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Review article

Nanodrugs alleviate acute kidney injury: Manipulate RONS at kidney

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ABSTRACT

Currently, there are no clinical drugs available to treat acute kidney injury (AKI). Given the high prevalence and high mortality rate of AKI, the development of drugs to effectively treat AKI is a huge unmet medical need and a research hotspot. Although existing evidence fully demonstrates that reactive oxygen and nitrogen species (RONS) burst at the AKI site is a major contributor to AKI progression, the heterogeneity, complexity, and unique physiological structure of the kidney make most antioxidant and anti-inflammatory small molecule drugs ineffective because of the lack of kidney targeting and side effects. Recently, nanodrugs with intrinsic kidney targeting through the control of size, shape, and surface properties have opened exciting prospects for the treatment of AKI. Many antioxidant nanodrugs have emerged to address the limitations of current AKI treatments. In this review, we systematically summarized for the first time about the emerging nanodrugs that exploit the pathological and physiological features of the kidney to overcome the limitations of traditional small-molecule drugs to achieve high AKI efficacy. First, we analyzed the pathological structural characteristics of AKI and the main pathological mechanism of AKI: hypoxia, harmful substance accumulation-induced RONS burst at the renal site despite the multifactorial initiation and heterogeneity of AKI. Subsequently, we introduced the strategies used to improve renal targeting and reviewed advances of nanodrugs for AKI: nano-RONS-sacrificial agents, antioxidant nanozymes, and nanocarriers for antioxidants and anti-inflammatory drugs. These nanodrugs have demonstrated excellent therapeutic effects, such as greatly reducing oxidative stress damage, restoring renal function, and low side effects. Finally, we discussed the challenges and future directions for translating nanodrugs into clinical AKI treatment.

1. Introduction :

The kidney, as one of the most important organs in maintaining body homeostasis, receives 20–25% of blood perfusion, allowing it to efficiently remove metabolic wastes; however, the high solute exchange at the renal tubules causes the kidneys to have a high oxygen (O_2) demand (~7% of the body's total O_2 consumption) [1]. As a result, the kidney is always exposed to high levels of harmful substances and at risk of hypoxia [2–4]. Acute kidney injury (AKI) is defined as a rapid decline of kidney function over a short period (<7 days), which is characterized by high morbidity and mortality [5]. In the current COVID-19 pandemic context, AKI is a widespread concern because it affects up to ~35.6% of patients with severe COVID-19 [6]. In fact, many other factors can also lead to AKI, such as perioperative, sepsis, nephrotoxic drug, rhabdomyolysis, malignancy, etc. [7] (Fig. 1a). Up to 13 million new AKI cases occur each year worldwide [8], affecting 10–15% of hospitalized patients and over 50% of ICU patients [9]. Many of these individuals develop chronic kidney disease (9.1% of the world's total population),

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Fig. 1. Etiology of AKI and distal multi-organ dysfunction caused by AKI. There is a variety of common factors that can lead to AKI, such as malignancy, sepsis, perioperative period, and nephrotoxic drugs (a). Besides, AKI predisposes lead to distal multi-organ dysfunction such as cardiovascular diseases, acute lung injury, brain dysfunction, liver dysfunction, and systemic inflammation to increase mortality in AKI patients by systemic or organ-specific hemodynamic, fluid, and immune

Fig. 2. The scope and focus of this article. The excessive production of RONS contributes critically to the development of various AKI. Harnessing RONS appears to be the most effective strategy to restore the redox balance and ameliorate renal injury. RONS-scavenging nanomaterials used for AKI antioxidant therapy are divided into three categories: nano-RONS-sacrificial agents; antioxidant nanozymes and nanocarriers for antioxidants and anti-inflammatory drugs.



Fig. 3. Overview of AKI pathology. (A) Renal microcirculation structure and O_2 shunting. The high O_2 consumption for tubular reabsorption aggravated the burden of hypoxia in kidney (i). The series connection of glomerular capillary network and peritubular capillary network (ii). The oxygen shunts between the countercurrent parallel arranged interlobular arteries and veins (iii, v), descending limb, and ascending limb (iv). AV, arterial-to-venous. **(B)** Schematic illustration of harmful substance accumulation in typical AKI. (i) Schematic structure of the glomerular filtration barrier (GFB). GFB comprises three specialized layers: endothelial fenestration (60–100 nm), glomerular basement membrane (reticular slit ~10 nm), and podocytes with filtration slit (7–11 nm). The red arrow shows the filtration characteristics of GFB. (ii) During AKI, the damaged GFB allows more filtration of proteins and harmful substances in the renal tubules and severe oxidative stress.



Fig. 4. Overview of AKI pathology. (A) Pathophysiological response of typical AKI. **(i)** Operation, sepsis, and nephrotoxic drugs can induce oxidative stress, microcirculation dysfunction, inflammation, and adaptive response in kidney. (ii) In perioperative AKI, the I/R or hypoperfusion to kidney during perioperative period reduces O₂ supply to tubular epithelium cells and induces severe oxidative stress. Hemoglobin release caused by hemolysis brings toxic to renal tubules. (iii) Sepsis induces disproportionate vascular resistance between the glomerular afferent and efferent small arteries and heterogeneous change of the renal microcirculation. The release of DAMPs and/or the presence of PAMPs in kidney activate innate immunity to induce inflammation and damage renal microcirculation. (iv) The nephrotoxic drugs that accumulate in kidneys will trigger severe oxidative stress and followed by cell death in both renal tubular epithelium cells and endothelial cells. (v) Overall, these changes can result in constriction of blood vessels in the kidney, decreased renal blood flow, GFR, tubular secretion, and urine output. Schematic illustration of renal tubular pathological mechanism in perioperative AKI **(B)**, S-AKI **(C)** and drug induced AKI **(D)**.

renal failure, multi-organ dysfunction, and even death (Fig. 1b) because of no effective treatment for AKI in clinical (only supportive treatment), which brings a heavy medical burden to the family and society [10]. For example, only dialysis-associated costs exceed 6% of the entire health insurance budget in the United States [11].

Diverse etiologies lead to heterogeneous AKI pathogenesis, which also poses a significant obstacle to its treatment [12–15]. However, all types of AKI are closely related to the excess reactive oxygen and nitrogen species (RONS) after summarizing the pathophysiological processes of various types of AKI [16,17]. If RONS in the injured kidneys are not eliminated in time, AKI will progress to irreversible renal fibrosis and renal failure, suggesting that RONS clearance is an imperative strategy for AKI treatment [18]. However, conventional antioxidants (direct eliminate RONS) and anti-inflammatory drugs (indirect eliminate RONS) have low renal targeting and high side effects, and may even be harmful (change renal blood flow or bring metabolism burden of high-dose drugs to the kidneys) in AKI due to the unique function and structure of the kidneys [19–21].

While nano-antioxidant therapy has advanced rapidly over the past decades, its therapeutic potential in AKI has received insufficient attention and exploitation from nanomedicine researchers, which can be attributed to the unsatisfactory progress in developing AKI antioxidant nanomaterials from a biomedical standpoint [22]. Many nano-researchers have a limited understanding of kidney physiology and AKI pathological process, which cause most of the current nanomedicine researches to stay on 'proof-of-concept studies (preclinical research, that support a scientific rationale but do not address the important questions in the broader drug development pipeline, like safety, efficacy, dosing regimen) because of lack of precise fit for clinical treatment problems. Meanwhile, most biomedical researchers, on the other hand, lack sufficient expertise in nanomaterials to fully identify and embrace the therapeutic promise of nano-antioxidants in AKI.

To help remove this barrier, herein we present the pathological mechanisms of typical AKI and highlighted the lethal role of various RONS in AKI. We focused on the different RONS sources in AKI, including the mitochondrial respiratory chain, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX), nitric oxide synthase (NOS), xanthine oxidase (XO), and myeloperoxidase (MPO) [23-26]. Next, we summarize the most significant breakthroughs in nanomaterials for antioxidant treatment in AKI, paying close attention to their RONS scavenging capabilities and renal targeting strategies. Specifically, these nanomaterials are divided into three parts: nano-RONS-sacrificial agents; antioxidant nanozymes; and nanocarriers for antioxidants and anti-inflammatory drugs (Fig. 2). Finally, we provide a thorough discussion of the prospects and opportunities in the field of AKI nanotherapeutics and highlight the limitations of current work from a clinical translational perspective. We hope that this review will also serve as a reference for developing more tailored AKI nanodrugs, improve understanding and appreciation of nanomaterials among the biomedical community, and stimulate more interdisciplinary researches to advance AKI therapeutics.

2. Overview of AKI pathology

To excrete various metabolic wastes from the blood into the urine, the kidney has many unique physiologic structures that make them more at risk of injury than other organs [27,28]. Overall, the kidney is particularly vulnerable to two factors: hypoxia and accumulation of harmful substances.

The kidney is susceptible to hypoxia despite receiving 20% of the cardiac output because blood flows through most organs to provide O_2 and nutrients, but the primary purpose through the kidneys is for purification [29,30]. Consequently, the kidney requires a large amount of O_2 from the circulatory system to replenish energy for reabsorption (Fig.3A, i) [31]. Unfortunately, the complex structure and function of the kidney lead to a physiological state in which the tubules themselves

are on the verge of suffocating [32]. The renal microcirculation is divided into two separate but interconnected capillary networks: the glomerular capillary network for filtration and the peritubular capillary network for reabsorption (Fig.3A, ii) [33]. This series of connections means that any blockage of upstream blood flow causes ischemia in the downstream vessels. In addition, an arterial infarction in one renal segment cannot be compensated for by other arteries because of no inter-arterial anastomosis between different renal artery segments [34]. Moreover, the O₂ delivery efficiency in the kidney is decreased by the diffuse O2 shunts between the cortical arteries and veins, as well as between the direct vessels of the descending and ascending limbs of the medulla (Fig. 3A, iii-iv) [35]. The O₂ shunt originates from the countercurrent arrangement of arteries and veins (i.e., arteries and veins are aligned in parallel and blood flow in opposite directions), allowing O₂ to travel down a concentration gradient between arterial and venous blood (Fig. 3A, v) [36].

Harmful substances in blood are mainly divided into two categories: exogenous substances like nephrotoxic drugs and pathogen-associated molecular patterns (PAMPs), and endogenous substances like inflammatory factors and damage-associated molecular patterns (DAMPs) [37]. The kidney is easily exposed to high circulating harmful substances because of its high proportion of the blood supply [38]. Moreover, kidney damage further accelerates harmful substance accumulation, forming a vicious cycle due to the organ's unique physiological structure (Fig. 3B, i) [39]. The glomerular filtration system bears the brunt of the damage when the kidney experiences ischemia or is exposed to harmful substances [40]. For instance, podocyte damage, glycocalyx loss and even apoptotic cell death are observed in AKI [41-45] (Fig.3B, ii). Renal tubular filtration system lesions allow harmful substances to more easily cross the barrier and accumulate in the renal tubules (Fig. 3B, iii). The harmful substances accumulation causes oxidative stress, inflammation, and adaptive responses in the renal tubules, which are the primary causes of renal tubular damage and impaired renal function [46].

Many factors cause kidney damage by affecting renal perfusion (mainly causing renal hypoxia) and harmful substances, including surgery, malignancy, cardiopulmonary dysfunction, hepatorenal syndrome, sepsis, and nephrotoxic drugs [47]. Among these, perioperative AKI, sepsis-associated AKI (S-AKI), and drug-induced AKI are the most common clinical causes (Fig.4A, i).

2.1. Perioperative AKI

Perioperative procedures are often accompanied by perioperative hemorrhage, hemolysis, persistent hypoperfusion, ischemia/reperfusion (I/R), and atherosclerotic plaque, which lead to low perfusion pressure beyond the kidney's regulable range [13,48]. Subsequently, the sympathetic nerves and renin-angiotensin-aldosterone system (RAAS) are activated to induce strong constriction of small inlet arteries (Fig.4A, ii), a significant reduction in renal blood flows, and a rapid decrease in glomerular filtration rate (GFR). Moreover, the free hemoglobin released by hemolysis can leak into extravascular tissues to cause the kidney damage when erythrocytes in the blood are exposed to air (i.e., wound exposure) or artificial surfaces [14,49-52]. Ultimately, ischemia-induced hypoxia and harmful substances (e.g., free hemoglobin, nonsteroidal anti-inflammatory drugs) administered during surgery lead to severe oxidative stress in renal tubule and induce AKI (Fig.4B, i-ii), with proximal tubular brush border loss and cast formations as the main pathological features [53] (Fig. 4B, iii).

2.2. Sepsis-associated AKI

Sepsis is a systemic inflammatory response syndrome caused by infection. AKI is one of the most common and serious complications in sepsis [54,55]. The decrease of GFR is not induced in S-AKI by inadequate renal perfusion, but by the disproportionate vascular resistance between the glomerular afferent and efferent small arteries (i.e.,



Fig. 5. Schematic illustration of RONS generation by mitochondrial respiratory chain. Complex I can create O_2^- in two ways. The first is during traditional forward electron transport, the electron leakage from FMN to O_2 results in the creation of O_2^- (**A**). The other way is related to the reverse transport of electrons. After I/R injury, the high proton driving force in the inner mitochondrial membrane, facilitates reverse electron transport at complex I, causing an O_2^- burst (**B**). Some proapoptotic compounds inhibit succinate coenzyme Q oxidoreductase activity in complex II, resulting in a direct single-electron reduction of O_2^- by the reduced ironsulfur cluster of complex II and the generation of O_2^- (**C**). The oxidation/reduction cycle of quinone generates unstable semiquinone intermediates that move freely within the complexes and are prone to leak electrons, resulting in the formation of O_2^- (**D**).

excessive dilatation of the efferent small arteries) [56]. In addition, overall renal hypoperfusion does not exclude the possibility of intrarenal perfusion redistribution due to microcirculatory dysfunction [57] (Fig. 4A, iii). Heterogeneous changes in the renal microcirculation occur and lead to the development of local hypoxia even without major blood flow instability. On the other hand, DAMPs and PAMPs abundantly exist in the circulation and cause systemic inflammation during sepsis [58]. DAMPs and PAMPs eventually enter the kidney through the circulatory system and are exposed to Toll-like receptors (TLR) on the surface of renal tubular epithelial cells (RTECs) during sepsis [59]. In addition, pro-inflammatory factors and recruited immune cells may migrate to RTECs from kidney microcirculation. Together, these lead to inflammation and oxidative stress damage to RTECs [60] (Fig.4C, i-ii). Hypoxia and inflammation rarely induce direct RTEC death, and the tubules exhibit only partially heterogeneous histopathological lesions thanks to the cellular adaptive response-characterized by intercellular signaling, metabolic reprogramming, and mitochondrial quality control-in S-AKI [61-65] (Fig. 4C, iii). Consequently, tissue biopsies from patients with S-AKI do not show diffuse tubular cell necrosis, but rather heterogeneous, focal, and patchy tubular injury [66,67].

2.3. Drug-induced AKI

Renal tubules are frequently exposed to potentially nephrotoxic drugs from the blood like antibiotics, chemotherapeutic agents, and contrast agents, etc [3,68]. These nephrotoxic drugs not only induce apoptosis or necrosis of RTECs by oxidative stress, but are also toxic to endothelial cells in renal microcirculation, severely impairing both renal structure and function (Fig.4A, iv) [69,70]. We take cisplatin (CP) as an example to illustrate the process of drug-induced AKI. Nephrotoxicity is the main dose-limiting factor for CP, with 30% of patients developing AKI after CP application [71]. CP is delivered from the basolateral circulation via the synergistic transport of organic cation transporter 2 (OCT2) and copper transporter 1(Ctr1) (Fig. 4D, i) [72]. CP entering cells induces massive RONS production via multiple pathways, which then causes lipid peroxidation and changes the structure and permeability of biological membranes; oxidizes intracellular biomolecules to promote DNA damage and apoptosis, and activates phosphoinositide 3-kinase (PI3K), Bcl-2-associated X (Bax), and p53 proteins to induce cell death pathways (Fig.4D, ii-iii). In addition, increased tumor necrosis factor α (TNF- α) expression induced by CP triggers the inflammatory cascade and plays an important role in CP-induced nephrotoxicity [73] (Fig.4D, iv). Furthermore, the cytotoxicity of CP affects endothelial cells as well, causing endothelial dysfunction and aberrant vasoconstriction, resulting in decreased GFR.

As described above, numerous complicated pathophysiological processes interweave to induce structural and functional kidney damage in AKI (Fig. 4A, v). We propose that the accumulation of multiple harmful substances, as well as renal hypoxia caused by hemodynamic disturbances, are the primary sources of pathological cellular responses in AKI.

3. RONS and AKI

In various types of AKI, harmful substance accumulation in the tubules leads to disrupted renal redox balance by inducing immune cells, endothelial cells, and RTECs to produce large amounts of RONS [74]. Furthermore, kidney hypoxia from persistent hypoperfusion, I/R, or microcirculatory disturbances causes intracellular mitochondria to produce large amounts of RONS [75]. Therefore, RONS overproduction is a central mechanism for the induction of oxidative stress, inflammation, adaptive response, and adaptive responses in AKI.

3.1. RONS

RONS are free radicals with one or more unpaired electrons including hydroxyl radicals (\cdot OH), superoxide anions (O_2^-), hydrogen peroxide (H_2O_2), and hypochlorous acid (HOCl), nitric oxide radicals (NO \cdot), and peroxynitrite (ONOO⁻), etc [76]. As important intracellular and intercellular signaling molecules, RONS are regionally and quantitatively limited, depending on the regulation of the intracellular antioxidant system [23,77]. Endogenous antioxidant systems primarily consist of enzymatic (e.g., superoxide dismutase [SOD], catalase [CAT], glutathione peroxidase [GPx], and thioredoxin [TRX]) and non-enzymatic antioxidants (e.g., glutathione, vitamins, or their analogs [vitamins A, C, and E; coenzyme Q10, and flavonoids], and metabolites [e.g., bilirubin, melatonin]) [78]. However, an RONS burst rapidly depletes antioxidant enzymes, destroys cell structure integrity and



Fig. 6. Schematic illustration of RONS generation by NOX2. Two independent events are required for the activation of $gp91^{phox}$, resulting in the assembly of the cytosolic regulatory proteins ($p40^{phox}$, $p47^{phox}$, and $p67^{phox}$) with the flavocytochrome b558. One of the two events is the activation of protein kinases such as protein kinase C (PKC) and Akt, which phosphorylate the autoinhibitory region of $p47^{phox}$, thus relieving its inhibition from the autoinhibitory loop and enabling $p47^{phox}$ to bind with $p22^{phox}$ (A). The second event starts with the replacement of GDP residue with GTP by a guanine nucleotide exchange factor (GEF), resulting in a conformational change of Rac protein by relieving inhibition from Rho GDP-dissociation inhibitor (Rho GDI), promoting its binding with $p67^{phox}$, and finally, resulting in the formation of the active complex (B). Angiotensin II, inflammatory stimuli, and I/R can activate both events to trigger the generation of O_2^- .

function, and ultimately induces cellular damage or even death during AKI [79]. Therefore, uncovering the RONS source is essential to understanding AKI pathogenesis and designing tailored antioxidant nanodrugs. In general, RONS are mainly derived from five sources in AKI: mitochondrial respiratory chain, NOX, NOS, XO, and MPO.

3.1.1. Mitochondrial respiratory chain

The kidneys are one of the organs with the highest mitochondrial quantity, second only to the heart [80]. The mitochondria, as an intracellular 'energy factory', is the efficient producer of ATP via oxidative phosphorylation by a series of enzymes (i.e., the mitochondrial respiratory chain) on the inner mitochondrial membrane, which consists of five membrane protein complexes (I, II, III, IV, and V) and two-electron carriers (membrane-bound ubiquinone [coenzyme Q10] and cytochrome c) [76].

In pathological states like ischemia, anaerobic metabolism leads to intracellular lactic acid accumulation, and the intracellular Na⁺/H⁺ exchanger is activated to restore the acid-base balance. The accumulated intracellular Na⁺ activates Na⁺/Ca²⁺ exchanger in a reverse mode, leading to an overload of intracellular Ca²⁺ [79]. After reperfusion, the increased intra- and extracellular H⁺ gradient aggravate this process. Accumulated Ca²⁺ induces the mitochondrial permeability transition pore (mPTP) opening, with subsequent mitochondrial inner membrane depolarization and respiratory inhibition [81,82]. Meanwhile, the energy depletion caused by ischemia and hypoxia leads to a reduction of respiratory chain-related proteins and electron carriers activities, resulting in the electrons leakage and RONS production (Fig. 5A) [83]. During ischemia, electrons are shifted to succinate, which acts as an electron store in the absence of O₂. After reperfusion, accumulated succinate facilitates reverse electron transport at complex I and causes an O_2^- burst by rapidly oxidizing to establish a high proton driving force in the inner mitochondrial membrane [84] (Fig. 5B). Some toxic substances (e.g., nephrotoxicity CP) inhibit succinate coenzyme Q oxidoreductase activity in complex II and generate O_2^- by a direct single-electron reduction of O_2 with the reduced iron-sulfur cluster of complex II [85] (Fig. 5C). In addition, the oxidation/reduction cycle of quinone is prone to leak electrons to form O_2^- during ischemia in AKI [86] (Fig. 5D).

Overall, oxidative stress generated by mitochondria is clearly a crucial disrupting element in RTEC damage. Notably, mitochondria serve as both a source and an assault target of RONS [87], indicating that removing excess RONS generated by mitochondria is a promising strategy for AKI.

3.1.2. NOX

The NOX family is a class of enzyme complexes with seven identified members (NOX1-5 and dual oxidase 1–2 [DUOX1-2]), which can generate O_2^- or H_2O_2 through electron transfer at the cytoplasmic membrane [88]. NOX is tissue-specific, with NOX2 and NOX4 being the major isoforms expressed in the vasculature and kidney [89]. Each has distinct activation mechanisms and creates diverse RONS, with NOX2 producing O_2^- and NOX4 producing H_2O_2 due to their various structures.

NOX2 is highly expressed in immune cells and kidney endothelial cells, and its catalytic core is a heterodimer composed of two membranebound subunits: gp91^{phox} and p22^{phox}, which form the flavonoid cytochrome *b*558 complex [90,91]. When the cytoplasmic subunits p47^{phox}, p40^{phox}, p67^{phox} (Fig. 6A), and Rac (Fig. 6B) translocate to the plasma membrane and bind to cytochrome *b*558 to form a complex, electrons are transferred from intracellular NADPH to O₂ to form O₂⁻, with



Fig. 7. Schematic illustration of RONS generation by other enzymes. (A) In eNOS, electron transmission is strictly controlled, and the interconversion of its cofactor BH_4 with its oxidized radical form BH_3H^+ serves as a critical step. Under stimulation, the uncoupling of eNOS induces electrons to be delivered to O_2 instead of arginine, resulting in the production of O2-- rather than NO. (B) When macrophages are activated by stimulation, the expression of iNOS is up-regulated to produce a large number of NO. NO could further react with oxygen and other reactive intermediates to form RONS, including nitrogen dioxide radical (-NO₂), peroxynitrite (ONOO⁻), nitrous acid (HNO₂), and nitrogen peroxide (NO₂⁺). (C) For XDH, xanthine is oxidized to uric acid, and electrons are transferred via 2 Fe–S centers to the FAD where NAD⁺ is reduced to NADH. For XO, xanthine is oxidized to uric acid, and electrons are transferred to O₂⁻ and H₂O₂. In AKI, an irreversible transition from XDH to XO leads to the high production of RONS. (D) During inflammation, neutrophils release NETs along with a large amount of MPO, which catalyze the generation of HOCI.

phosphorylation of p47^{phox} and activation of Rac play a crucial role in the assembly of the complex [92]. During surgery, elevated plasma angiotensin II (Ang II) levels cause T cells to produce O_2^{-} by NOX2 [93]. During sepsis, circulating lipopolysaccharide (LPS) and various inflammatory factors (e.g., TNF- α , LPS, phorbol myristate acetate (PMA), formylated methionyl-leucyl-phenylalanine (fMLP), etc.) phosphorylate $p47^{phox}$ and activate NOX2 to generate O_2^{-} [94]. NOX4, the most highly expressed NOX in the kidney, is abundantly expressed in mitochondrial membranes of proximal RTECs, and plays an important role in maintaining the kidney physiological functions (e.g., stimulating channel proteins activity) [95,96]. The activity of NOX4 is largely controlled by its expression level, independent of Rac activation or the presence of p47^{phox}/p67^{phox} proteins. However, NOX4 activity requires the presence of p22^{phox} [97]. The protein and mRNA levels of NOX4 and its docking subunit p22^{phox} can be upregulated by CP stimulation, which in turn induces RONS production. Downregulation of NOX4 reduces CP-activated programmed cell death, reduces inflammatory responses, and restores renal function by blocking the RONS production [98,99]. NOX4 also plays an important role in Toll-like receptors 4 (TLR4)-mediated renal damage in I/R-induced AKI (I/R-AKI). Following I/R stimulation, NOX4 is highly increased in proximal RTECs and forms a trimer with gp96 (the endoplasmic reticulum molecular chaperone of TLR) and TLR4, facilitating RONS generation and promoting apoptosis

[100]. Similarly, the upregulation of NOX4 expression in the kidney has been found in S-AKI as well [101].

3.1.3. Other RONS-producing enzymes

In addition to NOX, there are other RONS-producing enzymes in AKI including NOS, XO, and MPO [76]. NOS are a group of enzymes that catalyze the generation of nitric oxide (NO) from L-arginine. They are divided into three isoforms: neuronal NOS (nNOS), inducible NOS (iNOS), and endothelial NOS (eNOS) [102]. Among them, eNOS is the main source of vascular endothelial NO and is also directly involved in O_2^{-} production. eNOS is a homodimeric enzyme consisting of a reductase and an oxygenase structural domain with its dimerization interface having a binding site for the cofactor tetrahydrobiopterin (BH₄) and the substrate L-arginine [103]. L-arginine undergoes two consecutive monooxygenation reactions in the presence of BH4 to generate NO and L-citrulline. In eNOS, electron transmission is strictly controlled, and the interconversion of its cofactor BH4 with its oxidized radical form BH3H⁺ serves as a critical step [104]. During kidney I/R, eNOS is uncoupled from its cofactor BH4, and electrons are delivered to O2 instead of arginine, resulting in the production of O_2^{-} rather than NO [105]. Furthermore, $ONOO^-$ can oxidize BH_4 to BH_2 in cells with oxidative stress, which cannot participate in the BH₄ and BH₃H⁺ cycle, causing 'uncoupling' and O₂⁻⁻ formation [106] (Fig. 7A). In contrast-induced



Fig. 8. Schematic illustration of RONS crosstalk. (A) Overproduction of RONS in mitochondria causes the opening of mPTP and IMAC, leading to mitochondrial depolarization and RONS diffusion to neighboring mitochondria. (B, C) RONS crosstalk between mitochondria and NOX.

AKI, contrast agents induce elevated levels of asymmetric dimethylarginine (ADMA, an endogenous inhibitor of eNOS), to increased eNOS uncoupling to form O_2^- [107]. Similarly, I/R and S-AKI can also induce increased ADMA levels [108,109]. iNOS is mostly expressed in macrophages and its activation is associated with the inflammatory process [110]. iNOS activation induces significantly higher NO production than other NOS isozymes [102]. iNOS is upregulated in the kidney during I/R and S-AKI and causes significant NO synthesis, which requires high O_2 consumption and further aggravates renal hypoxia [111,112]. Furthermore, high NO levels compete with SOD for O_2^- to form ONOO⁻ and other RONS to exacerbate renal injury via nitration of proteins and lipids [113] (Fig. 7B).

Xanthine oxidoreductase (XOR) is a soluble cytosolic enzyme that catalyzes the oxidation of hypoxanthine to xanthine and xanthine to uric acid in turn [25]. XOR expression levels are low in most tissues but are relatively high in the kidney and vascular endothelium. Stimuli such as inflammatory factors, growth factors, hypoxia, and hormones can increase XOR expression [114]. In mammals, XOR can exist in two forms: xanthine dehydrogenase (XDH) and XO, which adopt NAD⁺ and O₂ as electron acceptors, respectively. XO directly transfers electrons to O₂ to form O_2^- and H₂O₂ through single- and two-electron reduction reactions, respectively [115]. In AKI, an irreversible transition from XDH to XO leads to the high production of H₂O₂ and O₂ [116] (Fig. 7C).

MPO is a heme-containing cofactor heme protease released by neutrophils, monocytes, and some macrophages. MPO catalyzes H_2O_2 and chloride to form HOCl [117,118]. In AKI, neutrophils flow into the kidney to release neutrophil extracellular trap (NET), a network of DNA complexed with histones and neutrophil granule proteins, including MPO [119]. MPO catalyzes production of HOCl to trigger oxidative tissue damage and cellular dysfunction (Fig. 7D). In AKI, HOCl-mediated tissue injury has been demonstrated by specific biomarkers, such as the chlorinated product of tyrosine, 3-chlorotyrosine (Cl-Tyr) [120].

Taurine supplementation (an important HOCl scavenger) exerts an excellent renoprotective effect in AKI induced by ischemia, doxorubicin, and rhabdomyolysis [121–123].

3.2. RONS crosstalk and RONS-inflammation cycles

Interestingly, the various RONS are not formed in isolation but crosstalk to generate a complex amplified vicious circle [124]. The most classical version is RONS-induced RONS release (RIRR) in mitochondria, which includes both mPTP-dependent and non-dependent mechanisms (Fig. 8A) [125]. In the former, RONS overproduction causes the opening of mPTP and subsequently depolarization in the mitochondrial membrane, which increases mitochondrial RONS production by altering the proton gradient in the inner mitochondrial membrane. In the mPTP non-dependent route, RONS induces the opening of inner membrane anion channels (IMAC), allowing the electron transport chain to discharge RONS into the cytosol [126]. This RIRR triggers a positive feedback loop that stimulates RONS synthesis between neighboring mitochondria because renal tubules have extremely dense mitochondria [127]. In addition, there is also crosstalk between mitochondria and NOX. NOX-derived RONS can promote the phosphorylation and opening of mitochondrial adenosine triphosphate-sensitive potassium K channels (mt-K_{ATP}), decreasing mitochondrial membrane potential depolarization and inducing mitochondrial RONS production (Fig. 8B) [128]. In turn, protein kinase C epsilon (PKC-e), triggered by mitochondrial RONS, activates NOX2 via promoting the phosphorylation of $p47^{phox}$ subunit and thereby inducing RONS production [129] (Fig. 8C).

As a highly active substance, RONS can destroy various biological molecules and cause widespread oxidative stress in cells, which acts as death signals to induce various programmed or non-programmed cell deaths [130,131]. A strong inflammatory response is triggered when large amounts of DAMPs are released along with cell deaths [132].



Fig. 9. Advantages of nanomedicine in AKI treatment. Nanomedicines exhibit a variety of exciting advantages over conventional drugs such as material diversity (A), flexible size, and shape (B). In addition, nanomedicines can be modified with targeting molecules to localize lesion sites (C). Nanomaterials can also act as drug delivery platforms to improve the biocompatibility, stability, and even to achieve the controlled release of drugs (D).

Inflammation is inextricably linked to oxidative stress injury in AKI [133]. Activated immune cells and endothelial cells secrete chemokines (e.g., chemokine [C-X-C motif] ligand 1 (CXCL1), CXCL8) and cytokines (e.g., TNF- α , interleukin-6 [IL-6]) that recruit more immune cells to the kidney [134]. Notably, RTECs can also be activated by inflammatory factors through pattern recognition receptors (e.g., TLR2, 4, 9, etc.) and express various adhesion molecules (e.g., E-selectin, P-selectin, intercellular adhesion molecule-1 [ICAM-1]), and complement receptors that are involved in inflammation amplification [135]. Activated immune cells induce RONS production by NOX, NOS, and MPO to promote a vicious cycle of oxidative stress and inflammation. Renal parenchymal cell death and inflammatory infiltration cause the loss of nephrons and a dramatic decrease in renal function [136].

Overall, it is vital to clear the excessive production of RONS during AKI and restore the renal redox balance in order to reduce renal injury and inflammation and thus halt the progression of kidney disease.

4. Advantages of nanodrugs in AKI treatment

Harnessing the excess RONS in renal system is an effective strategy for AKI treatment. Some small molecule antioxidants such as N-acetylcysteine (NAC), amifostine (AMF), and L-carnitine have been adopted in the adjuvant treatment of AKI [137–140]. However, these drugs have failed to become primary treatment for AKI owing to the low kidney targeting. They also inevitably increase the kidney excretory burden. The sensitive, damaged kidney has difficulty withstanding the unpredictable and even toxic side effects of drugs and their metabolites, which are detrimental to already impaired kidney function [141,142]. Thus, more effective, stable, and less toxic AKI medications are urgently needed to meet the challenges posed by its high mortality and poor prognosis.

The rapid advancement of nanotechnology and strong potential of different RONS scavenging nanodrugs are currently paving the way for novel AKI treatments. While the kidney microstructure complicates AKI treatment with traditional antioxidant and anti-inflammatory drugs, it opens the door to nanodrugs with special physicochemical features [16]. Moreover, the high biostability and compatibility of nanodrugs allow them superior efficacy in AKI treatment. Importantly, the unique size and diverse surface modification strategies of nanodrugs provide significant advantages for their renal targeting. Currently, various component nanodrugs with various sizes and morphologies have been designed to accumulate in renal tissue for AKI antioxidant therapy [16, 143–145] (Fig. 9A–B). Specifically, nanoparticles with a diameter of <6 nm can achieve high renal accumulation more easily. In addition, large planar ultra-thin (2 nm) graphene oxide sheets and carbon nanotubes (200-300 nm long and 20-30 nm diameter) can cross through the GFB and accumulate in the renal tubules by morphological reconfigurations like sliding, squeezing, rolling, or folding the sheets or by orienting nanotubes perpendicular to the GFB [146-148]. Furthermore, the glomerular structure of injured kidneys is damaged during AKI, which allows nanoparticles with larger sizes to accumulate in the kidney. Recently, Yu et al. found that nanoparticles with particle sizes of 100 nm demonstrate good renal accumulation in a mouse model of I/R-AKI, with longer ischemia times showing greater nanoparticle accumulation in the kidney [149].

In addition to exploiting the intrinsic renal targeting properties of nanomaterials, active targeting facilitates the active uptake of nanomaterials by specific cells [150] (Fig. 9C). Overproduction of RONS during AKI has been shown to impact the physiology of kidney-associated cells such as RTECs, endothelial cells, and macrophages, prompting them to express elevated levels of cytokine receptors and cell adhesion molecules in AKI. This specialized inflammatory state

Table 1

Receptors highly expressed in kidney-associated cells during AKI and their specific ligands.

Cell	Pathological manifestation during AKI	Receptor	Ligand	Reference
RTECs	1. Produce excess RONS;	ICAM-1, VCAM-1	VLA-4, LFA- 1 ITGα: βα	[152]
	inflammatory cytokines/	TLR9	TLR9 antagonist	[151]
	chemokines and interact with	CD44	Hyaluronic acid	[154–156]
	immune cells; 3. Adaptive	Folic acid receptor	Folic acid	[157]
	response (down- regulated expression of ion transporter,	kidney injury molecule- 1 (Kim-1)	Serine	[158]
	stagnated cell cycle, etc.);	CXCR4	CXCR4 antagonist	[159]
	4. Apoptosis, necrosis and exfoliation;	Megalin receptor	Low molecular weight chitosan	[160]
Endothelial	1. Produce excess	E-selectin	Sialic acid	[161]
cells	RONS; 2. Produce pro- inflammatory cytokines/ chemokines and interact with immune cells; 3. Apoptosis and necrosis;	P-selectin ICAM-1	Fucoidan ITGα _L β ₂	[162]
Macrophages	1. Produce excess RONS; 2. Respond to and amplify inflammatory signals; 3. Produce pro- inflammatory cytokines/ chemokines or anti-inflammatory cytokines;	ICAM-1	ΙΤGα _L β ₂	[151]

provides an environmental foundation for nano-researchers to tailor specific ligands of nanomaterials to target injured kidneys (Table 1). For example, macrophage extracellular vesicles can achieve specific, efficient renal targeting and uptake through the interaction of integrins on their surface with ICAM-1, which is highly expressed on the surfaces of RTECs, endothelial cells and macrophages during AKI [151].

At present, many kinds of antioxidant nanodrugs with high RONS scavenging efficacy, renal accumulation, biostability, and minimal toxicity have been developed to treat AKI. To be specific, these nanodrugs can be divided into three categories based on their antioxidant mechanism. Firstly, nano-RNOS sacrificial agents act as disposable reductants to scavenge excessive RONS relying on the changeable element valence. Secondly, antioxidant nanozymes with regenerable active centers can mimic endogenous antioxidant enzymes to continuously catalyze RONS detoxification. Thirdly, some nanomaterials serve as carriers rather than active agents to load various antioxidants and anti-inflammatory drugs to eliminate RONS directly or indirectly.

5. Nano-RONS-sacrificial agents

In recent years, a variety of nano antioxidants were applied to treat AKI, including DNA origami, metal compounds, and other nanosacrificial agents (Table 2). Most of them act as active reductants to sacrifice themselves to protect endogenous biomolecules by reacting with RONS rapidly, which are denoted as nano-RONS-sacrificial agents.

5.1. DNA origami

Theoretically, DNA can be used as a strong RONS scavenger because of its abundant nucleophilic groups with high reactivity for electrophilic RONS. High levels of RONS disrupt vital cellular processes in many oxidative stress related diseases by attacking DNA due to their high reactivity [76,79,173]. Unfortunately, unlike tumor tissues which have developed efficient mechanisms of RONS detoxification (mainly involving enhancement of antioxidant abilities and upregulation of pro-survival and pro-repair molecules), normal tissues such as kidneys are difficult to cope with large-scale oxidative stress in time [174,175]. Correspondingly, the administration of exogenous accessible DNA can directly react with RONS to reduce cell damage and alleviate AKI. Moreover, DNA has excellent inherent biocompatibility and biodegradability [176,177]. Therefore, DNA is extremely promising as a drug

Table 2

Nano-RONS-sacrificial agents for AKI antioxidant therapy.

Categories	Nanomaterial	Mechanism	Scavenged RONS	Size	Kidney-targeting strategy
DNA origami	Rec-DON; Tri-DON; Tub-DON [163]	DNA bases → oxidized DNA bases (e.g., guanine → 8-oxoguanine)	ABTS∙, O ₂ [−] , •OH	Rec-DON (90 nm × 60 nm); Tri-DON (120 nm per edge); Tub-DON (400 nm long)	Morphological reconfiguration (sliding, squeezing, rolling, or folding)
	tFNAs [164]		/	~11.7 nm	Small particle size
	siP53@L-sTD [<mark>165</mark>]		/	6 nm	Small particle size
	rDNAs [166]		ABTS-, -OH	$90 \times 60 \text{ nm}$	Morphological reconfiguration
Metal compound nano- RONS-sacrificial agents	POM [167]	$\mathrm{Mo}^{5+} ightarrow \mathrm{Mo}^{6+}$	ABTS·, O_2^{-} , H ₂ O ₂ , ·OH	<10 nm	Small particle size
	TPNs [168]	$Ti_3C_2 \rightarrow TiOx$	ABTS·, O_2^- , H ₂ O ₂ , ·OH	Lateral size: ~200 nm	Morphological reconfiguration
Other nano-RONS-sacrificial agents	SeCQDs [169]	Selenium \rightarrow Selenic acid	ABTS \cdot , O ₂ , H ₂ O ₂ , \cdot OH	Diameter: ~40 nm Height: ~2 nm	Morphological reconfiguration
U U	BP NSs [170]	$BP \ NSs \rightarrow P_x O_y^{n.}$	H ₂ O ₂ , OH, O ₂	Lateral size: 225.8 \pm 4.0 nm; Thickness: 3.8–4.5 nm	Morphological reconfiguration
	h-GQDs [171]	C–OH (phenol-like groups) serving as H-atom donors	ABTS∙, ∙OH, O2 [−] , DPPH∙	4.4–4.8 nm	Small particle size
	PDA-CNDs [172]	Polyaniline serving as H-atom donors	ABTS·, $O_2^{\cdot-}$, DPPH·	~4.92 nm	Small particle size



Fig. 10. DNA origami for AKI treatment. (A) Schematic of tFNAs as a therapeutic agent for RM-induced AKI. (B) Quantification analysis of relative fluorescence intensity in healthy and AKI mice of different organs 0.5 h after injected with Cy5 labeled tFNAs. (C) Analysis of Cre levels of in different groups. Adapted with permission from Ref. [164], copyright 2021. (D) In vivo biodistribution of intravenously injected Cy5.5-sTds in healthy nude mice. (E) Cellular uptake efficiency of L-sTd TCMK-1 cells pretreated with poly inosinate (poly-I) or megalin siRNA (siMeg). (F) The apoptotic damage visualized by annexin V staining in kidney sections after different treatments. (G) BUN levels estimated in blood samples of mice after different treatments. Adapted with permission from Ref. [165], copyright 2020. (H) Schematic illustration of preferential renal accumulation and multi-stage sequential therapy of rDON for AKI treatment. Adapted with permission from Ref. [166], copyright 2021.

for AKI antioxidative treatment. However, DNA is restricted by low stability and rapid degradation caused by ubiquitous nucleases in vivo [178]. Interestingly, tightly folded and three-dimensional conformational DNA nanostructures exhibit superior nuclease resistance over linear or circular DNA duplexes due to the presence of spatial site resistance. For example, one enzyme unit (U) of DNase I degrades 65 ng of double-stranded plasmid DNA in only 5 min, whereas 2 ng of 24-helical bundle DNA origami does so in ~60 min [179]. Recently, Jiang et al. constructed three different shapes of tightly folded DNA molecules (rectangular DNA origami nanostructures, rec-DON; triangular DNA origami nanostructures, tri-DON; and tubular DNA origami nanostructures, tub-DON) to treat AKI with high therapeutic effect [163]. These fully tightly folded DNA origami exhibited higher renal accumulation and lower hepatic metabolism compared with single-stranded unfolded DNA molecules and incompletely folded DNA molecules in vivo due to their lack of sticky ends, tightly folded structure, and proper sizes. Moreover, these DONs were effective in neutralizing ABTS radicals and endogenous RONS (\cdot OH, $O_2^{\cdot-}$, and H_2O_2). Especially, rec-DON (the best antioxidant in vitro) exhibited particularly preferential renal accumulation in AKI mice and was effective in restoring renal function, as evidenced by reduced serum blood urea nitrogen (BUN) and creatinine (Cre); restored renal clearance, renal SOD levels, and reduced histopathological tubular casts after intravenously injecting rec-DON.

Rec-DON had a far lower effective dose than NAC: 10 μ g/mouse of rec-DON had a therapeutic effect equivalent to 4.2 mg/mouse of NAC. Similarly, Zhang et al. developed a stable tetrahedral framework nucleic acid (tFNAs) for AKI antioxidant treatment (Fig. 10A) [164]. tFNAs had high stability and were stable in DNase-rich cell lysates for up to 9 h tFNAs were preferentially taken up by the kidney (Fig. 10B), and renal function was recovered in the rhabdomyolysis-induced AKI (RM-AKI) mouse model (Fig. 10C).

DNA origami can further improve the effect of AKI treatment when are adopted as delivery carriers for a specialized functional oligonucleotide. For example, Thai et al. developed a tetrahedral framework nucleic acid with an unnatural L-deoxyribose backbone (L-sTd)-loaded short interfering RNA (siRNA) of p53 to efficiently treat I/R-AKI [165]. L-sTd had higher serum stability than D-sTd with a natural sugar backbone (D-deoxyribose bone) due to its unnatural sugar backbone and were enriched in the kidney result from its small size (Fig. 10D). Importantly, L-sTd were successfully taken up by RTECs by megalin-mediated internalization (Fig. 10E). The siRNA of p53 (siP53) was loaded onto the L-sTd vector by hybridization (siP53@L-sTd). The siP53@L-sTd exhibited prolonged retention in circulation and increased renal distribution over time compared with naked siP53 because free siRNA was unstable in vivo. After siP53@L-sTd treatment, the expression of caspase-3, a downstream component of the p53-driven apoptotic



Fig. 11. Metal compound nano-sacrificial agents for AKI treatment. (A) Schematic illustration of preferential renal accumulation and antioxidant effect of POM nanoclusters for AKI treatment. **(B)** Representative longitudinal PET imaging of ⁸⁹Zr-POM in mice with AKI. **(C)** Measurement of DNA damage (8-OHdG) in renal tissue homogenates from each group. **(D)** BUN levels in the blood serum from each group. Adapted with permission from Ref. [167], copyright 2018. **(E)** Schematic of the TPNS synthesis process and their activity as redox-mediated artificial non-enzymatic antioxidant nanoplatforms for AKI treatment. **(F)** XPS patterns of TPNS in the Ti_{2p} region before and after various RONS scavenging (left), and statistical graph of different valence states of Ti in the TPNS before and after various RONS scavenging (right). **(G)** TEM images of TPNS after incubating with H₂O₂. **(H)** The fluorescence signal of cy5.5-TPNS in heart, liver, spleen, lung, and kidney. **(I)** BUN levels in serum from AKI mice after different treatments. Adapted with permission from Ref. [168], copyright 2021.

signaling cascade, was significantly reduced, and the morphology and renal function markers were greatly recovered as well (Fig. 10F-G). The pathological process of I/R-AKI was divided into two phases, namely the oxidative stress phase induced by RONS overproduction (peaking at 8 h) and the inflammatory phase caused by immune system activation (complement protein C5a levels begin to rise at 8 h postoperatively). Very recently, Chen et al. developed a DNA origami loaded with nucleic acid adaptors of complement protein C5a (ac5a-rDNAs) for the sequential treatment of I/R-AKI (Fig. 10H) [166]. The ac5a-rDNAs highly targeted the kidney and exhibited prolonged renal retention (~30% residual after 12 h) in the I/R-AKI mouse model due to their dense structure and ultra-thin thickness. The ac5a-rDNAs demonstrated an excellent sequential treatment effect of I/R-AKI. When the ac5a-rDNAs were intravenously injected into mice at 2 h postoperatively, the renal MDA levels were significantly lower in the treated group at 4 h postoperatively and the renal c5a levels were significantly decreased at 8 h postoperatively compared with the control group.

5.2. Metal compound nano-RONS-sacrificial agents

Many transition metal compounds have reducing activity and can scavenge RONS by accepting electrons from RONS. Currently, the transition metal nanocomplexes adopted in the treatment of AKI mainly include molybdenum (Mo)-based polyoxometalate (POM) and Ti-MXenes [167,168].

Mo is a trace element essential for human survival. Molybdenum cofactor, which acts as a prosthetic group for various enzymes such as XDH, aldehyde oxidase, and nitrate reductase, plays an integral role in many metabolic activities [180,181]. Mo-based compounds have great potential for RONS removal based on their multivariable valence states (primarily including Mo (III), Mo (IV), Mo (V), and Mo (VI)) [182]. Recently, Ni et al. developed a Mo-based POM for AKI treatment by efficiently eliminating RONS (Fig. 11A) [167]. Mo in POM switched between Mo5+ and Mo6+ to significantly scavenger broad-spectrum RONS both in vivo and in vitro. Moreover, POM was able to accumulate in the kidney based on the ultra-small hydrodynamic diameter of nanoclusters (<10 nm) (Fig. 11B). POM nanoclusters effectively reduced oxidative DNA damage and lipid peroxidation and induced an effective recovery of renal function (Fig. 11C-D). Very recently, Zhao et al. adopted ultrathin Ti₃C₂ MXene nanosheets (TPNs) for AKI antioxidant treatment (Fig. 11E) [168]. The stability of TPNs was improved by modifying polyvinyl pyrrolidone (PVP) under physiological conditions. TPNs had efficient and broad-spectrum RONS (H2O2, ·OH, O2) scavenging capabilities via their inherent reductive properties of Ti₃C₂. RONS were easily adsorbed onto the [Ti₃C] sites, and were scavenged by redox reactions and generated oxygenated nanosheets (i.e., TiOx species). Furthermore, TPNs sizes were significantly reduced by myeloperoxidase action or reaction with RONS, and degraded to Ti^{2+} , Ti^{3+} , and Ti⁴⁺ oxides (TiO₂) with negligible risk of adverse responses (Fig. 11F-G). Notably, TPNs with a high planar/thickness ratio had



Fig. 12. Other nano-RONS-sacrificial agents for AKI treatment. (A) A scheme showing the specific renal accumulation of SeCQDs allows prevention and treatment of AKI. **(B)** MIP PET images for 89 Zr-DFO-SeCQDs in healthy ICR mice. **(C)** Cre serum concentrations of groups in the RM-AKI animal model. Adapted with permission from Ref. [169], copyright 2020. **(D)** Accumulation of BPNSs in kidney reacted with RONS to protect the renal function. **(E)** Raman spectra of BPNSs reacted with H₂O₂. **(F)** Representative cy5 intensity of in vivo images at different time points after i.v. injection of cy5-BPNSs. **(G)** Cre analysis after different treatments. Adapted with permission from Ref. [170], copyright 2020.

significant renal targeting ability, similar to two-dimensional DNA nanosheets (Fig. 11H). After TPNs treatment, the renal function indexes and pathological tissue sections were restored in the RM-AKI mouse model (Fig. 11I).

5.3. Other nano-RONS-sacrificial agents

Many inorganic non-metallic elements also have varying valence states and show antioxidant activity. Among these, selenium, phosphorus, and carbon are essential elements for human physiology [183, 184]. Currently, nanoparticles based on these elements have been adopted for AKI treatment, with excellent therapeutic effects and extremely low side effects [185–189]. For example, Rosenkranz et al. adopted selenium-doped carbon quantum dots (SeCQDs) for AKI antioxidant therapy (Fig. 12A) [169]. Selenium is an essential human micronutrient that is involved in the production of 25 selenoproteins with redox activity [190]. SeCQDs had a higher selenium concentration (6.43%), and the doped selenium reacts with RONS (H_2O_2 , $\cdot OH$, O_2^-) to form selenic acid. Moreover, SeCQDs injected intravenously accumulated in the kidney and followed by a slow clearance of SeCQDs from the kidney but a small amount remained over the 72 h (Fig. 12B). SeCODs showed superior renal protection versus AMF in both RM-AKI and CP-induced AKI (CP-AKI) models with lowered Cre and BUN concentrations and reduced tubular casts (Fig. 12C). Black phosphorus (BP), as soft 2D nanomaterials, have excellent intrinsic kidney targeting ability and high RONS scavenging ability [191]. Very recently, Hou et al. developed BP nanosheets (BP NSs) for AKI treatment (Fig. 12D) [170]. BP NSs have a strong RONS (H_2O_2 , OH, O_2) scavenging ability because phosphorus is prone to be oxidized by RONS to generate non-toxic phosphate ions (Fig. 12E). Additionally, BP NSs passed the GFB longitudinally by coiling and folding, and were taken up preferentially by the kidney (Fig. 12F). Furthermore, BP NSs exhibited better exhibited better

Table 3	
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Nanozymes for AKI antioxidant therapy.

	10				
Categories	Nanomaterials	Enzyme-mimicking ability	Scavenged RONS	Size	Kidney-targeting strategy
Cerium oxide nanozymes	Ceria NPs [193]	POD, CAT, SOD	ABTS·, H_2O_2 , O_2^- , ·OH	~ 4 nm	Small particle size
	CNPs [194]	CAT	H_2O_2	~9.7 nm	Small particle size
Noble metal nanozymes	Pt NPs-PVP [195]	CAT, SOD, POD	ABTS-, H ₂ O ₂ , O ₂ , ·OH, DPPH-	~3 nm	Small particle size
	Ir NPs-PVP [196]	CAT, SOD, POD	ABTS-, H ₂ O ₂ , O ₂ , ·OH, DPPH-	3–4 nm	Small particle size
	RuO ₂ NPs [197]	CAT, SOD, GPx	$H_2O_2, O_2^{-}, \cdot OH$	~5.4 nm	Small particle size
	Au NCs-NAC [198]	CAT, SOD, POD	ABTS, O_2^- , OH	$\sim 2 \text{ nm}$	Small particle size
Other nanozymes	Cu _{5.4} O USNPs [199]	CAT, SOD, GPx	$H_2O_2, O_2^{-}, \cdot OH$	~4.5 nm	Small particle size
	PB NZs [200]	CAT, SOD, POD	ABTS-, H ₂ O ₂ , O ₂ , ·OH, DPPH-	4.5 nm	Small particle size
	CaPB NPs [201]	CAT, SOD, POD, GPx	H ₂ O ₂ , O ₂ , ·OH, DPPH·, ONOO	~5.3 nm	Small particle size
	MMPP [202]	SOD	ABTS, O_2^{-} , OH	~4.5 nm	Small particle size



Fig. 13. Cerium oxide nanozymes for AKI treatment. (A) Schematic illustration of catalytic activity tunable CNPs that context-dependently regulate RONS in vivo. **(B)** The survival rate of HK-2 cells (a) and ES-2 cells (b) upon treatments with 10 µM DDP and different concentrations of CNPs at pH 7.4 and pH 6.6. **(C)** Schematic illustration of the context-dependent catalase-like activity of CNPs under different pH conditions. **(D)** Images of the dissected tumors from groups of nude mice fed with sterile water after treatment. **(E)** Serum BUN levels of nude mice after different treatments. Adapted with permission from Ref. [194], copyright 2021.

renal function index recovery than AMF and NAC as well (Fig. 12G).

These nano-sacrificial agents still need further improvement for AKI treatment. These DNA origamis are still not stable enough in the body, most not exceeding one day. Additionally, DNA origami is very expensive to treat AKI, especially for those nucleic acids that require postmodification. In addition, the metabolism and accumulation of specific metal elements, Se, P, etc. in other Nano-RONS-sacrificial agents are still unclear in vivo, and their long-term toxicity has rarely been studied in AKI.

6. Antioxidant nanozymes

Antioxidant enzymes (e.g., SOD, CAT) are more efficient and durable compared with the sacrificial agent of RONS because these enzymes catalyze RONS without being sacrificed by them. However, direct supplementation with natural antioxidant enzymes is difficult for the treatment of AKI because natural enzymes are less stable and hard to target the kidneys. Recently, specially designed nanomaterials have been discovered to exhibit the properties of some natural antioxidant enzymes (nanozymes), such as SOD, CAT, and GPx [192]. These nanozymes have outstanding advantages over natural enzymes due to their modifiable physicochemical properties, high biostability, and diverse catalytic activities. Currently, a variety of antioxidant nanozymes have been used for AKI treatment (Table 3), which are mainly divided into cerium oxide enzymes, noble metal enzymes, and others. These nanozymes usually have the activity of at least one antioxidant enzyme and can scavenge other RONS through sacrificial or other effects.

6.1. Cerium oxide nanozymes

The enzyme-mimetic activity of cerium oxide originates from the redox cycle between Ce (III) and Ce (IV) [203,204]. The CeO₂ crystal on the nanoscale is prone to lose O atoms to form internal vacancies, and part of Ce (IV) is reduced to the unstable Ce (III). Ce (IV) and low surface defect formation energy play a key role in the oxidation process, whereas Ce (III) and free electrons in the O vacancy lattice are important in the reduction process [192]. The redox-mimetic enzymatic activity of cerium oxide is determined by its surface oxidation state. When the Ce (III)/Ce (IV) ratio in cerium oxide is high, it is more likely to exhibit SOD-mimetic activity: $O_2^{-} + Ce^{3+} + 2H^+ \rightarrow H_2O_2 + Ce^{4+}; O_2^{-} + Ce^{4+} \rightarrow H_2O_2 + Ce^{4+}; O_2^{-} + Ce^{4+}; O_2^{-}; O_2^{-} + Ce^{4+}; O_2^{-} + C$ $O_2 + Ce^{3+}$. When the Ce (III)/Ce (IV) ratio is low, it tends to exhibit CAT-like activity: $2Ce^{4+} + H_2O_2 \rightarrow Ce^{3+} + O_2 + 2H^+$ [205]. In addition, cerium oxide can successfully scavenge other harmful radicals through valence switching such as ·OH, ·NO, and ONOO⁻ [206]. Therefore, cerium oxide nanozymes is very promising in the treatment of AKI [193]. For instance, Weng et al. developed PEG-modified ceria nanoparticles (CNPs) for high-efficiency treatment of platinum-induced AKI under the premise of maintaining platinum-based anticancer effects (Fig. 13A) [194]. Oxidative stress is one of the main anti-tumor mechanisms of platinum-based chemotherapeutic agents [207]. Antioxidants (e.g., NAC, vitamin E) promote lung tumor cell proliferation and accelerate lung cancer progression by reducing RONS, mitigating DNA damage, and inhibiting p53 expression [208,209]. Notably, CNPs showed different antioxidant activities under different pH conditions (Fig. 13B). The rate of H₂O₂ decomposition catalyzed by CNPs under neutral conditions was significantly higher than that under acidic



Fig. 14. Noble metal nanozymes for AKI treatment. (A) Scheme represents the renal accumulation of broad-spectrum antioxidant Pt NPs-PVP for AKI treatment. **(B)** -OH scavenging efficiencies at different concentrations of Pt NPs-PVP. **(C)** Analysis of BUN levels in the blood serum of indicated groups in both the AKI and healthy animal model. Adapted with permission from Ref. [195], copyright 2021. **(D)** Schematic illustration of broad-spectrum antioxidant and anti-inflammatory activities of ultrasmall Au NCs-NAC for AKI alleviation as compared with NAC. **(I)** O_2^- scavenging activity of NAC and Au NCs-NAC. **(E)** The quantitative analysis of Au NCs-NAC in the major organs of AKI mice. Adapted with permission from Ref. [198], copyright 2021.

conditions. Under acidic conditions, excess H⁺ inhibited the conversion of Ce⁴⁺ to Ce³⁺, which in turn disturbed the re-exposure of the active catalytic center (Ce³⁺) and blocked the antioxidant cycle of CNPs (Fig. 13C). The pH-dependent antioxidant property of CNPs effectively protected the kidney from anticancer drugs at the renal site without affecting the tumor site anticancer effect because the pH of the tumor microenvironment (pH 6.0–6.6) differed significantly from that of normal tissues such as kidneys (pH 7.4) (Fig. 13D). Moreover, CNPs had similar renoprotective effects in cyclophosphamide-induced AKI mice (Fig. 13E).

6.2. Noble metal nanozymes

Noble metal nanoparticles have been widely developed for biomedical applications, including bio-diagnostics, biosensing, and medical therapies [210,211]. More importantly, lots of noble metal nanoparticles have high intrinsic catalytic activity due to their incompletely filled d-electron orbitals and small energy level spacing [212]. Currently, ultra-small-sized gold [198], platinum [195], Ir [196], and Ru [197] nanoparticles have been developed for the treatment of AKI, and these nanoparticles are often passively targeted to renal tissue to eliminate various RONS thanks to their variety of antioxidant enzyme properties. Among them, platinum nanoparticles (Pt NPs) have attracted much attention for their broad-spectrum and efficient RONS quenching activity by mimicking a variety of enzymes, including CAT, SOD, and NADH-coenzyme Q reductase. Moreover, Pt NPs are catalytically active over wide pH and temperature ranges due to their high stability as noble metals [213]. Recently, Zhang et al. synthesized PVP-coated ultra-small Pt NPs (~3 nm) via a simple nucleation-reduction method to serve as a

multi-enzyme mimic for AKI antioxidant therapy (Fig. 14A) [195]. Pt NPs-PVP exhibited efficient H₂O₂, ·OH, and O₂ scavenging abilities thanks to the widely exposed active site (Fig. 14B). In the RM-AKI mouse model, Pt NPs-PVP reduced renal DNA damage and lipid peroxidation levels by scavenging renal RONS and restoring the renal redox environment (i.e., increased SOD levels) and indicators of renal function. Importantly, the renoprotective effect of Pt NPs-PVP in AKI mice was significantly stronger than that of AMF (Fig. 14C). Very recently, Zhang et al. employed the NAC as a reductant and capping to synthesize ultrasmall gold nanoclusters (Au NCs) to provide effective AKI alleviation [198]. Au NCs had multienzyme mimetic properties like POD, SOD, and CAT. Moreover, Au NCs-NAC scavenged multiple RONS more efficiently than both alone thanks to the presence of NAC ligands and the multi-enzyme mimicking activity of Au NCs (Fig. 14D). Notably, Au NCs-NAC demonstrated preferential renal enrichment because of their ultra-small particle sizes (2 nm) (Fig. 14E), and Au NCs-NAC group showed significantly lower RONS levels and apoptotic cells in renal tissues than free NAC group, at the same dose after 14 days of treatment in RM-AKI mice.

6.3. Other nanozymes

Other antioxidant nanozymes have also been used in AKI treatment, including copper (Cu) nanozymes [199], Prussian blue (PB) nanozymes [200], and melanin nanozymes [202]. These nanozymes all have properties of various types of antioxidant enzymes and small size for AKI treatment. Sun et al. developed PEG-modified natural melanin nanoparticles (MMPPs) with ultra-small hydrodynamic size (~4.5 nm) and efficient scavenging ability for many types of toxic RONS (O_2^- , ·OH, and

Table 4

Nanocarriers for antioxidants or anti-inflammatory drugs for AKI treatment.

Categories	Nanomaterials	Cargo	Size	Kidney-targeting strategy
Antioxidant nanocarriers for	HA-NPs [156]	\$\$-31	~53 nm	Target CD44
mitochondria	SC-TK-SS31 [158]		1	Target KIM-1
	$N-NP_{CoO10}$ [221]	CoQ10	~120 nm	Respond to inflammatory signals from the
		-		kidney
	Atv/PTP-TCeria NPs	Atorvastatin, Ceria	\sim 43.1 \pm 7.50 nm	Leakage to the injured-kidney
	[222]			
	TLC [160]	Curcumin	/	Specifically internalized by RTECs via Megalin-
				mediated endocytosis
	SAP-MT [223]	Mito-TEMPO	10–20 nm	Intrarenal injection
Nanocarriers for anti-	MNP-ODN2088 [153]	TLR9 antagonist ODN2088	300-400 nm	Transported by blood and endocytosed by
inflammatory drugs				RTECs
	DNA nanocrafts [224]	IL-33	Thickness: ~4 nm	Morphological reconfiguration
	SAP hydrogel-based	anti-TNF- α and hepatocyte growth	diameter ~10-20 nm (in	Intrarenal injection
	DDS [225]	factor	pure water)	
	SA-NPs [161]	Dexamethasone	$95.39\pm0.29~\text{nm}$	Target E-selectin
	MSC-exos [152]	miR-125b-5p	$134.4\pm3.9~\text{nm}$	Target ICAM-1, VCAM-1
	MSC-EVs [226]	TFAM mRNA, mtDNA, and mitochondrial proteins	~160 nm	Home to sites of inflammatory kidney
	MSC-FVs [227]	miB-200a-3n	~120 nm	Home to sites of inflammatory kidney
	$II_{-10} + FV_{s}$ [151]	II10	134 nm	Home to sites of inflammatory kidney
	FV/BGD [228]	MSC-FVs	Nanofibers: (diameters	Intrarenal injection
		MOG EV5	4_7 nm):	inducidu injection
			FVs: (50-200 nm)	
	KMP2-EVs [229]	MSC-EVs	Nanofibers: (diameters	Intrarenal injection
			10–20 nm)	
Nanocarriers for antioxidants	FGP nanodots [230]	Gallic acid	diameter: 1~2 nm:	Small particle size
			thickness: ~3 nm	Ī
	PLGA-oltipraz NPs	Oltipraz	~100 nm	Leakage to the injured-kidney
	[149]	1		0 9 9
	nHA/PLBR [155]	Bilirubin	$226.9\pm4.5~\text{nm}$	Target CD44
	RAPs [231]	Iodinated contrast medium	170 nm	/
	Fe-Cur CPNs [232]	Curcumin	<10 nm	Small particle size
	HA-CUR [154]	Curcumin	/	Target CD44
	OSA-Fucoidan/Cur	Curcumin	~100 nm	Target P-selectin
	[162]			
	Se @TE NPs [233]	Tea polyphenol	$191.4\pm5.11~\text{nm}$	/
	NEQ [234]	Quercetin	~8 nm	Small particle size
	Eda-MNPs [235]	Edaravone	$374.0\pm12.2~\text{nm}$	Leakage to the injured-kidney
	BA-N [236]	BAPTA-AM	115 nm	/

ABTS·) for AKI treatment. Similarly, PB nanoparticles can mimic various biological enzymes (e.g., POD, CAT, and SOD), possibly due to their ability to interconvert in different forms, including Prussian white (PW), Berlin green (BG), and Prussian yellow (PY) [214]. Here, we take copper nanozymes as a representative example to illustrate how this class of nanozymes to treat AKI. Copper is an essential trace metal in many human proteins and enzymes. Nano-copper (0) has a strong quantum confinement effect on electrons and can decompose the O-O single bond in H₂O₂ and O₂, but cannot decompose ·OH [215,216]. Cuprous oxide (Cu₂O) can promote electron transfer reactions to deactivate H₂O₂ or ·OH [217]. Therefore, the catalytic activity of copper (0) and Cu₂O can be combined to obtain various RONS catalytic activities. Recently, Liu et al. developed an ultra-small hybrid nanoparticle containing Cu (0) and Cu (I) (Cu_{5.4}O USNPs) to effectively treat AKI [199]. The Cu_{5.4}O USNPs had highly SOD-, CAT- and GPX-like activities, and efficiently decomposed ·OH because of their mixed Cu (0) and Cu (I). Furthermore, the stability of Cu₂O coating on Cu nanoclusters was improved by the electron-hole separation between Cu₂O and Cu. Cu_{5.4}O USNPs were able to display considerable and diversified RONS scavenging capabilities $(H_2O_2, \cdot OH, and O_2)$ at very low dosages (tens of ng/ml). In the RM-AKI animal model, the protective impact of Cu₅₄O USNPs was demonstrated by restored of renal function markers, and reduced of tubular casts.

Nanozymes have become an ideal substitute for natural enzymes, but some limitations of nanozymes need be overcome in practical clinical application. Many nanozymes (like Pt nanoparticles and PB nanozymes) have POD-like properties, which can convert H_2O_2 into more cytotoxic ·OH. In addition, most of the nanozymes contain elements that are not necessary for life. Their metabolism and accumulation in vivo need to be further studied, especially for those chemically inert metal nanozymes, such as Pt, Ir, and Au, etc. These nanozymes may persist in the body for a long time and may cause adverse effects on the body. Conversely, FDA-approved PB nanozymes and natural melanin nanoparticles hold great promise for clinical translation thanks to their excellent biocompatibility and metabolisability.

7. Nanocarriers for antioxidants and anti-inflammatory drugs

Nanomaterials can also be used as carriers for small-molecule antioxidant drugs to overcome their poor renal targeting and strong side effects [157,159,218-220]. According to the source of RONS in AKI, these nano-drug delivery systems can be divided into three categories First, mitochondria-related (Table **4**). nanodrugs reduce mitochondria-derived RONS or maintain mitochondrial stability. Second, nanocarriers for anti-inflammatory drugs to effectively reduce oxidative stress in AKI because various enzymes such as NOX, iNOS, and MPO are highly expressed or activated in inflammatory cells during AKI. The activities of these enzymes are closely and positively correlated with the levels of inflammatory factors in AKI. Third, nanocarriers for antioxidant drugs, mainly including natural antioxidant drugs and synthetic antioxidant drugs.

7.1. Antioxidant nanocarriers for mitochondria

Mitochondrial-derived RONS are the main sources of AKI. Therefore, mitochondria are critical therapeutic targets for AKI. The current mitochondria-targeting nanodrugs mainly protect mitochondria and



Fig. 15. Antioxidant nanocarriers for mitochondria in AKI treatment. (A) The structure of NPs and the proposed mechanism for NPs to produce enhanced AKI alleviative effect. **(B)** AKI mice were injected intravenously with Cy5-SS-31 or Cy5-NPs with or without pretreatment of HA for 0.5 h and then visualized 4 h after administration. **(C)** Cre at day 2 in AKI mice after different treatment. Adapted with permission from Ref. [156], copyright 2019. **(D)** Chemical structure of SC-TK-SS31 and the schematic illustration showing the relief of AKI by SC-TK-SS31. Adapted with permission from Ref. [158], copyright 2020. **(E)** Schematic representation of neutrophil membrane-enveloped nanoparticles encapsulating Coenzyme Q10 for the neutralization of proinflammatory cytokines and prevention of oxidative damage in the renal I/R injury. **(F)** Bio-distribution of NP_{CoQ10} and N-NP_{CoQ10} was examined via in vivo imaging instruments. **(G)** Percentage of apoptotic HK-2 cells after different treatments. The levels of MDA **(H)**, and BUN **(I)** detected in I/R injury mice kidneys after different treatments. **(J)** The semi-quantification of tubular injury in indicated treated groups. Adapted with permission from Ref. [221], copyright 2020.

reduce mitochondria-derived RONS in three ways: protecting mitochondrial crest structure, maintaining mitochondrial respiratory chain, and mitochondria-targeted antioxidant therapy.

SS-31, an extensively researched mitochondrial targeting peptide, can selectively bind to cardiolipin of the inner mitochondrial membrane to protect mitochondrial crest structure through electrostatic and hydrophobic interactions [237,238]. However, SS-31 is unstable and lacks renal targeting in vivo, thus cannot be directly applied in the treatment of AKI. Recently, Liu et al. designed pH-responsive hyaluronic acid (HA) based nanocomplexes to deliver SS-31 for efficient AKI treatment (Fig. 15A) [156]. The positively charged SS-31 bonded to the negatively charged HA first and then formed nanocomposites with the positively charged CS (HA-NPs). HA specifically bonded to CD44, which was highly expressed in inflammatory vascular endothelial cells in AKI. After HA-NPs were taken up via the interaction between CD44 and HA and then entered lysosomes, the latter's low pH environment broke the electrostatic equilibrium of HA-NPs to release SS-31. Subsequently, the SS-31 was able to scavenge excess RONS by protecting mitochondrial crest structure, and restored renal function in the S-AKI mouse model (Fig. 15B-C). Very recently, Liu et al. developed a novel renal-targeted chitosan-based drug carrier for (SC-TK-SS-31) SS-31 delivery in therapy of AKI (Fig. 15D) [158]. The renoprotective effect of SC-TK-SS-31 contained two parts. Firstly, L-serine-modified chitosan with PEG (SC)

specifically bonded to KIM-1, which was highly expressed in damaged RTECs. Secondly, RONS-sensitive thioketone (TK) group changed from hydrophobicity to hydrophilic after reacting with RONS to achieve controllable release of SS-31. The SC-TK-SS-31 greatly enhanced the therapeutic effects of SS-31 in the I/R-AKI rat model by protecting mitochondria, attenuating oxidative stress, inflammatory response, and apoptosis due to the effective renal distribution and RONS-responsive drug release behaviors.

Coenzyme Q10 (CoQ10), an important electron carrier in the mitochondrial electronic respiratory chain, is an effective RONS scavenger [239]. However, CoQ10 is hydrophobic and cannot be directly used in AKI treatment. Recently, Liu et al. developed neutrophil membrane-encapsulated CoQ10 for AKI treatment (Fig. 15E) [221]. CoQ10 was first encapsulated with amphiphilic polyethylene glycol-polylactic acid by an emulsion approach and then coated with leukocyte neutrophil membrane (N-NP_{CoO10}). N-NP_{CoO10} inherited the antigenic properties of neutrophil membranes (as nano-baits) to absorb and neutralize complex pathological molecules. The signaling molecules on the neutrophil membrane responded to inflammatory signals in the kidney during AKI, allowing more precise and specific CoQ10 delivery (Fig. 15F). Moreover, N-NP_{CoQ10} reduced mitochondrial damage in RTECs by releasing CoQ10 to maintain the stability of mitochondrial respiratory chain, and significantly ameliorating renal injury in a mouse



Fig. 16. Anti-inflammatory nanomaterials for AKI treatment. (A) Selective nanoparticle-mediated targeting of renal tubular Toll-like receptor 9 attenuates ischemic AKI. Adapted with permission from Ref. [153], copyright 2020. (B) Nanocrafts showed selective kidney accumulation after intravenous injection and sustained release of IL-33 to induce rapid expansion of Tregs and ILC2s. Tregs can secrete IL-10 and ILC 2s can secrete cytokines IL-4 and IL-13 to promote M2 macrophage polarization, which contributes to renoprotection and tissue repair in AKI. (C) Ex vivo organ images of mice at different times in each group. (D) Serum creatinine and BUN (E) levels at 120 h after surgery in different treatments. (F) Semiquantitative assessment of tubular injury in mice at 120 h after I/R. Adapted with permission from Ref. [224], copyright 2021. (G) Schematic illustration of renoprotective effect of MSC-EVs for AKI treatment. (H) Serum BUN levels in mice with or without intravenous EV administration on day 3 after AKI. Adapted with permission from Ref. [226], copyright 2021.

model of I/R-AKI (Fig. 15G-J).

Mitochondrial-targeted antioxidant therapy is also an effective strategy to protect mitochondria and eliminate RONS in AKI. Lipophilic cationic triphenyl phosphorus (TPP) is a highly efficient mitochondrial targeting molecule because it can accumulate in mitochondria with the help of $\Delta \phi$ (positive outside and negative inside) [240]. Several TPP-modified nanodrugs have been adopted to deliver different antioxidants (e.g., TEMPO [223], curcumin [160] and cerium oxide [222]) to mitochondria for the treatment of AKI. For example, Yu et al. developed TPP-functionalized ceria nanoparticles (Atv/PTP-TCeria NPs) for AKI mitochondria-targeted antioxidant therapy [222]. TPP-modified ceria nanoparticles first were prepared by adding TPP in the solvothermal synthesis of ceria. Subsequently, RONS-responsive polymer mPEG-TK-PLGA was coated on the surface of the nanoparticles and finally loaded atorvastatin to create multifunctional targeting nanoparticles (Atv/PTP-TCeria NPs). TPP mediated the entry of Atv/PTP-TCeria NPs into mitochondria, and atorvastatin was released under the high concentration of RONS in mitochondria. As a result, the cerium and atorvastatin worked together to scavenge excess RONS in

mitochondria, significantly inhibiting the inflammatory response, and mitigating renal injury in IR-AKI mice at a very low drug dose.

7.2. Nanocarriers for anti-inflammatory drugs

At present, nano-*anti*-inflammatory drugs in AKI treatment are mainly divided into two categories: First, nanocarriers loaded with antiinflammatory drugs (e.g., TLR9 antagonist [153], immune modulator glucocorticoid [161], and anti-TNF- α [225]) for improved renal targeting and therapeutic effects. Second, mesenchymal stem cell (MSC)-derived exosomes with intrinsic renal targeting and anti-inflammatory effects were also adopted for AKI treatment [151, 152,226,227]. For example, Han et al. packaged ODN2088 (a TLR9 antagonist) into polylactic acid-glycolic acid copolymer nanoparticles (MNPs) to treat I/R-AKI (Fig. 16A) [153]. Systemic ODN2088 administration caused strong side effects because TLR9 was also distributed in other vital organs. MNPs demonstrated excellent kidney targeting ability of 30-fold selectivity over other organs and endocytosed into RTECs. Subsequently, MNPs significantly attenuated renal injury and restored



Fig. 17. Nanocarriers for antioxidants for AKI treatment. (A) Application of PLGA-Oltipraz nanoparticles with a particle size of 100 nm in I/R-induced AKI. **(B)** PLGA NPs with different particle sizes and free DiR were intravenously injected in renal I/R model of mice immediately after surgery. Near-infrared fluorescence images of ischemia-reperfusion (IR) kidneys (dotted box) and contralateral kidneys of RIRI mouse at the indicated time after injection.**(C)** BUN level at 24 h in mice with and without AKI. **(D)** Western blot analysis of protein levels of Nrf2 and downstream NQO1, GCLC and Gpx2 in IR mice on days 3 and 7 after RIRI. Adapted with permission from Ref. [149], copyright 2019. **(E)** Schematic illustration of nHA/PLBR alleviates AKI via preferential inflamed kidney accumulation and antioxidant/anti-inflammatory capacity. Adapted with permission from Ref. [155], copyright 2021.

renal function in I/R-AKI mice by reducing neutrophil and macrophage infiltrations. Recently, Li et al. developed DNA nanocrafts for AKI anti-inflammatory treatment (Fig. 16B) [224]. DNA nanocrafts were constructed with two-dimensional DNA origami as carriers, single-stranded DNA as joints, and immunomodulator interleukin-33 (IL-33) as cargos. DNA nanocrafts exhibited effective aggregation and long-term retention in the kidney due to their tightly folded and soft

laminar structure (Fig. 16C). Subsequently, IL-33 was then released slowly in the kidney as DNA breaking, causing a rapid expansion of renal type 2 innate lymphoid cells, M2 macrophages, and regulatory T cells, significantly ameliorating I/R-induced renal injury (Fig. 16D–F).

MSCs can create a microenvironment conducive to repairing damaged tissue [241]. MSC exosomes (MSCs-EVs) is nanoscale cell membrane vesicles and have the same therapeutic effects as MSCs

without the disadvantages of MSCs such as immunogenicity and embolism [242]. MSCs-EVs have anti-inflammatory effects to alleviate AKI injury by inhibiting CCl2-induced macrophage activation because MSCs-EVs contain abundant C-C motif chemokine receptor 2 [243]; MSCs-EVs also reduce the production of inflammatory factors by upregulating the expressions of autophagy-related genes (ATG5/ATG7) in RTECs [244]. However, the mechanism of MSCs-EVs targeting damaged renal tissue requires further exploration. Very recently, Cao et al. revealed that the membrane proteins of very late antigen 4 and lymphocyte function-associated antigen 1 in MSCs-EVs specifically bonded to VCAM-1 and ICAM-1 respectively to induce MSCs-EVs to target the site of renal injury [152]. In addition, MSCs-EVs had the high levels of miR-125b-5p expression to inhibit apoptosis of proximal RTECs by regulating Bcl-2 and Bax. Recently, Zhao et al. also found that MSC-EVs attenuated mitochondrial damage and inflammatory responses by reversing mitochondrial DNA (mtDNA) deletion and defective mitochondrial oxidative phosphorylation in I/R-AKI (Fig. 16G) [226]. This effect was at least partly dependent on the mitochondrial transcription factor A (TFAM) pathway, which was the major binding and packaging protein for mtDNA. After intravenous injection, MSC-EVS reduced the proportion of apoptotic renal cells, restored the renal function index, attenuated mitochondrial damage, and reduced the level of inflammatory cell infiltration (Fig. 16H). In addition, Cao et al. reported that MSC-EVs activated the Keap1-Nrf2 signaling pathway by increasing miR-200a-3p expression in RTECs. As a result, MSC-EVs enhanced mitochondrial function and promoted recovery of renal function [227]. However, MSC-EVs have poor biostability under systemic administration. Their membrane proteins, which may be critical for MSC-EVs to exert their therapeutic effects, are susceptible to degradation by various enzymes and rapid clearance in vivo. Nanohydrogels loaded MSC-EVs effectively improved MSC-EVs stability in vivo [229]. For example, Zhang et al. wrapped MSC-EVs into Arg-Gly-Asp peptide (RGD)-biotin hydrogels to increase their stability, retention, and bioavailability by the binding ability of RGD to the surface integrins of MSC-EVs. As a result, RGD-biotin MSC-EVs hydrogel was more effective than MSC-EVs themselves in treating I/R-AKI [228].

7.3. Nanocarriers for antioxidants

Currently, nanocarriers have been widely developed to improve the bioavailability and renal targeting ability of traditional antioxidant drugs for high-efficient treatment of AKI, including curcumin [154,160, 162,232], polyphenol [233], bilirubin [155], oltipraz [149], edaravone [235], and BAPTA-AM [236]. For example, Yu et al. developed polylactic acid-hydroxyacetic acid (PLGA) nanodrugs loaded with oltipraz for AKI treatment (Fig. 17A) [149]. Oltipraz activated the Nrf2 signaling pathway and initiated the expression of antioxidant genes to alleviate oxidative stress damage in AKI. However, oltipraz was poorly water-soluble and difficult to accumulate in injured kidney sites. Interestingly, PLGA-oltipraz nanoparticles with a size of 100 nm were mainly accumulated in RTECs in kidneys with more severe I/R injury (i.e., longer ligation time), which was related to the degree of GFB impairment (Fig. 17B). PLGA-oltipraz NPs treatment effectively attenuated oxidative stress by activating Nrf2 to initiate the expressions of downstream antioxidant genes in I/R-induced AKI (Fig. 17C-D). Actively targeting injured kidney tissue has also been adopted for the delivery of antioxidant drugs for AKI treatment. For example, Huang et al. developed HA-coated polylysine-bilirubin nanoparticles (PLBR) to treat AKI (Fig. 17E) [155]. Bilirubin first self-assembled with polylysine to prepare PLBR nanoparticles, and then covered with hyaluronic acid to form nHA/PLBR nanoparticles. The nHA/PLBR nanoparticles actively targeted injured kidney tissue due to the specific interaction between CD44 and HA, and demonstrated strong antioxidant and anti-inflammatory effects in a rat model of I/R-AKI. Interestingly, antioxidants can also bind to contrast agents to prevent renal injury from the source. For example, Liu et al. developed nephroprotective angiographic polymers

(RAPs) based nanoparticles for computed tomography (CT) imaging [231]. The nephroprotective angiographic polymer consisted of phenylboronic acid pinacol ester (PAPE) to scavenge RONS. As a result, PAPE of RAPs efficiently scavenged contrast agent-induced RONS production.

The biggest bottleneck of nanocarriers is their small enough size for renal targeting because of the limitation of the glomerular filtration barrier. The glomerular filtration system allows the passage of nanocarriers up to 100 nm even in severe glomerular filtration barrier damage^{125]}. In order to reduce the size of nanocarriers, the drug loading efficiency of nanocarriers may become low, and the difficulty of nanocarrier preparation is also increased. MSCs-EVs have natural AKI targeting properties, but are not stable in vivo. The stability of MSCs-EVs can be improved to a certain extent by modifying MSCs-EVs, but it may cause the size of MSCs-EVs to be too large and lose their renal targeting properties.

8. Challenges and outlook

As shown throughout this review, diverse antioxidant nanodrugs are being explored to harness RONS to effectively treat AKI, and have demonstrated success in improving renal targeting, effectively reducing oxidative stress damage, and low side effects. However, as described below, the clinical application of antioxidant nanodrugs in AKI treatment still faces great challenges.

First, interspecies differences are the most significant challenges for the clinical translation of antioxidant nanodrugs. All current researches on antioxidant nanodrugs are based on rodent models. In fact, there are huge differences in AKI disease models between rodents and humans [245]. For example, mouse kidney tissue has a much higher capillary density and mitochondrial density compared with humans because the metabolic rate of mice is almost seven times that of humans [246]. Therefore, the mouse AKI model has higher concentrations of RONS and more severe oxidative stress damage compared with humans [247]. In addition, the rodents are basically genetically identical or inbred animals in AKI in order to reduce experimental influence factors and improve data stability [248]. Patients with AKI have high diverse genetic diversity [249-251], which may affect the efficacy of nanodrugs. Moreover, current animal models of AKI do not reflect the complete characteristics of clinical AKI patients. Generally, human AKI occurs in the context of diabetes, cardiovascular disease, obesity [47], etc., which can significantly increase the susceptibility to AKI and ultimately affect the efficacy of nanodrugs once these nanodrugs are translated into the clinic. Consequently, different model animals are encouraged for multidimensional efficacy verification. For instance, a zebrafish AKI model has emerged as the zebrafish kidney develops and functions quite similarly to that of humans; indeed, their key pronephros genes have been identified as homologous with humans [252]. To facilitate these developments, nephrologists should be invited to participate in such studies, to increase their collaborative, interdisciplinary contributions. Second, further studies on various properties of nanodrugs are needed to realize their intended applications in AKI therapy. The size, surface charge, three-dimensional morphology, surface groups, and composition of nanodrugs are not only related to the passage of nanodrugs through the glomerular filtration system, but are also closely related to the uptake by RTECs and the role of inflammatory cells [253]. These fundamental properties underline the significance of the 'structure-function' relationship and serve as useful guidelines for the development of kidney-targeted nanodrugs [254]. Accordingly, researchers should dedicate to get the optimal choice of fundamental parameters through standardized screening. Finally, biocompatibility and long-term safety of nanodrugs also need to be considered, which should be evaluated by strictly defined criteria. In general, nanodrugs with FDA-approved drugs or adjuvants will be more conducive to clinical translation (Fig. 18).

To date, research of antioxidative nanodrugs for the treatment of AKI



Fig. 18. Future direction for clinical translation of nanodrugs in AKI treatment. (A) the clinical application of antioxidant nanodrugs in AKI treatment still faces great challenges including the species differences between model animals and humans, optimization of the fundamental and biocompatibility and safety of nanomaterials. To address these challenges, researchers are encouraged to conduct tailored design of nanodrugs, adopt diversified animal models and employ strict criteria to evaluate the fundamental parameters of nanodrugs in future works. Besides, more nephrologists should be invited to participate in the studies, to increase their collaborative, interdisciplinary contributions. (B) The Pharmaceutical marketing processes after preclinical studies.

is promising but still in its infancy. Nanodrugs for clinical AKI will require extensive multidisciplinary efforts in many different aspects of medicine, cell biology, and nanotechnology. It is anticipated that this review will serve as a valuable reference for scientists across different disciplinary backgrounds involved in AKI treatment, and contributes valuable inspiration in designing high-efficiency nanodrugs for AKI treatment.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work.

Declaration of competing interest

The authors declare no conflict of interest, financial or otherwise.

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