Immunological mechanisms and novel therapeutic strategies for sepsis-associated acute kidney injury (Review)

LU XU[1*], WEI JIANG[2*], LIN SONG[2], JING WANG[2], JIANGQUAN YU[1] and RUIQIANG ZHENG[1]

[1]Department of Critical Care Medicine, The Yangzhou Clinical College of Xuzhou Medical University, Yangzhou, Jiangsu 225001, P.R. China; [2]Department of Critical Care Medicine, Northern Jiangsu People's Hospital Affiliated to Yangzhou University, Yangzhou, Jiangsu 225001, P.R. China

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Abstract. Sepsis is a life-threatening clinical syndrome characterized by a dysregulated host immune response to infection, with its pathogenesis closely linked to the aberrant activation and dysfunction of various immune cells. The kidney is among the most vulnerable organs in sepsis. The development of acute kidney injury (AKI) in sepsis, referred to as sepsis-associated AKI (SA-AKI), is often associated with significantly increased mortality. Despite its clinical impact, specific and effective therapies for SA-AKI remain scarce. Increasing evidence highlights that complex intrarenal inflammatory processes, primarily driven by diverse immune cell populations, are central to the onset and progression of SA-AKI. The present review provides a comprehensive analysis of the roles of both innate and adaptive immune cells, such as macrophages, neutrophils, dendritic cells, natural killer cells, natural killer T (NKT) cells, B cells and T cells, in SA-AKI and explores potential therapeutic strategies, offering a theoretical foundation and insights for the development of more effective prevention and treatment approaches.

Contents

Correspondence to: Professor Jiangquan Yu or Professor Ruiqiang Zheng, Department of Critical Care Medicine, The Yangzhou Clinical College of Xuzhou Medical University, 98 Nantong West Road, Yangzhou, Jiangsu 225001, P.R. China
E-mail: yujiangquan2021@163.com
E-mail: zhengruiqiang2021@163.com

*Contributed equally

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1. Introduction

Sepsis is a life-threatening syndrome resulting from a dysregulated host response to infection, which can progress to multiple organ dysfunction syndrome with a mortality rate approaching 40% (1,2). Immune homeostasis plays a pivotal role in the complex pathophysiology of sepsis and is directly linked to clinical outcomes. Sepsis disrupts immune balance, leading to a state of immunosuppression. The mechanisms underlying this immune dysregulation are multifactorial, including excessive anti-inflammatory cytokine release, abnormal apoptosis of immune effector cells, over-proliferation of immunosuppressive cells and upregulation of immune checkpoint molecules (3). Sepsis inflicts extensive damage to multiple organs, including the kidneys, liver, lungs, circulatory system, gastrointestinal tract, blood and central nervous system. Among these, the kidneys are often the first organs affected during sepsis (4). Acute kidney injury (AKI), one of the most common and severe complications of sepsis, occurs in >50% of sepsis cases and is associated with significantly increased mortality (5). In sepsis, the kidneys undergo a series of alterations, including hemodynamic changes, microcirculatory dysfunction, endothelial injury, inflammatory responses, oxidative stress and direct tubular damage (6). Furthermore, immune responses driven by various immune cells, such as macrophages, neutrophils, dendritic cells (DCs), natural killer (NK) cells, natural killer T (NKT) cells, B cells and T cells, play a pivotal role in the development and progression of sepsis-associated AKI (SA-AKI) (Fig. 1). Damage-associated molecular patterns (DAMPs) are recognized by Toll-like receptors (TLRs), activating immune cells and initiating an inflammatory cascade (7). Upon sensing damage signals, innate immune cells not only help control tissue injury but also initiate adaptive immune responses. These immune cells synergistically contribute to the onset, progression and

persistence of disease. In sepsis, immune cell roles differ between the early hyperinflammatory phase and the later immunosuppressive phase. The early phase is characterized by a pro-inflammatory response marked by a cytokine storm. Following this excessive inflammation, patients either gradually recover or transition into a state of persistent immunosuppression, characterized by immune cell exhaustion (8-16); key features of this progression are summarized in Table I. However, the roles of mast cells and innate lymphoid cells (ILCs) in SA-AKI remain insufficiently studied, and their exact mechanisms are still unclear (Fig. 1). Therefore, precise targeting of immune cells may offer a promising strategy for preventing and treating SA-AKI.

2. Role of macrophages in SA-AKI

Under physiological conditions, the kidneys harbor a notable population of resident macrophages from birth. These macrophages primarily include those derived from yolk sac erythroid progenitors, fetal liver erythroid progenitors and hematopoietic stem cells (17). During early embryogenesis, yolk sac-derived macrophages play a predominant role (18). In adulthood, macrophage populations are sustained through two distinct mechanisms: The self-renewal of fetal liver erythroid progenitor-derived and hematopoietic stem cell-derived macrophages and the replacement of macrophages by monocyte-derived cells (17). Kidney resident macrophages (KRMs) and recruited macrophages perform distinct functions within the kidney. In the context of SA-AKI, macrophages play a pivotal role in driving both injury and repair through a complex interplay of polarization, metabolic reprogramming and signaling pathways, as summarized in Fig. 2.

Protective role of kidney-resident macrophages. As tissue-resident immune cells, KRMs are essential for maintaining normal kidney function. These macrophages are complex, highly adaptable renal resident mononuclear phagocytes with diverse functions, which originate from the yolk sac during early embryogenesis and persist in the kidney throughout development (19,20). KRMs help maintain systemic homeostasis through various mechanisms, such as clearing cellular debris, modulating local inflammation and promoting tissue repair (21). In adult tissues, KRMs possess self-renewal capabilities with minimal input from peripheral blood, helping sustain renal homeostasis, monitor the immune microenvironment, promote angiogenesis and mitigate AKI. Following kidney injury, KRMs aid in tissue repair and regeneration (22). Additionally, KRMs can reduce renal injury by selectively inhibiting interleukin (IL)-6 production from endothelial cells through IL-1 receptor antagonist expression (23). Furthermore, KRMs regulate renal sympathetic nerve activity, influencing salt and water balance and further promoting renal function recovery (24).

Inflammatory recruitment of monocytes in SA-AKI. In SA-AKI, monocyte recruitment is a critical pathophysiological event. This process involves multiple mechanisms that synergistically contribute to uncontrolled inflammation and exacerbated renal injury. These mechanisms include the release of chemoattractants, expression of adhesion molecules, activation of inflammatory cascades and microcirculatory dysfunction (25). During sepsis, renal tubular epithelial cells upregulate the expression of C-C motif ligand chemokine 2 (CCL2) at both the mRNA and protein levels through the combined actions of chemokine receptors CCR2 and C-X3-C motif chemokine receptor 1 (CX3CR1); this upregulation drives monocyte chemotaxis (26). Moreover, the endothelial glycocalyx, produced by vascular endothelial cells, undergoes degradation during sepsis due to inflammatory responses and oxidative stress. The glycocalyx, a critical component of the vascular endothelial barrier, when damaged, increases vascular permeability, facilitating the contact and adhesion of monocytes to endothelial cells (27). Monocytes infiltrating the kidney can differentiate into M1 or M2 macrophages, exerting pro-inflammatory or anti-inflammatory effects, respectively. Notably, a specific monocyte subset, such as Ly6Chigh monocytes, strongly adheres to the renal vascular wall in a CX3CR1-dependent manner during the early stages of sepsis. This subset plays a protective role via CX3CR1-dependent adhesion mechanisms (28).

Macrophage polarization and inflammation regulation. Sepsis is primarily induced by lipopolysaccharide (LPS) released from Gram-negative bacteria. LPS binds to TLRs on renal cells, triggering the release of DAMPs (29). These molecules act as endogenous 'danger signals', recognized by receptors on macrophages, leading to their activation. This activation results in the extensive release of inflammatory cytokines, such as tumor necrosis factor-α (TNF-α), IL-1β, IL-6 and the chemoattractant CCL2, initiating a cytokine storm and exacerbating renal inflammatory injury (30,31). Macrophages exhibit high plasticity and can polarize into distinct phenotypes, typically classified as M1 and M2. M1 macrophages primarily contribute to inflammation by releasing pro-inflammatory cytokines (such as TNF-α, IL-1β and IL-6) and reactive oxygen species (ROS), driving inflammation and tissue damage. By contrast, M2 macrophages are involved in tissue repair and inflammation resolution (32). Thus, modulation of macrophage polarization represents a potential strategy for alleviating renal injury in SA-AKI. Macrophage polarization is a dynamic process and excessive suppression of M1 polarization may impair pathogen clearance, hindering tissue healing. Conversely, overactivation of M2 macrophages can lead to immunosuppression, increasing infection risk (33,34). Therefore, precise regulation of the M1/M2 balance is critical to avoid adverse outcomes.

Metabolic reprogramming and polarization of macrophages. Macrophage metabolic reprogramming plays a pivotal role in SA-AKI. During sepsis, macrophages undergo significant metabolic changes to support the inflammatory response and cellular survival (35). This reprogramming involves a shift from fatty acid oxidation (FAO) to a dual reliance on glycolysis and FAO. M1 macrophages predominantly utilize aerobic glycolysis to rapidly initiate immune responses, while M2 macrophages rely on oxidative phosphorylation (OXPHOS) to exert anti-inflammatory effects and prevent tissue damage (36). In the early stages of sepsis, macrophages activate the AKT/mammalian target of rapamycin (mTOR)/hypoxia-inducible factor-1α signaling pathway, which enhances glycolytic enzyme activity and suppresses the tricarboxylic acid (TCA)

Table I. Evolution of immune cell functions across sepsis phases.

Cells	High inflammatory phase	Immunosuppressive phase	(Refs.)
Macrophages	Predominantly composed of M1 macrophages; increased production of pro-inflammatory cytokines.	Predominantly composed of M2 macrophages; endotoxin tolerance; decreased production of pro-inflammatory cytokines; increased production of anti-inflammatory cytokines.	(9)
Neutrophils	Increased release of inflammatory mediators such as ROS, proteases and cytokines.	Increased number of immature neutrophils; neutrophils with high PD-L1 expression induce T cell apoptosis and transdifferentiation into Tregs.	(10,11)
DCs	Activates lymphocytes and participates in inflammatory responses through mechanisms such as TLR4 and TLR9	The reduced synthesis of IL-6 and IL-12 by DCs promotes the differentiation of Th cells into Tregs within the microenvironment; transformation of the immune tolerance state; increased secretion of anti-inflammatory cytokine IL-10; decreased antigen-presenting function.	(12,13)
NK cells	Increased production of proinflammatory cytokines	Decreased NK cell quantity and cytotoxicity; weakened immune response.	(14)
B cells	Increased expression of PD-1/PD-L1	Increased secretion of anti-inflammatory cytokine IL-10.	(15)
T cells	Increased Th17 cell proportion	Increased number of Tregs; decreased production of pro-inflammatory cytokines; increased production of anti-inflammatory cytokines.	(16)

ROS, reactive oxygen species; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; Tregs, regulatory T cells; Th, T helper; TLR4, Toll-like receptor; IL, interleukin; DCs, dendritic cells; NK, natural killer.

cycle, initiating glycolysis to generate ATP, supporting cell survival and pro-inflammatory responses (35). However, excessive glycolysis can induce immunosuppression, impairing host defense and immune function. This immunosuppressive state is characterized by pro-inflammatory cytokines (such as TNF-α, IL-6 and CCL2) and T-cell-recruiting chemoattractants, as well as anti-inflammatory cytokines (such as IL-4, IL-10) (37). Nevertheless, this metabolic shift can impair mitochondrial function and reduce ATP production. Limiting glycolysis can mitigate the inflammatory response (38,39). While the transition from OXPHOS to aerobic glycolysis is essential for renal survival in early sepsis, failure to restore OXPHOS in the later stages may result in persistent inflammation and renal fibrosis (35). During the late inflammatory phase, cells activate peroxisome proliferator-activated receptor-γ coactivator 1α and carnitine palmitoyltransferase 1 through mediators such as sirtuin (Sirt)6, signal transducer and activator of transcription 3 (STAT3) and sirtuin 1, promoting a metabolic shift back to OXPHOS. Restoration of OXPHOS stimulates mitochondrial biogenesis, generates ATP and exerts anti-inflammatory effects, promoting renal function recovery (35). Additionally, lactate, a key metabolite in macrophage metabolism, influences the macrophage phenotype through lactylation, further impacting disease progression (40).

Amino acid metabolism, which regulates macrophage activation, is one of the earliest metabolic alterations during macrophage polarization. Arginine, glutamine and serine metabolism play pivotal roles in this process (41). Arginine catabolism regulates macrophage activation primarily through inducible nitric oxide synthase (iNOS) and arginase 1 (Arg1). iNOS, predominantly expressed in M1 macrophages, catalyzes the synthesis of nitric oxide and L-citrulline from arginine. Nitric oxide, a ROS, helps M1 macrophages combat pathogen invasion (40-42). By contrast, Arg1, highly expressed in M2 macrophages, catalyzes the hydrolysis of arginine into urea and L-ornithine. The metabolites of L-ornithine, including polyamines and proline, influence macrophage proliferation and collagen synthesis (42-44). A distinctive feature of M2 macrophages is their increased glutamine metabolism, with one-third of the carbon in TCA cycle metabolites of M2 macrophages derived from glutamine. Glutaminolysis generates α-ketoglutarate (α-KG), which enhances M2 macrophage activation and governs metabolic reprogramming through Jmjd3-dependent regulation. Additionally, α-KG, via a prolyl hydroxylase-dependent mechanism, inhibits the NF-κB pathway, thereby limiting M1 macrophage activation and modulating IKKβ activity (45). Serine metabolism also plays a pivotal role in macrophage functional polarization. It has been shown that serine metabolism suppresses insulin-like growth factor-1 (IGF1) transcription by increasing the promoter abundance of H3K27me3 through S-adenosylmethionine. Deficiency in serine metabolism alters M1 macrophage polarization and modulates Janus kinase (JAK)/STAT1 signaling via IGF1-dependent p38 activation (46).

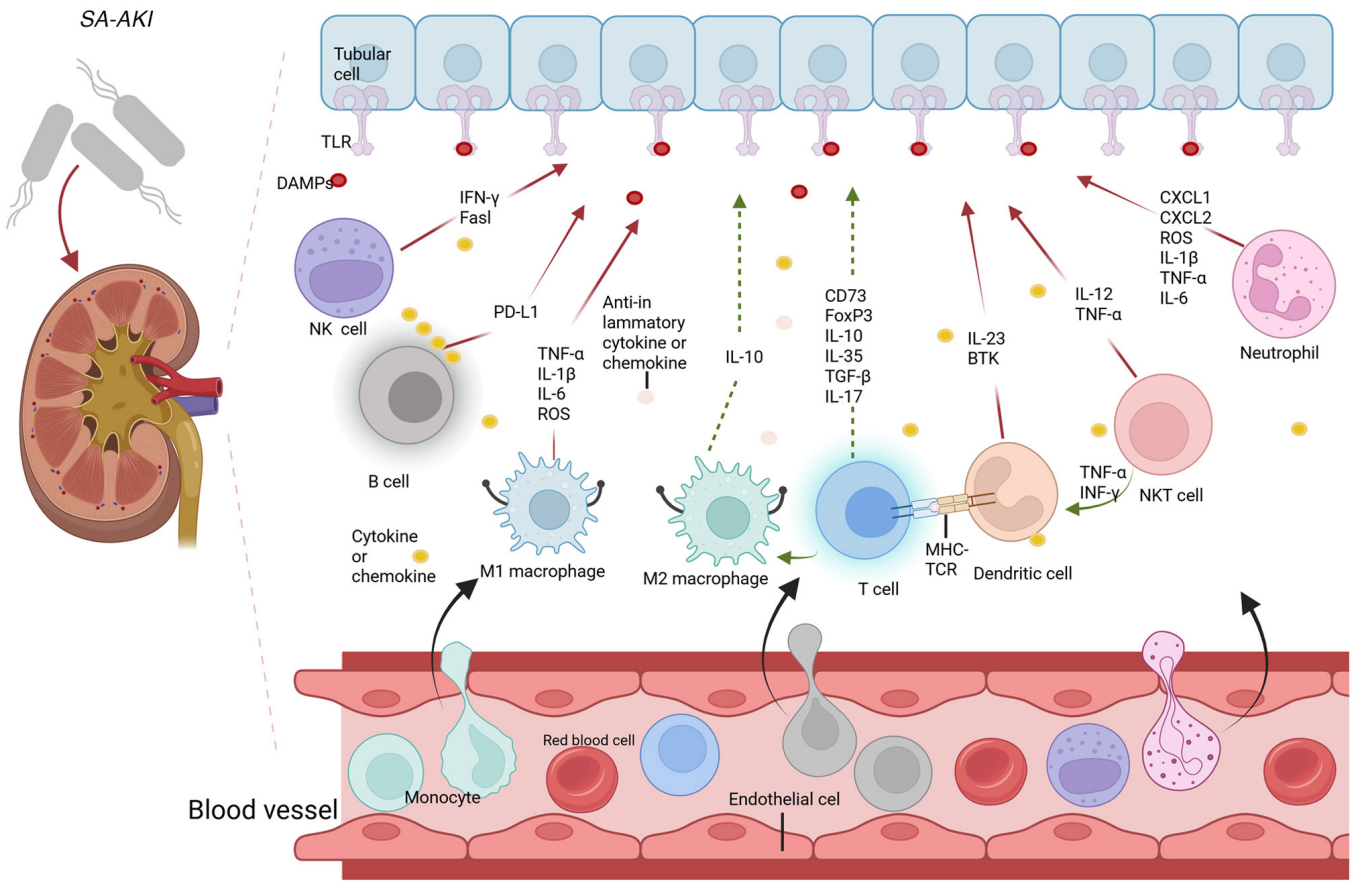

Figure 1. Immune response in SA-AKI. SA-AKI, sepsis-associated acute kidney injury; NK, natural killer; NKT, natural killer T; TLR, Toll-like receptor; DAMPs, damage-associated molecular patterns; IFN-γ, interferon-γ; FasL, Fas ligand; PD-L1, programmed death-ligand 1; TNF-α, Tumor Necrosis Factor-α; IL, interleukin; ROS, reactive oxygen species; FoxP3, forkhead box P3; TGF-β, transforming growth factor-β; BTK, Bruton's tyrosine kinase; CXCL1/2, C-X-C motif chemokine ligand 1/2; MHC, major histocompatibility complex; TCR, T-cell antigen receptor; CD73, ecto-5'-nucleotidase.

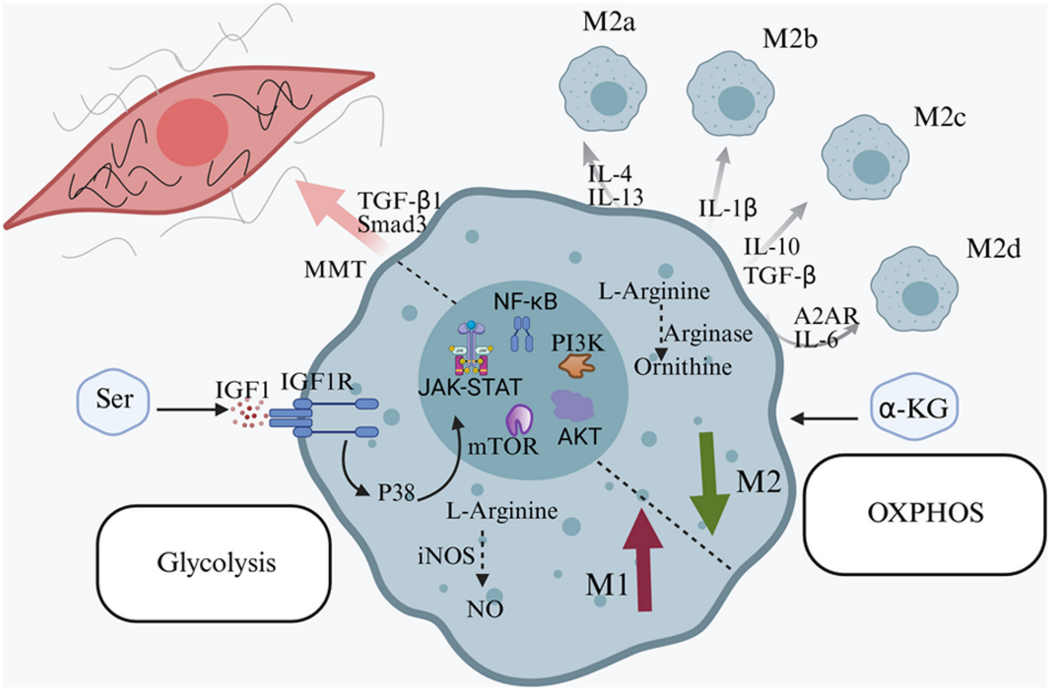

Figure 2. Role of macrophages in sepsis-associated acute kidney injury. NF-κB, nuclear factor-κB; JAK, Janus kinase; STAT, signal transducer and activator of transcription; mTOR, mammalian target of rapamycin; IGF1, insulin-like growth factor 1; IGF1R, insulin-like growth factor 1 receptor; IL, interleukin; TGF, transforming growth factor; Ser, Serine; A2AR, adenosineA2A receptor; P38, mitogen-activated protein kinase 14; MMT, macrophage-to-myofibroblast transition; α-KG, α-ketoglutarate; iNOS, inducible nitric oxide synthase.

In conclusion, during SA-AKI, macrophage metabolic reprogramming may be a critical component of the host defense response. However, specific regulatory strategies require further investigation to precisely modulate macrophage metabolism for therapeutic purposes.

NF-κB signaling pathway and macrophage inflammatory regulation. NF-κB is a dimeric transcription factor composed of five protein family members and is present in nearly all human cells (47); it plays a critical role in inflammation and immunity by regulating the expression of a broad range of chemoattractants, cytokines, transcription factors and regulatory proteins (47). The binding of LPS to its receptor, TLR4, on macrophages activates the myeloid differentiation primary response 88 (MyD88)-dependent signaling pathway. This pathway activates the IKK complex, which phosphorylates IκB proteins, leading to their ubiquitination and proteasomal degradation. Degradation of IκB releases NF-κB dimers, such as p50/RelA (p65), allowing their translocation to the nucleus (48). Within the nucleus, NF-κB binds to specific κB sites on DNA via its Rel homology domain, promoting the transcription of inflammatory genes, including TNF-α and IL-1β, thereby amplifying the inflammatory response (48). The NF-κB pathway interacts extensively with other signaling pathways. For instance, the PI3K/AKT/NF-κB signaling pathway plays a pivotal role in regulating macrophage polarization (49). Moreover, complex regulatory interactions exist between NF-κB and pathways such as the MAPK and STAT pathways.

PI3K/AKT/mTOR signaling pathway and macrophage inflammatory regulation. The PI3K/AKT/mTOR signaling pathway is a critical cascade that governs various cellular processes, including growth, proliferation, survival, metabolism and migration (50). A study has shown that LPS-induced activation of TLR4 in macrophages triggers the PI3K/AKT/mTOR pathway, leading to the production of muscle-type pyruvate kinase isozyme, which then facilitates the acetylation of high mobility group box 1 (HMGB1). Acetylated HMGB1 promotes LPS uptake by macrophages and inhibits macrophage apoptosis (51). This pathway is also essential for regulating macrophage polarization towards M1 or M2 phenotypes. Androulidaki *et al* (52) demonstrated that AKT1 modulates macrophage polarization upon LPS stimulation. AKT1 deficiency promotes M1 polarization, while AKT2 deficiency favors M2 polarization. For instance, Aquaporin 1 has been shown to mitigate SA-AKI by promoting M2 polarization via the PI3K/AKT pathway (53,54).

JAK/STAT signaling pathway and macrophage-mediated inflammation regulation. The JAK/STAT pathway is a key mechanism in cell communication, enabling cells to respond to external stimuli (55); it plays a critical role in various physiological and pathological processes, including cell proliferation, metabolism, immune response and inflammation (55). During sepsis, the release of large quantities of pro-inflammatory cytokines (such as TNF-α, IL-6 and IL-1β) activates the JAK/STAT signaling pathway. Activated STAT proteins translocate to the nucleus, driving the transcription of additional inflammatory mediators, thus amplifying the inflammatory response and contributing to kidney damage (56,57). STAT inhibitors can effectively reduce inflammation by restoring the CD11blowF4/80high macrophage population, which exhibits potential anti-inflammatory properties, thus protecting the kidneys from injury (58). For example, curcumin has been demonstrated to alleviate inflammation and apoptosis by modulating the JAK2/STAT3 pathway, mitigating SA-AKI (59).

The JAK/STAT pathway also regulates immune cell function. In sepsis, this pathway influences macrophage activation and differentiation, enabling macrophages to produce inflammatory cytokines through receptor-interacting serine/threonine-protein kinase and the NLRP3 inflammasome, thus impacting the intensity and duration of the immune response (51,56). For instance, mesenchymal stem cells (MSCs) with upregulated heme oxygenase-1 expression can ameliorate SA-AKI by activating the JAK/STAT3 pathway (60). Moreover, blocking TLR4/TNF1 can promote a phenotypic shift of M1 macrophages towards the M2 phenotype by inhibiting STAT1/STAT3 expression and increasing Suppressor of cytokine signaling 3 expression (61). Acyl-CoA thioesterase 11, an IL-1β-associated gene involved in fatty acid metabolism, promotes the accumulation of fatty acids, such as eicosatetraenoic acid (EA) and stearic acid, within macrophages (62). This accumulation inhibits JAK/STAT signaling activation via palmitoylation of interferon-γ (IFN-γ) receptor 2 at the C261 site (62). Eicosatetraenoic acid has also been shown to alleviate sepsis-associated organ damage via the same pathway (62). Additionally, macrophages expressing the chemokine CCL5 activate several pathways related to immune and inflammatory responses, including IL-6/JAK/STAT3 signaling, TGF-β signaling and inflammatory responses, recruiting neutrophils and exacerbating SA-AKI (63). In summary, the JAK/STAT signaling pathway plays a complex role in the pathophysiology of SA-AKI. By regulating inflammatory responses, immune modulation and apoptosis, this pathway contributes to the initiation and progression of renal injury. Thus, targeting the JAK/STAT pathway may offer novel therapeutic strategies for SA-AKI.

Precise regulation of diverse macrophage phenotypes. Accumulative evidence suggests that the M1/M2 dichotomy does not fully encompass the complex behaviors and functions of macrophages *in vivo* (26,64,65). Macrophages may exhibit multiple phenotypes and even co-express both M1 and M2 markers simultaneously. For example, macrophages can display mixed M1/M2 phenotypes, which are essential for regulating the assembly and structure of the extracellular matrix (66). Additionally, M2 macrophages represent not a single phenotype but several subtypes, including M2a, M2b, M2c and M2d, each characterized by distinct surface markers, cytokine secretion profiles and immune effector functions (67,68). M2a and M2b macrophages are particularly prevalent in renal tissue. M2a macrophages, typically induced by IL-4 or IL-13, express high levels of Arg1 and the mannose receptor and are primarily involved in wound healing, fibrosis and allergic responses (67). M2b macrophages, stimulated by immune complexes or IL-1β, exhibit immunomodulatory and anti-inflammatory effects. These cells produce anti-inflammatory cytokines such as IL-10, while also secreting pro-inflammatory cytokines such as IL-1β and TNF-α, thereby participating in immune complex-mediated diseases (69). In the later stages of sepsis, promoting the M2b macrophage phenotype may help maintain immune homeostasis and facilitate tissue healing. However,

the activity of M2b macrophages must be precisely regulated to prevent exacerbation of inflammation or suppression of immune responses. M2c macrophages, induced by IL-10 or TGF-β, are primarily involved in immunosuppression and tissue remodeling. They express surface markers such as CD163 and signal regulatory protein α (SIRPα) (67,68). M2d macrophages, induced by adenosine A2A receptor agonists or IL-6, play a major role in tumor angiogenesis and immunosuppression (67). Future research should focus on investigating M2 macrophage subtypes and their specific functions in SA-AKI, providing a theoretical foundation for more targeted therapies.

Macrophage-to-myofibroblast transition (MMT). Fibrosis, a common pathological feature of chronic disorders, is characterized by excessive activation of myofibroblasts and abnormal deposition of extracellular matrix in tissues (70). Macrophages can directly transdifferentiate into myofibroblasts via MMT, promoting renal fibrosis (71,72). Recently, MMT has been recognized as a novel source of myofibroblasts and plays a critical role in fibrotic processes across multiple organs. The regulatory mechanisms underlying MMT remain incompletely understood, but the TGF-β1/Smad3 signaling cascade is the most extensively studied pathway (73,74). Although no direct evidence currently links MMT to SA-AKI, a study has confirmed increased expression of TGF-β R2 and phosphorylated Smad3 in the kidneys of septic mice (75). Given the critical role of the TGF-β1/Smad3 pathway in MMT, it is hypothesized that MMT may contribute to the development and progression of renal fibrosis following SA-AKI. Therapeutic strategies targeting MMT hold promise for improving the long-term prognosis of SA-AKI, although further experimental validation is needed.

Novel macrophage-based immunomodulatory therapies. Catalytic nanoparticles offer a promising alternative to conventional anti-infective therapies by modulating innate immune responses and engineering macrophages for immunotherapy, thus providing innovative treatment options for infectious diseases such as sepsis. For example, ultrasound-responsive piezoelectric catalytic nanoparticles enhance macrophage-mediated antibacterial phagocytosis and bactericidal activity through intracellular piezoelectric catalysis (76). Bone marrow-derived macrophages co-cultured with these piezoelectric nanoparticles form piezoelectric macrophages, which, upon activation via ultrasound irradiation, can be utilized in adoptive cell therapy. This approach has proven effective against immunosuppressive bacterial infections, including sepsis (76). However, challenges remain in targeting these piezoelectric nanomaterials to macrophages and kidneys, as they are typically non-degradable and considered biologically inert, necessitating further investigation into their long-term effects and biosafety. Another novel nanoparticle modulates metabolic reprogramming in macrophages to mitigate the septic cytokine storm (77). Additionally, engineered apoptotic extracellular vesicles derived from macrophages can alleviate symptoms in septic patients by clearing toxins and regulating inflammatory responses (78). Nicotinamide adenine dinucleotide (NAD^+), an immunomodulator, shows promise for sepsis treatment. Co-incubation of LPS-activated macrophages with NAD^+-loaded lipid nanoparticles not only reduces the production of pro-inflammatory cytokines and ROS by macrophages but also enhances their viability (79). Moreover, nanoparticles formed by coordination between Ce^{3+} and astragalin (CeAst nanoparticles), encapsulated with macrophage membranes and modified with a kidney-targeting peptide, form the CeAst@MK system. This nanoplatform enables precise kidney targeting and promotes M2 macrophage polarization (80). The CeAst@MK system exhibits excellent biocompatibility and *in vivo* safety, indicating notable potential for clinical translation. A novel system of mannose-conjugated, PEGylated graphene oxide nanoparticles loaded with a sesquiterpene lactone (GMO@GO@PEG@MAN) not only targets the kidneys but also binds to macrophages and promotes the transition from M1 to M2 macrophages (81). Given the promising outcomes of these macrophage-based therapies in sepsis treatment, they hold notable potential for managing SA-AKI. Ongoing optimization of therapeutic strategies, deeper exploration of underlying mechanisms and enhanced clinical translational research are expected to improve the prognosis of patients with SA-AKI. As an emerging therapeutic approach, macrophage-based therapy shows broad potential in SA-AKI management. Through continuous refinement of treatment strategies and further investigation into its mechanisms, new avenues for improving patient outcomes in SA-AKI are anticipated.

3. Role of neutrophils in SA-AKI

Neutrophils are a critical component of the first line of defense against invading microorganisms, playing a key role in infection control and the mediation of inflammatory responses (Fig. 3). Neutrophils constitute ~70% of the total white blood cell count in circulation, making them the most abundant type of leukocyte. However, under normal physiological conditions, the number of neutrophils in the kidney is relatively low. Neutrophils primarily function in immune surveillance, clearing small quantities of pathogens or cellular debris that enter the kidney (82); they are typically maintained in a non-activated state to prevent unnecessary damage to renal tissues (82). In sepsis, excessive neutrophil activation can lead to an uncontrolled inflammatory response. Analysis of the large MIMIC-IV database has shown that an elevated neutrophil-to-lymphocyte-to-platelet ratio is strongly associated with an increased risk and severity of SA-AKI (83), indicating a notable role for neutrophils in the pathophysiology of SA-AKI. Similar to macrophages, neutrophils display phenotypic heterogeneity, with N1 neutrophils being pro-inflammatory and N2 neutrophils being anti-inflammatory (84). Neutrophils isolated from the kidneys of cecal ligation and puncture (CLP) mice exhibit a CD11bhigh, CD54high and CD95high profile, indicating an N1 phenotype (85,86). Upon LPS stimulation, CD54 expression on neutrophils increases, which correlates with enhanced phagocytosis and ROS production (87).

During SA-AKI, significant neutrophil recruitment and infiltration occur in the kidneys. Sepsis triggers a systemic inflammatory response, leading to endothelial cell activation and upregulation of various adhesion molecules, such as P-selectin, E-selectin and intercellular adhesion molecule-1 (88). These adhesion molecules interact with ligands on the neutrophil surface, promoting neutrophil adhesion from

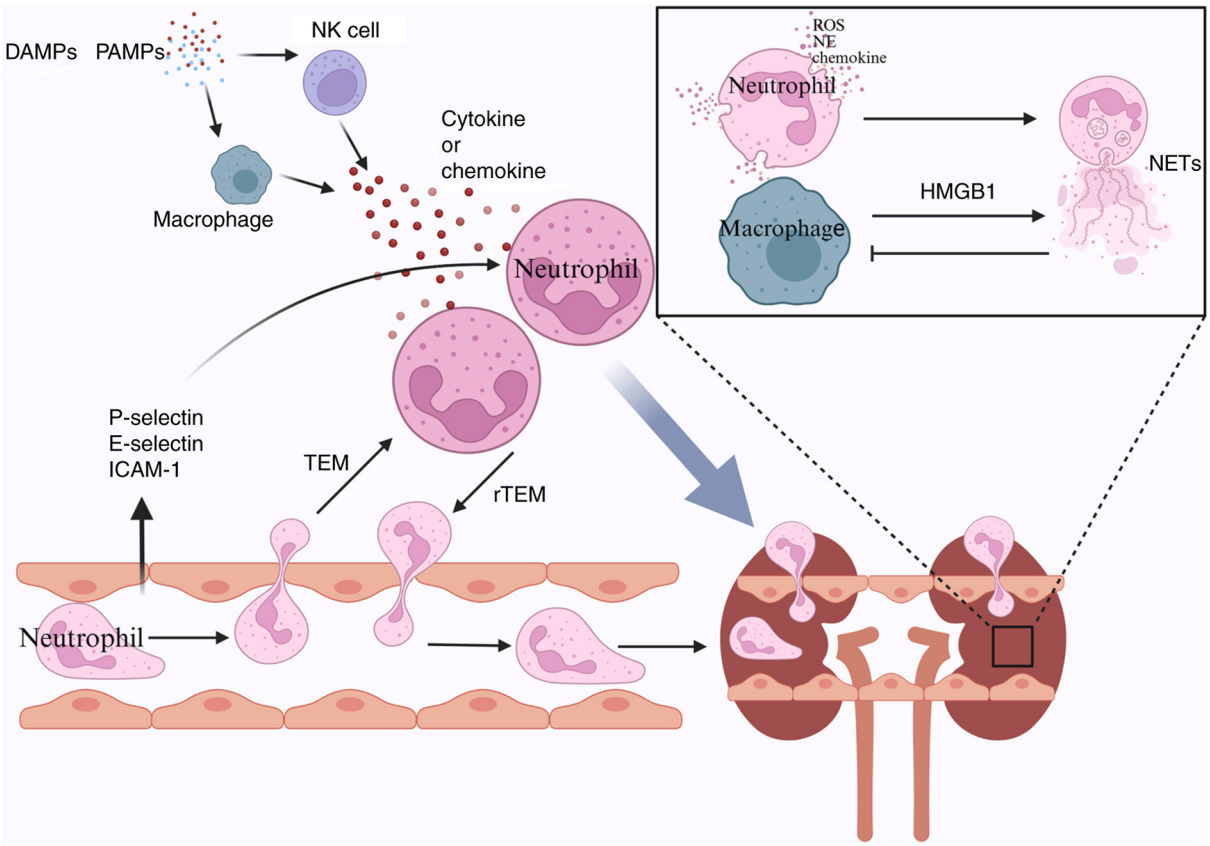

Figure 3. Role of neutrophils in sepsis-associated acute kidney injury. DAMPs, damage-associated molecular patterns; PAMPs, pathogen-associated molecular patterns; NK, natural killer; TEM, transendothelial migration; rTEM, reverse transendothelial migration; ROS, reactive oxygen species; HMGB1, high mobility group box 1 protein; NETs, neutrophil extracellular traps; NE, neutrophil elastase; ICAM-1, intercellular adhesion molecule-1.

the circulation to the renal vascular endothelium and their subsequent migration into renal tissue (88). Additionally, one study indicated that the release of DAMPs and pathogen-associated molecular patterns activates monocytes/macrophages and DCs, leading to the secretion of pro-inflammatory cytokines and chemokines, which initiate neutrophil recruitment into renal tissue (89-91). Other research has highlighted a sharp increase in classical pro-inflammatory chemokines and cytokines, such as C-X-C motif chemokine ligand (CXCL)1 and CXCL2, during SA-AKI (88,89). Neutrophils follow the CXCL1 and/or CXCL2 gradient to the sites of infection and uncontrolled levels of these chemokines may enhance tissue damage by over-activating neutrophils (92,93). Once recruited to the kidneys, neutrophils primarily accumulate around microvessels, with subsequent infiltration into the renal tubulointerstitium (94). Upon tissue infiltration, neutrophils are further activated, releasing inflammatory mediators such as ROS, proteases (such as neutrophil elastase) and cytokines (95). Excessive ROS production plays a key role in sepsis and SA-AKI, causing direct damage to renal tubular epithelial cells through lipid peroxidation, protein denaturation and DNA damage (96). Neutrophil elastase degrades the extracellular matrix, disrupting the structural integrity of renal tissue (97). In contrast to most studies that rely on reducing systemic neutrophil counts or inflammatory cytokines, one study demonstrated that renal injury during systemic inflammation was not significantly alleviated after specifically targeting neutrophil recruitment into the kidney. This finding suggests that the uncontrolled systemic inflammatory response, rather than local neutrophil recruitment into the kidney, dominates the pathogenesis of kidney injury in SA-AKI. However, the authors of this study also acknowledged the limitation that the specific mechanisms by which individual circulating proinflammatory mediators contribute to renal injury remain to be elucidated (98). This study likely focuses on the role of circulating inflammatory mediators in the early stages of the disease, whereas other studies emphasize the local effects of neutrophils in the kidneys during disease progression. Moreover, neutrophils recruited to sites of inflammation often undergo apoptosis. Insufficient clearance of apoptotic neutrophils can result in the persistence and worsening of inflammation (99). In patients with SA-AKI, peripheral blood mononuclear cells express high levels of the anti-phagocytic signal, involving leukocyte surface antigen CD47 and SIRPα. This signal facilitates the clearance of apoptotic neutrophils, promoting the resolution of inflammation and repair of tissue injury (100).

Neutrophil metabolic reprogramming. Neutrophil metabolic reprogramming refers to the adjustment of metabolic pathways in response to physiological or pathological conditions. Typically, neutrophils utilize multiple metabolic pathways, including glycolysis (101), the pentose phosphate pathway (PPP) and FAO, to support immune functions such as chemotaxis, ROS production, neutrophil extracellular trap (NET) formation and degranulation (102). Under normal conditions,

glycolysis serves as the primary energy source. However, in inflammatory or tumor microenvironments, neutrophils may shift to alternative metabolic pathways, such as FAO, to sustain effector functions. A study has shown that during sepsis, levels of glycolysis, PPP and fatty acid amide hydrolase are elevated in neutrophils (103). 2-deoxy-D-glucose alleviates excessive inflammatory responses by enhancing neutrophil recruitment, highlighting the link between metabolic regulation and infection/inflammation (104). Furthermore, during the acute phase of sepsis, the long non-coding RNA GSEC (containing a G-quadruplex sequence) is upregulated in sepsis-induced neutrophils, enhancing the transcription and translation of 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3 mRNA, which promotes neutrophil glycolysis and the production of inflammatory cytokines such as TNF-α, IL-1β and IL-6 (35). Thus, neutrophil metabolic reprogramming in SA-AKI likely contributes to the increased release of ROS, NETs and other factors, exacerbating disease progression. This process represents an interesting area for future investigation in SA-AKI.

NETs. Additionally, NETs play a notable role in the development of SA-AKI. NETs are web-like structures composed of DNA, histones and antimicrobial proteins, released by activated neutrophils (105). The formation of NETs is regulated by the pore-forming protein gasdermin D and depends on NADPH oxidase and neutrophil elastase activity (106). NETs can suppress macrophage phagocytosis, leading to persistent inflammation and tissue damage. Inhibiting NET formation may alleviate SA-AKI by restoring the infiltration and survival of $GAS6^+$ macrophages, promoting the clearance of damaged cells and the resolution of inflammation (107). However, while NETs provide a fibrous scaffold to entangle bacteria or pathogens, excessive activation of NETs can worsen inflammation and tissue injury (108). Furthermore, prolonged disturbances in the pro-/anti-inflammatory balance lead to pathogenic NET formation, which is a hallmark of systemic inflammatory response syndrome (107). NETs can exacerbate kidney damage by releasing cytokines and histones. Histones within NETs directly damage renal tubular epithelial cells (109), while the DNA component can activate the complement system (110), thereby intensifying the inflammatory response. Notably, defective NET formation has been shown to be protective in SA-AKI models (111).

Reverse transendothelial migration (rTEM) of neutrophils. Neutrophils do not remain fixed at the site of inflammation; they can exit via a process known as rTEM (112,113), in which neutrophils move back across the endothelium from the interstitial space into the bloodstream. This re-migration occurs through interactions between neutrophil surface molecules, such as β2 integrins, and corresponding ligands on vascular endothelial cells, with regulation by various cytokines and chemoattractants. rTEM plays a dual role: On the one hand, it may help reduce local inflammatory damage by decreasing neutrophil numbers in the affected tissue (114), while on the other hand, activated neutrophils re-entering the circulation can carry inflammatory mediators, releasing them into the bloodstream and potentially causing remote organ damage (115). For example, one study showed that extracellular vesicles derived from endothelial cells exacerbate remote lung injury by promoting rTEM (116). It is plausible that rTEM also contributes significantly to SA-AKI, warranting further investigation.

Neutrophil-associated biomarkers. Additionally, neutrophil gelatinase-associated lipocalin (NGAL) is crucial in the pathogenesis and progression of SA-AKI. NGAL functions as a notable renal growth factor, facilitating the differentiation of renal progenitor cells into renal tubular epithelial cells (117). During the initial stages of AKI, NGAL is upregulated in a compensatory manner to promote tubular repair and regeneration (117). NGAL, primarily secreted by neutrophils, is also produced by endothelial cells upon stimulation by TNF-α, LPS and IL-1β (118). After the kidney sustains ischemic, septic or nephrotoxic injury, it releases large amounts of NGAL into both urine and serum. Thus, NGAL is considered a promising early biomarker for SA-AKI (119-122). Beyond serving as an early diagnostic biomarker, serum and urine NGAL can predict the progression of AKI to CKD in patients with SA-AKI (123).

Novel therapeutic strategies based on neutrophil immunoregulation. Numerous innovative nanotechnology-based therapies targeting neutrophils have been developed. In diseases associated with neutrophil infiltration, neutrophils serve not only as therapeutic targets but also as ideal carriers for targeted drug delivery (124). For example, a targeted nanodrug delivery platform, Ac-PGP (a peptide sequence that targets the CXCR2 receptor on neutrophils)-tetrahedral framework nucleic acid (tFNA), utilizes tFNA and a neutrophil hitchhiking mechanism (125). DNA-based nanorobots have also been employed to target, load and modulate neutrophils for precise drug delivery and anti-inflammatory effects (125,126). Ly6G nanoparticles loaded with a selective phosphodiesterase 4 inhibitor can effectively suppress the release of cytokines and chemoattractants from activated neutrophils, preventing organ damage caused by excessive neutrophil accumulation and migration (127). Additionally, nanomaterials loaded with astragaloside IV, a natural compound with anti-inflammatory and antioxidant properties, can precisely target neutrophils and inhibit NET formation, mitigating sepsis-induced inflammatory responses and organ damage (128). Similarly, nanomaterials loaded with Coenzyme Q10, an antioxidant, significantly enhance kidney delivery efficiency, offering a new approach to alleviating kidney damage (129). Nanozymes, nanomaterials with enzyme-like activities, also play a vital role in SA-AKI treatment by catalyzing specific biochemical reactions and protecting the kidneys through mechanisms such as scavenging excess ROS and modulating inflammatory signaling pathways (130). Neutrophil-targeted nanodrug delivery systems provide novel strategies for SA-AKI treatment by enabling precise intervention in neutrophil-mediated kidney injury, optimizing nanocarrier design and facilitating clinical translation.

Although studies targeting neutrophil-mediated injury pathways have shown promising results, neutropenia remains a high-risk condition in critically ill septic patients (131). Compared with non-neutropenic patients, severe sepsis triggers a distinct inflammatory response in neutropenic patients (131). Levels of IL-6, IL-8 and granulocyte colony-stimulating factor

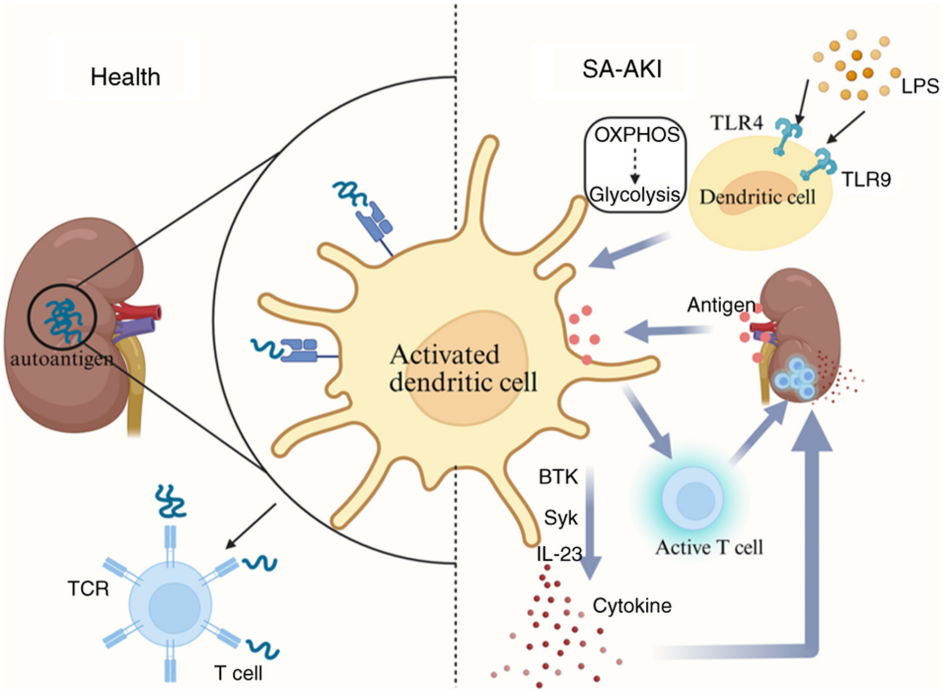

Figure 4. Role of dendritic cells in SA-AKI. SA-AKI, sepsis-associated acute kidney injury; LPS, lipopolysaccharide; BTK, Bruton's tyrosine kinase; Syk, spleen tyrosine kinase; TLR, Toll-like receptor; TCR, T-cell antigen receptor; OXPHOS, oxidative phosphorylation.

(CSF) are significantly elevated in neutropenic septic patients and are independently associated with an increased risk of AKI (131). Therefore, the development of therapeutic strategies targeting neutrophils must be carefully balanced to avoid excessive suppression of their functions, which could impair renal repair.

4. Role of DCs in SA-AKI

DCs, the most abundant resident leukocytes in the kidney, play a critical role in renal immunity by forming a sophisticated immune sentinel system that continuously monitors the tubulointerstitial compartment (132) (Fig. 4). Under normal physiological conditions, DCs primarily maintain immune tolerance and prevent autoimmune responses (133); they constantly sample and present autoantigens and low-molecular-weight antigens from the glomeruli and tubules to T lymphocytes, thereby promoting T cell tolerance and preventing attacks on renal tissues (133,134). Additionally, DCs have the capacity to recognize and clear apoptotic cells and debris, preventing excessive activation of inflammatory responses (133). However, under pathological conditions, DCs undergo notable changes. Upon recognition of DAMPs, DCs undergo metabolic reprogramming, shifting from OXPHOS to glycolysis to generate an immunogenic response (135). This metabolic shift is accompanied by phenotypic maturation, enabling DCs to specialize in T cell stimulation and activate innate immune cells (136). Mature DCs then migrate to inflamed tissues and lymph nodes, enhancing their antigen-presenting capacity by upregulating major histocompatibility complex (MHC) molecules and T cell co-stimulatory proteins on their cell membranes, thus facilitating T cell activation and initiating an immune response (137,138).

DCs play an even more critical role in sepsis, where they modulate the adaptive immune response to infection by producing pro-inflammatory cytokines and chemokines that guide lymphocyte activation and lineage commitment (139). DCs may also mediate T cell infiltration into the kidney, initiating inflammatory responses that contribute to the onset and progression of SA-AKI, potentially through antigen uptake from peritubular capillaries (139). DCs mediate the link between TLRs and sepsis. TLR4 and TLR9, key members of the TLR family, are closely associated with sepsis-induced inflammatory responses. TLR4 serves as the cellular receptor for LPS on the DC surface; the binding of LPS to TLR4 activates downstream signaling pathways, leading to the activation of NF-κB, a transcription factor that regulates gene expression during LPS-induced inflammatory responses in both kidney damage and sepsis (140). Triggered by endogenously released mitochondrial DNA during sepsis, TLR9 activates DCs. The activated DCs then produce IL-23, which induces γδ T cells to produce IL-17A, thereby promoting the development of SA-AKI (141). Based on these mechanisms, developing specific inhibitors targeting TLR4 or TLR9 could be an effective strategy to mitigate the progression of the inflammatory cascade in SA-AKI (140). Furthermore, LPS activates TLR4 signaling through two distinct pathways: Via the plasma membrane through the Toll/IL-1 receptor domain-containing adapter protein (TIRAP)-MyD88 adapter complex and via endosomes through the TRIF-related adaptor molecule-Toll/IL-1 receptor domain-containing adapter inducing IFN-β (TRAM-TRIF) adapter complex. In DCs, the p110δ subunit of PI3K acts as a key mediator, promoting the transition of TLR4 signaling from the pro-inflammatory TIRAP-MyD88-dependent phase to the anti-inflammatory TRAM-TRIF-dependent phase (142). Therefore, using DCs as vehicles through genetic modification

or drug delivery approaches to enhance the anti-inflammatory effects of the p110δ subunit presents a promising therapeutic strategy for SA-AKI.

In addition to TLR4 and TLR9-related mechanisms, DCs influence the progression of SA-AKI through the release of inflammatory cytokines, a process regulated by the spleen tyrosine kinase (Syk) signaling pathway (143). Inhibition of Syk signaling has been shown to limit the inflammatory cascade in SA-AKI (144). Concurrently, research has identified that activation of Bruton's tyrosine kinase (BTK) in DCs leads to a significant increase in biochemical markers associated with subacute kidney injury. During the onset of SA-AKI, BTK is activated in DCs, neutrophils and B cells, and inhibiting BTK signaling improves renal function following AKI (145). Therefore, inhibiting both the Syk and BTK signaling pathways in innate immune cells may serve as an effective strategy to attenuate the progression of the inflammatory cascade in SA-AKI.

Techniques involving the *ex vivo* expansion, modification and reinfusion of immune cells, such as chimeric antigen receptor T cell immunotherapy and DC-based therapies (146,147), have been widely studied and applied in oncology. The technology for isolating and culturing DCs *ex vivo* is well-established, providing a solid foundation for clinical translation. However, in the field of sepsis, clinical trials involving DC reinfusion have not yet been initiated and remain limited to animal studies. Reinfusion of mouse bone marrow cells, differentiated into DCs (BMDCs) *ex vivo* using granulocyte-macrophage CSF and IL-4, into the lungs of CLP mice effectively protected against lung injury caused by fungal infection and reduced mortality following secondary injury (148). Similarly, reinfusion of BMDCs via intraperitoneal injection in CLP mice promoted a shift in lymphocyte differentiation towards T helper 1 (Th1) cells, reduced regulatory T lymphocyte differentiation and significantly improved pathological damage and dysfunction in multiple organs (149). Given the demonstrated clinical safety in other contexts, exogenous supplementation of DCs could be considered in septic patients.

5. Role of mast cells in SA-AKI

Mast cells are granule-rich immune cells distributed throughout the body, particularly in areas commonly exposed to microbes, such as mucosal tissues, skin and connective tissues (150). These cells interact with pathogens through surface and intracellular receptors, including pattern recognition receptors, bacterial toxin receptors, antimicrobial peptides, complement proteins and Fc receptors (151). While mast cells are traditionally associated with allergic reactions, atopic asthma and other IgE-mediated allergic diseases (152), studies have highlighted their broader immunomodulatory roles. These include enhancing host resistance in certain bacterial or parasitic infection models and even providing defense against specific animal venoms (152). This functional diversity is especially evident in sepsis. In the early stages of infection, mast cells activate neutrophils by releasing IL-6 and suppressing TNF, thereby enhancing their bactericidal activity (150,153-156). However, in severe sepsis, excessive mast cell activation exacerbates the systemic inflammatory response and increases mortality. Despite this, in models of sepsis and ischemia-reperfusion injury, mast cells can modulate TNF levels through the release of anti-inflammatory mediators, such as protease 4 (a homolog of mouse mast cell protease), which suppresses neutrophil overactivation, reduces inflammation and mitigates renal impairment (152,157). In the context of kidney disease, mast cells display a dual role. In anti-glomerular basement membrane antibody-induced glomerulonephritis, mast cells reduce glomerular injury by initiating repair mechanisms (158). By contrast, in cisplatin-induced AKI, mast cells exacerbate the condition through a TNF-dependent pathway (159). While the specific role of mast cells in SA-AKI remains unclear, existing evidence suggests their potential importance. Mast cells may combat infection via rapid inflammatory responses and influence disease progression through immunomodulation. Current understanding of this mechanism largely relies on non-sepsis models, such as cisplatin-induced and ischemia-reperfusion injury models. However, the unique immune microenvironment in sepsis may alter the manifestation of these mechanisms, and their direct role in SA-AKI requires further validation.

Given the complex and diverse roles of mast cells, future multicenter, large-scale clinical studies are urgently needed. These studies should focus on the specific association between mast cells and SA-AKI and further elucidate their immunoregulatory functions, repair mechanisms and interactions with the renal microenvironment. Such investigations are expected to provide novel insights and therapeutic strategies for the treatment of SA-AKI.

6. Role of NK cells and NKT cells in SA-AKI

NK cells are large granular lymphocytes derived from the bone marrow, constituting ~15% of all circulating lymphocytes. Fig. 5 provides a schematic overview of the roles and mechanisms of NK cells in the pathogenesis of SA-AKI. As vital components of the innate immune system, NK cells are capable of directly lysing tumor cells and other target cells (160,161); however, their function is dualistic. While NK cells are critical for immune defense, excessive activation may result in attacks on normal cells, leading to shock and multiple organ failure (MOF) (162). The mechanisms of NK cell action manifest in two primary ways: i) Direct cytolysis via azurophilic granules within the cytoplasm; and ii) the secretion of pro-inflammatory cytokines, such as IFNs and TNF, to modulate the activities of other immune cells (160,163). The activity of NK cells is regulated by a balance of activating and inhibitory receptors on their surface. Most healthy cells express MHC class I molecules, which deliver inhibitory signals that suppress NK cell activity (164). In humans, NK cells are typically divided into two subsets: i) CD56bright NK cells, predominantly found in lymphoid organs; and ii) CD56dim NK cells, which are mainly located in peripheral blood. CD56bright NK cells primarily exert immunoregulatory functions through cytokine secretion, while CD56dim NK cells exhibit potent cytotoxic capabilities (165,166). Notably, CD56bright NK cells often express tissue-resident markers in the healthy kidney and may play a key role in renal defense against infections (167). However, in patients with renal fibrosis and chronic kidney disease (CKD), a substantial number of CD56bright NK cells

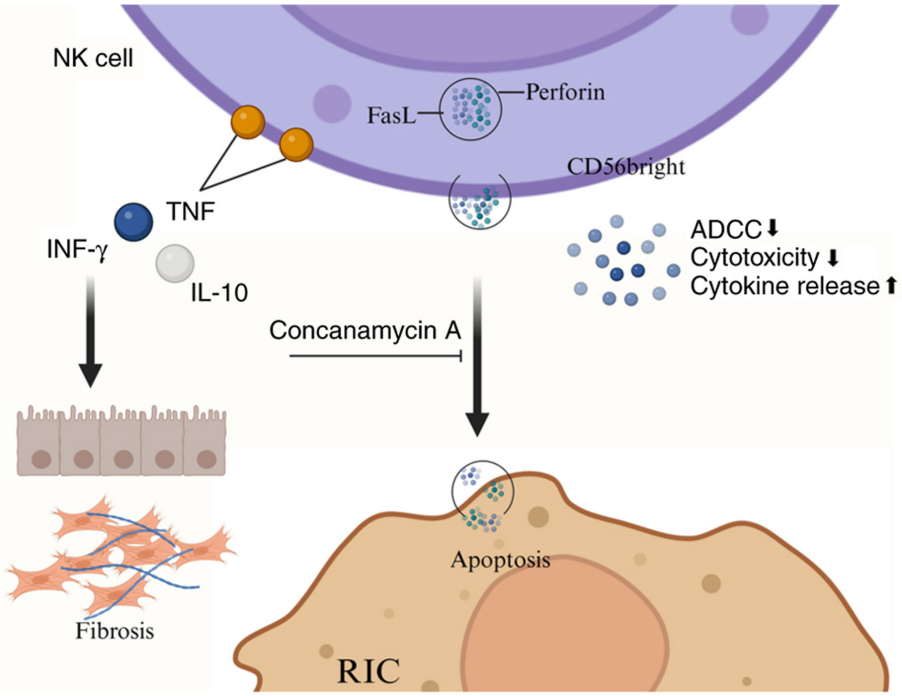

Figure 5. Role of NK cells in sepsis-associated acute kidney injury. RIC, renal intrinsic cell; ADCC, antibody-dependent cellular cytotoxicity; NK, natural killer; IFN-γ, interferon-γ; TNF, tumor necrosis factor; FasL, Fas ligand; IL-10, interleukin-10.

accumulate in the renal tubulointerstitium, where they produce IFN-γ and contribute to the progression of renal fibrosis (168). In the context of SA-AKI, targeted treatment strategies could be developed based on the distinct characteristics of these NK cell subsets. For example, the cytotoxic function of CD56dim NK cells could be harnessed to clear damaged cells, while the activity of CD56bright NK cells could be modulated to prevent excessive inflammatory responses. Furthermore, NK cells produce a wide range of cytotoxic effector molecules, including Fas ligand (FasL) and perforin. Notably, stimulation with bacterial components such as LPS leads to a significant increase in the proportion of perforin-positive cells (169,170). Stimulated human $CD56^+$ NK cell subsets can damage intrinsic renal cells, including renal tubular epithelial cells and glomerular endothelial cells. Inhibition of the perforin-mediated pathway with concanamycin A can reduce the cytotoxicity of $CD56^+$ NK cells against glomerular endothelial cells (169,171).

In sepsis-related research, a decrease in human NK cell counts has been observed within 1 day of sepsis onset, which increases the risk of hospital-acquired infections and sepsis-related complications (168). Additionally, NK cell function is impaired in critically ill septic patients, accompanied by reduced cytokine secretion (172). A further study has indicated that lower levels of NK cells and other immune cells elevate mortality risk in septic patients, whereas those with higher NK cell levels tend to have longer survival times (173). A case report described a patient with pulmonary squamous cell carcinoma who developed sepsis and showed a poor response to conventional therapy. Following NK cell infusion therapy, the patient's infection markers initially decreased but later increased. While the long-term efficacy of NK cell therapy requires further investigation, optimizing treatment regimens holds promise for improving NK cell survival and therapeutic outcomes (174). The aforementioned case report suggests that NK cell therapy can enhance patient physical function, increase cytokine levels with antitumor activity and reduce pro-inflammatory cytokines; it also provides insights for SA-AKI treatment: Monitoring NK cell count and function during therapy and selecting the appropriate timing for intervention. For instance, administering appropriate stimulation or supplementation before NK cell numbers severely decline may enhance treatment efficacy, whereas restoring function is necessary if NK cell activity is already impaired. Future research should focus on optimizing NK cell treatment strategies, including selecting suitable cell sources and determining the optimal infusion doses and frequencies, to improve their survival and efficacy in SA-AKI treatment.

In addition to NK cells, NKT cells represent a unique subset of immune cells that exhibit characteristics of both T cells and NK cells. As innate lymphocytes bridging innate and adaptive immune responses, NKT cells are present in extremely low numbers in the blood, accounting for <0.1% of human peripheral blood mononuclear cells (175). Based on the variability of the T cell receptor (TCR) chain, NKT cells can be classified into two types: Type I (iNKT cells) and type II (vNKT cells) (174,176). Among these, iNKT cells are the predominant subtype in humans, expressing the Va-24 and Ja-18 chains; they differentiate into mature iNKT cells upon recognition of glycolipid antigens presented by CD1d molecules (177). Furthermore, various cytokines secreted by iNKT cells play a potent regulatory role in the maturation of DCs, positioning iNKT cells as a critical link between innate and adaptive immunity (177). A reciprocal regulatory relationship exists between iNKT and vNKT cells, with vNKT cells suppressing iNKT cell-mediated inflammatory responses. This interaction may influence disease progression during

the onset and development of SA-AKI. Therefore, in treating SA-AKI, it is essential to consider not only the overall status of NKT cells but also the interactions between different subsets (178,179). Like NK cells, NKT cells express activating receptors, inhibitory receptors and cytokine receptors (such as IL-12 and TNF-α receptors) (167); they also possess the NK1.1 antigen and an intermediate TCR (171). NKT cells recognize lipids and glycolipids presented by CD1d molecules (180) and can be activated through TCR engagement, exhibiting potent cytotoxic functions and directly participating in the clearance of infectious agents (167). This dual functionality provides a more comprehensive perspective for understanding the pathophysiology of SA-AKI and offers potential therapeutic targets.

The role of iNKT cells in immune functions is multifaceted. On the one hand, a study has demonstrated that iNKT cells can mediate macrophage inflammatory responses to pathogenic microorganisms by regulating macrophage quantity and phenotype, optimizing immune factor release, enhancing host defense capacity and improving macrophage killing efficiency (181). On the other hand, research on sepsis has revealed that iNKT cells exacerbate the inflammatory response during the early stages of sepsis, worsening its severity. iNKT cell-deficient mice exhibit a certain level of protection against sepsis (182), whereas CD1-deficient mice, lacking both iNKT and vNKT cells, do not show this protective effect (183). During the development of AKI, NKT cells are known to highly express inflammatory regulators, modulating the production of cytokines involved in injury and complement activation, indicating their involvement in AKI pathogenesis through inflammatory mechanisms (184). SA-AKI can lead to MOF, including AKI (167,185). Upon stimulation by cytokines or bacterial components, NKT cells are activated. Similar to NK cells, they can damage renal tubular epithelial cells via the TNF-α/FasL system and injure vascular endothelial cells through a perforin-mediated pathway. These independent mechanisms contribute to the induction of SA-AKI (171). Relevant studies support this view: In patients with SA-AKI undergoing continuous renal replacement therapy (CRRT), the expression of perforin in $CD56^+$ NK cells and $CD56^+$ T cells (that is, NKT cells) is elevated, with FasL expression significantly upregulated in these $CD56^+$ T cells (167,169). This suggests that both the TNF-α/FasL system and perforin play critical roles in the progression of SA-AKI. Future strategies for SA-AKI treatment could focus on regulating NKT cell activation. Additionally, this phenomenon suggests that CRRT may be linked to NKT cell activation. Subsequent therapeutic approaches could consider combining CRRT with treatments targeting NKT cells to enhance CRRT efficacy and improve the prognosis of patients with SA-AKI by modulating NKT cell activation.

7. Role of ILCs in SA-AKI

ILCs are critical components of the innate immune system, playing essential roles in immune responses, inflammation and tissue healing (186). Although ILCs lack lineage-specific surface markers or antigen receptors typical of other immune cells, they are critical for maintaining protective immunity, homeostasis and inflammatory responses (187). The role of ILCs in the kidney is becoming increasingly recognized, with evidence suggesting their involvement in immune surveillance, homeostasis maintenance and disease progression within the kidney (188). Despite their lack of antigen-specific reactivity, ILCs share key transcriptional regulators with T lymphocytes and possess the ability to produce cytokines (189). ILCs are classified into three main subsets: Group 1 ILCs (ILC1s), group 2 ILCs (ILC2s) and group 3 ILCs (ILC3s), each functionally associated with Th1, Th2 and Th17 cells, respectively (190). Among these, ILC2-derived cytokines, such as IL-4 and IL-13, play a key role in driving macrophage polarization towards the M2 phenotype (191). As aforementioned, appropriate M2 macrophage activation is essential for ameliorating SA-AKI.

Kidney-resident ILC2s express receptors for IL-25 (IL-17RB) and IL-33 (T1/ST2), which, when activated by their respective cytokines, promote ILC2 expansion *in vivo* (192). While ILC2s exert protective effects in the kidney, their impact depends on renal IL-33 levels. During kidney injury and disease, IL-33, released from vascular endothelial cells and/or renal tubular epithelial cells, activates kidney-resident ILC2s (193). Studies on ILC2 function have shown varying results. For instance, Akcay *et al* (194) found that recombinant IL-33 exacerbated AKI in a cisplatin-induced model by promoting $CD4^+$ T cell-mediated CXCL1 production. However, soluble ST2, which neutralizes IL-33, reduced the severity of AKI. This suggests that in cisplatin-induced AKI, IL-33 aggravates kidney damage by activating the ST2 signaling pathway and promoting inflammation. Conversely, Cao *et al* (195) observed that in an ischemia-reperfusion-induced AKI model, IL-33 pretreatment improved renal injury by activating ILC2s, promoting M2 macrophage polarization and aiding renal function recovery. These studies indicate that the role of IL-33 in AKI is context-dependent, influenced by factors such as the type of injury, inflammatory environment and immune cell composition. The role of ILC2s in SA-AKI remains unclear. Unlike non-infection-induced AKI, SA-AKI pathogenesis is more complex and it is uncertain whether IL-33 activates ILC2s through similar mechanisms. However, a study has shown that during sepsis, plasma IL-33 levels are significantly elevated in young mice, promoting the egress of ILC2s from the bone marrow. This alteration may affect the accumulation and function of ILC2s in the kidney (196). Therefore, when studying the functions of ILC2s in SA-AKI, factors such as the experimental model and conditions must be carefully considered. Further research into the specific signaling pathways activated by IL-33 in different AKI models, along with the roles of ILC2s in these pathways, could provide a theoretical foundation for developing more effective therapeutic strategies for SA-AKI.

Research on the role of ILCs in SA-AKI is still limited and their precise mechanisms of action are not fully understood. Given the preliminary evidence supporting the involvement of ILCs in other types of AKI, further investigation into the functions and mechanisms of ILC subsets in SA-AKI is crucial for advancing our understanding and treatment of this condition.

8. Role of adaptive immune cells in SA-AKI

B cells. B cells, a key subset of lymphocytes, play an essential role in the immune response. As summarized in Fig. 6,

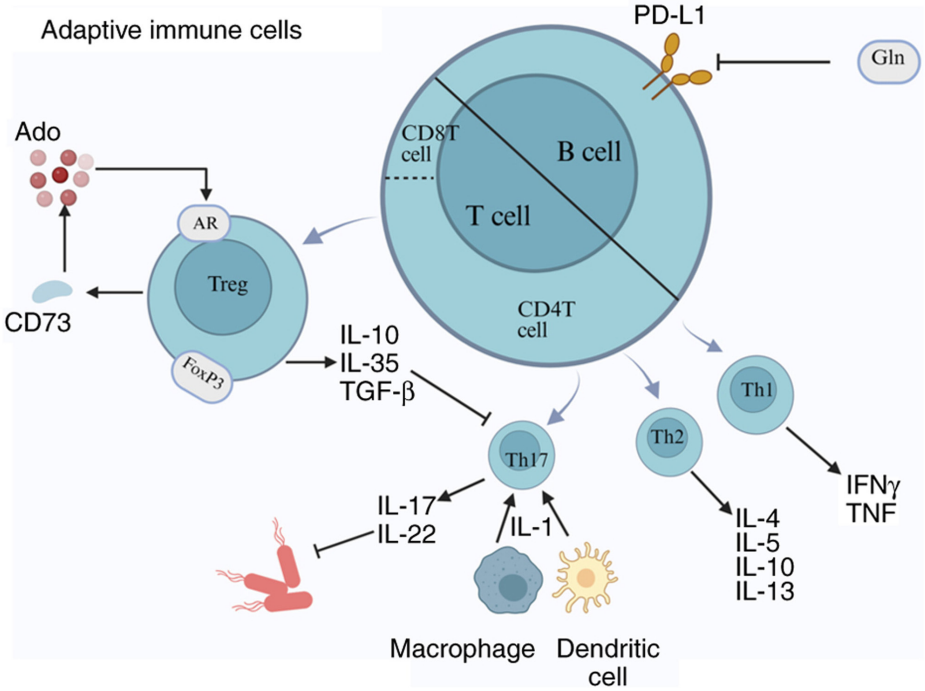

Figure 6. Role of adaptive immune cells in sepsis-associated acute kidney injury. Tregs, regulatory T cells; Ado, adenosine; AR, adenosine receptor; IL, interleukin; TGF-β, transforming growth factor-β; PD-L1, programmed death-ligand 1; Gln, glutamine; FoxP3, forkhead box P3; IFNγ, interferon-γ.

B cells produce antibodies, presenting antigens and secreting cytokines, thereby mediating both adaptive and innate immune responses, maintaining immune balance and renal homeostasis (197). However, due to their pathogenic role in organ transplantation and autoimmune diseases, B cells are considered to have detrimental effects in AKI (198). In a cisplatin-induced AKI model, Inaba *et al* (199) observed that renal B cells were a significant source of CCL7, promoting the recruitment of neutrophils and monocytes to the injured kidney and exacerbating AKI severity. Similarly, in a study of unilateral ureteral obstruction-induced AKI, Han *et al* (200), found that early accumulation of B cells in the kidney accelerated the mobilization and infiltration of monocytes/macrophages, aggravating fibrosis induced by AKI. Clinical studies on SA-AKI have shown an association between the plasma lymphocyte ratio and renal function, with 1 study revealing that septic patients who recovered renal function had fewer B lymphocytes at hospital admission (201). Sepsis increases the expression of programmed death-ligand 1 (PD-L1) on B lymphocytes. Programmed cell death protein 1 (PD-1) impairs immunity by inducing apoptosis, inhibiting T-cell activation, increasing IL-10 production and rendering T cells unresponsive while reducing their cytokine secretion, leading to T-cell exhaustion. Glutamine administration has been shown to reduce the expression of PD-1/PD-L1 on B cells, alleviating kidney damage (202).

T cells. Under normal physiological conditions, T cells play a pivotal role in maintaining renal immune homeostasis (203) (Fig. 6); they regulate immune responses, preventing autoimmune reactions and excessive inflammation, thereby protecting the kidneys from damage. T cells continuously monitor renal tissues, identifying and eliminating potential pathogens or abnormal cells to preserve kidney health (204). Following the onset of SA-AKI, T cells, as key immune cells combating pathogen infections, play a decisive role in the pathogenesis and progression of the disease.

T cell subsets exert distinct immunomodulatory functions in the kidneys. T lymphocytes can be classified into two major subsets: $CD4^+$ Th cells and $CD8^+$ T cells. Th cells are further divided into Th1, Th2 and Th17 subsets. Th1 cells primarily produce IFN-γ and TNF-α, exerting pro-inflammatory effects. Th2 cells secrete IL-4, IL-5, IL-10 and IL-13 (205), predominantly mediating anti-inflammatory effects. Th17 cells mainly produce IL-17 and IL-22 (206). After kidney injury, IL-1 secreted by renal DCs and macrophages promotes the differentiation and activation of Th17 cells (207). Th17 cells infiltrate the renal parenchyma during murine AKI, defend against extracellular pathogens through the production of their signature cytokine IL-17 and play a pivotal role in promoting autoimmune diseases and tissue inflammation (208).

Regulatory T (Treg) cells are a unique subset of $CD4^+$ T cells, comprising a small fraction of the total $CD4^+$ T cell population; they mediate tissue repair by synthesizing pro-repair molecules that promote regeneration and play a critical role in anti-inflammatory processes (209,210). Treg cells exert protective effects through several mechanisms. For instance, they express CD73 (ecto-5'-nucleotidase), an enzyme that catalyzes the production of extracellular adenosine (211). Adenosine binding to the A2A receptor on Treg cells increases their surface expression of PD-1, which is essential for their suppression of innate immune responses (7). Additionally, Treg cells can be identified by the expression of the transcription factor Forkhead Box P3 and employ multiple mechanisms to suppress other immune cells (212). These cells

secrete anti-inflammatory mediators such as IL-10, IL-35 and TGF-β, inhibit Th17 cell activity, promote their own proliferation, suppress excessive T lymphocyte responses and reduce pro-inflammatory mediators, thus directly inhibiting innate immune responses (213,214). Moreover, an imbalance in the Th17/Treg ratio is believed to be associated with the occurrence and severity of SA-AKI (215). Targeted regulation of Treg cells may potentially improve renal function. The α7 nicotinic acetylcholine receptor (α7nAChR), highly expressed on Treg cells, can modulate Treg cell activity. Shi *et al* (216) demonstrated that the α7nAChR agonist PNU-282987 ameliorated CLP-induced AKI by activating Treg cells. While the immunosuppressive function of Treg cells is beneficial in mitigating inflammatory injury, excessive immunosuppression in infections such as sepsis may impair the ability of the host to clear pathogens (217). A study has indicated that fish oil emulsion alleviates kidney damage under septic conditions by reversing elevated Treg cell expression and downregulating inflammatory mediators (218). Future research should focus on developing strategies to precisely modulate Treg cell activity, potentially enhancing Treg cell recruitment to renal tissues while avoiding systemic immunosuppression.

In sepsis, lymphocyte dysfunction occurs not only in peripheral blood cells but also in target organs (219). T cell priming is regulated by a balance of positive and negative co-stimulatory molecules, with imbalances in these molecules (also known as immune checkpoint molecules) being closely linked to immune dysfunction (220). A common feature of sepsis-associated immunosuppression is impaired lymphocyte function and increased expression of inhibitory checkpoint molecules such as PD-1. Activation of the PD-1/PD-L1 pathway by lactate can induce immunosuppression by promoting lymphocyte apoptosis in SA-AKI. Blocking the lactate receptor or PD-1/PD-L1 can restore lymphocyte function and alleviate kidney damage (221). Additionally, MSCs can restore the balance between Th17 and Treg cells via the galectin-9/T-cell immunoglobulin and mucin domain-containing molecule-3 pathway, reduce inflammatory cell infiltration and reestablish the equilibrium between pro-inflammatory and anti-inflammatory responses, thus improving SA-AKI (222). Dysregulation of T cells can also lead to the abnormal release of immunomodulatory molecules, such as excessive inflammatory cytokines, exacerbating tissue inflammatory injury. In this context, glutamine has been shown to alleviate SA-AKI by balancing T cell polarization and reducing T cell apoptosis (223). Given the imbalance in T cell subsets in patients with SA-AKI, future therapeutic strategies should aim to selectively expand protective T lymphocyte subsets or suppress damaging T cell subsets.

Several potential therapeutic targets related to T cells in SA-AKI have been identified. In addition to α7nAChR agonists, MSCs and anti-PD-L1 antibodies, recombinant human soluble thrombomodulin (rTM), a single-transmembrane, multi-domain glycoprotein receptor for thrombin, has emerged as a promising candidate (224). rTM not only reduces the upregulation of pro-inflammatory cytokines and chemoattractants induced by LPS, thereby decreasing leukocyte infiltration into the kidneys, but also mitigates kidney damage by reducing the accumulation of $CD4^+$ T cells, $CD11c^+$ cells and $F4/80^+$ cells in SA-AKI. This effect is mediated through enhanced phosphorylation of c-Jun, which diminishes cytokine production and apoptosis signaling (224). Additionally, CD28 plays a role in regulating TNF-α and IL-10 homeostasis, influencing the expression of chemoattractants. Through the CD28 pathway, T cells modulate renal function during sepsis (225).

In addition to therapeutic targets, certain T cell-related biomarkers may serve as predictors for SA-AKI. Ma *et al* (226) demonstrated that T cell knock-out mice exhibit reduced inflammatory cytokine secretion in renal tissue after LPS injection and that T cell suppression alleviates sepsis-induced inflammation and kidney damage. Therefore, T cell hyperactivation or upregulation could serve as a biomarker for worsening SA-AKI, and therapies targeting T cells or blocking receptors for inflammatory cytokine secretion may offer benefits in treating SA-AKI (226). Elevated plasma levels of IL-10 and soluble CD25 (a marker of Treg cells) in patients with SA-AKI may also serve as novel biomarkers (227). Moreover, ATP content in $CD4^+$ T cells (ATP_CD4) has been shown to correlate with survival in sepsis patients. Low ATP_CD4 levels at 48 h post-onset may indicate a higher likelihood of complete renal recovery, making it a potential prognostic indicator (228).

Future research should focus on elucidating the mechanisms of T cells in SA-AKI, including interactions among different subsets and signaling pathways. Integrating the regulation of immune checkpoint molecules, MSCs application, exploration of potential therapeutic targets and the development of biomarkers will contribute to the formulation of comprehensive treatment strategies to improve the prognosis of patients with SA-AKI.

9. Potential persistent adverse effects following treatment

Although treatment for SA-AKI significantly alleviates the complex inflammatory response within the kidney, the potential for persistent adverse effects following treatment warrants attention. Even after the acute phase of AKI resolves, renal injury may result in permanent nephron loss or maladaptive repair, ultimately leading to CKD or accelerating the progression of pre-existing CKD (229). Furthermore, sepsis-induced immunosuppression represents a prolonged and complex state of immune dysfunction. Even after the acute inflammatory response is controlled, the immune system may remain dysregulated, increasing the risk of subsequent infections and abnormal responses during tissue healing (16). Additionally, sepsis often involves multiple organs, leading to intricate organ-organ interactions (230). AKI can modulate the function of other vital organs through inter-organ crosstalk. TNF-α and IL-1, key mediators of renal injury, also play central roles in the pathophysiology of cardiac dysfunction during sepsis (231). During SA-AKI, renal injury not only triggers immune responses in lung tissue, including monocyte, neutrophil and $CD8^+$ T cell infiltration, but also increases inflammatory cytokine production and activates immune cells that impair intestinal barrier function and increase permeability. Intestinal hyperpermeability is a common factor exacerbating renal failure (232). These complex interactions suggest that dysfunction in organs beyond the kidney may persist or worsen, adversely impacting renal recovery. Therefore, the therapeutic strategy for SA-AKI should focus not only on mitigating renal inflammation but

also on addressing the potential for long-term adverse effects following treatment.

10. Conclusion

The present review systematically summarized the mechanisms of various immune cells in SA-AKI and discussed potential therapeutic strategies, encompassing both innate and adaptive immunity and introducing innovative approaches such as nanotechnology and cell therapy. However, several limitations remain. First, some mechanistic studies cited in the present review are based on non-septic AKI models (such as cisplatin-induced or ischemia-reperfusion injury), which, while simulating certain pathological features of kidney injury, differ significantly from the immune microenvironment of patients with sepsis. Sepsis-specific phenomena, such as immunoparalysis and endotoxin tolerance, are difficult to replicate fully in these models, limiting the direct applicability of their findings to SA-AKI. Second, the roles of certain immune cells (such as mast cells and ILCs) in SA-AKI are still discussed primarily through inference or indirect evidence, particularly concerning their specific functions in sepsis. Further experimental validation using sepsis-specific models is necessary to confirm these roles. Finally, while the present review has introduced various novel therapeutic strategies based on nanotechnology and cell therapy, the application of these strategies in treating SA-AKI remains challenging. Most nanomaterials lack clinical evaluations for long-term safety and biocompatibility. Although some animal studies have shown positive results, the human immune system's response to nanomaterials may differ. Additionally, targeted therapies for the kidneys require further research. The stability of the preparation process and quality control in the clinical translation of nanomaterials are also key factors affecting long-term safety. Therefore, long-term safety testing and large-scale clinical studies are needed to ensure the sustainability and reliability of these treatments. In conclusion, future research should focus on the development and application of sepsis-specific animal models, enhance spatiotemporal analysis of the dynamic functions of immune cells and promote the translation of basic research into clinical applications, ultimately providing a more reliable foundation for precision immunotherapy in SA-AKI.

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Authors' contributions

LX, WJ, JY and RZ wrote the main manuscript text. LS and JW modified the details of the manuscript. Data authentication is not applicable. All of the authors read and approved the final version of the manuscript.

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Competing interests

The authors declare that they have no competing interests.

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