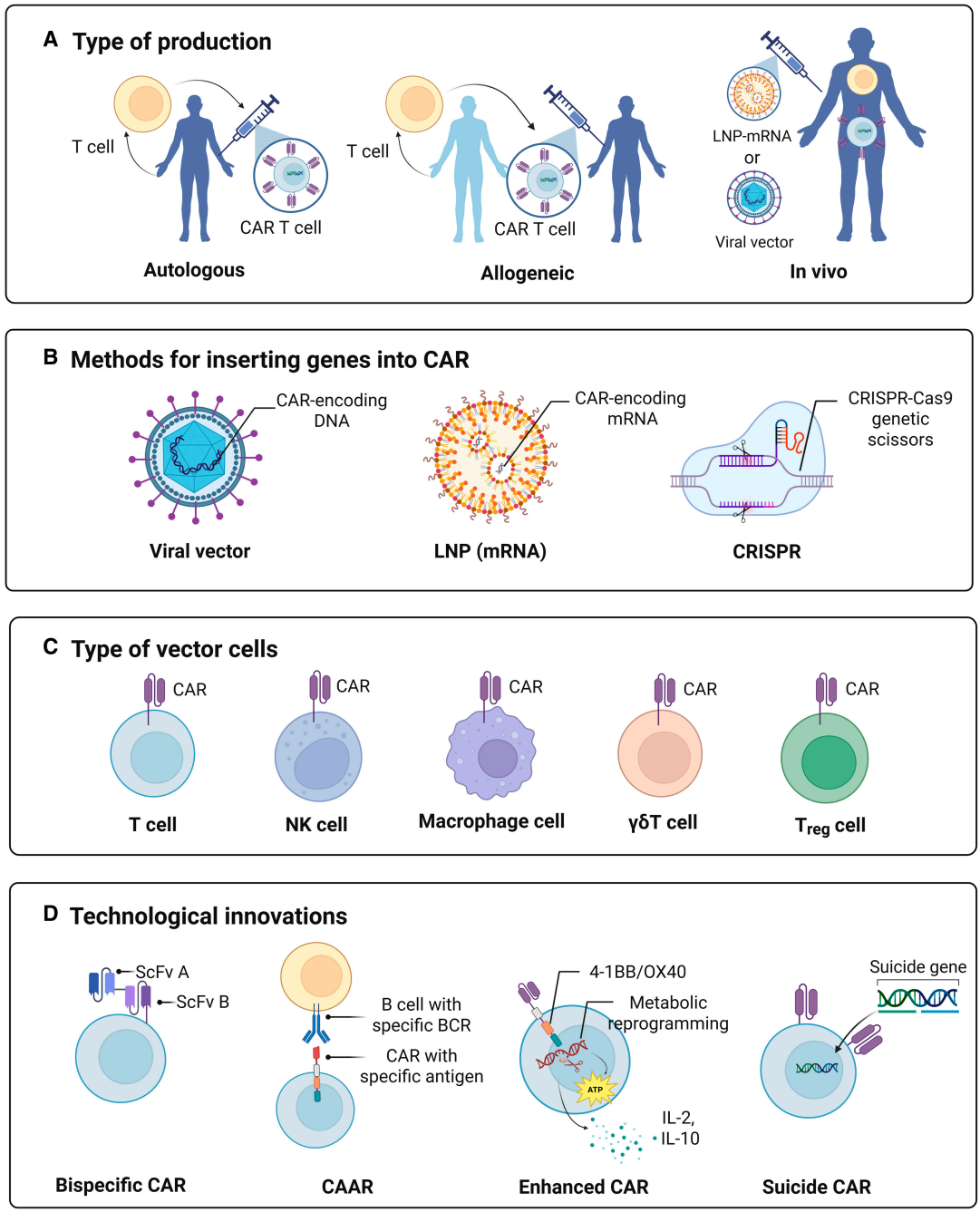

Fig. 4. (A) Several different methods for producing CAR-T cells. (B) Different methods for transducing genes into CARs. (C) Different vector cell types for CAR. (D) Several innovative designs for CAR-T cells. Bispecific CARs can simultaneously target 2 antigens to enhance therapeutic breadth; CAARs eliminate pathogenic B cells by expressing disease-specific autoantigens; enhanced CARs integrate costimulatory signaling and metabolic reprogramming to improve cellular persistence and function; suicide CARs incorporate controllable genes to enable precise regulation and reduce toxicity risk. LNP, lipid nanoparticle; mRNA, messenger RNA; NK, natural killer; T_{reg}, regulatory T; ScFv, single-chain variable fragment; CAAR, chimeric autoantibody receptor.

Anti-CD19 CAR-T cells

In preclinical research, anti-CD19 CAR-T cell therapy has demonstrated effectiveness in removing autoreactive B cells and reducing renal IgG immunodeposition and inflammatory cell infiltration in a mouse model of SLE [71,72]. Additionally, this therapy has been effective in preventing and delaying the onset of SLE in mice [73]. These promising results have paved the way for further clinical investigations. A young female patient with severe refractory SLE and grade IIIA active LN received anti-CD19 CAR-T cell therapy. This intervention led to the depletion of circulating B cells, a rapid decrease in disease activity, the resolution of proteinuria, and a significant improvement in renal damage. There were no relapses or treatment-related adverse events during 18 months of follow-up [4]. The same research group subsequently treated and analyzed 5 patients with refractory adult SLE in depth, all of whom showed significant improvement in symptoms, disappearance of renal inflammatory manifestations, and immunophenotypic analyses that

Table 2. Ongoing clinical trials of CAR-T cell therapy for AIKDs

Disease	CAR target(s)	Cell source	Manufacturing type	CAR-T product name	Clinical trial number	Phase and estimated enrollment	Study duration
Lupus nephritis (LN)	CD19	T cell	Autologous	N/A	NCT06585514	I/II, 18	2024–2025
		T cell	Autologous	KYV-101-001	NCT05938725	I/II, 32	2023–2026
		T cell	Autologous	KYV-101-003	NCT06342960	I/II, 32	2022–2029
		T cell	Autologous	Rapcabtagene auto-leucel	NCT06581198	II, 144	2024–2030
		T cell	Autologous	CNCT19	NCT05930314	I, 12	2023–2025
		T cell	Autologous	YTB323	NCT05798117	I/II, 24	2023–2026
		T cell	Autologous	CABA-201	NCT06121297	I/II, 12	2024–2027
		T cell	Autologous	SYNCAR-001 + STK-009 (Orthogonal IL-2)	NCT06544330	I, 42	2024–2041
		T cell	Allogeneic	SC291	NCT06294236	I, 36	2024–2028
		T cell	Autologous	KYV-101	NCT06152172 (not yet recruiting)	I, 24	2024–2028
		NK cell	Allogeneic	NKX019-102	NCT06557265	I, 21	2024–2027
		T cell	Allogeneic	ATA3219	NCT06429800 (not yet recruiting)	I, 26	2024–2029
	CD20	T cell	Allogeneic	ADI-001	NCT06375993 (not yet recruiting)	I, 40	2024–2027
	BCMA	T cell	Autologous	PRG-1801	NCT06277427	N/A, 24	2024–2027
		T cell	Autologous	PRG-1801	NCT06497387	I, 30	2024–2028
	CD19/CD20	T cell	Autologous	IMPT-514	NCT06153095	I/II, 30	2024–2027
		T cell	Autologous	Zamto-Cel	NCT06708845 (not yet recruiting)	I, 48	2025–2026
	CD19/BCMA	T cell	Autologous	BH002	NCT06350110	I/II, 75	2024–2025
		T cell	Autologous	PRG-2311	NCT06497361	I, 30	2024–2028
		T cell	Allogeneic	N/A	NCT06681337 (not yet recruiting)	I, 10	2024–2025
		T cell	Autologous	FKC288	NCT06285279	I, 24	2024–2028
	CD19/CD20/CD22	T cell	Autologous	LCAR-AIO	NCT06653556 (not yet recruiting)	I, 34	2024–2029

(Continued)

Table 2. (Continued)

Disease	CAR target(s)	Cell source	Manufacturing type	CAR-T product name	Clinical trial number	Phase and estimated enrollment	Study duration
ANCA-associated glomerulonephritis	CD19	T cell	Autologous	N/A	NCT06508346	Observational, 12	2024–2027
		T cell	Autologous	N/A	NCT06056921	I, 24	2023–2026
		T cell	Autologous	RD06-04	NCT06548607	I, 20	2024–2027
		T cell	Autologous	RD06-04	NCT06549296	I, 12	2024–2027
		T cell	Allogeneic	SC291	NCT06294236	I, 36	2024–2028
		T cell	Autologous	RD06-04	NCT06548620 (not yet recruiting)	I, 18	2024–2027
		T cell	Allogeneic	BRL-301	NCT05859997	N/A, 15	2023–2025
		T cell	Autologous	N/A	NCT06420154 (not yet recruiting)	I, 9	2024–2027
		T cell	Autologous	KYV-101	NCT06590545 (not yet recruiting)	I/II, 8	2025–2027
		T cell	Autologous	KYV-101	NCT06152172 (not yet recruiting)	I, 24	2024–2028
		T cell	Autologous	ATMP	NCT06685042 (not yet recruiting)	I/II, 8	2024–2025
	BCMA	T cell	Autologous	PRG-1801	NCT06277427	N/A, 24	2024–2027
	CD19/CD20	T cell	Autologous	IMPT-514	NCT06462144	I, 36	2024–2026
	CD19/BCMA	T cell	Autologous	BH002	NCT06350110	I/II, 75	2024–2025
		T cell	Autologous	FKC288	NCT06285279	I, 24	2024–2028
	CD19/CD3E	T cell	Autologous	N/A	NCT06373081	N/A, 6	2024–2026
Multidrug-resistant nephrotic syndrome (MDR-SRNS)	BCMA/CD70	T cell	Autologous	N/A	NCT06553898	I, 18	2024–2027
IgA nephropathy (IgAN)	CD19	T cell	Autologous	IM19	NCT06690359 (not yet recruiting)	I, 12	2024–2026
Membranous nephropathy (MN)	CD19	T cell	Autologous	IM19	NCT06690359 (not yet recruiting)	I, 12	2024–2026
	CD19/BCMA	T cell	Autologous	FKC288	NCT06285279	I, 24	2024–2028
Immune nephritis	CD19/BCMA	T cell	Autologous	N/A	NCT05085418	I, 9	2021–2024
	CD19	NK cell	Autologous	KN5501	NCT06469190	I, 36	2024–2026

ANCA, anti-neutrophil cytoplasmic antibody; N/A, not applicable; NK, natural killer

revealed that the reconstituted B cells were predominantly initial B cells [5]. However, one patient continued to have low-level proteinuria at 3 months, suggesting that CAR-T cell therapy may have limited efficacy in cases where irreversible renal damage has already occurred. More recent follow-up data have shown that 8 patients with refractory SLE combined with LN maintained disease inactivity, pathogenic autoantibody deficiency, and stable levels of vaccine-associated protective antibodies for 29 months [6].

Compared to adults, pediatric SLE is often characterized by more aggressive disease phenotypes, a higher incidence of renal involvement, and an increased burden of treatment-related morbidity [74]. Building upon the promising outcomes observed in adult cohorts, CD19-CAR T cell therapy has emerged as a potentially valuable strategy for children with severe, treatment-refractory disease. Preliminary clinical reports have demonstrated favorable tolerability and notable therapeutic responses in pediatric patients. For example, in a 15-year-old girl with severe SLE and class IV LN, CAR-T cell therapy minimized renal inflammation and preserved remaining renal function [75]. We also reported 2 pediatric patients with refractory SLE who received CAR-T therapy. Both exhibited complete B cell depletion, significant reductions in autoantibody titers, and clinical improvement within 4 to 5 months post-infusion. One of these patients with grade IV LN underwent a repeat renal biopsy, which showed a reduction in acute inflammatory indices, although chronic damage remained, highlighting the challenges of reversing established structural injury [76]. While these findings underscore the feasibility and potential efficacy of anti-CD19 CAR-T cells in pediatric SLE, further research is essential to optimize dosing strategies, evaluate long-term safety, and address developmental and immunologic considerations unique to the pediatric population. These efforts will be critical to positioning CAR-T therapy as a transformative option in the management of childhood-onset SLE.

Encouraged by the initial success of CD19-targeting CAR-T cell therapy in SLE and LN, there is growing interest in extending this approach to other antibody-mediated AIKDs, particularly AAGN. Preclinical data have provided early proof of concept for this approach. In a murine model of anti-neutrophil cytoplasmic autoantibody-associated vasculitis, anti-CD19 CAR-T cells were shown to effectively migrate to the kidneys and continuously eliminate B cells, and prevent the development of AAGN. However, clinical evidence remains absent. To bridge this gap, we have initiated a prospective, 2-year follow-up study (NCT06508346) to evaluate the safety and efficacy of anti-CD19 CAR-T cell therapy in patients with refractory AAGN, marking a critical step toward clinical translation. Clinical trials are now exploring CD19 CAR-T cell therapy in other AIKDs, such as IgAN and MN, where the results are highly anticipated.

Anti-BCMA CAR-T cells

Notably, complete exhaustion of autoantibodies was not observed with anti-CD19 CAR-T cell therapy, either in clinical trials of LN [5,6] or in preclinical models of AAGN [77]. This suggests that CD19-negative but BCMA-expressing pathogenic PCs—especially LLPCs—may persist and continue to drive disease. LLPCs have been implicated in refractory LN and are associated with disease severity [78]. There are reports that anti-BCMA CAR-T therapy can serve as a salvage treatment in patients with other autoimmune diseases who failed anti-CD19 CAR-T infusion, suggesting that PC depletion may improve outcomes in refractory cases [79]. However, their depletion also poses risks, as LLPCs are critical for maintaining protective immunity. Prior studies have shown that extensive depletion of LLPCs can rapidly reduce vaccine-induced IgG levels [80]. Based on this, multiple clinical trials have begun to explore the feasibility of using BCMA as a standalone target or in combination with CD19 for CAR-T cell therapy in AIKDs. A phase I clinical study of BCMA-CD19 CAR-T cells in SLE patients showed a marked reduction in anti-Sjögren syndrome B antibody autoantibodies following treatment, suggesting successful elimination of pathogenic antibodies predominantly produced by LLPCs [37]. In some cases, although hepatitis B surface antibody titers dropped to nearly undetectable levels, they rapidly recovered after revaccination, indicating that immune memory may be preserved in certain patients. Compared to CD19 CAR-T therapy alone, BCMA-CD19 CAR-T treatment resulted in a more pronounced decline in IgG levels, but only mild, manageable infection events were observed. Nevertheless, thoroughly evaluating the long-term safety of LLPC-targeting strategies remains essential, particularly in balancing the risk–benefit trade-off between pathogenic antibody clearance and preservation of protective immunity. Engineering CARs to selectively recognize pathogenic rather than protective LLPCs may represent a key strategy to address this challenge.

CAR-T_{reg} cells

T_{reg} cells maintain immune tolerance by preventing the activation and proliferation of autoreactive T cells [81]. Although polyclonal T_{reg} therapies have shown efficacy in treating autoimmune diseases, their nonspecific immunosuppression raises safety concerns [82]. Recent studies have introduced CAR technology into T_{reg} cells to produce antigen-specific CAR-T_{reg} cells, which can accurately recognize and immunomodulate disease-associated antigens, thereby restoring immune homeostasis and attenuating tissue inflammatory damage [58,83]. Reduced T_{reg} cell numbers and defective T_{reg} function are closely associated with the development and progression of various AIKDs [84–86]. Preclinical studies have found that secondary transfer of T_{reg} cells reduces B cell counts and attenuates symptoms in a mouse model of chronic graft-versus-host disease with SLE [87]. Prevention of AIKD progression by T_{reg} cells has been demonstrated across various animal models, including LN [88], anti-glomerular basement membrane disease [89], and IgAN [90]. Therefore, CAR-T_{reg} cell therapy for AIKDs is highly feasible, and the future development of a targeted delivery system for CAR-T_{reg} cells is expected to achieve precise regulation of the local immune microenvironment in the kidney. However, there are some potential concerns before CAR-T_{reg} cells can be used in the clinic, as contaminated effector T cells may be transduced by T_{reg} cells, which may exacerbate autoimmune perturbations. Prolonged suppression of immune surveillance functions may lead to increased susceptibility to infection or malignancy. In addition, CAR-T_{reg} may undergo functional exhaustion or transdifferentiation into an effector T cell phenotype in the inflammatory microenvironment.

Barriers and Advanced Strategies for CAR-T Cell Therapy in AIKDs

While CAR-T cell therapy holds significant promise for patients with multidrug-resistant and refractory AIKDs, several key considerations and challenges still need to be addressed in its clinical application. A thorough evaluation of these factors is

essential to achieve the best possible therapeutic outcomes for patients. Continued research in these areas will help improve the overall feasibility and widespread adoption of this innovative treatment strategy.

Patients, optimal selection of therapeutic targets, and timing of treatment

CAR-T cell therapy in AIKDs is still in the exploratory stage, and the key to its success lies in 3 dimensions. The first dimension involves the precise identification of potential beneficiaries, necessitating a departure from traditional clinicopathological classifications. This involves retrospective analysis of patient subgroups that respond well to CAR-T cell therapy and the establishment of a precise immunophenotyping and cell therapy efficacy prediction model on the basis of the single-cell multiomic features of the disease, both before and after treatment. The second dimension focuses on the precise selection of dynamic targets for CAR-T cells. Patients with various AIKDs may display distinct immune features and antigen expression patterns at different stages of the disease. For example, the early stage of MN is dominated by podocyte antigens such as PLA2R/THSD7A, but there may be antigen escape and increased expression of other novel antigens in relapsed patients [91]. In addition, disease typing based on different interferon pathways can be used to guide target selection in LN patients, and type I/II LN patients may have different B cell subpopulations driving them [92,93]. The third dimension is the timing of the intervention window. At present, CAR-T cell therapy is utilized primarily for patients who are resistant to multiple drugs. These patients often have intricate medical histories with prolonged treatment courses. The combined side effects of various treatments, along with disease relapse, can lead to irreversible kidney damage, such as glomerulosclerosis and fibrosis, especially when the immune system's ability to adapt is diminished. However, owing to the potential nephrotoxicity associated with CAR-T cell therapy, most clinical trials require a glomerular filtration rate of at least 30 ml/min/1.73 m^2. This requirement may cause some patients to miss the optimal timing for treatment and limit the benefits they can gain from CAR-T cell therapy. Intervening as early as possible during the acute, immunologically active phase of the disease, before extensive fibrosis occurs, may be advantageous for maximizing treatment efficacy. Additionally, clinical trials in patients with aggressive B cell lymphoma have shown that CAR-T cell therapy may offer superior clinical benefit as a first-line treatment compared with conventional approaches [94,95]. Whether CAR-T therapy can be used in the early stage of AIKDs remains an important question. Exploring its potential to improve efficacy and prognosis in patients at low to intermediate risk will be a major focus of future research. The establishment of a standardized risk–benefit scoring system related to CAR-T cell therapy may be beneficial in the future to guide clinical decision making. In addition, comprehensive pretreatment assessment of organ function, including repeated renal biopsy, is essential to ensure that patients with residual renal function can tolerate CAR-T cell therapy.

Management of adverse reactions associated with CAR-T cell therapy

Early common adverse reactions associated with CAR-T cell therapy include CRS and immune effector cell-associated neurotoxicity syndrome (ICANS). CRS is characterized by a severe systemic inflammatory response resulting from the in vivo overactivation and proliferation of CAR-T cells. These cells produce large amounts of cytokines, such as IL-6 and TNF-α, which can disrupt the integrity of the blood–brain barrier and subsequently trigger a neurotoxic response [96,97]. However, clinical data suggest that the incidence of CRS and ICANS in patients with autoimmune diseases is significantly lower than that in patients with cancer, which may be related to a lower pathological B cell load [4–6,98]. Effective treatments for CRS include glucocorticoids or tolizumab, an IL-6 neutralizing antibody [97]. Close monitoring and active assessment of vital signs, neurological symptoms, and inflammatory markers during the initial post-infusion phase are essential to ensure patient safety and optimize CAR-T cell efficacy. Furthermore, the U.S. Food and Drug Administration reported that prolonged expansion and sustained activity of CAR-T cells could provoke an excessive immune response, potentially increasing the risk of developing T cell malignancies [99]. Future development of modifiable CAR structures and the integration of suicide gene safety switches will aid in achieving dynamic monitoring and the urgent elimination of T cell activity. Predictive models based on machine learning algorithms integrating multiomic inflammatory biomarkers will facilitate CRS/ICANS risk stratification management. Hypogammaglobulinemia due to B cell depletion is a long-term CAR-T therapy side effect that requires attention and may increase the risk of opportunistic infections. Risk reduction strategies include intravenous immunoglobulin replacement and prophylactic anti-infective therapy [99,100]. Notably, long-term safety data on whether CAR-T cell therapy could interfere with the underdeveloped immune systems of pediatric patients are lacking.

Nephrotoxicity associated with CAR-T cell therapy, particularly acute kidney injury (AKI), should not be overlooked in patients with AIKDs. A recent systematic review of studies of AKI after CAR-T cell therapy revealed that 22% of 694 patients with hematologic malignancies experienced AKI, with the majority recovering their renal function after symptomatic treatment [101]. Secondary fluid loss and a reduction in effective blood volume due to CRS are often considered the most common causes of concomitant AKI, as the massive release of cytokines may exacerbate damage to podocytes and endothelial cells [102,103]. The nephrotoxicity resulting from pretreatment with chemotherapeutic agents may also trigger the development of AKI [104]. However, no cases of AKI have been reported in patients with AIKDs treated with CAR-T cells, which contradicts the hypothesis that AKI is more likely to occur in patients with limited renal reserve. This discrepancy may be attributed to small sample sizes or the avoidance of conditions such as tumor lysis syndrome, which has been observed to cause AKI in patients with hematologic tumors [105]. In conclusion, pretreatment renal risk assessment as well as close post-treatment monitoring of renal function and urine output are necessary. The development of early biomarkers of kidney injury will facilitate risk prediction modeling. For patients with preexisting renal insufficiency, a more thorough evaluation of the risks and benefits of CAR-T cell therapy is necessary, and the optimal dose of the lymphocyte removal regimen should be rationally selected.

Relapse and retreatment

Relapse after CAR-T cell therapy remains a major clinical management challenge in AIKDs. However, the relapse rate following CAR-T treatment for AIKDs remains inconsistent across studies.

Evidence from hematologic malignancies suggests that the depth of initial treatment response may be a key predictor of long-term remission following CAR-T cell therapy [106–108]. In patients with SLE, relapse has been reported due to insufficient CAR-T cell infusion doses during initial treatment [37]. Optimizing CAR-T cell manufacturing conditions, increasing the number of infused cells, and employing genetic engineering strategies to develop metabolically enhanced CAR-T cells may help improve the depth of the initial response. Currently, retreatment strategies after relapse are still under exploration. Depending on the severity of relapse, short-term corticosteroids or immunosuppressive therapies may be effective in mild cases, whereas moderate to severe relapses may require consideration of a second CAR-T cell infusion. If the initial therapy was effective, reinfusion of cryopreserved CAR-T cells can be attempted, although the potential development of anti-CAR antibodies due to immunogenicity must be considered. Switching therapeutic targets (e.g., using BCMA or CD38 instead of CD19) or exploring non-CAR-T cell-based immunotherapies (such as CAR-natural killer cells) may also help reinduce durable remission. Long-term follow-up and dynamic monitoring of B cell reconstitution, autoantibody profiles, and changes in the immune microenvironment are essential for identifying patients at high risk of relapse. Furthermore, optimizing CAR constructs, such as through the use of humanized designs or the incorporation of constitutive activation domains, may help reduce the risk of relapse.

Impact of the kidney immune microenvironment

Certain AIKDs, such as LN and IgAN, are more prone to developing a localized renal immune microenvironment, making it challenging to ensure the effective infiltration and persistence of CAR-T cells within the kidney [12,109]. However, unlike the highly immunosuppressive microenvironment of solid tumors, the immune milieu in AIKDs is characterized by active inflammation and a lack of suppressive barriers, which may facilitate tissue infiltration by CAR-T cells. Future studies are warranted to investigate whether renal CAR-T cell persistence and expansion are impaired in patients with treatment failure or disease relapse compared to those who achieve long-term remission. In the field of solid tumor immunotherapy, approaches such as coexpression of chemokine receptors (e.g., CXCR5) [110] and engineered local delivery systems (e.g., penetrative hydrogels or nanoparticle carriers) [111,112] have been explored to enhance T cell localization and tissue penetration. These strategies hold similar promise in AIKDs, especially in patients where suboptimal CAR-T efficacy is linked to the renal immune microenvironment. Additionally, CAR-engineered cell-derived exosomes represent a novel method for targeted renal delivery [113]. The development of intelligent, kidney-targeted CAR-T delivery systems may not only improve therapeutic efficacy but also reduce systemic toxicity, offering a more durable and precise immunotherapeutic approach for AIKDs.

Conclusion and Perspectives

CAR-T cell therapy represents a breakthrough advancement over conventional B cell depletion therapies in AIKDs, enabling deeper and more sustained elimination of pathogenic B cells to induce immune reset and disease remission. However, clinical evidence remains limited regarding its long-term safety, durable efficacy, and relapse control. Challenges persist in personalized CAR-T design, optimal target selection, and precise patient stratification. Moving forward, deeper mechanistic insights into CAR-T biology, innovative production strategies, and improved risk assessment models may transform CAR-T therapy from a last-resort option to a frontline intervention for AIKDs. This evolution may ultimately establish a new treatment paradigm centered on precision immune remodeling.

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