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Molecular mechanisms and therapeutic interventions in acute kidney injury: a literature review

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Abstract

Acute kidney injury (AKI) is a clinical challenge characterized by elevated morbidity and a substantial impact on individual health and socioeconomic factors. A comprehensive examination of the molecular pathways behind AKI is essential for its prevention and management. In recent years, vigorous research in the domain of AKI has concentrated on pathophysiological characteristics, early identification, and therapeutic approaches across many aetiologies and highlighted the principal themes of oxidative stress, inflammatory response, apoptosis, necrosis, and immunological response. This review comprehensively reviewed the molecular mechanisms underlying AKI, including oxidative stress, inflammatory pathways, immune cell-mediated injury, activation of the renin-angiotensin-aldosterone (RAAS) system, mitochondrial damage and autophagy, apoptosis, necrosis, etc. Inflammatory pathways are involved in the injuries in all four structural components of the kidney. We also summarized therapeutic techniques and pharmacological agents associated with the aforementioned molecular pathways. This work aims to clarify the molecular mechanisms of AKI thoroughly, offer novel insights for further investigations of AKI, and facilitate the formulation of efficient therapeutic methods to avert the progression of AKI.

Keywords Acute kidney injury, Molecular mechanisms, Therapeutic interventions, Complement, Oxidative stress, Inflammation

Introduction

Acute kidney injury (AKI) refers to the sudden damage to the renal parenchyma or sharp decline in kidney function, resulting from a range of factors with diverse underlying mechanisms. AKI can be broadly categorized into pre-renal AKI, which is centered on decreased glomerular filtration rate (GFR) due to decreased renal perfusion, and post-renal AKI, which is centered on urinary tract obstruction. The rest are renal AKI in which the structures of the nephron, such as glomeruli, tubules, vasculature, and renal tubules are affected (Table 1) [1]. AKI is a heavy health burden worldwide, with a global incidence of approximately 21.6% and 33.7% in adults and children, respectively, and an overall mortality rate of 23.9% and 13.8% in adults and children in 2013 [2]. AKI is significantly associated with in-hospital adverse events and progression to chronic kidney disease (CKD) and greatly increases the risk of long-term morbidity and mortality [3–5].

Although the clinical significance of AKI is widely recognized, there is still a lack of specific therapeutic options

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Table 1 Types of AKI

Type	Causes	Pathophysiology and conditions
Pre-renal AKI	Decreased systemic tissue perfusion	Reduced circulating blood volume: vomiting, diarrhea, diuretic use, sepsis, anaphylaxis, etc.
		Reduced cardiac output: cardiac failure, etc.
		Systemic vasodilatation: septic shock, advanced liver disease, etc.
	Selective reduction of renal blood flow	Drugs that affect glomerular blood flow.
		Renal arterial obstruction: renal artery thrombosis, renal artery stenosis, etc.
Intra-renal AKI	Glomeruli	Deposition of immune complexes and immune-mediated systemic diseases such as systemic lupus erythematosus, granulomatous polyangiitis, etc.
	Tubules	Nephrotoxic drugs such as aminoglycosides, cisplatin, heavy metals (e.g., lead and mercury), solvents (e.g., ethylene glycol), contrast-induced ATN, ischaemic ATN, etc.
	Vascular structure	Renal vein thrombosis, renal artery stenosis, etc.
	Interstitium	Drug-induced AIN such as NSAIDs and penicillin, microbial infections such as Legionella or Streptococcus spp.
Post-renal AKI	Urinary tract obstruction	Kidney stones, prostatic hyperplasia, prostate cancer, etc.

Note AKI: acute kidney injury, ATN: acute tubular necrosis, AIN: acute interstitial nephritis

for AKI so far. Diverse molecular mechanisms have been reported to contribute to the parenchymal damage of kidneys in AKI, including complement activation [6], oxidative stress [7], and inflammation [7, 8]. Delving into these molecular mechanisms underlying the pathological processes of AKI is an important approach to identify specific biomarkers and potential therapeutic targets.

Here in this review, we summarized the molecular mechanisms and corresponding interventions of AKI in the literature, aiming to comprehensively and thoroughly understand the pathogenic molecular mechanisms of AKI and to provide assistance for future research on specific prevention and treatment strategies for AKI. For ease of description, the molecular mechanisms are summarized based on the four main components of the kidney, the glomeruli, tubules, vasculature, and interstitium. Interventions for individual mechanisms are also presented.

Underlying molecular mechanisms of glomerular injury in AKI

Immune complex deposition

Glomeruli are susceptible to commonly affected by injury caused by deposition of immune complexes in systemic immune and autoimmune disorders [9, 10]. Deposited immune complexes stimulate circulating immune cells, which subsequently release cytokines and vasoactive substances, creating a pro-inflammatory milieu after the deposition of immune complexes [11]. In IgA nephropathy, stimulatory circulating immune complexes containing galactose-deficient Immunoglobulin A1 induced the production of transforming growth factor-beta (TGF-β), which stimulated the production of extracellular matrix (ECM) proteins and promoted the synthesis of laminin, leading to the proliferation of mesangial cells [12].

Immune complexes activate complement via the classical pathway and have been reported in various types of glomerulonephritis [13], leading to damage to glomerular capillary walls, glomerular basement membrane, and other structures and inflammatory cell recruitment [14]. Complement Component 3a (C3a) and Complement Component 5a (C5a) formed by complement activation have potent proinflammatory functions and create the membrane attack complex (MAC) that can induce cell activation or lysis [15]. Activation of the complement system forms the C5a-C5a receptor1 axis to promote podocyte injury and disrupt the glomerular filtration barrier by enhancing Dynamin-related protein 1-mediated mitochondrial fission [16].

Activation of renin-angiotensin-aldosterone system (RAAS)

Reduced renal blood flow, particularly in the presence of pre-renal AKI, results in a diminished GFR, prompting para-glomerular cells to secrete increased amounts of renin, activating the RAAS system. Prolonged activation of the RAAS results in renal hypoxia, vasoconstriction, glomerulosclerosis, and glomerular interstitial fibrosis [17]. Angiotensin II (AngII) induces glomerulosclerosis through the upregulation of TGF-β in rat renal cells, leading to enhanced production of ECM proteins [18]. AngII has also been shown to enhance the expression of toll-like receptor 4 (TLR4), which in turn activates nuclear factor-kappa B (NF-κB) in mesangial cells, amplifying the inflammatory response [19]. Moreover, hyperactivation of RAAS promotes oxidative stress to exacerbate kidney damage [20]. Research indicates that angiotensin-converting enzyme inhibitors and AngII receptor blockers are associated with improved survival outcomes in AKI, although they may also contribute to a heightened likelihood of complications, including acute renal failure and hyperkalemia [21]. Spironolactone, another RAAS system inhibitor, antagonizes aldosterone receptors but poses a danger of hyperkalemia [22]. However, it was reported that spironolactone treatment after 24 h of ischemic injury leading to AKI can improve renal inflammation and mitigate the progression from AKI to CKD [23].

Underlying molecular mechanisms of renal tubular injury in AKI

Activation of the complement system

The proximal tubules are the primary location of damage during renal ischemia-reperfusion injury (IRI), and complement activation on ischemic renal tubules significantly contributes to ischemic AKI [24]. Complement activation is mediated via three distinct pathways: the classical, lectin, and alternative pathways. Although these three pathways have different initiation mechanisms, they ultimately converge on C3 cleavage, leading to the activation of C3 and C5 and forming MAC, which induces cell activation or cleavage [15]. Data on complement mechanisms in AKI are mainly from animal models. The lectin complement pathway is activated in the renal tubules of mice with AKI in rhabdomyolysis, probably through an aberrant pattern of fucosyltransferase 2-dependent cytosolic fucosylation, recognized by the pattern-recognition molecule collectin-11 and in a C4-independent bypass manner [25]. Stimulation of TGF-β1 production in cultured mouse renal tubular cells after complement activation by C3a and C5a binding to C5a receptor and C3a receptor, and stimulation of proximal tubular epithelial cells by MAC leading to increased expression of type IV collagen mediate renal fibrosis resulting in the transition from AKI to CKD [26]. Furthermore, C3a mediates podocyte injury through TLR4/NF-κB-P65 signaling during IRI-AKI and post-injury fibrosis [27]. Ongoing complement-inhibiting drugs are currently used to treat a variety of kidney diseases causing AKI and exhibit promising efficacy (Table 2).

Table 2 Complement therapeutics for adult kidney diseases

Name	Target	Disease	Status	NCT
Eculizumab	C5	anti-GBM	Phase 2	NCT06513338
		ANCA-Associated Vasculitis	Phase 2	NCT01275287
		MPGN	Phase 2	NCT02093533
CCX168 (Avacopan)	C5a receptor	ANCA-Associated Vasculitis	Phase 3	NCT02994927
		IgAN	Phase 2	NCT06676579
AMY-101	C3	Complement Mediated Diseases	Phase 1	NCT03316521
Pegcetacoplan	C3	C3G or IC-MPGN	Phase 3	NCT05809531
LNP023	C3a receptor	IgAN	Phase 2	NCT03373461

Note: C5: Complement Component 5, C5a: Complement Component 5a, anti-GBM: anti-glomerular basement membrane, ANCA: anti-neutrophil cytoplasmic autoantibodies, MPGN: membranoproliferative glomerulonephritis, IgAN: IgA nephropathy, C1: Complement Component 1, C3: Complement Component 3, C3G: C3 glomerulopathy, IC-MPGN: immune-complex membranoproliferative glomerulonephritis, C3a: Complement Component 3a

Mitochondrial impairment and autophagy pathway

Mitochondria serves as a principal source of cellular energy, with the proximal tubule being the primary locus of mitochondrial failure in AKI [28]. Mitochondrial damage seems to occur prior to the clinical manifestations of AKI following the onset of injury [29]. Electron microscopy revealed mitochondrial swelling, accompanied by minimal acute renal function impairment within 60 min of occluding a renal vessel [30]. Mitochondrial injury results in elevated reactive oxygen species (ROS), which subsequently exacerbates mitochondrial damage [31]. To reduce harm, the body activates mitochondrial autophagy to remove surplus or impaired mitochondria [32]. Augmented mitochondrial autophagy facilitates cell survival initially, while excessive activation of mitochondrial autophagy results in cell death and tissue injury [33]. Research indicates that the mitochondria-targeted antioxidant 10-(6'-plastoquinonyl) decylrhodamine 19 enhances renal blood flow and protects endothelial cells following renal ischemia-reperfusion [34].

Oxidative stress

The kidney utilizes substantial quantities of oxygen to provide energy for tubular reabsorption; consequently, renal tubules are particularly vulnerable to ischemia and hypoxic damage [35]. Ischemia and hypoxia in renal tubular cells elevate endogenous free radical production and disrupt mitochondrial oxidative phosphorylation, resulting in excessive ROS, while minimal ROS and free radicals can confer advantages to biological systems, their surplus induces oxidative stress, inflicting damage on various cellular structures, including membranes, proteins, lipids, and DNA [36, 37]. The oxidative stress processes of AKI primarily encompass ROS production, nitric oxide depletion, damage-associated molecular patterns (DAMPs) formation, toll-like receptors (TLRs) activation, autophagy, and microvascular dysfunction [38]. In IRI, DAMPs released from necrotic renal tubular cells activate TLRs on renal cells, initiating a cascade in inhibitor of NF-κB, resulting in its release and facilitating the nuclear translocation of NF-κB, within the nucleus, NF-κB drives the expression of inflammatory cytokines, oxidative bursts, and inflammatory responses, thereby exacerbating the injury process [39]. Prolonged exposure to oxidative stress stimuli in kidney tissue results in an initial inflammatory phase, subsequently leading to the excessive production of fibrous tissue, which compromises organ function and may result in CKD [40].

Antioxidant treatment shows promising results in AKI (Table 3). N-acetylcysteine (NAC) helps to mitigate contrast-induced AKI (CI-AKI), while Au NCs-NAC (ultrasmall gold nanoclusters measuring 1–2 nm, capped with NAC) exhibit significantly enhanced therapeutic efficacy compared to NAC alone [41, 42]. Vitamin C sequesters

Table 3 Antioxidants for the treatment of AKI and the corresponding mechanisms

Antioxidants	Mechanisms
SkQR1 [34]	Protection of mitochondria
NAC [41]	Reduction of CI-AKI
Vitamin C [43]	Capturing RNS and ROS
Vitamin E [44]	Reducing the incidence of CI-AKI in CKD patients
Lipoic acid [45]	Inhibit oxidative stress and inflammatory response
Coenzyme Q10 [46]	Antiperoxidant, anti-apoptotic, and anti-inflammatory protection

Note: SkQR1:10-(6'-plastoquinonyl) decylrhodamine 19, NAC: N-acetylcysteine, RNS: Reactive nitrogen species, ROS: Reactive oxygen species, AKI: Acute kidney injury, CKD: Chronic kidney disease, CI-AKI: Contrast-associated acute kidney injury

Table 4 Ongoing antioxidants

Name	Disease	Status	NCT
Allopurinol and Trimetazidine	CI-AKI	Phase 4	NCT05540184
Melatonin	Antibiotic-associated AKI	Phase 3	NCT05084196
Nitric Oxide	AKI in acute-type aortic dissection patients	Phase 4	NCT06622291
Pentoxifylline	AKI	Phase 2 Phase 3	NCT02951299
Alprostadil, Sodium Ferulate and Dopamine	Pediatric AKI	Phase 4	NCT03892447

Note: AKI: acute kidney injury, CI-AKI: Contrast-associated acute kidney injury

reactive nitrogen species and ROS and replenishes endogenous glutathione levels, establishing its role as a vital antioxidant [43]. Preventive oral vitamin E in conjunction with a 0.9% saline infusion has been demonstrated to diminish the occurrence of CI-AKI in patients with CKD undergoing elective coronary angiography, as opposed to saline alone [44]. Lipoic acid decreases signs of oxidative stress and inflammatory response and has a preventative effect on the course of severe AKI [45]. Coenzyme Q10 possesses anti-peroxidative, anti-apoptotic, and anti-inflammatory properties and offers renoprotection after AKI [46]. Alongside topical treatments, the body possesses endogenous antioxidant systems that can alleviate damage from oxidative stress [47]. The clinical trials of antioxidants are currently being conducted vigorously and demonstrate favorable therapeutic outcomes (Table 4).

Inflammatory pathways

Damaged cells and immune cells release various cytokines (e.g., tumor necrosis factor (TNF), interleukin (IL)) and chemokines that attract neutrophils and macrophages from the bloodstream to the damaged site [48, 49]. Numerous studies indicate that pro-inflammatory cytokines and chemokines rely on NF-κB, binding to specific DNA regulatory elements, and triggering the expression of various inflammatory genes [50]. Tacrolimus can reduce the nuclear translocation of NF-κB, while glucocorticoids suppress the DNA-binding function of NF-κB [51]. In addition, glucocorticoids may be an effective therapeutic approach for septic AKI by mitigating mitochondrial damage, apoptosis, and anti-inflammatory [52].

Other inflammatory pathways are also involved in tubular injury in AKI. Research has demonstrated that NOD-like receptor family, pyrin domain containing 3 (NLRP3) inflammasome has an important role in CI-AKI models [53]. Remdesivir can suppress the activation of the NLRP3 inflammasome, therefore mitigating AKI [54]. TLR4 activates the NLRP3 inflammasome and the mitogen-activated protein kinases (MAPKs) phosphorylation inflammatory pathway, hence facilitating inflammatory reactions, inhibition of TLR4 confers a protective effect against sepsis-induced AKI in mice and represents a potential therapeutic approach for AKI [55, 56]. Furthermore, the thioredoxin-interacting protein facilitates the endoplasmic reticulum (ER) stress-mediated formation of the NLRP3 inflammasome complex and associates oxidative stress with the activation of the NLRP3 inflammasome, instigating mitochondria stress-induced apoptosis and promoting inflammatory cell death, thioredoxin-interacting protein may be a potential therapeutic target for AKI [57, 58].

The MAPK kinase signaling pathway activated by ROS from oxidative stress promotes the activation of activator protein-1, which regulates the modulation of pro-inflammatory cytokines and chemokines [59, 60]. Metformin mitigates inflammation, oxidative stress, and ER stress in renal tubular cells by activating 5' Adenosine monophosphate-activated Protein Kinase in preclinical AKI models [61]. Pioglitazone improved IRI-AKI by attenuating oxidative stress and NLRP3 inflammasome activation [62]. The inflammasome-IL-1α/IL-1β-IL-1Receptor system is a pivotal component of renal inflammation and its systemic repercussions, with anti-inflammatory treatment utilizing IL-1 receptor antagonists being a viable option [63, 64]. Mast cells cause AKI through the production of TNF, and the application of TNF blockers (e.g., infliximab) protects renal function [65, 66]. Anti-inflammatory drugs for the treatment of AKI are summarized in Table 5. The ongoing clinical trials of anti-inflammatory drugs are summarized in Table 6.

Endoplasmic reticulum (ER) stress

The ER serves as the principal location for protein synthesis and processing, lipid metabolism, and signal transduction in the cell [67]. The accumulation of newly synthesized unfolded proteins due to ischemia, hypoxia, and oxidative stress induces ER stress, if ER stress is

Table 5 Anti-inflammatory drugs for the treatment of AKI and the corresponding mechanisms

Anti-inflammatory drugs	Mechanisms
Tacrolimus [51]	Blockade nuclear translocation of the NF-κB subunit
Glucocorticoids [51, 52]	Inhibit the DNA-binding activity of NF-κB and reduce mitochondrial damage and apoptosis.
Remdesivir [54]	Inhibit the activation of the NLRP3 inflammasome
Metformin [61]	Inhibit inflammation, apoptosis, oxidative stress, ER stress
Pioglitazone [62]	Inhibit inflammation and oxidative stress
IL-1 receptor antagonists [63, 64]	Inhibit inflammasome-IL-1α/IL-1β-IL-1Receptor system
Infliximab [66]	Inhibit TNF

Note: NF-κB: Nuclear factor-kappa B, NLRP3: NOD-like receptor family, pyrin domain containing 3, ER: Endoplasmic reticulum, IL: Interleukin, TNF: Tumor necrosis factor

Table 6 Anti-inflammatory ongoing medicines

Name	Disease	Status	NCT
CXA-10	AKI (Nontraumatic)	Phase 1	NCT02127190
Ibuprofen	AKI after running in the heat	Phase 1	NCT06247462
TIN816	Septic AKI	Phase 2	NCT05996835
Pirfenidone	Septic AKI	Phase 4	NCT02530359
Curcumin	Colistin-induced Nephrotoxicity	Phase 3	NCT05613361
Dexamethasone	AKI after adult cardiac surgery	Phase 1	NCT06783634

Note: AKI: Acute kidney injury

severe or prolonged, it ultimately results in cellular apoptosis, protein degradation, and translational attenuation [68]. Overall, In AKI, mild to moderate ER stress confers a protective effect on the kidneys, but severe ER stress worsens AKI [69]. The toxicity of clinically significant nephrotoxic agents, such as cisplatin and gentamicin, is markedly diminished in cells preconditioned with ER stress inducers [70]. However, TUG891 activates the G protein-coupled receptor 120, mitigating ER stress and apoptosis in cisplatin-induced AKI, thereby preserving kidney integrity [71]. Furthermore, ER stress is closely related to autophagy, which has a protective effect on ER stress-induced renal cell apoptosis, rapamycin enhances autophagy activity by inhibiting the mammalian target of rapamycin complex 1 to protect renal cells from ER stress-induced apoptosis [72].

Apoptosis and necrosis pathways

Proximal tubular cells exhibit significant metabolic activity and are susceptible to hypoxia and ischemia, rendering them a frequent locus for apoptosis and necrosis in AKI [35]. AKI encompasses several forms of renal cell death, including apoptosis, necrosis, pyroptosis, apoptosis-like necrosis, and ferroptosis [73]. Exposure of renal tubular cells to cisplatin results in tubular cell damage and mortality [74]. Cellular apoptosis and necrosis depend on trauma severity. Apoptosis involves intrinsic and extrinsic pathways and their interactions. Stress triggers the intrinsic pathway, releasing cytochrome c via Bcl-2-associated X protein/Bcl-2 antagonist killer 1-induced mitochondrial permeabilization, which activates caspase-9 and caspase-3, initiating apoptosis, in contrast, the extrinsic pathway involves Fas ligands binding death receptors, activating caspase-8, which triggers caspase-3 and cleaves BH3-interacting domain death agonist (Bid) into truncated Bid, which translocates to mitochondria, amplifying the intrinsic pathway and apoptotic cascade [8]. Selective reduction of pro-apoptotic genes, including Bax and Bak, reduces renal tubular cell apoptosis and offers protection against ischemia AKI [75]. Modulating specific apoptotic pathways may be advantageous for renal protection, the apoptosis of myofibroblast populations aids in renal recovery following IRI-AKI [76]. Recent discoveries indicate that ferroptosis plays a significant role in AKI. Ferroptosis is an iron-dependent form of cell death marked by the depletion of membrane lipid peroxidation products and plasma membrane polyunsaturated fatty acids, distinguishing it from apoptosis and necrosis [77]. Inhibition of necrosis and ferroptosis has demonstrated beneficial effects in many models of AKI [78].

Autophagy pathways

The induction of autophagy in proximal tubules during acute tubulointerstitial nephritis demonstrated that autophagy serves a nephroprotective function in AKI, nevertheless, excessive autophagy ultimately results in cellular demise [79]. Fibroblast growth factor 10 (FGF10) has been demonstrated to mitigate renal IRI-AKI by preventing excessive autophagy [80]. Autophagy may significantly modulate the inflammatory response in AKI, making the autophagy-inflammation axis a promising therapeutic target for AKI [81].

Underlying molecular mechanisms of renal vascular injury in AKI

Vascular endothelial damage

Under typical circumstances, endothelial cells perform activities including anticoagulation, anti-inflammation, vascular tone modulation, and release of vasoactive cytokines [82]. Damage to endothelial cells results in heightened secretion of the vasoconstrictor endothelin and diminished secretion of the vasodilator nitric oxide, causing sustained renal vasoconstriction, impaired renal perfusion, and aggravated renal injury [83]. Research indicates that the endothelin system is upregulated in AKI patients, this upregulation can promote the

progression from AKI to CKD, and the use of selective antagonists of the endothelin-a receptor or non-dihydropyridine calcium channel blockers to block the endothelin system can protect the kidneys [84]. Meta-analyses indicate that the administration of inducible nitric oxide correlates with a diminished risk of AKI in individuals undergoing cardiac surgery, but it markedly elevates the risk of AKI in patients suffering from acute respiratory distress syndrome [85]. Furthermore, in the presence of ischemia and hypoxia, endothelial cells elevate the synthesis of ROS, and elevated levels of ROS inflict additional harm on endothelial cells [86].

Renal artery thrombosis and renal artery thromboembolism

Renal artery thromboembolism is a rare yet significant etiology of AKI, the formation of a thrombus in one or both arteries supplying blood to the kidneys results in diminished renal perfusion, potentially causing AKI [87]. Intact vascular endothelial cells possess anticoagulant properties; but upon activation due to endothelial injury, they facilitate renal artery thrombosis by initiating the blood coagulation cascade through the synthesis of procoagulant factors that enhance the generation and spread of thrombin [88]. Notably, renal artery thrombosis may arise as a secondary complication of coronavirus infection [89].

Vascular thinning

Vascular thinning denotes the diminishment of capillaries or a decrease in density, and the diminished density of renal microvessels may be a significant characteristic of the progression from AKI to CKD [90]. Contemporary therapies for vascular atrophy concentrate on protecting and rehabilitating the capillary network, numerous studies have suggested that the severity of AKI may be mitigated and the prognosis enhanced by facilitating neovascularization and protecting existing arteries [91].

Underling molecular mechanisms of renal interstitial injury in AKI

Immune cells-mediated damage

The renal interstitium houses the majority of the renal immune system, predominantly including dendritic cells, along with macrophages and fibroblasts [92]. Dendritic cells collect and deliver antigens to initiate adaptive immune responses [10]. Antigen-presenting cells, including dendritic cells and macrophages, convey antigens to naive T lymphocytes, triggering their activation and differentiation, CD4 + T helper cells are essential for coordinating immune responses by aiding B cells and activating cytotoxic CD8 + T cells, B lymphocytes mature into plasma cells, which generate antibodies that combat infections and facilitate their eradication [93]. B lymphocytes also secrete chemokines C-C motif-ligand 7 (CCL7), which recruit neutrophils and monocytes to the kidney during AKI [94]. Neutrophils contribute to inflammation by secreting cytokines, ROS, proteases, and other substances into renal tissue [95]. Macrophages are classified into type 1 and type 2, with M1 macrophages generating pro-inflammatory cytokines to promote inflammation, and M2 macrophages exhibit anti-inflammatory and pro-fibrotic properties [96]. Furthermore, interferon-γ, secreted by natural killer cells, activates M1 macrophages within renal tissue [97]. Various inflammatory cells release several inflammatory factors, infiltrate the renal interstitium, and aggravate renal injury [10].

Renal interstitial fibrosis

In AKI, renal interstitial cells generate significant quantities of inflammatory mediators, initiating sustained inflammatory responses that result in renal interstitial fibrosis and subsequently impair the recovery of kidney function [98]. Renal interstitial fibrosis is an irreversible phenomenon marked by the abnormal buildup of ECM, influenced by many cellular and molecular pathways [99]. During AKI, transitory Wnt-β-catenin signaling facilitates repair and regeneration, while persistent upregulation promotes renal fibrosis [100]. Snail 1-mediated partial transformation of epithelial cells into mesenchymal cells facilitates renal fibrosis in mice [101]. Additionally, AngII facilitates renal fibrosis by activating Janus kinases and MAPKs, promoting intracellular calcium influx via Ca^{2+} channels and enhancing the signaling pathways of TGF-β [102]. FGF23 is increased in individuals with AKI, and enhancement of FGF23 activates TGF-β and Wnt/β-catenin, promoting renal fibrosis and contributing to the transition from AKI to CKD [103, 104]. Research indicates that pirfenidone is a suitable choice for placebo-controlled trials in individuals with advanced CKD [105]. Subsequent investigations indicate that long-acting sustained-release pirfenidone did not enhance the clinical progression of septic AKI, however, it is safe and does not cause adverse effects [106].

The underlying molecular mechanisms in the four components of the kidney are summarized in Fig. 1. Inflammatory pathways are involved in the injuries in all four components. The reported mechanisms are not independent of each other, but rather interlinked with each other (Fig. 2).

Conclusions

AKI is a critical concern in nephrology, inflicting considerable harm on both physical and mental health, while its elevated incidence and fatality rates place a tremendous strain on the healthcare system. The clinical diagnosis of AKI relies on changes in serum creatinine levels and urine output, lacking definitive methodologies. It is imperative to investigate the molecular pathways to

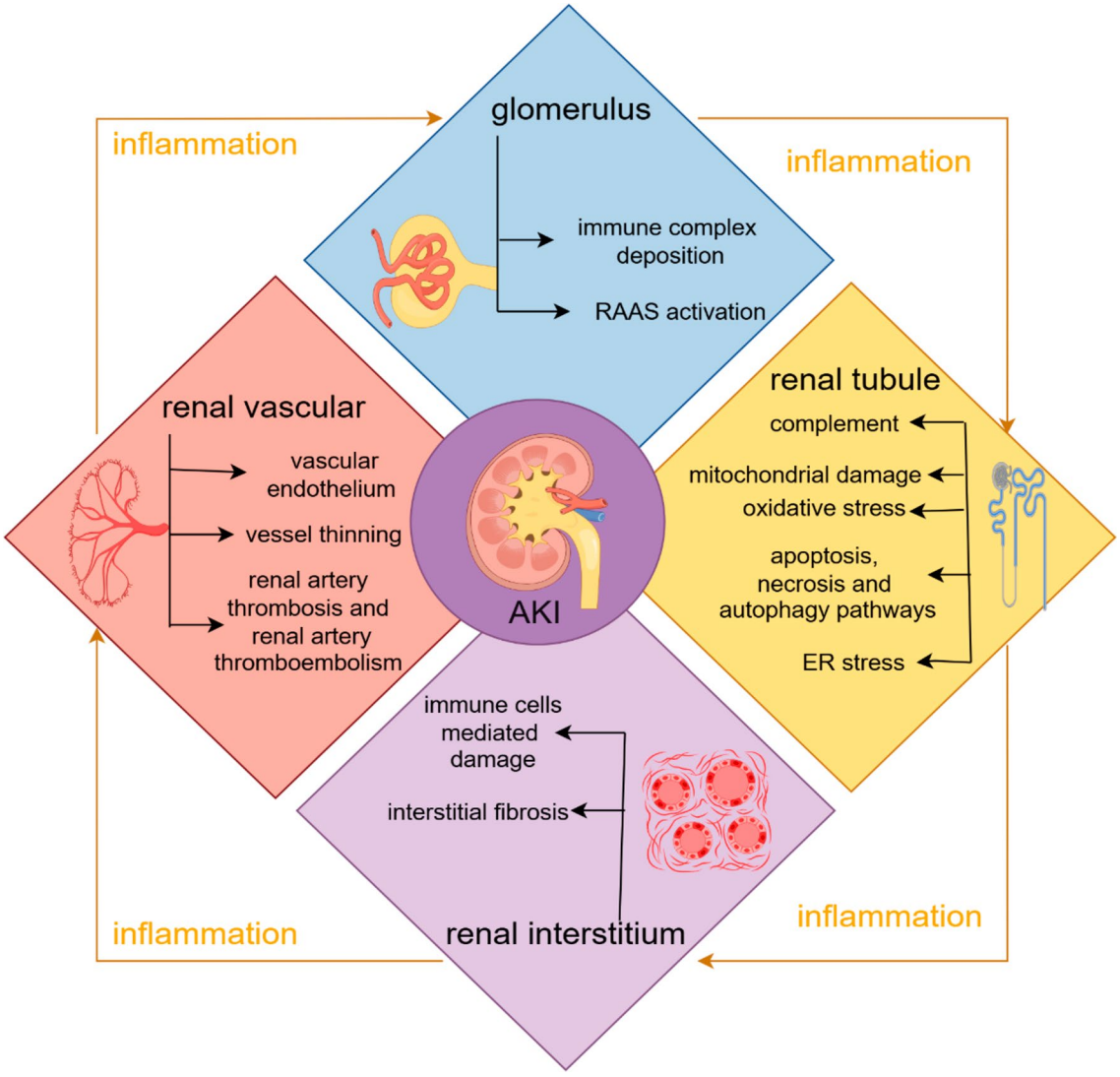

Fig. 1 Underlying molecular mechanisms of the pathogenesis of AKI (by Figdraw). Notes: Inflammatory pathways contribute to injuries in all four components of kidney. Abbreviations: RAAS: Renin-angiotensin-aldosterone system; ER: Endoplasmic reticulum; AKI: Acute kidney injury

create highly specific and readily observable diagnostic tools and to develop therapeutic agents targeting these mechanisms.

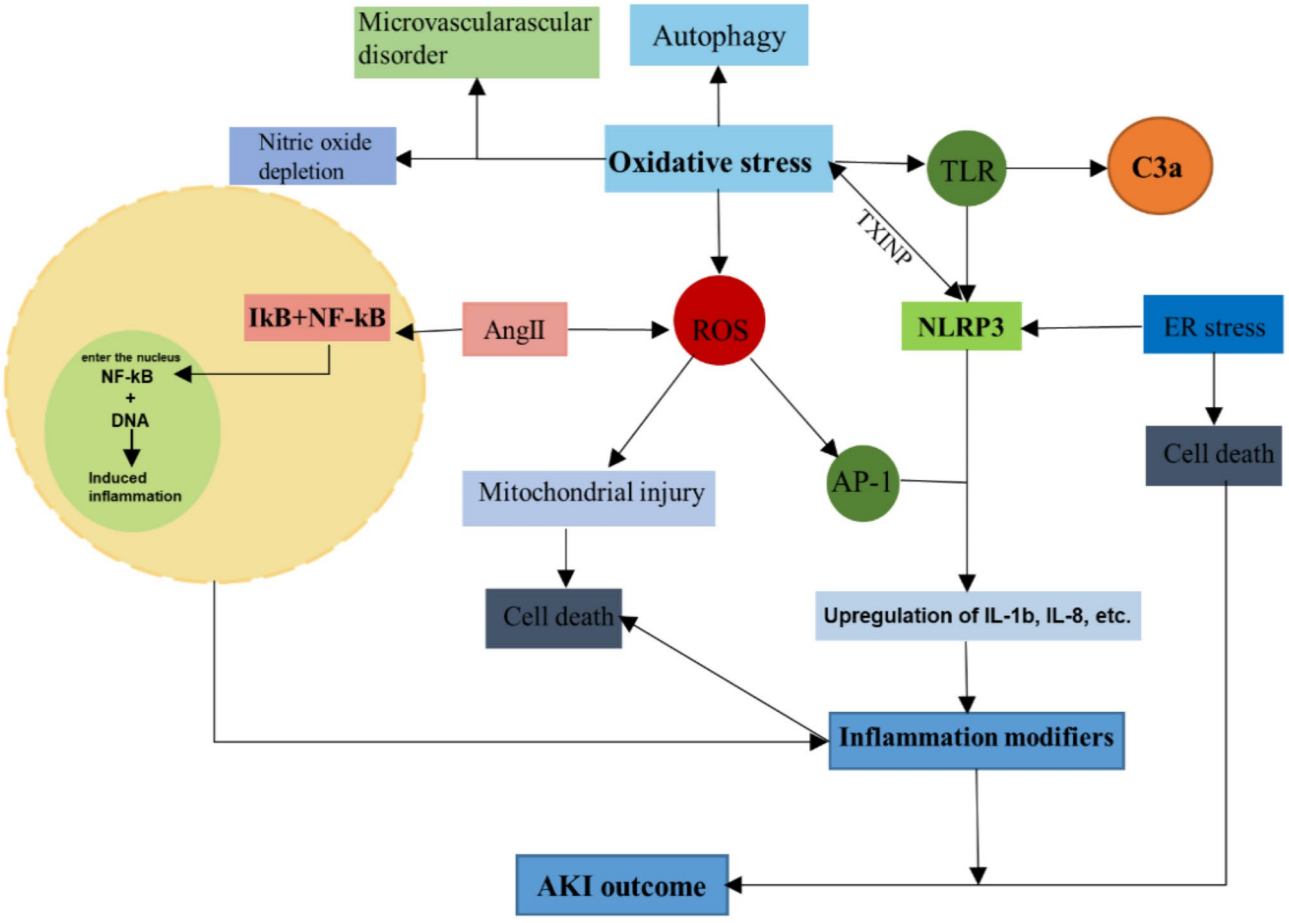

Fig. 2 Interlinkages among mechanisms underlying AKI. Abbreviations: ROS: Reactive oxygen species; AngII: Angiotensin II; NF-κB: Nuclear factor-kappa B; IκB: Inhibitor of NF-Kb; TLR: Toll-like receptor; TXNIP: Thioredoxin-interacting protein; IL: Interleukin; C3a: Complement Components 3a; NLRP3: NOD-like receptor family, Pyrin domain containing 3; ER: Endoplasmic reticulum; AP-1: Activator protein-1; AKI: Acute kidney injury

Abbreviations

AKI	Acute kidney injury
AngII	Angiotensin II
Bid	BH3-interacting domain death agonist
CCL7	Chemokines C-C motif-ligand 7
CI-AKI	Mitigate contrast-induced AKI
CKD	Chronic kidney disease
C3a	Complement Components 3a
C5a	Complement Components 5a
DAMPs	Damage-associated molecular patterns
ECM	Extracellular matrix
ER	Endoplasmic reticulum
FGF10	Fibroblast growth factor 10
GFR	Decreased glomerular filtration rate
IL	Interleukin
IRI	Ischemia-reperfusion injury
MAC	Membrane attack complex
MAPKs	Mitogen-activated protein kinases
NAC	N-acetylcysteine
NF-κB	Transcription factor-kappa B
NLRP3	NOD-like receptor family, pyrin domain containing 3
RAAS	Renin-angiotensin-aldosterone system
ROS	Reactive oxygen species
TGF-β	Transforming growth factor-β
TLR4	Toll-like receptor 4
TNF	Tumor necrosis factor

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JH did literature research, extracted the data, and drafted the manuscript. YF designed the research and reviewed the manuscript. All authors reviewed the manuscript. All authors read and approved the final manuscript.

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