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Review

Nanomedicine embraces the treatment and prevention of acute kidney injury to chronic kidney disease transition: evidence, challenges, and opportunities

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Abstract

Acute kidney injury (AKI), a common kidney disease in which renal function decreases rapidly due to various etiologic factors, is an important risk factor for chronic kidney disease (CKD). The pathogenesis of AKI leading to CKD is complex, and effective treatments are still lacking, which seriously affects the prognosis and quality of life of patients with kidney disease. Nanomedicine, a discipline at the intersection of medicine and nanotechnology, has emerged as a promising avenue for treating kidney diseases ranging from AKI to CKD. Increasing evidence has validated the therapeutic potential of nanomedicine in AKI; however, little attention has been paid to its effect on AKI for patients with CKD. In this review, we systematically emphasize the major pathophysiology of the AKI-to-CKD transition and summarize the treatment effects of nanomedicine on this transition. Furthermore, we discuss the key role of nanomedicine in the regulation of targeted drug delivery, inflammation, oxidative stress, ferroptosis, and apoptosis during the transition from AKI to CKD. Additionally, this review demonstrates that the integration of nanomedicine into nephrology offers unprecedented precision and efficacy in the management of conditions ranging from AKI to CKD, including the design and preparation of multifunctional nanocarriers to overcome biological barriers and deliver therapeutics specifically to renal cells. In summary, nanomedicine holds significant potential for revolutionizing the management of AKI-to-CKD transition, thereby providing a promising opportunity for the future treatment of kidney diseases.

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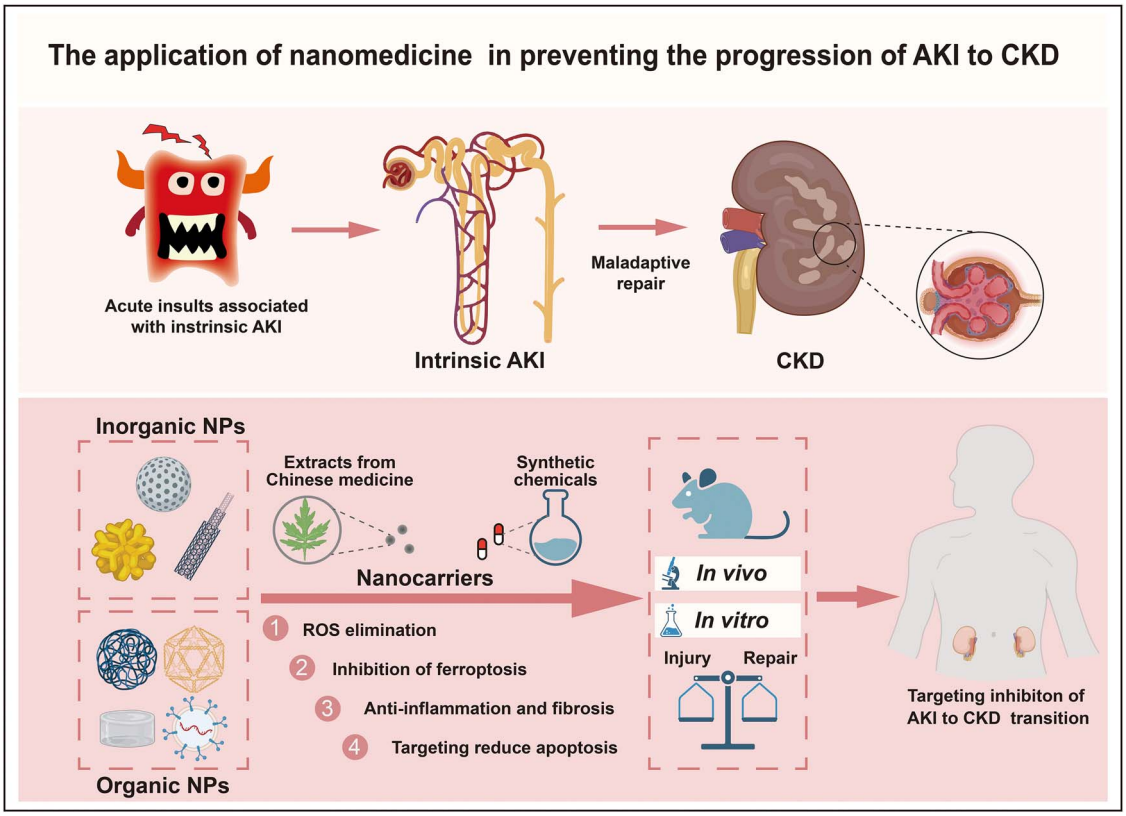
Graphical Abstract



Keywords: Nanomedicine; Acute kidney injury; Chronic kidney disease; Treatment

Highlights

- Maladaptive repair following AKI has been a longstanding challenge in the progression of CKD.
- We explored the mechanisms of nanomedicine for different pathological processes.
- This review is the first to shed light on the potential of targeted nanomaterials as therapeutic interventions against the AKI-to-CKD transition.
- Targeting nanotechnology currently offers new insights into potential therapeutic strategies.

Background

Acute kidney injury (AKI) is a common clinical kidney disease complication and has been considered a benign and reversible clinical syndrome, but recent clinical and experimental studies have indicated a close association between AKI and chronic kidney disease (CKD) [1]. During AKI, distinct pathological manifestations, including renal tubular epithelial cell injury, inflammatory cell infiltration, and impaired vascular function, can trigger intricate self-repair mechanisms in the kidney [2]. When maladaptive repair occurs, the proliferation and activation of fibroblasts within the renal interstitium, along with the deposition of extracellular matrix components, further increase the likelihood of progression to CKD [3].

According to etiological classification, the pathogenesis of AKI can be categorized into decreased renal perfusion, intrinsic renal disease, and urinary obstruction [4]. Diverse and complex etiologies lead to obvious obstacles in AKI treatment [5]. Conventional treatments often involve low efficiency and delayed diagnosis while primarily focusing on support management for patients with AKI. Strategies for halting or slowing down the transition to CKD are limited to traditional approaches. Therefore, novel approaches, including pharmaceuticals and technologies, that can provide precise, user-friendly, and highly efficient therapeutics for AKI-related CKD treatment are urgently required. Nanomedicine has recently emerged as a potential solution to address these issues and offers new therapeutic strategies for renal diseases [6–8].

Nanomedicine is a branch of medicine that involves the use of nanoparticles (NPs) for the diagnosis, monitoring, prevention, and treatment of diverse diseases. In nanomedicine, NPs have a profound impact on cellular interactions, transport mechanisms, biodistribution, and pharmacokinetics because of their distinctive physical and chemical attributes [9–11]. NPs possess various advantages and serve as therapeutic delivery carriers with enhanced efficacy and improved stability [12–14], thereby enabling precise and controlled release of various payloads, such as small molecule drugs, peptides, proteins, DNA, RNA, and their combinations, over an extended period of time [15]. Inspired by the benefits of NPs, the combination of nanomedicine with conventional treatments could slow down the progression of AKI to CKD.

In this review, we provide a comprehensive overview of the recent advancements in the transition from AKI to CKD.

In the first section, we present the critical biological mechanism of AKI-to-CKD transition, which can potentially inspire novel syntheses, engineering strategies, and applications in nanomedicine. Next, we briefly provide an overview of the engineered nanomaterials currently used for kidney diseases to inspire the novel design of nanomaterials for targeted therapeutic development. Subsequently, we summarize the applications of nanomedicine to address various pathogenic mechanisms for the treatment of AKI and prevention of its progression to CKD. In particular, we highlight the advantages of nanomedicine in promoting the efficacy of nanoscale treatments for theranostic applications. By enhancing our understanding of the intricate interactions between NPs and the kidney, we aim to propel the field of nanomedicine forward and expand its application in the management of renal diseases.

Review

Potential mechanisms of AKI-to-CKD transition

Despite comprehensive research efforts directed toward unraveling the mechanisms governing the transition from AKI to CKD, effective therapeutic strategies for preventing this progression have not yet been identified. One reason for this is that the pathogenesis of AKI is multifaceted, as each patient exhibits significant heterogeneity of underlying conditions. Therefore, we provide an overview of the current understanding of the mechanisms underlying AKI progression to CKD, as shown in Figure 1. The biological mechanisms underlying the AKI-to-CKD transition involve processes that can be effectively targeted by the unique capabilities of nanomedicines. Their ability to provide controlled, sustained release of drugs ensures consistent therapeutic levels, addressing the chronic nature of AKI progression. Additionally, the multifunctional nature of nanomedicines allows for target delivery of anti-inflammatory, antioxidant, and antifibrotic agents, tackling multiple pathways as described. These approaches hold the promise of improving outcomes for patients by providing more precise, effective, and safer treatments.

Reactive oxygen species and mitochondrial dysfunction

AKI is a common kidney disease caused by many factors, including ischemia–reperfusion injury (IRI), nephrotoxins, and sepsis, and is characterized by a reduction in renal blood flow [16]. Hypoperfusion is a well-known activator of renal damage via the production of reactive oxygen species (ROS), which includes the commonly observed free-radical superoxide anion, hydroxyl radical, and the non-radical oxidant hydrogen peroxide [17]. Normally, endogenous antioxidants are generated and counterbalance the overwhelming oxidant production to protect against mild or early stages of injury. However, severe injuries can enhance ROS production, induce cell death, and promote vascular dysfunction, inflammation, and cell cytotoxicity, which are typically observed during the transition from AKI to CKD [18]. Prolonged exposure to increased oxidative stress often results in chronic inflammation of the kidney microenvironment. This process results in a harmful cycle by activating the nuclear transcription factor κB, which mobilizes immune cell activation and recruitment. Therefore, inflammatory cytokines associated with oxidative stress promote pathological damage by inducing apoptosis and fibrosis, thus playing a vital role in CKD [19].

Mitochondria serve as essential regulators of ROS and the delicate balance of ROS regulation within the mitochondria is highly vulnerable to oxidative stress-induced impairment. One study innovatively employed a mitochondrial membrane-potential-dependent dye for intravital imaging using multi-photon microscopy, enabling the observation of mitochondrial structure, membrane potential, and functional changes within the proximal tubules *in vivo* [20]. The results demonstrated that depletion of ATP and changes in the structure of mitochondria, which lead to alterations and dysfunction of energy metabolism, are observed in the initial stage of AKI [20,21]. Other studies also confirmed the pivotal role of mitochondrial homeostasis as a mediator in the transition from AKI to CKD [22,23]. The deletion of genes that are aberrantly expressed when AKI occurs can alleviate progressive renal injury and fibrosis, and promote subsequent renal restoration [24,25].

p53 regulation

p53, which was originally identified as a well-known tumor suppressor, plays an important and paradoxical stress-dependent role in maintaining cell survival and promoting cell death. However, the discovery of novel functions of p53 that are important in the stress response and in maintaining cellular homeostasis promoted its use as an essential therapeutic target. How does p53 play a role in inducing proximal tubule injury? When AKI occurs, disruption of the cellular redox system leads to dramatically increased ROS levels in tumor endothelial cells (TECs). ROS can regulate p53 activity directly through redox modifications or indirectly by inducing signaling pathway responses to p53 activation. For example, ataxia telangiectasia mutated (ATM) and ATR (ATM and Rad3-related), which are oxidative stress-induced kinases, are activated in cisplatin (CP)-induced kidney injuries and subsequently contribute to the increased phosphorylation of p53 and TEC dysfunction [26]. Compared with their wild-type counterparts, p53 knockout mice are better protected from aristolochic acid-induced acute tubular injury and disease progression [27]. Furthermore, various severe and persistent stress stimuli, including hypoxia, DNA damage, inflammation, and nutrient stress, can activate p53 and play important roles in the progression of AKI to CKD. An experimental study demonstrated that G2/M cell cycle arrest triggers the upregulation of profibrogenic growth factors through the c-jun NH2-terminal kinase (JNK) signaling pathway in unilateral and severe IRI as well as in aristolochic acid-induced and unilateral ureteral obstruction (UUO) profibrotic AKI models. Treatment with a p53 or JNK inhibitor reversed G2/M cell cycle arrest and attenuated renal fibrosis [28]. Similarly, in TEC-specific p53 knockout AKI mice, renal injury, transforming growth factor β activation, and apoptosis were markedly improved compared to those in wild-type mice [29]. However, global p53 knockout mice develop more severe AKI than wild-type mice in response to IRI, likely because of increased inflammation, suggesting the importance of precise and targeted p53 knockout for further treatment [30].

Ferroptosis

Ferroptosis is a non-apoptotic regulated cell death process that manifests as an imbalance in the intracellular iron and

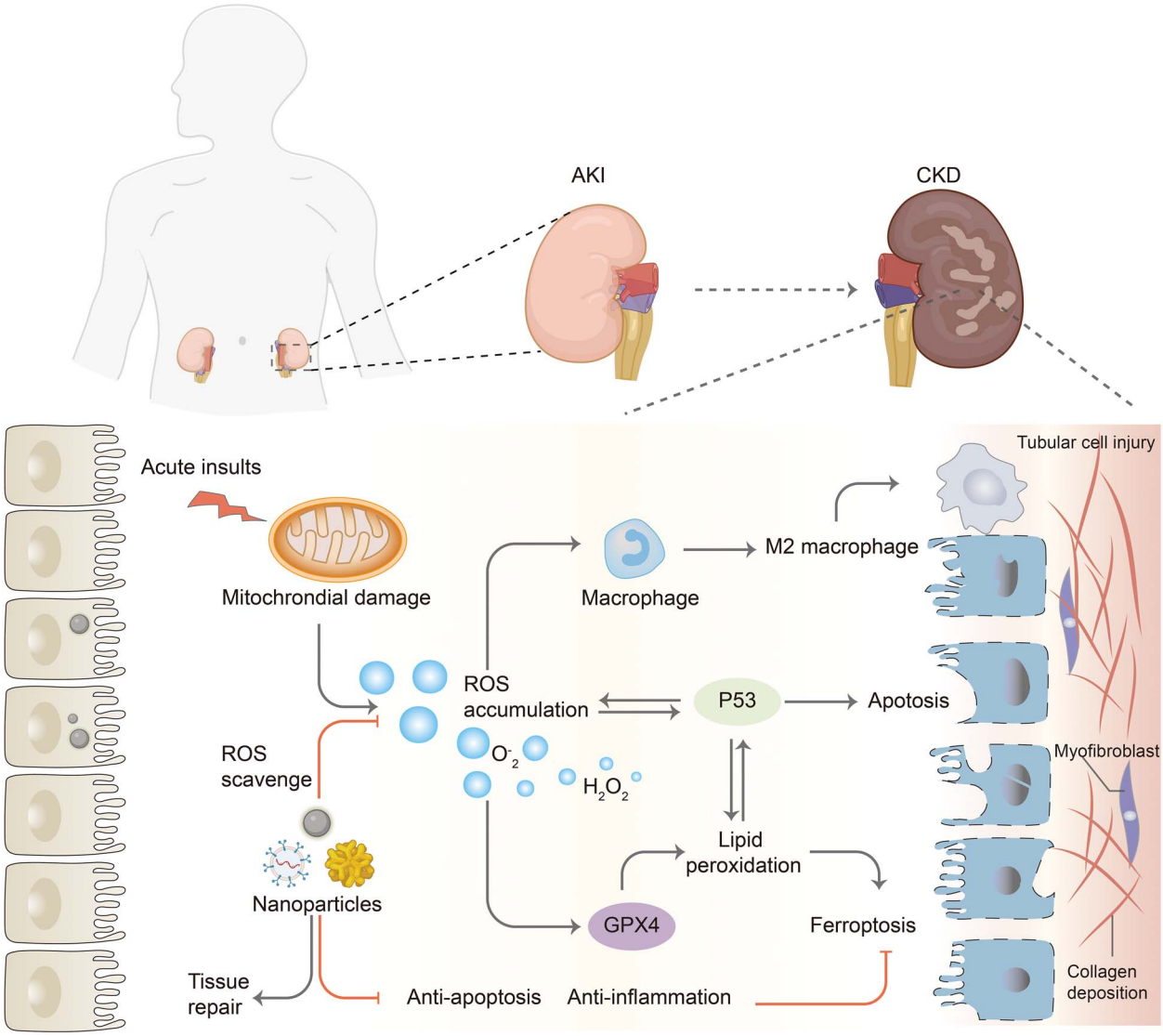


Figure 1. Potential mechanisms underlying AKI-to-CKD progression. Several mechanisms, including ROS accumulation, mitochondrial dysfunction, p53 activation, and lipid peroxidation damage, have been postulated to lead to maladaptive repair after AKI, potentially exacerbating the progression of CKD. These mechanisms can be independently induced by acute injury or interact synergistically to enhance their effects. These processes appear to involve the recruitment of tubular cells and macrophages, which also contribute to the secretion of profibrotic cytokines and pericyte transformation into myofibroblasts. Upon the application of NPs, tissue injuries can be repaired, and the progression from AKI to CKD can be halted through actions such as ROS scavenging as well as anti-apoptotic and anti-inflammatory pathways. *AKI* acute kidney injury, *CKD* chronic kidney disease, *ROS* reactive oxygen species, *NPs* nanoparticles

redox systems resulting from the overgeneration of toxic lipid-peroxidation products [31]. A recent study evidenced that ferroptosis is involved in the pathogenesis of AKI and its progression to CKD [32]. It regulates various metabolic processes involved at this stage, including inflammation, fibrosis, and cell death. The glutathione/glutathione peroxidase 4 (*Gpx4*) axis is the central defense pathway that prevents ferroptotic stress and ferroptosis. Researchers have used conditional knockout *Gpx4* mice after IRI and found that their kidneys not only exhibited severe tubular injury on Day 21, but also accumulated KIM^+KRT8^+ (damage-associated marker) tubular cells [33]. However, treatment with liproxstatin-1 (a ferroptosis inhibitor) prevents renal atrophy and reduces ferroptotic stress [34].

The regulatory mechanisms of ferroptosis are not independent; they are intricately associated with mitochondrial dysfunction in both AKI and CKD [35]. Mitochondria are central sites for intracellular iron metabolism and contain enzymes that play essential roles in redox reactions, ATP generation, DNA synthesis, and various cellular processes [36]. The accumulation of free iron in cells impairs mitochondrial biogenesis, resulting in further mitochondrial dysfunction. Disrupted energy metabolism results in ROS accumulation and decreased ATP production, which exacerbates ferroptosis and cell death [37,38]. Therefore, targeting the reduction of ferroptosis may serve as a novel direction for investigating the AKI-to-CKD transition.

Extracellular vesicle contents

Extracellular vesicles (EVs) are diverse membranous vesicles released by cells into the external environment that play important roles in intercellular communication and

regulation of physiological processes [39,40]. They are important mediators of the spread of pathological cargo from dysfunctional cells during AKI. Previous investigations evidenced that EVs derived from dysfunctional cells contain various pathological factors that produce an ideal microenvironment for inflammation and hyperimmunity. TEC-derived EVs containing increased microRNA-19b-3p mediate communication between macrophages and TECs, promoting M1 macrophage activation and tubulointerstitial inflammation in a lipopolysaccharide-induced AKI mouse model [41]. During AKI development, injured glomerular endothelial cell-derived EVs can induce neutrophil infiltration and inflammatory responses [42] and promote renal fibrosis through microRNA-150-containing EVs [43]. EV microRNA-21 (miR-21) from TECs also accelerated the development of kidney fibrosis by activating fibroblasts through the miR-21/phosphatase and tensin homolog (PTEN)/Akt pathway in a UUO mouse model [44]. Furthermore, EVs can be used as diagnostic markers because they contain cargo derived from the parental cells, mirroring the pathophysiological status of AKI [45]. Urinary exosomal activating transcription factor 3 was increased in patients with AKI even before serum creatinine was assessed, evidencing the potential of exosome-excreted activating transcription factor 3 as an early-stage biomarker for AKI [46]. These studies support the role of EVs in inflammation and fibrosis, two prominent pathological pathways involved in both AKI and the transition from AKI to CKD.

Nanoparticle classification

In recent years, nanotechnology has been extensively applied in nanomedicine because it addresses several issues associated with conventional therapeutic agents in the medical field [47–49]. NPs are versatile materials with diameters <100 nm that are classified into zero-dimensional (0D), 1D, 2D, and 3D structures [50]. While early-stage NPs were mostly composed of unmodified natural materials, engineered NPs have recently undergone various revolutionary developments and can be designed and produced with complex architectures, targeting capabilities, and controlled release systems to maximize efficacy and safety [51]. For example, photoacoustic/Raman-based nanoprobes can provide highly sensitive real-time intraoperative differentiation for photoacoustic imaging and theragnostics [52]. Moreover, a glucose nanosensor based on hydrogels and Ag-NPs was designed to detect the glucose concentration in the urine of diabetic patients [53]. Given the special role of the kidney in the filtration and absorption of drugs, an increasing number of studies have focused on the application of nanomedicine for the treatment of nephrological diseases. In this section, we summarize the properties and characteristics of NPs, which may lead to the development of innovative precision therapies comprising renal-protective materials for the prevention of AKI-to-CKD transition (Figure 2).

Polymeric NPs

Polymeric NPs are particles within the size range 1–1000 nm that are composed of natural or synthetic materials and appear in two forms, nanocapsules and nanospheres, distinguished by their morphological structures [54]. Depending on the desired properties and requirements of the NPs for a particular application, different methods can be employed for their synthesis, such as solvent evaporation [55], emulsification [56], and nanoprecipitation [57]. The unique properties and features of polymeric NPs, including biocompatibility, biodegradability, and nontoxicity, allow them to be used in a broad spectrum of applications. They are used as drug carriers in biomedical imaging, for biomarker detection, in disease treatment, and in other medical fields. Chitosan, a common natural polymer, is widely used as the shell material for polymeric nanocapsules. Unlike polyethylene glycol (PEG) and polyvinyl alcohol, chitosan is biodegradable, biocompatible, mucoadhesive, and has been widely used as a drug carrier. Additionally, NPs covered with chitosan can be modified using functional (amino) groups and surface cations. A positive charge can improve the interaction between NPs and the negatively charged glomerular capillary wall [58], allowing NPs to pass through the glomerular charge barrier more easily.

Compared to natural polymers, synthesized materials have demonstrated significant advantages in terms of quality and purity. These materials can be tailored to meet different pharmaceutical requirements, and possess various chemical, ionic, mechanical, solubility, and degradability properties [59]. The most commonly used synthesized materials include poly(lactic-co-glycolic acid) (PLGA), poly(ε-caprolactone), PEG, polyvinylpyrrolidone and Eudragit [60]. Among these, PLGA-based NPs are widely used for clinical diagnosis and treatment of diseases. Yu *et al*. designed PLGA-oltipraz NPs to treat IRI-AKI and renal fibrosis. Their results demonstrated that PLGA-oltipraz NPs improved cell viability and had greater antioxidative effects, lower malondialdehyde content, and higher superoxide dismutase activity, thereby significantly reducing renal tubular necrosis and fibrosis during the IRI recovery stage [61]. These findings reveal that polymeric NPs are a promising treatment strategy for AKI progression.

Inorganic NPs

Inorganic NPs include metallic, carbon-based, and magnetic iron oxide NPs, as well as quantum dot-based NPs composed of semiconductor materials. Owing to their controllable size, excellent biological stability, unique electrical/magnetic properties, and good biocompatibility, these NPs have been widely engineered for disease diagnosis, imaging, and biomedical treatments [62], thereby showing their great potential for applications in the medical field.

Gold-based NPs, among the most utilized metallic NPs, are excellent candidates for therapeutic strategies such as biosensor detection and as drug nanocarriers [63]. Multiple surface functionalities can be obtained when these materials are combined with different ligands. Moreover, the ability and properties of the nanosystem depend on the NP surface area. Generally, the smaller the NP size, the denser the surface atoms, which leads to closer interaction and recognition specificity [64]. For example, quantum-dot NPs possess tissue-accumulating properties and are ideal agents for monitoring long-term disease progression.

Commonly studied inorganic NPs also include iron oxide NPs, which can be classified into two types based on their size: ultrasmall superparamagnetic iron oxides (USPIO, <50 nm diameter) and SPIO (>50 nm diameter) [65]. Iversen *et al*. demonstrated that polyacrylic acid-coated magnetic iron oxide NPs are safe for use in healthy BALB/cJ mice and do not affect the glomerular filtration rate of their kidneys [66]. In addition, magnetic resonance imaging with USPIO particles

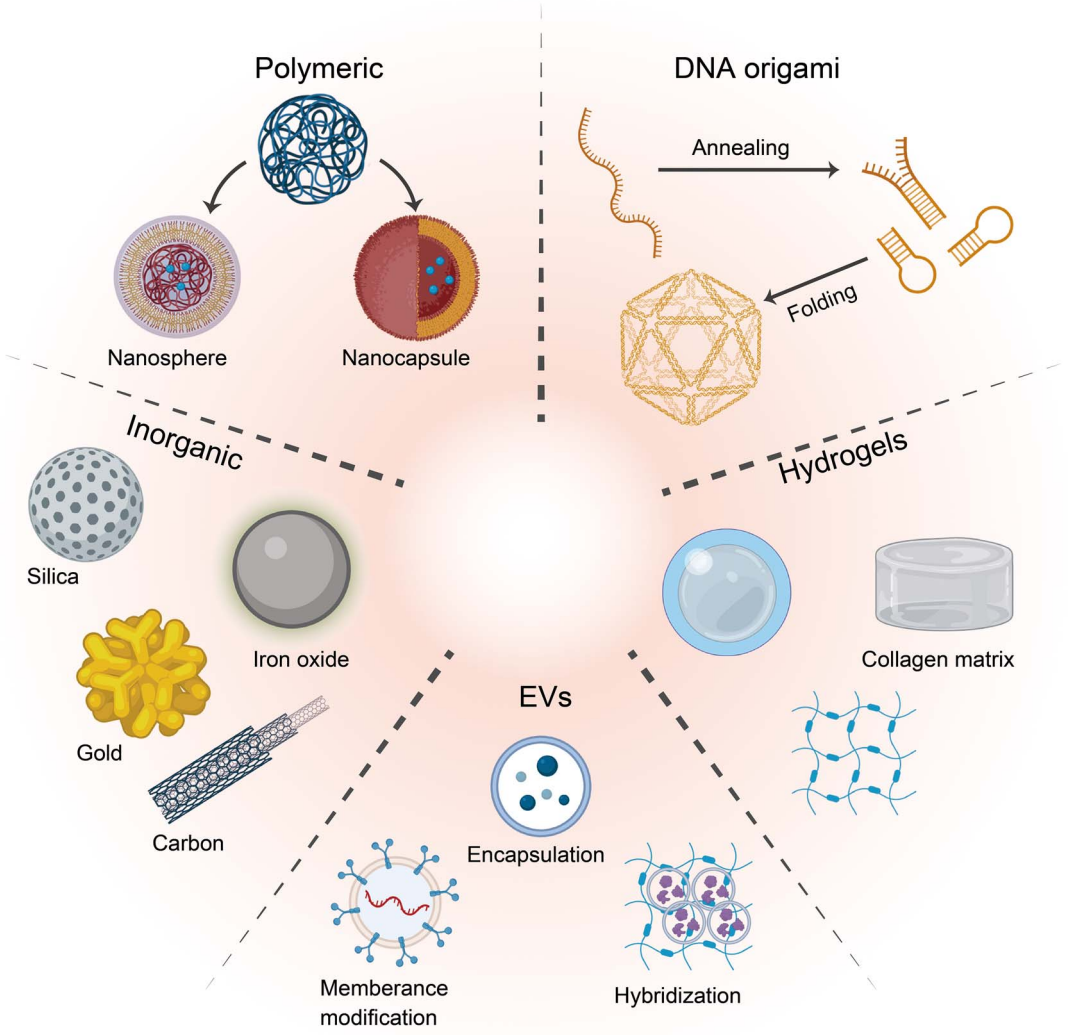


Figure 2. Summary of NPs employed for biomedical applications. The application of NPs in kidney treatment can be broadly categorized into five classes based on their size, shape, and chemical properties. The specific classifications and synthetic processes of NPs can also be modified through different targeting molecules to achieve more efficient targeted delivery. *NPs* nanoparticles, *EVs* extracellular vesicles

via intravenous injection appeared to successfully monitor inflammatory cell distribution within the kidney, which is used for the detection of renal transplant rejection [67]. These results suggest that iron oxide NPs are a promising tool for non-invasive and sensitive biomonitoring.

Hydrogels

Hydrogels are 3D hydrophilic polymer platforms that typically absorb large volumes of water while maintaining physical integrity [68]. They offer adjustable physicochemical properties such as mechanical strength, pore size, network structure, degradability, ligand presentation, and stimulus responsiveness [69]. The inherent hydrophobicity of traditional hydrogels has improved with the combination of hydrogels and nanomaterials, making hydrogel nanocomposite systems useful tools for facilitating localized therapies.

Currently, the prevalent routes of hydrogel administration for kidney treatment are intra-arterial, intraparenchymal, and intracapsular injections in the liquid phase [70]. Upon localization in the target tissue, hydrogels undergo gelation through different mechanisms, mainly involving self-assembly [71] or stimuli-responsive polymerization (e.g. pH, thermal, or electronic). With the degradation of gelatinized hydrogels, the controlled release of cargo payloads such as drugs, cyclic peptides, NPs, and biovesicles plays a pivotal role in their therapeutic effects [72]. In addition to serving as drug-loaded carriers, hydrogels can serve as engineered matrices with growth factors to provide suitable conditions for the self-renewal and differentiation of mesenchymal stem cells (MSCs) [73]. The therapeutic effect of EVs on kidney injury can be improved by encapsulation in thermosensitive injectable collagen hydrogels, which significantly increase the stability and long-term retention of EVs *in vivo* [74]. These engineered hydrogels can offer insights into AKI progression and be implemented for its localized treatment.

DNA origami

DNA origami is a new nanotechnology that facilitates the folding of long single-stranded DNA (scaffolds) into complex 2D or 3D nanostructures by exploiting intra- and inter-molecular Watson–Crick base pairings [75]. Such tightly folded 3D conformational DNA nanostructures

bypass some of the limitations of conventional linear and circular DNA duplexes, enabling the notable enhancement of nuclease resistance and origami stability. DNA origami nanostructures exhibit excellent properties including marked biocompatibility, low cytotoxicity, and high loading efficiency, thus offering potential advantages for targeted drug delivery [76]. Conventionally, single- or double-stranded DNA barely permeates the live cell membranes. However, recent studies have revealed that DNA nanostructures can be readily transported into cells with high cellular-uptake efficiency [77,78].

As a promising tool for drug delivery, various therapeutic cargos, including small molecules, proteins, and nucleic acids, can be delivered via DNA origami. Because DNA origami and cargo nucleic acids share the same type of molecule, employing exogenous nucleic acid strands [e.g. small interfering RNA (siRNA) and cytosine phosphate-guanine] as medicines to execute the corresponding functions is more convenient [79]. Overall, DNA origami has shown positive effects on cellular delivery, which makes DNA nanostructures good candidates as immunotherapeutic carriers. In the following sections, we summarize the application of DNA origami in the AKI-to-CKD transition.

Nanomedicine-dependent therapeutic methods for AKI-to-CKD progression

Glomerular filtration barrier structure

The nephron, composed of the renal corpuscle and tubular system, is the major unit for blood filtration and substance reabsorption. The renal corpuscle is formed by bundles of capillaries called glomeruli and is encapsulated by Bowman's capsule. The key process for achieving precise targeted transport and clearance of NPs is passing through the glomerular filtration barrier (GFB), which consists of glomerular endothelial cells (70–100 nm), podocytes (<12 nm), and the glomerular basement membrane (2–8 nm). In healthy states, molecules with molecular size >6–8 nm cannot freely pass through the GFB. In AKI, enlargement of endothelial-cell fenestrations, loosening of the basement membrane, and loss of podocytes are observed, collectively resulting in damage to the GFB. This compromised barrier facilitates the filtration of NPs and larger substances (Figure 3). NPs are engineered with surface ligands that bind specifically to receptors expressed in damaged kidney tissues. These ligands ensure that the nanomedicines precisely target the injury sites. Lawrence *et al*. demonstrated the feasibility of using a synthesized nano-delivery system (diameter ∼190 nm) to target podocytes by selectively binding to the melanocortin-1 receptor, indicating not only the potential of these systems to traverse the other two layers of the GFB [80], but also showing that passing through the GFB is determined by a variety of factors. By modulating NP characteristics such as size, charge, shape, and surface chemistry, it is possible to precisely control their interactions with distinct renal compartments and target specific cells [81].

Overall, the properties of the injured GFB, combined with the targeting characteristics of NPs, enable NPs to specifically address various injury mechanisms during the treatment of the AKI-to-CKD transition. This targeted approach leverages the unique pathophysiological features of the damaged kidney, allowing for precise intervention that can mitigate progression and improve outcomes.

NPs targeting ROS

Given the important role of ROS and mitochondrial dysfunction in the initiation and progression of AKI, ROS elimination appears to be a promising strategy for preventing AKI progression. Various types of nanomaterials provide innovative methods for the targeted delivery of renoprotective drugs and materials to achieve higher therapeutic efficacy (Table 1).

Polymeric NPs. As mentioned previously, PLGA is a commonly used and food and drug administration (FDA)-approved synthesized nanomaterial that is already used in clinical applications. Liu *et al*. generated gypenoside XLIX-loaded PLGA (PLGA-Gyp XLIX) NPs with a diameter of ∼120 nm, which selectively accumulated in the injured kidneys of a UUO mouse model. The therapeutic effect was evaluated initially, and at Days 3 and 7 following tail vein injections of NPs at a concentration of 5 mg/kg every other day. PLGA-Gyp XLIX NPs alleviated renal fibrosis mainly through the transforming growth factor β/SMAD family member 3 (SMAD3)-dependent signaling pathway [82]. Subsequent studies have demonstrated the recovery of mitochondrial and cellular functions by inducing mitochondrial biogenesis (MB), which is the main process in ROS production. They encapsulated formoterol (a PGC-1α agonist known as a stimulator of MB) in a polymeric matrix composed of PLGA-PEG NPs and evidenced sustained drug release, renal localization, and MB in rabbit renal TECs and male C57BL/6 mice [83].

In addition, chitosan has been demonstrated to be useful for AKI treatment. Liu *et al*. combined a prodrug (SC-TK-SS31) with L-serine-modified chitosan as a drug carrier for effective AKI therapy. By targeting L-serine to induce kidney injury molecule-1 (Kim-1), particularly in injured renal proximal tubules, the accumulation and therapeutic efficacies of SC-TK-SS31 in these tubules were improved by protecting against apoptosis from oxidative stress in the mitochondria [85] (Figure 4). Similarly, a chitosan-based carrier binding mangiferin, a polyphenol that protects against and attenuates oxidative stress, significantly improved the bioavailability and solubility of mangiferin and scavenged free radicals in renal cells [84]. Compared with neutrophil gelatinase associated lipocalin (NGAL) and Kim-1, which are early injury markers of AKI, CD44 may be associated with maladaptive repair and subsequent renal fibrosis after AKI [108]. Hyaluronic acid (HA) can inherently and specifically target CD44 receptors. Based on these findings, Hu *et al*. identified a cell-targeted drug delivery system that combined HA with curcumin to significantly alleviate the levels of pro-inflammatory cytokines and oxidative stress in an IRI-AKI murine model and HK-2 cells [86].

Inorganic NPs. Inorganic NPs, including ceria [109], selenium [110], quantum dots, and molybdenum, have been used to treat various ROS-related diseases, particularly AKI, owing to their inherent capability to effectively quench ROS. Graphene quantum dots (GQDs) exhibit ROS-scavenging activity and renal specificity. Wang *et al*. took advantage of GQDs and constructed phenol-like group-functionalized GQDs (h-GQDs) with an increased number of phenol-like groups and decreased number of carbonyl groups, which benefited the antioxidative activity of AKI treatment [88]. Similarly, Gao *et al*. modified carbon nanodots with *m*-phenylenediamine functional groups, which exhibited

Table 1. Nanomedicine-based therapeutic methods for AKI and CKD treatment

Type of nanomaterial		Payload	Size (nm)	Administration	Animal model	Mechanism of action	Ref.	Year
Polymeric	PLGA	Gyp-XLIX	120	Tail intravenous	UUO model	Inhibit renal fibrosis; reduce collagen deposition; reduce renal tubular necrosis	[82]	2021
	PLGA-PEG	Formoterol	442	Tail intravenous	RTECs and male C57BL/6 mice	Induce mitochondrial biogenesis	[83]	2021
	Chitosan	Mangiferin	<80	Coincubation	Kidney epithelial cells	Scavenge free radicals; maintain antioxidant enzymes activities	[84]	2020
	L-Serine-modified chitosan	SS-31	2.84	Tail intravenous	IRI-AKI	Reduce oxidative stress, inflammation, and cell apoptosis	[85]	2020
	Hyaluronic acid	Curcumin	-	Intravenous	IRI-AKI	Relieve oxidative stress damage	[86]	2018
	PAGA-b-PPBAE	Curcumin	143.12	Intraperitoneal	CP-AKI	Promote lipid degradation and autophagy	[87]	2024
Inorganic	h-GQDs	-	4.4–4.8	Intravenous	Glycerol-induced AKI	Antioxidative activity	[88]	2020
	PDA-CNDs	-	4.92	Intravenous	IRI-AKI; CP-AKI	Scavenge free radicals; against various oxidative stresses	[89]	2020
	SeCQDs	-	40	Intravenous	RM-AKI; CP-AKI	Antioxidative activity	[90]	2020
	POM	-	1	Intravenous	CP-AKI	Scavenge ROS; antioxidative activity	[91]	2018
	BPNS	-	225.8 ± 4.0	Intravenous	Glycerol-induced AKI	Scavenge ROS; antioxidative activity	[92]	2020
	PTP-TCeria	Atorvastatin	43.1 ± 7.50	Intravenous	LPS-induced AKI	Target mitochondria to scavenge excessive ROS	[93]	2020
DNA origami	DONs	-	90 × 60	Intravenous	Glycerol-induced AKI	Scavenge ROS	[94]	2018
	rDON	aC5a	90 × 60	Intravenous	IRI-AKI	Block c5a-mediated inflammation	[95]	2021
	tFNAs	Typ	16.93 ± 3.72	Intravenous	IRI-AKI	Increase antiapoptotic and antioxidative effect	[96]	2023
	tFNAs	-	11.7	Tail intravenous	Glycerol-induced AKI	Antioxidant effects	[97]	2021
Hydrogel	starPEG-heparin hydrogel	bFGF/EGF	25–50	Subcapsular injection	Glycerol-induced AKI	Antioxidative activity; renal tubular regeneration	[98]	2013
	KLDD hydrogel	MT	10–20	Under renal capsules	IRI-AKI	Mitochondrion-targeted antioxidant	[99]	2018
Liposomal	PEGylated liposomal	Prednisolone	-	Intravenous	IRI-AKI	Anti-inflammatory effects	[100]	2018
	TPP-decorated liposomes	Artesunate	81.13 ± 2.18	Intraperitoneal	CP-AKI	Anti-mitochondrial oxidative stress	[101]	2024
Hyaluronic acid	HA	nPLBR	226.9 ± 4.5	Intravenous	IRI-AKI	Relieve oxidative stress and inflammatory reactions	[102]	2021
	HA-assembled melanin	Dexamethasone	13.4	Tail intravenous	IRI-AKI	Anti-oxidative, anti-inflammation, and anti-apoptosis	[103]	2024
Nanomicelles	F127 microemulsions	Quercetin	<8	Intraperitoneal	Gentamicin-induced AKI	Reduce lipid peroxidation; enhance antioxidant defense systems	[104]	2021
	DSPE-PEG2000-NH2	Cur-TPP and Que	57.9 ± 1.4	Intravenous	CP-AKI	Antioxidant and anti- inflammatory	[105]	2024
Nanozymes	Gold	NAC	3–4	Intravenous	Glycerol-induced AKI	Anti-inflammatory/antioxidative effects	[106]	2021
	Pt NPs-PVP	-	3	Intravenous	Glycerol-induced AKI	RONS scavenging	[107]	2021

LPS lipopolysaccharide, *ROS* reactive oxygen species, *RONS* reactive oxygen/nitrogen species, *PLGA* poly (lactic-co-glycolic acid), *PEG* poly (ethylene glycol), *GQD* Graphene quantum dots, *PDA-CNDs* m-phenylenediamine-based carbon nanodots, *SeCQDs* Selenium-doped carbon quantum dots, *POM* molybdenum-based polyoxometalate, *BPNS* Black phosphorus nanosheets, *DONs* DNA origami nanostructure, *tFNA* tetrahedral framework nucleic acid, *Typ* typhaceae, *bFGF/EGF* basic fibroblast growth factor/epidermal growth factor, *MT* Mito-2,2,6,6-tetramethylpiperidine-N-oxyl, *TPP* triphenylphosphonium, *HA* hyaluronic acid, *nPLBR* ε-polylysine-bilirubin conjugate, *NAC* N-acetylcysteine, *Pt NPs-PVP* polyvinylpyrrolidone-coated ultrasmall platinum nanoparticles

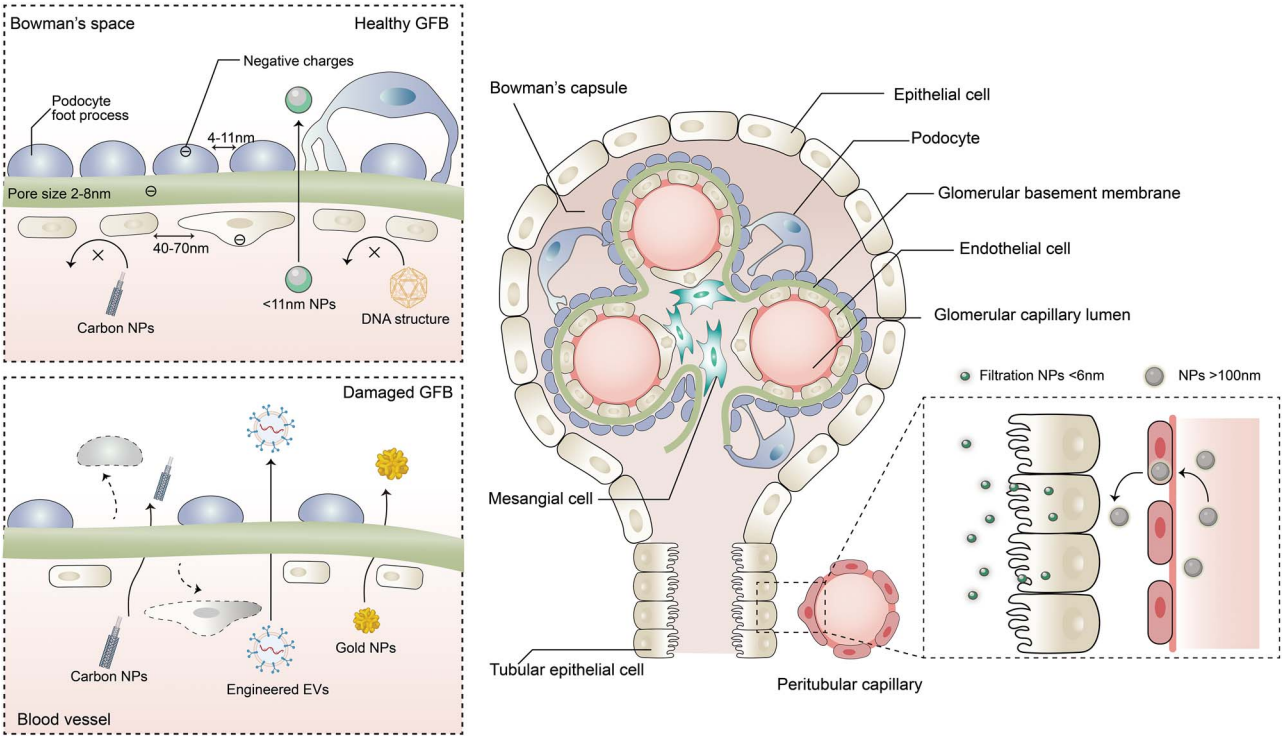


Figure 3. Schematic structure of renal filtration and accumulation of NPs. The renal GFB consists of podocytes, the glomerular basement membrane, and endothelial cells, all of which carry a negative charge. NPs ranging from 4 to 10 nm can freely pass through the GFB, those ranging from 10 to 100 nm can penetrate the endothelial layer but cannot pass through the intact GFB, while NPs >100 nm cannot cross the GFB under healthy conditions. However, in the event of AKI, the damaged barrier facilitates the filtration of NPs and larger substances. NPs <100 nm can breach the compromised GFB and enter proximal tubular epithelial cells. NPs >100 nm may access tubular cells through the peritubular capillaries surrounding the renal tubules. When NPs are engineered with targeting peptides, they can selectively accumulate within target cells. *NPS* nanoparticles, *EVs* extracellular vesicles, *AKI* acute kidney injury, *GFB* glomerular filtration barrier

excellent biocompatibility and safety *in vivo* without causing histological injury. *m*-Phenylenediamine-carbon nanodots may therefore serve as potential candidates for treating both CP-induced AKI (CP-AKI) and IRI-AKI because of their antioxidant activity [89]. Moreover, carbon quantum dots (CQDs) can be used as dopants for engineering materials containing trace elements such as selenium. Selenium-doped CQDs (SeCQDs) can improve cell viability by scavenging various free radicals, including superoxide anion radicals, hydroxyl radicals, and hydrogen peroxide, in the treatment of rhabdomyolysis-induced AKI (RM-AKI) and prevent CP-AKI injury [90]. In another study, Ni *et al*. synthesized molybdenum-based polyoxometalate nanoclusters with an ultra-small size (~10 nm), which demonstrated renal targeting and antioxidant activity to prevent AKI. In the CP-AKI mouse model, polyoxometalate successfully alleviated ROS-induced mitochondrial damage and inhibited the development of renal injury by scavenging excess ROS after intravenous administration at a dose of 1 mg per mouse [91].

DNA origami. DNA origami exhibits high reactivity toward electrophilic reactive oxygen/nitrogen species because of its abundant nucleophilic groups, and can thus serve as a potent active reductant [111]. Interactions with ROS play the role of safeguarding against endogenous biomolecules. During the onset of AKI, excessive ROS production from damaged mitochondria leads to the disruption of DNA integrity. Hence, exogenous DNA nanostructures can react directly with ROS to reduce cell damage and alleviate AKI progression.

Recently, Jiang *et al*. used a rectangular DNA origami nanostructure (Rec-DONs) and demonstrated that it preferentially targeted the kidneys and efficiently restored renal function in RM-AKI mice by scavenging ROS. Moreover, short single-stranded DNAs and partially folded scaffold DONs undergo rapid renal clearance [94]. Owing to their good biocompatibility, low immunogenicity, and rapid therapeutic responses, Rec-DONs play a pivotal role in AKI treatment. The contribution of oxidative stress and inflammation to AKI is magnified by the activation of C5a. Chen *et al*. equipped Rec-DONs with an anticomplement component 5a (aC5a) aptamer to selectively block C5a-mediated cytokine storms and relieve oxidative stress, which decreased renal malondialdehyde and C5a levels during multistage repair in IRI-AKI mice [95].

Recently, a research group employed a stable tetrahedral framework nucleic acid (tFNA) and a traditional Chinese medicinal extract of Typhaceae (Typ) to develop a tFNA-Typ complex that enhanced the bioavailability and stability of Typ. By alleviating mitochondrial oxidative stress and reducing cellular apoptosis following IRI, the restoration of mitochondrial function was facilitated, ultimately enhancing outcomes in IRI-AKI model mice [96]. Consistent with the findings of a previous study, tFNA protected TECs from cytotoxicity by scavenging excessive ROS [97].

Other materials. In addition to NPs, various other materials that can enhance the payload performance have been studied and these findings provide valuable insights for the

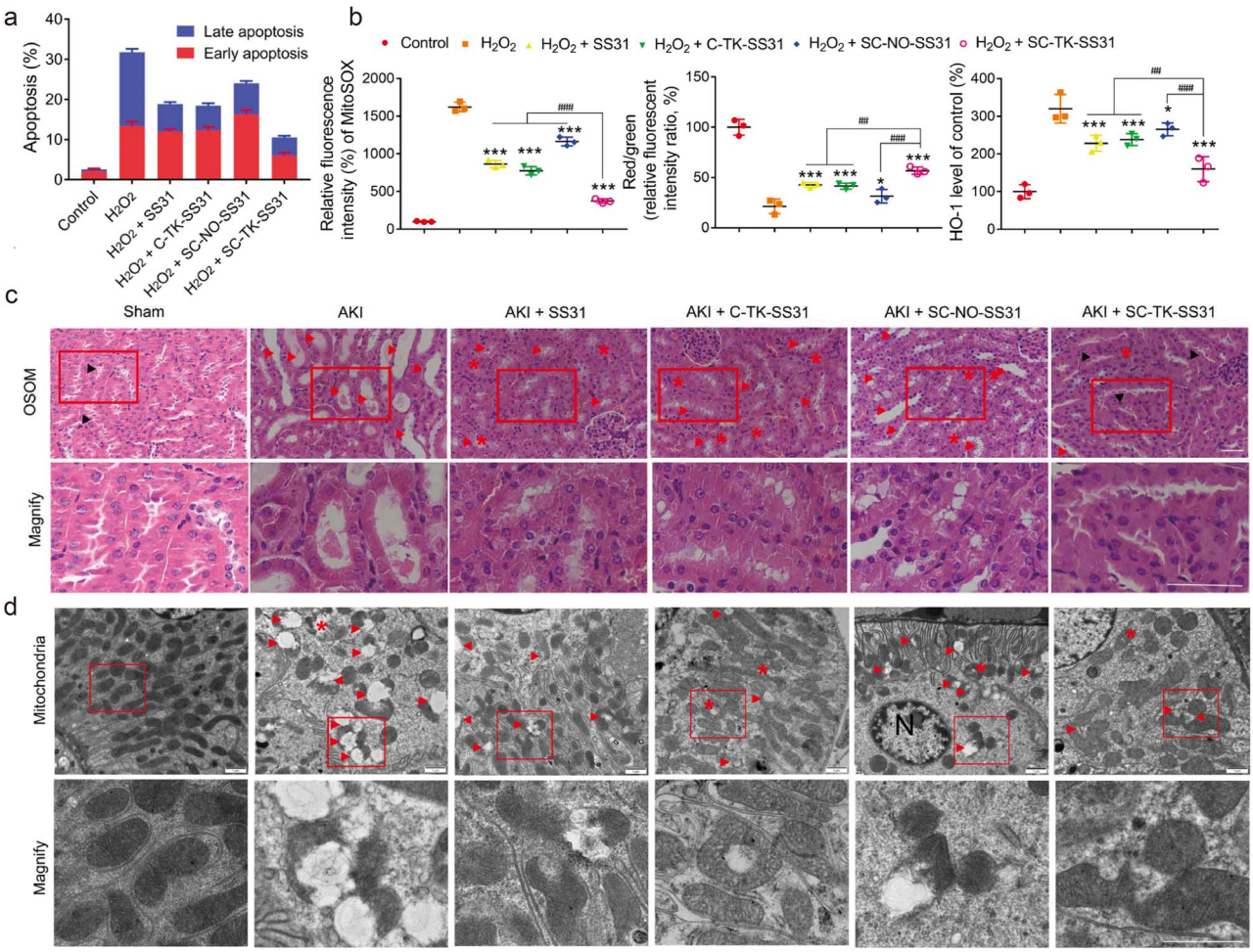


Figure 4. Therapeutic efficacy of SC-TK-SS-31 in AKI progression. (**a**) the percentage of apoptotic cells decreased, especially those in the early stage of apoptosis. $^{***}p<0.001$, $^{\#\#}p<0.01$ and $^{\#\#\#}p<0.001$ between groups.(**b**) SC-TK-SS31 treatment exhibited the highest reduction of mitochondrial ROS production as compared to the other three drugs. (**c**) In comparison with other groups, hematoxylin and eosin staining revealed that the SC-TK-SS31 treatment group has renal protective effects, as the brush borders were well preserved in proximal tubules. Scale bar, 50μm.The normal mice kidneys architecture with remarkable brush borders (shown as black arrowheads). Red arrowheads donate hyaline casts and cell sloughing. Asterisks donate adhesion.(**d**) Treatment of SC-TK-SS31 largely decreased the numbers of damaged mitochondria in proximal tubular cells of AKI mice [85]. Swollen mitochondria are noted with arrowheads. N, nucleus. Scale bar, 1μm. *OSOM* outer stripe of the outer medulla.© 2020 science advances. *AKI* acute kidney injury, *ROS* reactive oxygen species

future development of drug-delivery systems. For instance, a milestone advancement in cellular repair with local delivery was introduced by Tsurkan *et al.* in 2013, who combined multi-armed PEG (starPEG) and heparin to construct micrometer-sized hydrogel NPs [98]. They developed a new biohybrid platform that showed good flexibility, hydrophilic characteristics, and high affinity for various growth factors. The results showed antioxidant activity *in vitro* and renal tubular regeneration in a glycerol-induced AKI model generated via subcapsular injection. In 2017, Zhao *et al.* developed a more complex material with a self-assembling design strategy to generate an injectable self-assembling peptides (KLDD) hydrogel that prolonged the release time of mitochondrion-targeted antioxidants [99].

Lipid-based NPs facilitate the targeting and efficacy of selective drug compounds. Van Alem *et al.* established prednisolone-loaded conjugated PEGylated lipid NPs. At 96 h after injection, the accumulation of prednisolone in the inflamed kidney was enhanced and the proinflammatory state was improved in IRI-AKI model rats [100]. Enhancing the solubility of NP structures is necessary to expand their applications. One method is to use a microemulsion to encapsulate both hydrophobic and hydrophilic drug compounds in both the hydrophilic and lipophilic domains, as demonstrated by Rahdar *et al.* They encapsulated quercetin in an F127 microemulsion to improve its bioavailability. This nanoencapsulated quercetin restored renal ROS injury in gentamicin rats and even reversed gentamicin-induced renal fibrosis [104]. In addition, it has been shown that ultrasmall platinum [107] and gold [106] NPs possess multienzyme mimetic activity, including catalases, superoxide dismutases, and peroxidases, thereby demonstrating an excellent ability to eliminate reactive oxygen and nitrogen species. Furthermore, these nanozymes exhibited synergistic anti-inflammatory and antioxidative effects, as evidenced by reduced interleukin 6 (IL-6) and TNF-α levels. Therapies for carrier-based materials are summarized in Table 1.

Overall, excessive ROS production is a pivotal factor in the onset and progression of AKI to CKD. As described above, various nanomaterials and drugs have demonstrated significant efficacy in current AKI treatments by mitigating ROS levels and preventing renal fibrosis, thereby establishing a

foundational framework for the application of nanomaterials in the context of AKI.

NPs targeting ferroptosis

Ferroptosis, a new mode of regulated cell death, is associated with pathophysiological processes in many diseases. Precise intervention in the development of AKI by regulating ferroptosis has thus become a topic of interest. However, existing small-molecule ferroptosis inducers and kidney-targeted drug delivery strategies still have some limitations, such as poor solubility, unpredictable distribution, and short duration, so there is room for further innovation.

Nanomedicine provides new opportunities for ferroptosis-driven therapies (Table 2). Wang *et al*. designed nanozymes known as CaPB ($KCa(H_2O)_2[Fe^{III}(CN)_6]\cdot H_2O$) NPs that function as multienzyme mimetics and target ferroptosis to treat AKI [112]. After CaPB nanozyme treatment, the expression levels of GPX4, the key enzyme involved in peroxidation, significantly increased, whereas the expression of ACSL4 and PTGS-2 (ferroptosis facilitators) decreased in ferroptosis-induced cells. Furthermore, TEC morphology, anti-inflammatory marker expression, and impaired renal function were significantly restored *in vivo*. The pathological progression of IRI-induced renal fibrosis was effectively ameliorated, demonstrating the ability of this treatment to prevent the progression of AKI to CKD. Xie *et al*. synthesized gallic acid-gallium polyvinyl pyrrolidone NPs (GGP NPs) for AKI treatment. GGP NPs have strong iron-scavenging abilities because gallium can mimic iron ions and disrupt cellular iron metabolism [113]. These properties allow GGP NPs to ameliorate renal tubular injury in CP-AKI and IRI-AKI mouse models by reducing intracellular free iron levels and ferroptosis. Additionally, mitochondrial morphological damage was reversed by the pre-administration of GGP NPs. Deng *et al*. developed Se/albumin NPs, which have been shown to suppress ferroptosis by upregulating intracellular glutathione levels and GPX4 activity when used in CP-induced AKI therapy [114].

In addition to employing a nano-based approach that enables exogenous iron ions to disrupt ferroptosis, rationally designed carriers can also manipulate lipid peroxidation levels to regulate ferroptosis. Recently, Zhang *et al*. constructed a renal tubule-targeted polysialic acid-modified dexrazoxane (DXZ-PSA) [115]. When combined with a DXZ iron chelator, this formulation effectively mitigated ferroptosis and acted as a natural carrier capable of inhibiting complement-system reactions [130]. This innovative approach paves the way for a novel strategy for designing medications aimed at suppressing ferroptosis, thereby offering a promising opportunity to identify diverse targets for AKI treatment.

Engineered EVs for targeted therapy

In addition to their complex and powerful endocrine and paracrine functions, EVs, as natural vesicles released by cells, communicate with acceptor cells through proteins, lipids, and nucleic acids transport [131]. However, heterogeneity in the sizes and sources of native EVs, along with the high complexity of cargo biomolecules and inefficient targeting, remain critical barriers to their diagnostic and therapeutic applications. Hence, the reconstruction of EVs is imperative as it could aid in highly targeted delivery of therapeutic cargo to injured tissues (Table 2).

Membrane modification. Membrane modification is a common method to engineer EVs. Owing to the fluidity of the EV membrane, the components can be easily embedded in the EV surface bilayer. Zhang *et al*. successfully anchored a P-selectin-binding peptide (PBP) to the surface of EVs through hydrophobic reactions and demonstrated the ability of P-selectin to bind injured endothelial cells in AKI. The results confirmed that PBP-EVs accelerated renal recovery 3 and 7 days after severe IRI, as shown by a reduction in histological structure injury, inhibition of myofibroblast activation, and decreased expression of α-SMA^+ (alpha-smooth muscle actin) myofibroblasts on Day 28. This suggests that the nephroprotective effects of PBP-EVs in the extension phase of AKI and alleviation of fibrosis prevent further progression of AKI to CKD [117].

Another commonly employed approach to enhance the biofunction of EVs involves the co-incubation of donor cells with certain substances; therefore, beneficial molecules can be loaded into or onto the EV surface. For example, melatonin-stimulated MSCs increase the expression of anti-inflammatory and anti-fibrotic-related miRNAs in MSC-EVs. This process enhanced the ability of MSC-EVs to modulate CKD-related gene expression and hinder CKD progression [118].

Encapsulation. EVs can serve as carriers for a wide array of drugs and small molecules. The efficiency of targeting and drug transport can be further improved by modifying EV content. For example, it has been demonstrated that IL-10-encapsulated EVs are enriched in adhesion molecules such as integrin $\alpha 1\beta 1$, L2, and M2, which target TECs after ischemic AKI. Moreover, the therapeutic efficacy of these agents is demonstrated by the inhibition of rapamycin signaling, which consequently preserves mitochondrial homeostasis. This intervention significantly improved tubular atrophy, inflammatory cell infiltration, and fibrosis, and prevented progression to CKD [119]. In another study, Tang *et al*. developed a red blood cell-derived EV (REV)-based delivery platform using a Kim-1-targeted peptide (LTH) for the targeted delivery of therapeutic small interfering RNA (siRNA) siP65/siSnai1 into injured tubular cells. Treatment with REV-LTH-siRNA enhanced anti-tubulointerstitial inflammation and fibrosis in three mouse models, especially in the CKD model developed from ischemic AKI [120] (Figure 5). Collectively, these studies highlight the potential of engineered EVs as a promising therapeutic avenue for cargo delivery in AKI and CKD treatments.

Hybridization. EVs can not only undergo characteristic modifications through chemical or genetic approaches but also acquire additional functionalities by combining with nanomaterials. Enhancing the therapeutic effects of EVs by loading implanted scaffolds, such as hydrogels and collagen matrices, provides a new way to prolong the bioavailability of native EVs. Zhang *et al*. labeled human placenta-MSC-derived EVs with an RGD (Arg-Gly-Asp) hydrogel, which increased EV integrin-mediated loading and improved the stability and retention of EVs in the treatment of AKI [121]. Intrarenal injection of EV-RGD hydrogels ameliorated histopathological impairments and improved regeneration in the early stage of AKI. Masson staining showed that the occurrence of renal fibrosis was significantly attenuated on Day 28 during the chronic stage of AKI, demonstrating the improved efficacy

Table 2. Characteristics of nanomedicine for AKI and CKD treatment

Biological effect	Type of nanomaterial		Size (nm)	Administration	Animal model	Ref.	Year
Inhibition of ferroptosis	Nanozymes	CaPB	6 nm	Intravenous	IRI-AKI	[112]	2022
	Inorganic	Gallium	20	Intraperitoneal	CP-IRI; IRI-AKI	[113]	2022
	Inorganic	Se/albumin	96 ± 7.5	Intraperitoneal	CP-IRI	[114]	2022
	Polymeric	DXZ-PSA	-	Intravenous	CP-IRI; IRI-AKI	[115]	2023
	DNA origami	TDNs	18.79	-	Only CP-IRI cell model	[116]	2021
Anti-inflammation	EV membrane modification	PBP-EVs	97.33	Intravenous	IRI-AKI	[117]	2023
		Melatonin-MSCs coincubation	177.18 ± 2.84	Intravenous	CKD	[118]	2021
	EV encapsulation	IL-10^{+} EVs	134	Intravenous	IRI-AKI	[119]	2020
		REVLTH-siP65/siSnai1	100	Intravenous	IRI-AKI; UUO	[120]	2021
	EV hybridization	EV/RGD hydrogel	-	Intrarenal	IRI-AKI	[121]	2020
		KMP2-EVs hydrogel	-	Intrarenal	IRI-AKI	[122]	2019
		Col-EVs	-	Intrarenal	IRI-AKI	[74]	2020
Targeting reduces renal apoptosis	Nanocarbon	fCNT/siTrp53	300	Intravenous	CP-IRI	[11]	2016
	Chitosan	C-CS/sip53	110	Intravenous	IRI-AKI	[123]	2022
	Polymeric	PCX/sip53	127	Intravenous	CP-IRI; IRI-AKI	[124]	2022
	EV	MSC-EVs/sip53	134.4 ± 3.9	Intravenous	IRI-AKI	[125]	2021
	DNA origami	siP53@L-sTd	6	Intravenous	FA-AKI	[126]	2020
Attenuates renal fibrosis	Liposomal	CREKA-Lip	110	Tail intravenous	UUO	[127]	2020
	Inorganic	Lf-CONP	-	Intraperitoneal	UUO	[128]	2022
	Chitosan	CS/HA	45.67 ± 10.16	Tail intravenous	UUO	[129]	2020

MSC mesenchymal stem cell, *EV* extracellular vesicle, *FA* folic acid, *CP* cisplatin, *DXZ-PSA* dexrazoxane and polysialic acid, *TDNs* tetrahedral DNA nanostructures, *PBP* P-selectin binding peptide, *Col-EVs* collagen matrix-incorporated EVs, *CS* chitosan, *C-CS* CS modified with α-cyclam-p-toluic acid, *PCX* polymeric CXCR4 antagonist, *Lf-CONP* lactoferrin-cerium oxide nanoparticle

of the EV-RGD hydrogels in preventing the progression of AKI to CKD. Similarly, Zhou *et al*. developed an injectable MSC-EV-releasing peptide nanofiber hydrogel for kidney endothelial cell injury regeneration in an IRI-AKI mouse model [122].

NPs targeting p53

Conventional gene therapy involving RNA interference typically relies on various viral vectors such as lentiviruses and adenoviruses. However, concerns regarding the biosafety of viral delivery of genetic material have impeded its translational application in clinical trials. Consequently, nanomaterials present a novel alternative for non-viral delivery and have shown promising outcomes in the targeted regulation of gene expression. In 2016, Alidori *et al*. described an ammonium-functionalized carbon nanotube (fCNT)-mediated delivery platform to selectively transport several target genes, including *p53*, to renal proximal tubule cells in a CP-AKI mouse model. fCNT/si*p53*/siMep1b treatment significantly minimized renal injury and reduced immune infiltration as early as 11 days after CP injury, and both kidney and interstitial fibrosis levels were significantly lower than those in scrambled controls at 180 days [11]. Chitosan has long been used as a polymeric carrier for the delivery of siRNAs and drugs for many diseases [132]. For renal applications, modifications can be made by conjugating chitosan with α-cyclam-*p*-toluic acid (C-CS), which imparts the C-CS polymer with targeting properties to injured renal cells overexpressing the chemokine receptor CXCR4 in AKI [123]. Polymeric CXCR4 antagonist (PCX) siRNA-NPs also have a strong ability to deliver siRNA, effectively knocking down the expression of p53 and providing nephroprotective effects against tubular injury in AKI [124]. Several studies on RNA interference against p53 in the kidneys are presented in Table 2.

NPs targeting fibrosis

Recent advancements in nanomedicine have demonstrated the potential of NPs in targeting fibrosis, particularly in AKI-to-CKD transition. Li *et al*. designed PEGylated liposomes (CREKA-Lip), and by loading them with celastrol (CEL) successfully attenuated renal fibrosis and inflammation in UUO mouse models. The expression of α-SMA, collagen, and fibronectin were decreased when treated with CREKA-Lip/CEL [127]. Aslam Saifi *et al*. used lactoferrin-decorated cerium oxide NPs to enhance targeting efficiency to the kidneys and prevent fibrotic progression [128]. Midgley *et al*. utilized NP-enclosed antifibrotic biologics, bone morphogenetic protein 7 (BMP7), and hepatocyte growth factor (HGF)-NK1 to target delivery to CKD mouse models. The NPs system reversed the progression of renal fibrosis and eliminated collagen fiber deposition [129], as shown in Table 2. These studies collectively underscore the potential of NPs in providing targeted, efficient, and safe therapeutic strategies for combating fibrosis in CKD.

Perspectives

AKI is a common complication in critically ill patients and is often associated with long-term transitions including chronic dialysis dependence. Currently, standard strategies predominantly only prevent further deterioration of renal function [133].

Unlike traditional approaches, nanomedicine allows precise targeting at the molecular level, delivering therapeutics

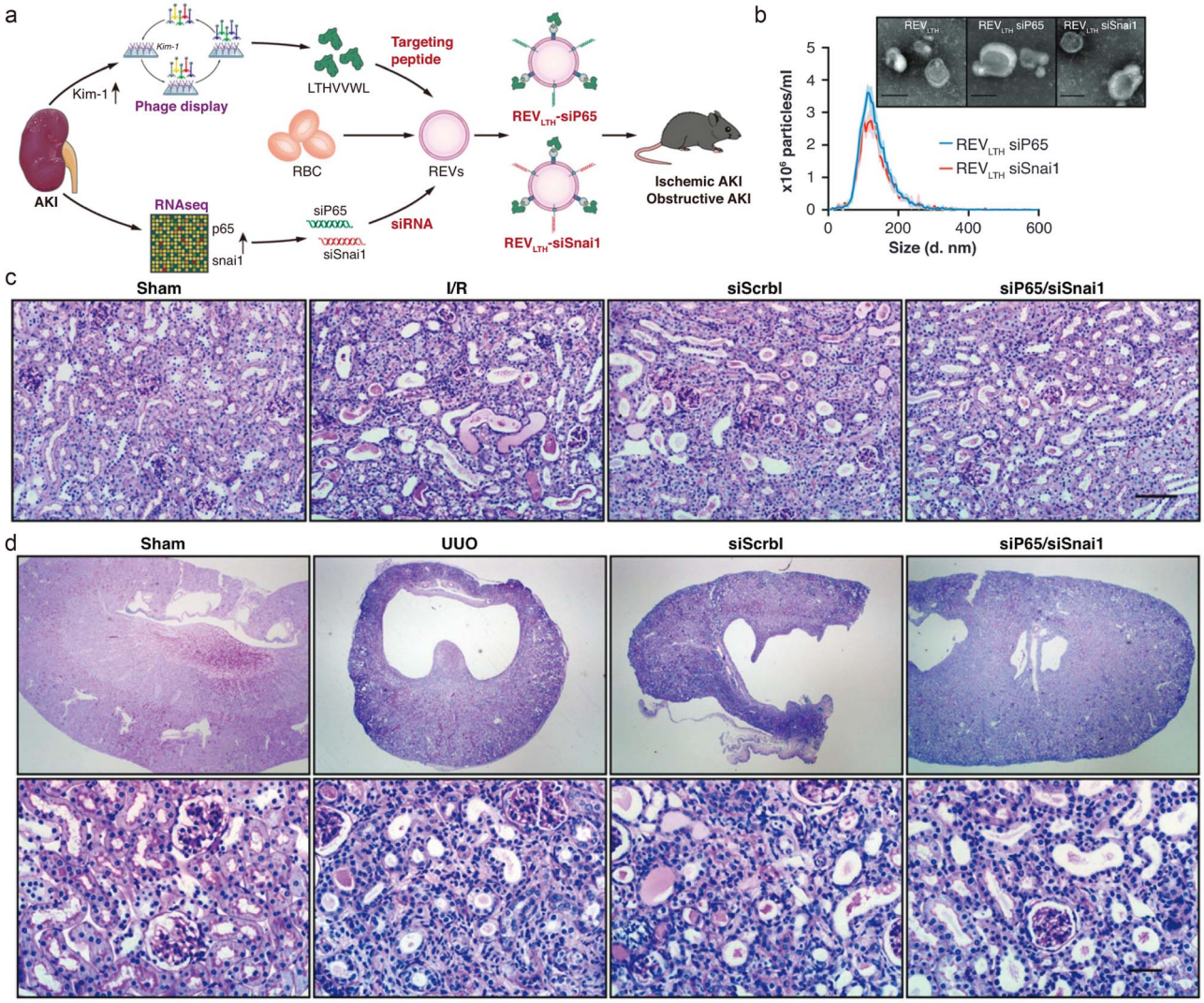


Figure 5. REVLTH-siP65/siSnai1 combination therapy alleviates AKI. (**a**) Scheme of the preparation of REV-based kidney-targeted RNA interference (RNAi) therapy against AKI. (**b**) Representative transmission electron microscopy images showing the size distribution of REVLTH-siP65 and REVLTH-siSnai1. (**c**) Representative images of periodic acid–Schiff (PAS) staining in IRI kidneys. (**d**) Representative images of PAS staining and quantification of kidney injury [120]. siRNA small interfering RNA, VVWL the displayed peptide of LTH.© 2021 American Society of Nephrology. *AKI* acute kidney injury

directly to affected renal cells with enhanced efficacy and minimal systemic side effects. NPs can encapsulate drugs, protect them from degradation, and ensure controlled release, thereby optimizing drug bioavailability and therapeutic outcomes. Most importantly, nanocarriers can overcome biological barriers such as the GFB, facilitating efficient drug delivery to the kidneys [80]. Moreover, nanomedicines offer controlled release mechanisms, ensuring sustained therapeutic levels of drugs over extended periods. Various nanomaterials offer different therapeutic targets and can be designed based on specific conditions (Table 3). For example, EVs exhibit excellent biocompatibility and serve as efficient carriers for drug delivery. Furthermore, they can be combined with other nanomaterials and show good biosafety in terms of their long-term effects. This is crucial in the context of AKI progression to CKD, in which prolonged intervention is necessary to halt disease progression and promote renal regeneration. Compared with physicochemical therapies such as dialysis or renal replacement therapy, nanomedicine, such as magnetic NP-assisted hemodialysis, provides high removal efficiency and reduces the side effects of conventional hemodialysis [134]. By targeting specific molecular pathways implicated in renal injury and fibrosis, nanomedicine has the potential to halt or even reverse the pathological processes that drive CKD development.

Despite the tremendous potential of nanomedicine, several challenges and limitations must be addressed. The first and foremost issues are long-term biocompatibility and safety. Because these materials interact with biological systems over extended periods, their potential for long-term toxicity or immune responses must be rigorously evaluated. Factors such as nanoparticle size, surface charge, and biocompatibility can influence pharmacokinetics and potential toxicity [135]. This is especially critical when considering the chronic nature of CKD, the nanoscale characteristics of NPs, and the mode of administration, because toxicity may lead to varying degrees of severity [136]. Moreover, the lack of preparation processes with standardized protocols, size control, and low-cost has led to variations in NP characteristics, rendering them unsuitable for scaled-up production. For example, the highly demanding

Table 3. Summary of nanomaterials in terms of therapeutic efficacy and biological safety evaluation in AKI and CKD treatment

Nanomaterial	Duration	Therapeutic efficacy	Biological safety assessment	Ref.
Polymeric	7 days	Scr and BUN	Fluorescence images of the major organs[a]	[82]
	24 h	Immunoblotting for PGC1a, ND1 expression	Adverse cardiac effects	[83]
Inorganic	7 days	Scr and BUN; Body weight; MDA; H&E staining	Body weight, eating, drinking, and activity; H&E staining images of major organs from mice 15 days	[88]
	7 days and 1 month	Scr and BUN; H&E staining; PET imaging	The renal sections of tubules, collecting ducts, glomeruli, and urethrae were collected and stained with H&E	[91]
DNA origami	24 h	Urinary protein levels; Scr and BUN; H&E staining	H&E staining of major organs after 4 days; Routine blood tests on Days 1 and 4 showed no apparent damage	[97]
Hydrogel	5 days	Renal histology and BrdU-positive cells	-	[98]
	5 days	IF; IHC; H&E staining	-	[99]
Liposomal	96 h and 4 days	IHC; H&E staining	Representative images of the NIR signal in the *in vivo* organs	[100]
	7 days	Scr and BUN; H&E and Masson staining; Tubulointerstitial fibrosis index	H&E staining of major organs. Blood routine analysis on day 5 post-injection; liver function examination	[101]
Nanomicelles	8 days	H&E and PAS; Scr and BUN	Fluorescence images of the major organs	[105]
Nanozymes	14 days	H&E and IF; Scr and BUN; Survival time	Fluorescence images of the major organs	[106]
	14 days	H&E and IF; Scr and BUN	H&E staining of major organs; body weight; AST and ALT; Scr and BUN	[107]
EV	28 days	H&E and PAS staining; Masson trichrome staining	-	[121]
	14 days	Scr and BUN; H&E and Masson staining; IHC	-	[122]

Scr serum creatinine, *BUN* blood urea nitrogen, *H&E* hematoxylin and eosin, *PAS* periodic acid-Schiff, *IHC* Immunohistochemistry, *IF* immunofluorescence, *AST* aspartate transaminase, *ALT* alanine transaminase [a]Major organs include heart, liver, spleen, lungs, and kidneys

purification steps for DNA nanostructures result in expensive production [137]. In addition, the etiology of AKI is complex, and the transition to CKD encompasses a spectrum of pathologies, making it challenging to develop a one-size-fits-all-nanomaterial-based approach. Interventions targeting specific AKI subtypes also require further investigation. Finally, all current AKI studies are based on rodent models, and the fine structure of mouse and human kidneys includes different innate and adaptive immune systems [138]. Large animal models, such as rabbits and dogs, provide opportunities to more closely model human AKI pathophysiology and can be deployed at different stages of preclinical therapeutic development. Clinical translation of nanomaterial-based therapies faces challenges related to regulatory approval and scalability. Transitioning from laboratory experiments to large-scale production for widespread clinical use requires careful consideration of the manufacturing processes, quality control, and standardization.

Conclusions

Nanomedicine has emerged as a promising tool for combating AKI and its progression to CKD because of its unique properties and versatility. Nanomaterials have shown significant potential for mitigating various pathways leading to CKD, such as excessive ROS production, ferroptosis, EV-mediated communication, and p53-mediated cellular responses. These nanomedicine-based approaches enable researchers to intervene in the early progression of AKI using efficient and convenient methods. The use of nanomedicine for preventing the transition from AKI to CKD represents a cutting-edge paradigm in the field of nephrology. These nanomaterials offer precise targeting and provide new hope for patients facing critical health challenges. Nevertheless, the road ahead is challenging. Further research is needed to enhance the specificity and targeted delivery of nanomaterials to renal tissues, which can potentially minimize off-target effects and maximize the therapeutic benefits. As we continue to uncover the capabilities of nanomaterials and address the associated limitations, the promise of more effective and personalized treatments for AKI-to-CKD transition increases, offering hope to countless patients worldwide.

Author contributions

Jia Li (Conceptualization [lead], Writing—review editing [supporting]), Jiayu Duan (Conceptualization [supporting], Writing—review editing [supporting]), Chaoyang Hua (Conceptualization [supporting], Writing—original draft [supporting], Writing——review & editing [supporting]), Shaokang Pan (Conceptualization [supporting], Writing—review & editing [supporting]), Guangpu Li (Conceptualization

[supporting], Writing—review & editing [supporting]), Qi Feng (Conceptualization [lead], Writing—original draft [equal], Writing—review & editing [supporting]), Dongwei Liu (Conceptualization [supporting], Writing—original draft [supporting], Writing—review & editing [equal], and Zhangsuo Liu (Conceptualization [equal], Funding acquisition [lead], Writing—review & editing [lead]).

Conflict of interest

None declared.

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Data availability

The data used to support the findings of this study are included within the paper.

References

1. Kurzhagen JT, Dellepiane S, Cantaluppi V, Rabb H AKI: an increasingly recognized risk factor for CKD development and progression. *J Nephrol* 2020;**33**:1171–87. https://doi.org/10.1007/s40620-020-00793-2.
2. Xiang Y, Fu Y, Wu W, Tang C, Dong Z Autophagy in acute kidney injury and maladaptive kidney repair. Burns. *Trauma* 2023;**11**:tkac059. https://doi.org/10.1093/burnst/tkac059.
3. Mack M, Yanagita M. Origin of myofibroblasts and cellular events triggering fibrosis. *Kidney Int* 2015;**87**:297–307. https://doi.org/10.1038/ki.2014.287.
4. Peerapornratana S, Manrique-Caballero CL, Gómez H, Kellum JA Acute kidney injury from sepsis: current concepts, epidemiology, pathophysiology, prevention and treatment. *Kidney Int* 2019;**96**:1083–99. https://doi.org/10.1016/j.kint.2019.05.026.
5. He L, Wei Q, Liu J, Yi M, Liu Y, Liu H. *et al.* AKI on CKD: heightened injury, suppressed repair, and the underlying mechanisms. *Kidney Int* 2017;**92**:1071–83. https://doi.org/10.1016/j.kint.2017.06.030.
6. Wang B, Xu J, Fu P, Ma L. MicroRNAs in septic acute kidney injury. *Burns & Trauma* 2023;**11**:tkad008. https://doi.org/10.1093/burnst/tkad008.
7. Adhikari A, Mondal S, Chatterjee T, das M, Biswas P, Ghosh R. *et al.* Redox nanomedicine ameliorates chronic kidney disease (CKD) by mitochondrial reconditioning in mice. *Commun Biol* 2021;**4**:1013. https://doi.org/10.1038/s42003-021-02546-8.
8. Lee T-Y, Lu H-H, Cheng H-T, Huang HC, Tsai YJ, Chang IH. *et al.* Delivery of nitric oxide with a pH-responsive nanocarrier for the treatment of renal fibrosis. *J Control Release* 2023;**354**:417–28. https://doi.org/10.1016/j.jconrel.2022.12.059.
9. Du B, Yu M, Zheng J. Transport and interactions of nanoparticles in the kidneys. *Nature Reviews Materials* 2018;**3**:358–74. https://doi.org/10.1038/s41578-018-0038-3.
10. Geo HN, Murugan DD, Chik Z, Norazit A, Foo YY, Leo BF. *et al.* Renal Nano-drug delivery for acute kidney injury: current status and future perspectives. *J Control Release* 2022;**343**:237–54. https://doi.org/10.1016/j.jconrel.2022.01.033.
11. Alidori S, Akhavein N, Thorek DLJ, Behling K, Romin Y, Queen D. *et al.* Targeted fibrillar nanocarbon RNAi treatment of acute kidney injury. *Sci Transl Med* 2016;**8**:331ra39. https://doi.org/10.1126/scitranslmed.aac9647.
12. Mitchell MJ, Billingsley MM, Haley RM, Wechsler ME, Peppas NA, Langer R Engineering precision nanoparticles for drug delivery. *Nat Rev Drug Discov* 2021;**20**:101–24. https://doi.org/10.1038/s41573-020-0090-8.
13. Couvreur P. Nanoparticles in drug delivery: past, present and future. *Adv Drug Deliv Rev* 2013;**65**:21–3. https://doi.org/10.1016/j.addr.2012.04.010.
14. Cho K, Wang X, Nie S, Chen Z(G, Shin DM Therapeutic nanoparticles for drug delivery in cancer. *Clin Cancer Res* 2008;**14**:1310–6. https://doi.org/10.1158/1078-0432.CCR-07-1441.
15. Ying Y, Tang Q, Han D, Mou S Nucleic acid nanotechnology for diagnostics and therapeutics in acute kidney injury. *Int J Mol Sci* 2022;**23**. https://doi.org/10.3390/ijms23063093.
16. Watchorn J, Huang D, Bramham K, Hutchings S Decreased renal cortical perfusion, independent of changes in renal blood flow and sublingual microcirculatory impairment, is associated with the severity of acute kidney injury in patients with septic shock. *Crit Care* 2022;**26**:261. https://doi.org/10.1186/s13054-022-04134-6.
17. Dennis JM, Witting PK. Protective role for antioxidants in acute kidney disease. *Nutrients* 2017;**9**. https://doi.org/10.3390/nu9070718.
18. Honda T, Hirakawa Y, Nangaku M. The role of oxidative stress and hypoxia in renal disease. *Kidney Res Clin Pract* 2019;**38**:414–26. https://doi.org/10.23876/j.krcp.19.063.
19. Li Z, Guo H, Li J, Ma T, Zhou S, Zhang Z. *et al.* Sulforaphane prevents type 2 diabetes-induced nephropathy via AMPK-mediated activation of lipid metabolic pathways and Nrf2 antioxidative function. *Clin Sci (Lond)* 2020;**134**:2469–87. https://doi.org/10.1042/CS20191088.
20. Hall AM, Rhodes GJ, Sandoval RM, Corridon PR, Molitoris BA In vivo multiphoton imaging of mitochondrial structure and function during acute kidney injury. *Kidney Int* 2013;**83**:72–83. https://doi.org/10.1038/ki.2012.328.
21. Tanaka S, Tanaka T, Kawakami T, Takano H, Sugahara M, Saito H. *et al.* Vascular adhesion protein-1 enhances neutrophil infiltration by generation of hydrogen peroxide in renal ischemia/reperfusion injury. *Kidney Int* 2017;**92**:154–64. https://doi.org/10.1016/j.kint.2017.01.014.
22. Tammaro A, Scantlebery AML, Rampanelli E, Borrelli C, Claessen N, Butter LM. *et al.* TREM1/3 deficiency impairs tissue repair after acute kidney injury and mitochondrial metabolic flexibility in tubular epithelial cells. *Front Immunol* 2019;**10**:1469. https://doi.org/10.3389/fimmu.2019.01469.
23. Mapuskar KA, Wen H, Holanda DG, Rastogi P, Steinbach E, Han R. *et al.* Persistent increase in mitochondrial superoxide mediates cisplatin-induced chronic kidney disease. *Redox Biol* 2019;**20**:98–106. https://doi.org/10.1016/j.redox.2018.09.020.
24. Wang J, Zhu P, Li R, Ren J, Zhou H Fundc1-dependent mitophagy is obligatory to ischemic preconditioning-conferred renoprotection in ischemic AKI via suppression of Drp1-mediated mitochondrial fission. *Redox Biol* 2020;**30**:101415. https://doi.org/10.1016/j.redox.2019.101415.
25. Perry HM, Huang L, Wilson RJ, Bajwa A, Sesaki H, Yan Z. *et al.* Dynamin-related protein 1 deficiency promotes recovery from AKI. *J Am Soc Nephrol* 2018;**29**:194–206. https://doi.org/10.1681/ASN.2017060659.
26. Jiang M, Dong Z. Regulation and pathological role of p53 in cisplatin nephrotoxicity. *J Pharmacol Exp Ther* 2008;**327**:300–7. https://doi.org/10.1124/jpet.108.139162.
27. Zhou L, Fu P, Huang XR, Liu F, Lai KN, Lan HY Activation of p53 promotes renal injury in acute aristolochic acid nephropathy.

J Am Soc Nephrol 2010;**21**:31–41. https://doi.org/10.1681/ASN.2008111133.
28. Yang L, Besschetnova TY, Brooks CR, Shah JV, Bonventre JV Epithelial cell cycle arrest in G2/M mediates kidney fibrosis after injury. *Nat Med* 2010;**16**:535–43. https://doi.org/10.1038/nm.2144.
29. Ying Y, Kim J, Westphal SN, Long KE, Padanilam BJ Targeted deletion of p53 in the proximal tubule prevents ischemic renal injury. *J Am Soc Nephrol* 2014;**25**:2707–16. https://doi.org/10.1681/ASN.2013121270.
30. Sutton TA, Hato T, Mai E, Yoshimoto M, Kuehl S, Anderson M. *et al.* p53 is renoprotective after ischemic kidney injury by reducing inflammation. *J Am Soc Nephrol* 2013;**24**:113–24. https://doi.org/10.1681/ASN.2012050469.
31. Yan H-F, Zou T, Tuo Q-Z, Xu S, Li H, Belaidi AA. *et al.* Ferroptosis: mechanisms and links with diseases. *Signal Transduct Target Ther* 2021;**6**:49. https://doi.org/10.1038/s41392-020-00428-9.
32. Ni L, Yuan C, Wu X. Targeting ferroptosis in acute kidney injury. *Cell Death Dis* 2022;**13**:182. https://doi.org/10.1038/s41419-022-04628-9.
33. Ide S, Kobayashi Y, Ide K, Strausser SA, Abe K, Herbek S. *et al.* Ferroptotic stress promotes the accumulation of pro-inflammatory proximal tubular cells in maladaptive renal repair. *elife* 2021;**10**:10. https://doi.org/10.7554/eLife.68603.
34. Zhang B, Chen X, Ru F, Gan Y, Li B, Xia W. *et al.* Liproxstatin-1 attenuates unilateral ureteral obstruction-induced renal fibrosis by inhibiting renal tubular epithelial cells ferroptosis. *Cell Death Dis* 2021;**12**:843. https://doi.org/10.1038/s41419-021-04137-1.
35. Guo R, Duan J, Pan S, Cheng F, Qiao Y, Feng Q. *et al.* The road from AKI to CKD: molecular mechanisms and therapeutic targets of Ferroptosis. *Cell Death Dis* 2023;**14**:426. https://doi.org/10.1038/s41419-023-05969-9.
36. Gao J, Zhou Q, Wu D, Chen L Mitochondrial iron metabolism and its role in diseases. *Clin Chim Acta* 2021;**513**:6–12. https://doi.org/10.1016/j.cca.2020.12.005.
37. Li Z, Lu S, Li X. The role of metabolic reprogramming in tubular epithelial cells during the progression of acute kidney injury. *Cell Mol Life Sci* 2021;**78**:5731–41. https://doi.org/10.1007/s00018-021-03892-w.
38. Zhu Z, Hu J, Chen Z, Feng J, Yang X, Liang W. *et al.* Transition of acute kidney injury to chronic kidney disease: role of metabolic reprogramming. *Metabolism* 2022;**131**:155194. https://doi.org/10.1016/j.metabol.2022.155194.
39. Cheng L, Hill AF. Therapeutically harnessing extracellular vesicles. *Nat Rev Drug Discov* 2022;**21**:379–99. https://doi.org/10.1038/s41573-022-00410-w.
40. Buzas EI. The roles of extracellular vesicles in the immune system. *Nat Rev Immunol* 2023;**23**:236–50. https://doi.org/10.1038/s41577-022-00763-8.
41. Lv L-L, Feng Y, Wu M, Wang B, Li ZL, Zhong X. *et al.* Exosomal miRNA-19b-3p of tubular epithelial cells promotes M1 macrophage activation in kidney injury. *Cell Death Differ* 2020;**27**:210–26. https://doi.org/10.1038/s41418-019-0349-y.
42. Mossberg M, Ståhl A-L, Kahn R, Kristoffersson AC, Tati R, Heijl C. *et al.* C1-inhibitor decreases the release of Vasculitis-like chemotactic endothelial microvesicles. *J Am Soc Nephrol* 2017;**28**:2472–81. https://doi.org/10.1681/ASN.2016060637.
43. Guan H, Peng R, Mao L, Fang F, Xu B, Chen M Injured tubular epithelial cells activate fibroblasts to promote kidney fibrosis through miR-150-containing exosomes. *Exp Cell Res* 2020;**392**:112007. https://doi.org/10.1016/j.yexcr.2020.112007.
44. Zhao S, Li W, Yu W, Rao T, Li H, Ruan Y. *et al.* Exosomal miR-21 from tubular cells contributes to renal fibrosis by activating fibroblasts via targeting PTEN in obstructed kidneys. *Theranostics* 2021;**11**:8660–73. https://doi.org/10.7150/thno.62820.
45. Murakami T, Oakes M, Ogura M, Tovar V, Yamamoto C, Mitsuhashi M Development of glomerulus-, tubule-, and collecting duct-specific mRNA assay in human urinary exosomes and microvesicles. *PLoS One* 2014;**9**:e109074. https://doi.org/10.1371/journal.pone.0109074.
46. Zhou H, Cheruvanky A, Hu X, Matsumoto T, Hiramatsu N, Cho ME. *et al.* Urinary exosomal transcription factors, a new class of biomarkers for renal disease. *Kidney Int* 2008;**74**:613–21. https://doi.org/10.1038/ki.2008.206.
47. Dilliard SA, Cheng Q, Siegwart DJ. On the mechanism of tissue-specific mRNA delivery by selective organ targeting nanoparticles. *Proc Natl Acad Sci USA* 2021;**118**. https://doi.org/10.1073/pnas.2109256118.
48. Dadfar SM, Roemhild K, Drude NI, von Stillfried S, Knüchel R, Kiessling F. *et al.* Iron oxide nanoparticles: diagnostic, therapeutic and theranostic applications. *Adv Drug Deliv Rev* 2019;**138**:302–25. https://doi.org/10.1016/j.addr.2019.01.005.
49. Lisik K, Krokosz A. Application of carbon nanoparticles in oncology and regenerative medicine. *Int J Mol Sci* 2021;**22**. https://doi.org/10.3390/ijms22158341.
50. Tiwari JN, Tiwari RN, Kim KS. Zero-dimensional, one-dimensional, two-dimensional and three-dimensional nanostructured materials for advanced electrochemical energy devices. *Prog Mater Sci* 2012;**57**:724–803. https://doi.org/10.1016/j.pmatsci.2011.08.003.
51. Waheed S, Li Z, Zhang F, Chiarini A, Armato U, Wu J Engineering nano-drug biointerface to overcome biological barriers toward precision drug delivery. *J Nanobiotechnology* 2022;**20**:395. https://doi.org/10.1186/s12951-022-01605-4.
52. Park E-Y, Oh D, Park S, Kim W, Kim C New contrast agents for photoacoustic imaging and theranostics: recent 5-year overview on phthalocyanine/naphthalocyanine-based nanoparticles. *APL Bioeng* 2021;**5**:031510. https://doi.org/10.1063/5.0047660.
53. Yetisen AK, Montelongo Y, da Cruz VF, Martinez-Hurtado JL, Neupane S, Butt H. *et al.* Reusable, robust, and accurate laser-generated photonic nanosensor. *Nano Lett* 2014;**14**:3587–93. https://doi.org/10.1021/nl5012504.
54. Łukasiewicz S, Szczepanowicz K, Podgórna K, Błasiak E, Majeed N, Ogren SOÖ. *et al.* Encapsulation of clozapine in polymeric nanocapsules and its biological effects. *Colloids Surf B Biointerfaces* 2016;**140**:342–52. https://doi.org/10.1016/j.colsurfb.2015.12.044.
55. Szczęch M, Szczepanowicz K. Polymeric Core-Shell nanoparticles prepared by spontaneous emulsification solvent evaporation and functionalized by the layer-by-layer method. *Nanomaterials (Basel)* 2020;**10**:10. https://doi.org/10.3390/nano10030496.
56. Souto EB, Souto SB, Campos JR, Severino P, Pashirova TN, Zakharova LY. *et al.* Nanoparticle delivery Systems in the Treatment of diabetes complications. *Molecules* 2019;**24**. https://doi.org/10.3390/molecules24234209.
57. Yan X, Bernard J, Ganachaud F. Nanoprecipitation as a simple and straightforward process to create complex polymeric colloidal morphologies. *Adv Colloid Interf Sci* 2021;**294**:102474. https://doi.org/10.1016/j.cis.2021.102474.
58. Oroojalian F, Charbgoo F, Hashemi M, Amani A, Yazdian-Robati R, Mokhtarzadeh A. *et al.* Recent advances in nanotechnology-based drug delivery systems for the kidney. *J Control Release* 2020;**321**:442–62. https://doi.org/10.1016/j.jconrel.2020.02.027.
59. da Silva Júnior WF, de Oliveira Pinheiro JG, Moreira CDLFA, de Souza FJJ, de Lima ÁAN. Chapter 15 - Alternative Technologies to Improve Solubility and Stability of Poorly Water-Soluble Drugs. In: Grumezescu AM, editor. *Multifunctional Systems for Combined Delivery, Biosensing and Diagnostics*: Elsevier; 2017. p. 281–305, https://doi.org/10.1016/B978-0-323-52725-5.00015-0.
60. Deng S, Gigliobianco MR, Censi R, di Martino P Polymeric Nanocapsules as Nanotechnological alternative for drug delivery system: current status, challenges and opportunities. *Nanomaterials (Basel)* 2020;**10**:10. https://doi.org/10.3390/nano10050847.
61. Yu H, Lin T, Chen W, Cao W, Zhang C, Wang T. *et al.* Size and temporal-dependent efficacy of oltipraz-loaded PLGA

nanoparticles for treatment of acute kidney injury and fibrosis. *Biomaterials* 2019;**219**:119368. https://doi.org/10.1016/j.biomaterials.2019.119368.
62. Huang H, Feng W, Chen Y, Shi J Inorganic nanoparticles in clinical trials and translations. *Nano Today* 2020;**35**:100972. https://doi.org/10.1016/j.nantod.2020.100972.
63. Fan J, Cheng Y, Sun M. Functionalized gold nanoparticles: synthesis, properties and biomedical applications. *Chem Rec* 2020;**20**:1474–504. https://doi.org/10.1002/tcr.202000087.
64. Kim H-M, Hong Jeong D, Lee H-Y, Park JH, Lee SK Improved stability of gold nanoparticles on the optical fiber and their application to refractive index sensor based on localized surface plasmon resonance. *Opt Laser Technol* 2019;**114**:171–8. https://doi.org/10.1016/j.optlastec.2019.02.002.
65. Neuwelt EA, Hamilton BE, Varallyay CG, Rooney WR, Edelman RD, Jacobs PM. *et al.* Ultrasmall superparamagnetic iron oxides (USPIOs): a future alternative magnetic resonance (MR) contrast agent for patients at risk for nephrogenic systemic fibrosis (NSF)? *Kidney Int* 2009;**75**:465–74. https://doi.org/10.1038/ki.2008.496.
66. Iversen NK, Frische S, Thomsen K, Laustsen C, Pedersen M, Hansen PBL. *et al.* Superparamagnetic iron oxide polyacrylic acid coated γ-Fe2O3 nanoparticles do not affect kidney function but cause acute effect on the cardiovascular function in healthy mice. *Toxicol Appl Pharmacol* 2013;**266**:276–88. https://doi.org/10.1016/j.taap.2012.10.014.
67. Schutter R, Lantinga VA, Borra RJH, Moers C MRI for diagnosis of post-renal transplant complications: current state-of-the-art and future perspectives. *MAGMA* 2020;**33**:49–61. https://doi.org/10.1007/s10334-019-00813-8.
68. Richbourg, Peppas NA. The swollen polymer network hypothesis: quantitative models of hydrogel swelling, stiffness, and solute transport. 2020;**105**:101243. https://doi.org/10.1016/j.progpolymsci.2020.101243.
69. Cao H, Duan L, Zhang Y, Cao J, Zhang K. Current hydrogel advances in physicochemical and biological response-driven biomedical application diversity. *Signal Transduct Target Ther* 2021;**6**:426. https://doi.org/10.1038/s41392-021-00830-x.
70. Jansen K, Schuurmans CL, Jansen J, Masereeuw R, Vermonden T Hydrogel-based cell therapies for kidney regeneration: current trends in biofabrication and in vivo repair. *Curr Pharm Des* 2017;**23**:3845–57. https://doi.org/10.2174/1381612823666170710155726.
71. Shaikh H, Rho JY, Macdougall LJ, Gurnani P, Lunn AM, Yang J. *et al.* Hydrogel and Organogel formation by hierarchical self-assembly of cyclic peptides nanotubes. *Chemistry* 2018;**24**:19066–74. https://doi.org/10.1002/chem.201804576.
72. Ahmed EM. Hydrogel: preparation, characterization, and applications: a review. *J Adv Res* 2015;**6**:105–21. https://doi.org/10.1016/j.jare.2013.07.006.
73. Feng G, Zhang J, Li Y, Nie Y, Zhu D, Wang R. *et al.* IGF-1 C domain-modified hydrogel enhances cell therapy for AKI. *J Am Soc Nephrol* 2016;**27**:2357–69. https://doi.org/10.1681/ASN.2015050578.
74. Liu Y, Cui J, Wang H, Hezam K, Zhao X, Huang H. *et al.* Enhanced therapeutic effects of MSC-derived extracellular vesicles with an injectable collagen matrix for experimental acute kidney injury treatment. *Stem Cell Res Ther* 2020;**11**:161. https://doi.org/10.1186/s13287-020-01668-w.
75. Pinheiro AV, Han D, Shih WM, Yan H Challenges and opportunities for structural DNA nanotechnology. *Nat Nanotechnol* 2011;**6**:763–72. https://doi.org/10.1038/nnano.2011.187.
76. Udomprasert A, Kangsamaksin T. DNA origami applications in cancer therapy. *Cancer Sci* 2017;**108**:1535–43. https://doi.org/10.1111/cas.13290.
77. Wang P, Rahman MA, Zhao Z, Weiss K, Zhang C, Chen Z. *et al.* Visualization of the cellular uptake and trafficking of DNA origami nanostructures in cancer cells. *J Am Chem Soc* 2018;**140**:2478–84. https://doi.org/10.1021/jacs.7b09024.
78. Mathur D, Galvan AR, Green CM, Liu K, Medintz IL Uptake and stability of DNA nanostructures in cells: a cross-sectional overview of the current state of the art. *Nanoscale* 2023;**15**:2516–28. https://doi.org/10.1039/D2NR05868E.
79. Dai L, Liu P, Hu X, Zhao X, Shao G, Tian Y DNA origami: an outstanding platform for functions in nanophotonics and cancer therapy. *Analyst* 2021;**146**:1807–19. https://doi.org/10.1039/D0AN02160A.
80. Lawrence MG, Altenburg MK, Sanford R, Willett JD, Bleasdale B, Ballou B. *et al.* Permeation of macromolecules into the renal glomerular basement membrane and capture by the tubules. *Proc Natl Acad Sci USA* 2017;**114**:2958–63. https://doi.org/10.1073/pnas.1616457114.
81. Ruggiero A, Villa CH, Bander E, Rey DA, Bergkvist M, Batt CA. *et al.* Paradoxical glomerular filtration of carbon nanotubes. *Proc Natl Acad Sci USA* 2010;**107**:12369–74. https://doi.org/10.1073/pnas.0913667107.
82. Liu Q, Chen X, Kan M, Yang J, Gong Q, Jin R. *et al.* Gypenoside XLIX loaded nanoparticles targeting therapy for renal fibrosis and its mechanism. *Eur J Pharmacol* 2021;**910**:174501. https://doi.org/10.1016/j.ejphar.2021.174501.
83. Vallorz EL, Blohm-Mangone K, Schnellmann RG, Mansour HM Formoterol PLGA-PEG nanoparticles induce mitochondrial biogenesis in renal proximal tubules. *AAPS J* 2021;**23**:88. https://doi.org/10.1208/s12248-021-00619-4.
84. Samadarsi R, Dutta D. Anti-oxidative effect of mangiferin-chitosan nanoparticles on oxidative stress-induced renal cells. *Int J Biol Macromol* 2020;**151**:36–46. https://doi.org/10.1016/j.ijbiomac.2020.02.112.
85. Liu D, Shu G, Jin F, Qi J, Xu X, Du Y. *et al.* ROS-responsive chitosan-SS31 prodrug for AKI therapy via rapid distribution in the kidney and long-term retention in the renal tubule. *Sci Adv* 2020;**6**:6. https://doi.org/10.1126/sciadv.abb7422.
86. Hu J-B, Li S-J, Kang X-Q, Qi J, Wu J-H, Wang X-J. *et al.* CD44-targeted hyaluronic acid-curcumin prodrug protects renal tubular epithelial cell survival from oxidative stress damage. *Carbohydr Polym* 2018;**193**:268–80. https://doi.org/10.1016/j.carbpol.2018.04.011.
87. Guo H, Lan T, Lu X, Geng K, Shen X, Mao H. *et al.* ROS-responsive curcumin-encapsulated nanoparticles for AKI therapy via promoting lipid degradation in renal tubules. *J Mater Chem B* 2024;**12**:3063–78. https://doi.org/10.1039/D3TB02318D.
88. Wang H, Yu D, Fang J, Zhou Y, Li D, Liu Z. *et al.* Phenol-like group functionalized graphene quantum dots structurally mimicking natural antioxidants for highly efficient acute kidney injury treatment. *Chem Sci* 2020;**11**:12721–30. https://doi.org/10.1039/D0SC03246H.
89. Gao J, Liu Y, Jiang B, Cao W, Kan Y, Chen W. *et al.* Phenylenediamine-based carbon Nanodots alleviate acute kidney injury via preferential renal accumulation and antioxidant capacity. *ACS Appl Mater Interfaces* 2020;**12**:31745–56. https://doi.org/10.1021/acsami.0c05041.
90. Rosenkrans ZT, Sun T, Jiang D, Chen W, Barnhart TE, Zhang Z. *et al.* Selenium-doped carbon quantum dots act as broad-Spectrum antioxidants for acute kidney injury management. *Adv Sci (Weinh)* 2020;**7**:2000420. https://doi.org/10.1002/advs.202000420.
91. Ni D, Jiang D, Kutyreff CJ, Lai J, Yan Y, Barnhart TE. *et al.* Molybdenum-based nanoclusters act as antioxidants and ameliorate acute kidney injury in mice. *Nat Commun* 2018;**9**:5421. https://doi.org/10.1038/s41467-018-07890-8.
92. Hou J, Wang H, Ge Z, Zuo T, Chen Q, Liu X. *et al.* Treating acute kidney injury with Antioxidative black phosphorus Nanosheets. *Nano Lett* 2020;**20**:1447–54. https://doi.org/10.1021/acs.nanolett.9b05218.
93. Yu H, Jin F, Liu D, Shu G, Wang X, Qi J. *et al.* ROS-responsive nano-drug delivery system combining mitochondria-targeting ceria nanoparticles with atorvastatin for acute kidney

injury. *Theranostics* 2020;**10**:2342–57. https://doi.org/10.7150/thno.40395.
94. Jiang D, Ge Z, Im H-J, England CG, Ni D, Hou J. *et al.* DNA origami nanostructures can exhibit preferential renal uptake and alleviate acute kidney injury. *Nat Biomed Eng* 2018;**2**:865–77. https://doi.org/10.1038/s41551-018-0317-8.
95. Chen Q, Ding F, Zhang S, Li Q, Liu X, Song H. *et al.* Sequential therapy of acute kidney injury with a DNA Nanodevice. *Nano Lett* 2021;**21**:4394–402. https://doi.org/10.1021/acs.nanolett.1c01044.
96. Yan R, Cui W, Ma W, Li J, Liu Z, Lin Y. Typhaneoside-tetrahedral framework nucleic acids system: mitochondrial recovery and Antioxidation for acute kidney injury treatment. *ACS Nano* 2023;**17**:8767–81. https://doi.org/10.1021/acsnano.3c02102.
97. Zhang Q, Lin S, Wang L, Peng S, Tian T, Li S. *et al.* Tetrahedral framework nucleic acids act as antioxidants in acute kidney injury treatment. *Chem Eng J* 2021;**413**:127426. https://doi.org/10.1016/j.cej.2020.127426.
98. Tsurkan MV, Hauser PV, Zieris A, Carvalhosa R, Bussolati B, Freudenberg U. *et al.* Growth factor delivery from hydrogel particle aggregates to promote tubular regeneration after acute kidney injury. *J Control Release* 2013;**167**:248–55. https://doi.org/10.1016/j.jconrel.2013.01.030.
99. Zhao M, Zhou Y, Liu S, Li L, Chen Y, Cheng J. *et al.* Control release of mitochondria-targeted antioxidant by injectable self-assembling peptide hydrogel ameliorated persistent mitochondrial dysfunction and inflammation after acute kidney injury. *Drug Deliv* 2018;**25**:546–54. https://doi.org/10.1080/10717544.2018.1440445.
100. van Alem CMA, Boonstra M, Prins J, Bezhaeva T, van Essen MF, Ruben JM. *et al.* Local delivery of liposomal prednisolone leads to an anti-inflammatory profile in renal ischaemia-reperfusion injury in the rat. *Nephrol Dial Transplant* 2018;**33**:44–53. https://doi.org/10.1093/ndt/gfx204.
101. Zhang J, Gu L, Jiang Y, Ma Y, Zhang Z, Shen S. *et al.* Artesunate-Nanoliposome-TPP, a novel drug delivery system that targets the mitochondria, attenuates cisplatin-induced acute kidney injury by suppressing oxidative stress and inflammatory effects. *Int J Nanomedicine* 2024;**19**:1385–408. https://doi.org/10.2147/IJN.S444076.
102. Huang Z-W, Shi Y, Zhai Y-Y, Du C-C, Zhai J, Yu R-J. *et al.* Hyaluronic acid coated bilirubin nanoparticles attenuate ischemia reperfusion-induced acute kidney injury. *J Control Release* 2021;**334**:275–89. https://doi.org/10.1016/j.jconrel.2021.04.033.
103. Sun J, Zhao X, Shen H, Dong J, Rong S, Cai W, *et al.* CD44-targeted melanin-based nanoplatform for alleviation of ischemia/reperfusion-induced acute kidney injury. *J Control Release* 2024;**368**:1–14. https://doi.org/10.1016/j.jconrel.2024.02.021.
104. Rahdar A, Hasanein P, Bilal M, Beyzaei H, Kyzas GZ. *et al.* Quercetin-loaded F127 nanomicelles: antioxidant activity and protection against renal injury induced by gentamicin in rats. *Life Sci* 2021;**276**:119420. https://doi.org/10.1016/j.lfs.2021.119420.
105. Zhao M, Guo J, Tian C, Yan M, Zhou Y, Liu C. *et al.* Dual-targeted nanoparticles with removing ROS inside and outside mitochondria for acute kidney injury treatment. *Nanomedicine* 2024;**55**:102725. https://doi.org/10.1016/j.nano.2023.102725.
106. Zhang D-Y, Tu T, Younis MR, Zhu KS, Liu H, Lei S. *et al.* Clinically translatable gold nanozymes with broad spectrum antioxidant and anti-inflammatory activity for alleviating acute kidney injury. *Theranostics* 2021;**11**:9904–17. https://doi.org/10.7150/thno.66518.
107. Zhang D-Y, Liu H, Younis MR, Lei S, Yang C, Lin J. *et al.* Ultrasmall platinum nanozymes as broad-spectrum antioxidants for theranostic application in acute kidney injury. *Chem Eng J* 2021;**409**:127371. https://doi.org/10.1016/j.cej.2020.127371.
108. Matsushita K, Toyoda T, Yamada T, Morikawa T, Ogawa K Specific expression of survivin, SOX9, and CD44 in renal tubules in adaptive and maladaptive repair processes after acute kidney injury in rats. *J Appl Toxicol* 2021;**41**:607–17. https://doi.org/10.1002/jat.4069.
109. Kim CK, Kim T, Choi I-Y, Soh M, Kim D, Kim YJ. *et al.* Ceria nanoparticles that can protect against ischemic stroke. *Angew Chem Int Ed Engl* 2012;**51**:11039–43. https://doi.org/10.1002/anie.201203780.
110. AlBasher G, Alfarraj S, Alarifi S, Alkhtani S, Almeer R, Alsultan N. *et al.* Nephroprotective role of selenium nanoparticles against glycerol-induced acute kidney injury in rats. *Biol Trace Elem Res* 2020;**194**:444–54. https://doi.org/10.1007/s12011-019-01793-5.
111. Liu M, Huang Q, Zhu Y, Chen L, Li Y, Gong Z. *et al.* Harnessing reactive oxygen/nitrogen species and inflammation: Nanodrugs for liver injury. *Materials Today Bio* 2022;**13**:100215. https://doi.org/10.1016/j.mtbio.2022.100215.
112. Wang K, Zhang Y, Mao W, Feng W, Lu S, Wan J. *et al.* Engineering Ultrasmall Ferroptosis-targeting and reactive oxygen/nitrogen species-scavenging Nanozyme for alleviating acute kidney injury. *Adv Funct Mater* 2022;**32**:2109221. https://doi.org/10.1002/adfm.202109221.
113. Xie X, Zhang Y, Su X, Wang J, Yao X, Lv D. *et al.* Targeting iron metabolism using gallium nanoparticles to suppress ferroptosis and effectively mitigate acute kidney injury. *Nano Res* 2022;**15**:6315–27. https://doi.org/10.1007/s12274-022-4257-y.
114. Deng L, Xiao M, Wu A, He D, Huang S, Deng T. *et al.* Se/albumin nanoparticles for inhibition of Ferroptosis in tubular epithelial cells during acute kidney injury. 2022;**5**:227–36. https://doi.org/10.1021/acsanm.1c02706.
115. Zhang Y, Wu J, An Q, Zhu H, Su X, Wang Y. *et al.* Renal tubule-targeted dexrazoxane suppresses ferroptosis in acute kidney injury by inhibiting ACMSD. *Nano Res* 2023;**16**:9701–14. https://doi.org/10.1007/s12274-023-5547-8.
116. Li J, Wei L, Zhang Y, Wu M Tetrahedral DNA nanostructures inhibit Ferroptosis and apoptosis in cisplatin-induced renal injury. *ACS Appl Bio Mater* 2021;**4**:5026–32. https://doi.org/10.1021/acsabm.1c00294.
117. Zhang K, Li R, Chen X, Yan H, Li H, Zhao X. *et al.* Renal endothelial cell-targeted extracellular vesicles protect the kidney from ischemic injury. *Adv Sci (Weinh)* 2023;**10**:e2204626. https://doi.org/10.1002/advs.202204626.
118. Yea J-H, Yoon YM, Lee JH, Yun CW, Lee SH Exosomes isolated from melatonin-stimulated mesenchymal stem cells improve kidney function by regulating inflammation and fibrosis in a chronic kidney disease mouse model. *J Tissue Eng* 2021;**12**:20417314211059624.
119. Tang T-T, Wang B, Wu M, Li ZL, Feng Y, Cao JY. *et al.* Extracellular vesicle-encapsulated IL-10 as novel nanotherapeutics against ischemic AKI. *Sci Adv* 2020;**6**:eaaz0748. https://doi.org/10.1126/sciadv.aaz0748.
120. Tang T-T, Wang B, Li Z-L, Wen Y, Feng ST, Wu M. *et al.* Kim-1 targeted extracellular vesicles: a new therapeutic platform for RNAi to treat AKI. *J Am Soc Nephrol* 2021;**32**:2467–83. https://doi.org/10.1681/ASN.2020111561.
121. Zhang C, Shang Y, Chen X, Midgley AC, Wang Z, Zhu D. *et al.* Supramolecular nanofibers containing arginine-glycine-aspartate (RGD) peptides boost therapeutic efficacy of extracellular vesicles in kidney repair. *ACS Nano* 2020;**14**:12133–47. https://doi.org/10.1021/acsnano.0c05681.
122. Zhou Y, Liu S, Zhao M, Wang C, Li L, Yuan Y. *et al.* Injectable extracellular vesicle-released self-assembling peptide nanofiber hydrogel as an enhanced cell-free therapy for tissue regeneration. *J Control Release* 2019;**316**:93–104. https://doi.org/10.1016/j.jconrel.2019.11.003.
123. Tang W, Panja S, Jogdeo CM, Tang S, Ding L, Yu A. *et al.* Modified chitosan for effective renal delivery of siRNA to treat

acute kidney injury. *Biomaterials* 2022;**285**:121562. https://doi.org/10.1016/j.biomaterials.2022.121562.
124. Tang W, Chen Y, Jang H-S, Hang Y, Jogdeo CM, Li J. *et al.* Preferential siRNA delivery to injured kidneys for combination treatment of acute kidney injury. *J Control Release* 2022;**341**:300–13. https://doi.org/10.1016/j.jconrel.2021.11.029.
125. Cao J-Y, Wang B, Tang T-T, Wen Y, Li ZL, Feng ST. *et al.* Exosomal miR-125b-5p deriving from mesenchymal stem cells promotes tubular repair by suppression of p53 in ischemic acute kidney injury. *Theranostics* 2021;**11**:5248–66. https://doi.org/10.7150/thno.54550.
126. Thai HBD, Kim K-R, Hong KT, Voitsitskyi T, Lee JS, Mao C. *et al.* Kidney-targeted cytosolic delivery of siRNA using a small-sized mirror DNA tetrahedron for enhanced potency. *ACS Cent Sci* 2020;**6**:2250–8. https://doi.org/10.1021/acscentsci.0c00763.
127. Li R, Li Y, Zhang J, Liu Q, Wu T, Zhou J. *et al.* Targeted delivery of celastrol to renal interstitial myofibroblasts using fibronectin-binding liposomes attenuates renal fibrosis and reduces systemic toxicity. *J Control Release* 2020;**320**:32–44. https://doi.org/10.1016/j.jconrel.2020.01.017.
128. Aslam Saifi M, Hirawat R, Godugu C. Lactoferrin-decorated cerium oxide nanoparticles prevent renal injury and fibrosis. *Biol Trace Elem Res* 2023;**201**:1837–45. https://doi.org/10.1007/s12011-022-03284-6.
129. Midgley AC, Wei Y, Zhu D, Gao F, Yan H, Khalique A. *et al.* Multifunctional natural polymer nanoparticles as Antifibrotic gene carriers for CKD therapy. *J Am Soc Nephrol* 2020;**31**:2292–311. https://doi.org/10.1681/ASN.2019111160.
130. Karlstetter M, Kopatz J, Aslanidis A, Shahraz A, Caramoy A, Linnartz-Gerlach B. *et al.* Polysialic acid blocks mononuclear phagocyte reactivity, inhibits complement activation, and protects from vascular damage in the retina. *EMBO Mol Med* 2017;**9**:154–66. https://doi.org/10.15252/emmm.201606627.
131. Quesenberry PJ, Goldberg LR, Aliotta JM, Dooner MS, Pereira MG, Wen S. *et al.* Cellular phenotype and extracellular vesicles: basic and clinical considerations. *Stem Cells Dev* 2014;**23**:1429–36. https://doi.org/10.1089/scd.2013.0594.
132. Bernkop-Schnürch A, Dünnhaupt S. Chitosan-based drug delivery systems. *Eur J Pharm Biopharm* 2012;**81**:463–9. https://doi.org/10.1016/j.ejpb.2012.04.007.
133. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. *Nephron Clinical Practice* 2012;**120**:c179–84. https://doi.org/10.1159/000339789.
134. Stamopoulos D, Bouziotis P, Benaki D, Kotsovassilis C, Zirogiannis PN Utilization of nanobiotechnology in haemodialysis: mock-dialysis experiments on homocysteine. *Nephrology Dialysis Transplantation* 2008;**23**:3234–9. https://doi.org/10.1093/ndt/gfn189.
135. Ba X, Ye T, Shang H, Tong Y, Huang Q, He Y. *et al.* Recent advances in nanomaterials for the treatment of acute kidney injury. *ACS Appl Mater Interfaces* 2024;**16**:12117–48. https://doi.org/10.1021/acsami.3c19308.
136. Yildirimer L, Thanh NTK, Loizidou M, Seifalian AM Toxicology and clinical potential of nanoparticles. *Nano Today* 2011;**6**:585–607. https://doi.org/10.1016/j.nantod.2011.10.001.
137. Wang P, Meyer TA, Pan V, Dutta PK, Ke Y The beauty and utility of DNA origami. *Chem* 2017;**2**:359–82. https://doi.org/10.1016/j.chempr.2017.02.009.
138. Packialakshmi B, Stewart IJ, Burmeister DM, Chung KK, Zhou X Large animal models for translational research in acute kidney injury. *Ren Fail* 2020;**42**:1042–58. https://doi.org/10.1080/0886022X.2020.1830108.