Efficacy of exosomes in acute kidney injury treatment and the associated mechanism (Review)

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Abstract. Acute kidney injury (AKI) is a syndrome characterized by rapid loss of renal function with a high morbidity and mortality. However, due to the complex pathophysiologic mechanisms of AKI, no specific treatment for this disease is currently available. Animal models have demonstrated the protective effects of exosomes on AKI; however, the underlying mechanisms require further investigation. The present review focuses on the efficacy of exosomes derived from different cell sources, including mesenchymal stem cells, endothelial progenitor cells and tubular epithelial cells, in the treatment of AKI and the associated mechanism. Furthermore, the effects of exosomal contents, including microRNAs, circular RNAs, long non-coding RNAs, messenger RNAs and proteins, on the repair of renal tubules, protection against renal tubular epithelial cell injury, protection against fibrosis, inhibition of early endoplasmic reticulum stress and mediation of inflammation during AKI are also summarized in the present review.

Contents

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Abbreviations: AKI, acute kidney injury; S-AKI, sepsis-induced AKI; Cis-AKI, cisplatin-induced AKI; V-AKI, vancomycin-induced AKI; I/R-AKI, ischemia-reperfusion-induced AKI; ROS, reactive oxygen species; EV, extracellular vesicle; MSC, mesenchymal stem cell; huMSC, human umbilical cord-derived MSC; hAEC, human amniotic epithelial cell; TEC, renal tubular epithelial cell; rIPC, remote ischemic preconditioning; NEXs, neutrophil cell membrane-engineered huMSC-secreted EVs

Key words: exosomes, AKI, MSC, macrophage

1. Introduction

Acute kidney injury (AKI) involves rapid deterioration of kidney function, typically occurring over a period of hours to days, and is defined by an increase in serum creatinine levels, a decrease in urine output or both. AKI occurs in 10-15% of hospitalized patients and >50% of patients in intensive care units. Since AKI is a highly heterogeneous disease, its complex pathophysiological mechanisms are not completely understood (1). Currently, no effective treatment or prevention method is available for AKI (1,2). AKI can be caused by several drugs and toxins, such as cisplatin-induced AKI (Cis-AKI) and vancomycin-induced AKI (V-AKI). In addition, sepsis-induced AKI (S-AKI) and ischemia-reperfusion (I/R)-induced AKI (I/R-AKI) are also commonly reported (3-5). The main pathogenic mechanisms of AKI are oxidative stress and cytotoxicity caused by the accumulation of reactive oxygen species (ROS) and toxins due to dysfunction of enzyme-promoted and non-enzyme-promoted antioxidant defense systems, resulting in renal tissue damage and renal dysfunction (6-9).

Extracellular vesicles (EVs) are a heterogeneous group of membrane-bound vesicles and EVs can be divided into micro-vesicles, exosomes and apoptotic bodies according to their size, biological processes and molecular markers (10). Exosomes are an important type of EV, with a size of 40-200 nm and an average diameter of 100 nm (10,11). Exosomes originate from endosomes and are secreted and released by a variety of cells, including mesenchymal stem cells (MSCs) and neutrophils (11). Increasing evidence suggests that exosomes serve an important role in intercellular communication, and the pathways related to exosome uptake include receptor-ligand binding, membrane fusion and endocytosis (10-13). For example, proteins, microRNAs (miRNAs/miRs), circular RNAs, lipids, DNA and long non-coding RNAs (lncRNAs) are delivered to target cells to regulate cell functions (10-15). Although the potential mechanisms underlying the targeted regulation of exosomes are diverse and complex, several studies have revealed the regulatory role of exosome-supported biomolecules in renal I/R injury (12,16,17). However, further investigation of the effects of exosomes on AKI progression is necessary. Exosomes secreted by cells and substances from different sources differ in terms of their efficacy and mechanism of action on AKI, which are discussed and summarized in the present review.

2. Therapeutic effect of exosomes on AKI

Effects of exosomes derived from MSCs on AKI. Previous studies have revealed that MSCs have the capacity for self-renewal, differentiation, immune regulation and nutritional support, and are essential in regenerative medicine because of their ability to create a microenvironment conducive to the repair of damaged tissues (17,18). Previously, a phase 1a clinical trial demonstrated that MSCs can increase renal blood flow and the glomerular filtration rate, and reduce inflammation in the kidneys after stenosis (18-20). The therapeutic effect of MSCs is generally considered to be mediated by the secretion of various factors, including cytokines, cell growth factors and exosomes (21). Exosome-rich components are recognized as key active therapeutic ingredients for MSC-based therapies. Compared with adult stem cell therapy, exosome therapy has certain advantages, including increased consistency, enhanced potency, greater scalability of manufacturing and a wide range of sources (22,23). MSCs can be isolated from a variety of tissues, including the bone marrow, fat, umbilical cord and placenta, and extracted from substances such as dental pulp, skin, blood and urine (10,24,25).

Exosomes from different types of MSCs can promote tubular repair, alleviate tubular epithelial cell damage, inhibit inflammation, oxidative stress and apoptosis, and alleviate renal I/R injury (14,18,26-30). Previous studies have shown that the transfusion of human umbilical cord-derived MSC (huMSC) exosomal miR-874-3p into a mouse model of Cis-AKI and transfection into Cis-HK-2 reduced the activation of necroptosis, and promoted mitochondrial homeostasis and the repair of tubular epithelial cell injury by targeting the receptor-interacting serine/threonine protein kinase 1 (RIPK1)/PGAM5 pathway (27,29). Adipose-derived stem cell-derived exosomal CIRCVMA21 and miR-342-5p alleviated lipopolysaccharide (LPS)-stimulated HK-2 cell damage, inhibited oxidative stress and inflammation, increased renal function, and restored normal tissue morphology by targeting miR-16-5P and inhibiting toll-like receptor 9 (3,31). In addition, physiological homeostasis of the plasma metabolome could be maintained in a male cat model of postrenal AKI, effectively improving renal function of the cats (3,25,28,31,32). Furthermore, the exosomes miR-199a-3p and miR-199a-5p from bone marrow mesenchymal stem cells also have effects on AKI. First, miR-199a-3p inhibits apoptosis and inflammation in I/R mouse models by activating the AKT/ERK pathway. Secondly, miR-199a-5p targeted immunoglobulin protein, inhibited apoptosis and alleviated endoplasmic reticulum stress in I/R mouse models (12,14).

In addition, human urine-derived stem cell (hUSC) exosomes carrying miR-146a-5p and miR-216a-5p also play a role. First, miR-146a-5p inhibits inflammation and apoptosis and promotes renal tubular cell proliferation by targeting interleukin-1 receptor-associated kinase-1. Second, miR-216a-5p targets the PTEN/Akt signaling pathway, inhibits inflammation and oxidative stress, and reduces I/R-AKI in mice (33,34). Furthermore, klotho, a reno-protective protein expressed by hUSCs, migrates to the site of kidney injury and carries out a protective role through a similar mechanism (35). In addition, ferroptosis is a unique mode of cell death induced by iron-mediated lipid peroxidation accumulation and plasma membrane rupture. Exosomes derived from hUSCs carry the lncRNA taurine upregulated 1 and regulate achaete-scute homolog 4-mediated iron death by interacting with serine/arginine-rich splicing factor 1 to inhibit tubular cell epithelial cell damage and alleviate kidney injury (36,37). Iron overload promotes M1 macrophage activation and subsequent inflammation (38). Therefore, future work should combine anti-ferroptosis and anti-inflammatory therapy to potentially increase the therapeutic efficacy of the treatment for inflammation. In combination with immunization and other methods, the application of MSC-exosome-mediated ferroptosis in the treatment of various diseases is expected to increase (36,38-41). Future studies may explore whether exosomes serve roles in other forms of cell death, such as copper-induced cell death, in the occurrence and development of disease (42).

Although studies have shown that exosomes derived from MSCs serve a positive role in the development of AKI (3,12,14,27,31,33,34,43), evidence from animal model studies is limited. This is partly because of ethical constraints; thus, the participation of regulatory bodies, such as ethical review committees, in exosome research is key. In addition, due to the shortcomings of MSCs, such as insufficient clinical validation, unstable sources and quality, and the complex physiological structure and mechanism of the human body, when MSCs are used as drugs, it is necessary to consider whether resistance or immune reactions may occur in the process, which may prevent initial therapeutic effects and exacerbate damage (10,40,41,44) (Fig. 1; Table I).

Efficacy of exosomes derived from other cells in AKI treatment and the associated mechanisms. In addition to MSCs, exosomes secreted by other cells and substances have therapeutic effects on AKI. Exosomes from the urine of premature infants were effective against Cis-AKI (45). Exosomal miR-30a-5p serves a role by activating MAPK8. It reduces the expression of cisplatin-induced cleaved caspase-3, monocyte chemoattractant protein-1 (MCP-1) and Bax, and increases Bcl-2 expression (45). Therefore, miR-30a-5p inhibits cell inflammation and apoptosis, and serves a protective role in the kidney. In V-AKI, human urinary exosomes may serve as biomarkers for drug-induced kidney injury, and exhibit potential as biomarkers, targets and therapeutics for immunomodulatory compounds (45,46).

Exosomal miR-486-5p from endothelial colony-forming cells is effective against I/R-AKI. Exosomal miR-486-5p serves an important role by targeting the PTEN/Akt pathway to alleviate renal tubular epithelial cell (TEC) inflammation and inhibit fibrosis (47,48). In mouse models of CLP, endothelial progenitor cell-derived exosomal miR-21-5p improved kidney function by inhibiting runt-related transcription factor 1 expression, apoptosis and inflammatory responses (49).

Human amniotic epithelial cells (hAECs) are non-MSCs that are isolated from the placental amniotic epithelial membrane. hAECs respond to immunomodulatory therapy, express anti-inflammatory proteins, including IL-10 and IL-12, and have the advantages of abundant sources, large quantities and genetic stability (50). In mice subjected to cecal ligation and puncture, hAEC-derived exosomes inhibited vascular cell adhesion factor 1 through immunomodulation, thereby controlling cellular inflammation and reducing fluorescein

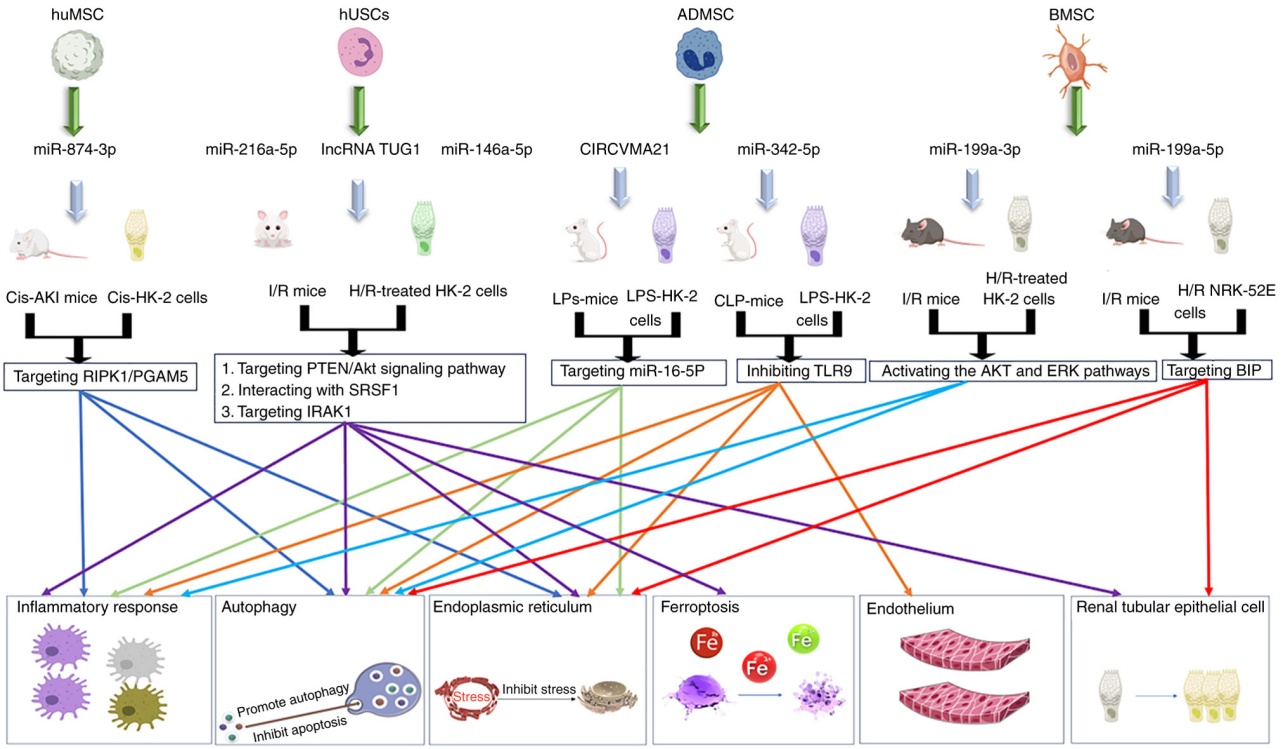

Figure 1. Exosomal contents of mesenchymal stem cells, such as proteins, lncRNAs and miRNAs, inhibit AKI-induced inflammation and apoptosis, and promote the proliferation of renal tubular epithelial cells by regulating various proteins involved in AKI or acting on certain pathways. ADMSC, adipose-derived mesenchymal stem cell; AKI, acute kidney injury; BIP, binding immunoglobulin protein; BMSC, bone marrow mesenchymal stem cell; Cis, cisplatin; Cis-AKI, Cis-induced AKI; CLP, cecal ligation and puncture; H/R, hypoxia/reoxygenation; huMSC, human umbilical cord-derived mesenchymal stem cell; I/R, ischemia-reperfusion; IRAK1, interleukin-1 receptor-associated kinase 1; lncRNA, long non-coding RNA; LPS, lipopolysaccharide; miR/miRNA, microRNA; RIPK1, receptor-interacting serine/threonine protein kinase 1; SRSF1, serine and arginine rich splicing factor 1; TLR9, toll-like receptor 9; hUSCs, human urine-derived stem cells.

isothiocyanate-dextran leakage. Therefore, the integrity of the endothelial monolayer and glomerular endothelial cells was protected, and the functional damage to endothelial cells induced by s-AKI was alleviated (51,52).

TECs are typically the site of injury caused by hypoxia, inflammation and toxins, and TEC injury serves a role in promoting disease progression. miR-19b-3p in exosomes from TECs activate the NF-κB signaling pathway in macrophages by targeting suppressor of cytokine-signaling-1. Increased p65 and phosphorylated-p65 protein levels increase the expression levels of MCP-1 and TNF-α, regulate the activation mechanism of M1 macrophages and promote the progression of renal tubulointerstitial inflammation facilitated by macrophages. Exosomal miR-19b-3p levels are positively associated with the severity of proteinuria (53-55). This finding is the opposite of the protective effect of mesenchymal stem cell exosomes on the kidneys reported in previous studies (33,53), and it is hypothesized that the inflammatory response in AKI may be caused by the exosome-mediated inflammatory pathway through the promotion of TEC macrophage activation. Therefore, miR-16b-3p is a potential target for the treatment of AKI (53,54).

The study also revealed that exosomes from the plasma of patients undergoing heart surgery were effective in mouse models of I/R. Exosomal miR-590-3p reduced I/R-induced oxidative stress by targeting RIPK1. Furthermore, LC3 II and Beclin-1 protein expression levels were decreased, p62 protein expression was increased, and TNF receptor-associated factor 6 could be targeted to regulate autophagy and alleviate LPS-induced AKI and podocyte apoptosis, which had a protective effect on the kidneys (55).

The therapeutic effect of cellular exosomes on S-AKI has also been investigated. Remote ischemic preconditioning (rIPC) also has a protective effect. rIPC is a beneficial stimulator triggered by transient I/R in remote tissues (2). Previous studies have revealed that rIPC has a beneficial effect on a variety of organs (56-59). After rIPC, the kidney promotes the expression of miR-21, which inhibits PTEN expression and NF-κB activity. Therefore, inhibition of HIF-1α abrogates renoprotection induced by rIPC in mice (2,56) (Fig. 2; Table II).

3. Novel advances in exosome therapy

Engineering exosomes. Several studies have shown that MSCs and other cell- and substance-derived exosomes have positive roles in the treatment and prevention of AKI (3,31,33,34,53,55,57). However, these exosomes are deficient in the treatment of AKI, and their therapeutic effects are limited. At present, no standard system exists for the mass production, separation and storage of exosomes. Therefore, the engineering of exosomes is necessary. This process can enhance the targeting of injured sites and treatment specificity or improve resistance to body clearance. The engineering of exosomes involves the modification of natural exosomes using biological and chemical engineering techniques, and

Table I. Role of the exosomal contents of MSCs in AKI.

First author/s, year	Exosome source	Model	Effect	Pathways	Contents	(Refs.)
Yu *et al*, 2023	huMSC	UUO mice; Cis HK-2 cells; Cis-NRK-52E cells; Cis-AKI mice	Anti-inflammation; anti-apoptotic; reduces oxidative stress	Targeting RIPK1/PGAM5	miR-874-3p	(27)
He *et al*, 2023	ADMSC	LPS-AKI mice; LPS-HK-2 cells	Anti-inflammation; anti-apoptotic; reduces oxidative stress; reduces cell damage	Targeting miR-16-5P	CIRCVMA21	(3)
Liu *et al*, 2023	ADMSC	LPS HK-2 cells; CLP mice	Anti-inflammation; anti-apoptotic; promotes autophagy; inhibits endoplasmic reticulum stress; maintains endothelial integrity	Inhibiting TLR9	miR-342-5p	(31)
Zhang *et al*, 2020	hUSC	H/R HK-2 cells; I/R mice	Anti-inflammation; anti-apoptotic; promotes the proliferation of HK-2 cells	Regulating the miR-216a-5p/PTEN/Akt signaling pathway	miR-216a-5p	(34)
Li *et al*, 2020	hUSC	IRI mice; H/R HK-2 cells	Anti-inflammation; anti-apoptotic; anti-oxidative	Targeting the 3'UTR of IRAK1 mRNA and inhibiting the activation NF-κB signaling	miR-146a-5p	(33)
Sun *et al*, 2022	hUSC	IRI mice; H/R HK-2 cells	Reduces the level of ROS; ameliorates ferroptosis; alleviates cell apoptosis	Interacting with SRSF1 to regulate ASCL4-mediated ferroptosis	lncRNA TUG1	(36)
Zhu *et al*, 2019	BMSC	H/R HK-2 cells; I/R mice	Anti-apoptotic; anti-inflammation	Downregulating Sema3A expression and thereby activating the AKT and ERK pathways	miR-199a-3p	(14)
Wang *et al*, 2019	BMSC	I/R rats; H/R NRK-52E cells	Anti-apoptotic; inhibits ER stress; reduces tubular necrosis	Targeting binding immunoglobulin protein	miR-199a-5p	(12)

3'UTR, 3' untranslated region; ADMSC, adipose-derived MSC; AKI, acute kidney injury; ASCL4, achaete-scute family bHLH transcription factor 4; BMSC, bone marrow MSC; Cis, cisplatin; Cis-AKI, Cis-induced AKI; CLP, cecal ligation and puncture; ER, endoplasmic reticulum; H/R, hypoxia/reoxygenation; huMSC, human umbilical cord-derived MSC; hUSC, human urine-derived stem cell; I/R, ischemia-reperfusion; IRAK1, interleukin-1 receptor associated kinase 1; IRI, ischemia reperfusion injury; lncRNA, long non-coding RNA; LPS, lipopolysaccharide; miR, microRNA; MSC, mesenchymal stem cell; RIPK1, receptor-interacting serine/threonine protein kinase 1; ROS, reactive oxygen species; Sema3A, semaphorin 3A; SRSF1, serine and arginine rich splicing factor 1; TLR9, toll-like receptor 9; UUO, unilateral ureteral obstruction.

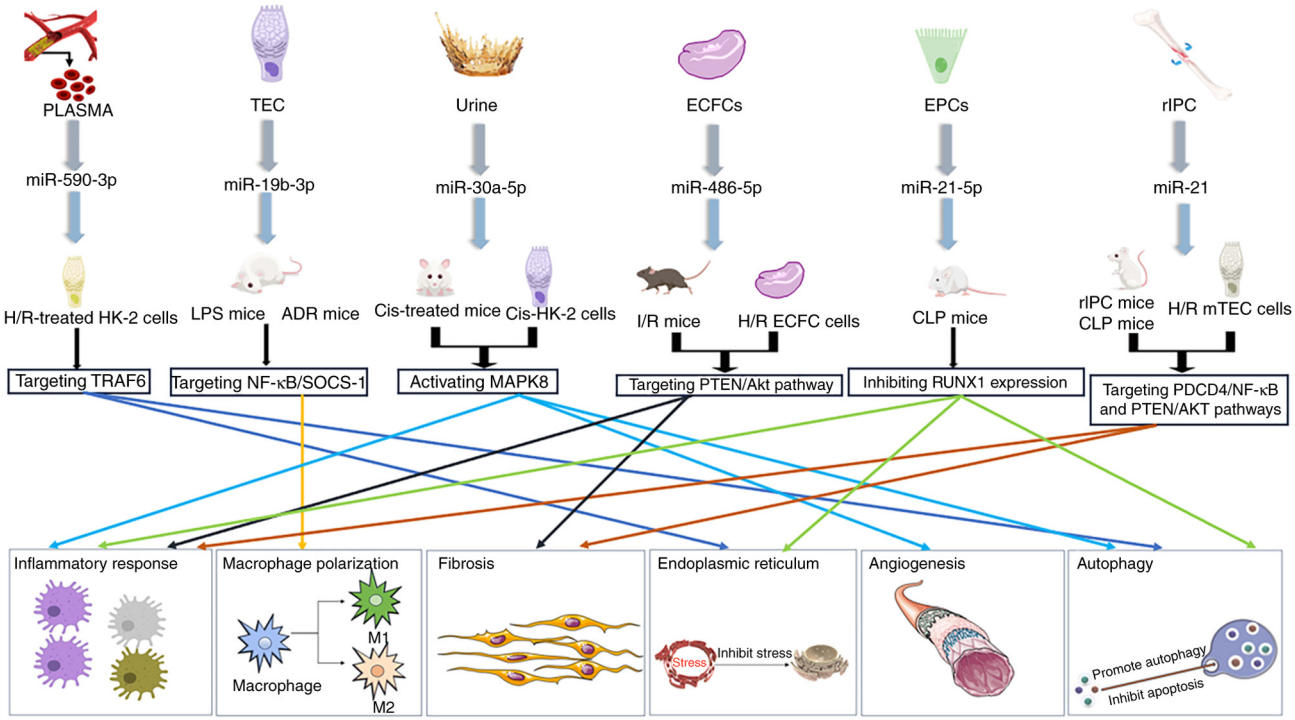

Figure 2. Exosomal contents from other cells and substances act on damaged kidney tissue, have anti-inflammatory and anti-apoptotic effects, and can promote vascular regeneration and inhibit fibrosis, thereby protecting the kidney. By contrast, exosomal content from TEC promotes macrophage activation, and thus, mediates inflammatory responses, a role opposite to that of other exosomes. ADR, adriamycin; Cis, cisplatin; CLP, cecal ligation and puncture; ECFC, endothelial colony-forming cell; EPC, endothelial progenitor cell; H/R, hypoxia/reoxygenation; I/R, ischemia-reperfusion; LPS, lipopolysaccharide; miR, microRNA; mTEC, mice tubular epithelial cells; PDCD4, programmed cell death 4; rIPC, remote ischemic preconditioning; RUNX1, runt-related transcription factor 1; SOCS-1, suppressor of cytokine signaling 1; TEC, renal tubular epithelial cell; TRAF6, TNF receptor associated factor 6.

the modification of endogenous and exogenous loads through bioengineering refers to the introduction of targeting motifs by genetically fusing membrane-bound proteins (60-62). Chemical engineering refers to the addition of substances such as antibodies, proteins and small molecules through lipid chemical reactions, membrane-bound protein chemical reactions or lipid-lipid interactions, amplifying the advantages and specific functions of various nano-delivery systems (55,60). To date, engineered exosomes have been studied for the treatment of a variety of diseases, such as Cis-AKI. huMSC-derived exosomes exhibit a low targeting ability and therapeutic specificity for tissue damage repair. Therefore, neutrophil cell membrane-engineered huMSC-sEVs (NEXs) have been developed to enhance the specificity of targeting huMSC-sEVs. NEXs effectively target the site of kidney injury, considerably reduce ROS levels, and strengthen anti-inflammatory, antioxidative stress and antiapoptotic effects (43). Exosome engineering provides a more accurate and personalized treatment outlook for AKI (10,43,62,63).

Smart nano-exosomes. Smart nano-exosomes are nano-cellular double vesicles that are present in the endosomal region of the majority of eukaryotes and the cytoplasm of several types of bacteria (64). Smart nano-exosomes are formed when multivesicular bodies are secreted together with fused plasma membranes through the exocytosis of intracellular vesicles (65). Nanomaterials with considerable pharmacokinetic, bioavailability and biodistribution properties, such as low toxicity and immunogenicity, penetrate other cells without being targeted by the immune system or toxic reactions, and enable more efficient penetration and delivery of cargoes carrying molecules (66). Thus, these materials have the potential to further elucidate complex biological responses, and represent a promising tool for the diagnosis and treatment of multiple diseases (64-66). Currently, nanoscale single-cell gene manipulation is an effective method to screen for intelligent exosomes that can be directly modified by stem cell modification to increase the 'intelligent' properties of exosomes (67-69). Nano-exosomes have been investigated for the treatment of viral diseases, cancer and cardiovascular diseases (70,71), but there is a gap in AKI research. Previous studies have shown that intelligent nano-exosomes are a rich source of potential biomarkers, and that their secretion into extracellular regions provides convenient conditions for the examination of body fluids such as urine and blood (72,73). Therefore, studies should explore whether they can be used as novel biomarkers for the diagnosis of AKI (68-73).

Applications of nanotechnology in AKI. Gene therapy and stem cell therapy use can improve the effectiveness of AKI treatment, but early use of stem cell therapy for AKI treatment requires research to confirm its long-term safety and assess the risk of developing fibrosis (74). Therefore, due to the rapid development of nanotechnology, nanotechnology has been used to develop early and accurate diagnostic methods and effective treatments for various kidney diseases (75). Modified TiO_2 nanotube arrays, nanosensor, nanotubes, nanorod, nanospheres and iron oxide nanoparticles have been developed, enabling

Table II. Role of the exosome contents of other cells and substance origin in AKI.

First author/s, year	Exosome source	Model	Effects	Pathways	Contents	(Refs.)
Zhang *et al*, 2021	EPCs	CLP mice	Anti-apoptotic; anti-inflammation; reduces oxidative stress	Inhibiting RUNX1 expression	miR-21-5p	(49)
Vinas *et al*, 2016	ECFCs	I/R mice; H/R ECFC cells	Anti-inflammation; inhibits fibrosis	Targeting PTEN and the Akt pathway	miR-486-5p	(47)
Lv *et al*, 2020	TEC	LPS mice; ADR mice	Promotes M1 macrophage activation; promotes inflammation	Leading to M1 phenotype polarization by targeting NF-κB/SOCS-1	miR-19b-3p	(53)
Ma *et al*, 2022	Urine	Cis-AKI mice; Cis HK-2 cells	Promotes cell regeneration; anti-apoptotic; anti-inflammation	Targeting and downregulating MAPK8	miR-30a-5p	(45)
Chen *et al*, 2022	Plasma	H/R HK-2 cells	Anti-apoptotic; reduces oxidative stress; promotes autophagy	Targeting TRAF6	miR-590-3p	(55)
Pan *et al*, 2019	rIPC	Limb rIPC; CLP mice; LPS mTEC cells	Anti-inflammation; anti-apoptotic	Targeting the downstream PDCD4/ NF-κB and PTEN/AKT pathways	miR-21	(2)

ADR, adriamycin; AKI, acute kidney injury; Cis, cisplatin; Cis-AKI, Cis-induced AKI; CLP, cecal ligation and puncture; ECFC, endothelial colony-forming cell; EPC, endothelial progenitor cell; H/R, hypoxia/reoxygenation; I/R, ischemia-reperfusion; LPS, lipopolysaccharide; miR, microRNA; mTEC, mouse tubular epithelial cells; PDCD4, programmed cell death 4; rIPC, remote ischemic preconditioning; RUNX1, runt-related transcription factor 1; SOCS-1, suppressor of cytokine signaling 1; TEC, renal tubular epithelial cell; TRAF6, TNF receptor associated factor 6.

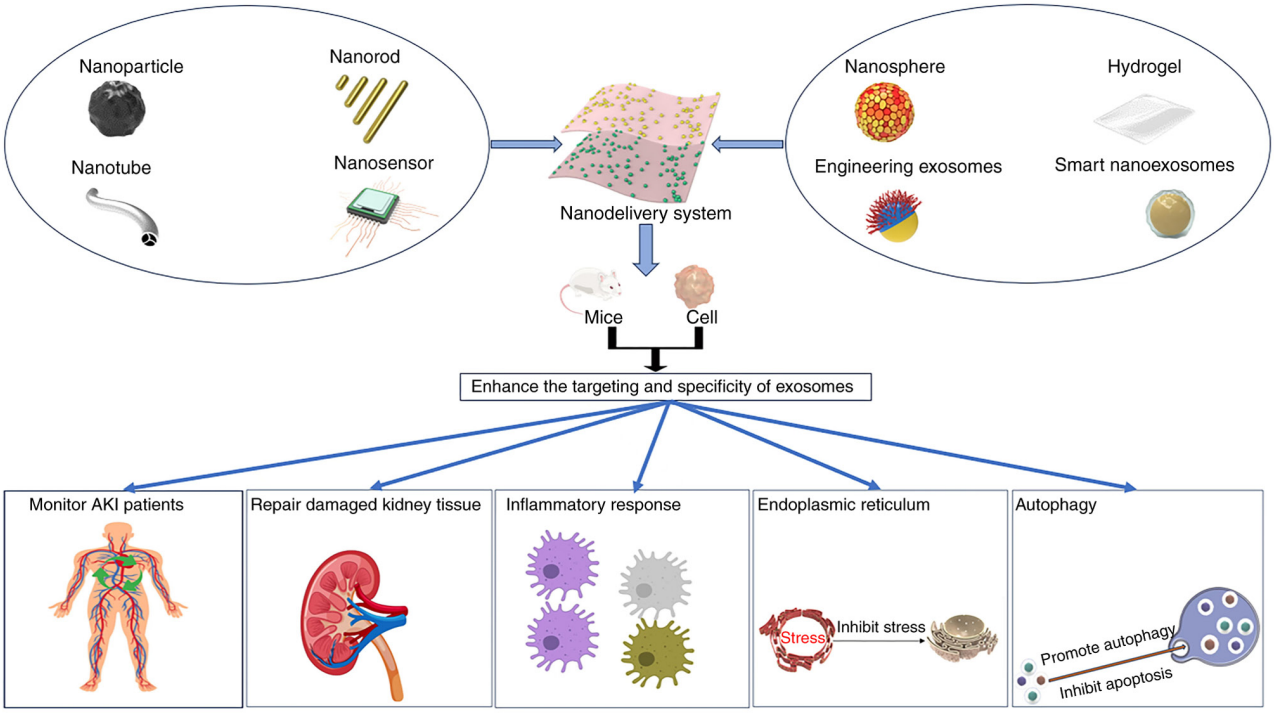

Figure 3. Nanodrug delivery systems can accurately deliver drugs to the damaged site of the kidney, which can inhibit inflammation and apoptosis. In addition, it can inhibit oxidative stress of endoplasmic reticulum, repair damaged kidney tissue, and monitor the physical condition of patients at an early stage. AKI, acute kidney injury.

researchers to sensitively, accurately and conveniently diagnose and continuously monitor the status of patients with AKI using methods such as biomarker monitoring, ultrasound detection and optical imaging (76). In addition, various delivery systems, including polymer nanoparticles, organic nanoparticles, inorganic nanoparticles, lipid nanoparticles and hydrogels, are currently available (74-76). Polymer nanoparticles can be modified with a variety of components that precisely control the characteristics of the nanoparticles, increasing the targeting ability and anti-inflammatory and antioxidant effects of the delivered exosomes (74,77). Inorganic nanoparticles, which can effectively clear ROS, provide a novel option for the treatment of various diseases caused by oxidative stress (78,79). Lipid nanoparticles use biocompatible and physiologically tolerated lipids to improve the solubility of hydrophobic drugs and enhance biocompatibility, making it easier for loaded drugs or exosomes to reach damaged sites, improving therapeutic efficacy and reducing systemic side effects (80,81).

In addition, hydrogels are also the focus of current research. Hydrogels are hydrophilic gels with 3D network structures composed of soft, biocompatible and biodegradable materials. Due to their advantages of high biocompatibility, injection flexibility and controllability, hydrogels can be easily injected (82,83). For example, hydrogels loaded with osteoinductive dental pulp stem cell-derived EVs enhance bone tissue remodeling and adhesion, and promote bone growth (82). The use of hydrogels as delivery systems has also been applied to the treatment of AKI. Studies have shown that the delivery of MSC-EVs to the injured site through hydrogels can increase the bioavailability of MSC-EVs, effectively alleviate the induced inflammatory response and reduce the remodeling of the extracellular matrix, which is expected to become an innovative treatment method for AKI (74,83-85). Finally, nanocarriers can assist in the delivery of small interfering RNAs between cells, increase their plasma stability and targeting, prolong their circulation time, and modulate their pharmacokinetics (86). Studies have prepared megalin-targeting polycationic polymyxin-polyethylenimine/DNA-nanoplexes for kidney-targeted gene delivery to improve gene transfection efficiency. This opens novel avenues for kidney gene therapy for AKI (68,87,88) (Fig. 3; Table III).

4. Conclusion

The present review summarizes the role and mechanism of exosomes derived from different cells and substances in AKI. Exosomes serve an important role in the occurrence and development of AKI by regulating certain pathways or targeting specific sites. For example, the exosome miR-874-3p from huMSC targets RIPK1/PGAM5 to inhibit inflammation and apoptosis. In addition, the exosome miR-216a-5p derived from hUSCs promotes the proliferation of HK-2 cells by targeting the PTEN/Akt signaling pathway. The therapeutic effects of exosomes from different sources on different pathological characteristics of AKI are also discussed by examining their reparative effects on renal tubule injury, and anti-inflammatory and anti-apoptotic effects. The roles of certain exosomes in promoting AKI are also discussed. For instance, the exosome miR-19b-3p derived from TEC can promote the activation of M1 macrophages and promote inflammation, thus promoting the development of AKI. Furthermore, future trends in the development of exosome therapy and some possible challenges, including ethical issues and unclear mechanisms of exosome action on damaged sites, are also discussed. Finally,

Table III. Role of engineered exosomes and nanotechnology in AKI.

First author/s, year	Exosome source	Model	Effects	Pathways	Contents	(Refs.)
Wu *et al*, 2022	NEX	Cis-AKI mice; Cis-NRK52E cells	Promotes cell proliferation; reduces the levels of ROS	NEX enhances the targeting of huMSC-sEVs	Engineered exosomes	(43)
Latifkar A *et al*, 2019	Nanotechnology	Mice; cells	Anti-inflammation; reduces oxidative stress; Monitor the status of patients with AKI	Enhance the targeting and specificity of exosomes	Polymer nanoparticles; hydrogels; smart nanoexosomes	(67,74-76)
Zhao *et al*, 2021						
Sun *et al*, 2019						
Mi *et al*, 2016						

AKI, acute kidney injury; Cis, cisplatin; Cis-AKI, Cis-induced AKI; huMSC-sEVs, human umbilical cord mesenchymal stem cells-derived small extracellular vesicles; NEX, neutrophil cell membrane-engineered huMSC-sEVs; ROS, reactive oxygen species.

the present review discusses the current development trends of exosome therapy and reveals that there are still several issues that remain to be solved. For instance, the field of engineering exosomes, nano-exosomes and gene-edited exosomes still needs to be explored, and the utilization of nanotechnology in these domains remains relatively rare. Unique therapeutic cargoes with biological and clinical therapeutic effects may be loaded into exosomes derived from various cells and substances, and further exploration of the pathogenesis of AKI and the mechanism of action of exosomes is needed. Subsequently, exosome therapy may provide more possibilities in regenerative medicine and the treatment of some diseases, and provides novel options with potential for the treatment of AKI.

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Availability of data and materials

Not applicable.

Authors' contributions

ZZ and MB conceived the present study and revised the manuscript. ZZ and MB wrote and revised the manuscript, and constructed and revised the figures. LS revised the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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