International Journal of Nanomedicine

Dovepress
Taylor & Francis Group

Open Access Full Text Article

REVIEW

Multifunctional Applications of Extracellular Nanovesicles for Acute Kidney Injury and Renal Fibrosis; a Mini Review

Ruizhe Xu[1], Shuainan Liu[2], Zhenhua Cui[1]

[1]Department of Nephrology, College of Medicine, Yanbian University, Yanji, Jilin, 133000, People's Republic of China; [2]Department of Dermatology, College of Medicine, Yanbian University, Yanji, Jilin, 133000, People's Republic of China

Correspondence: Zhenhua Cui, Department of Nephrology, College of Medicine, Yanbian University, Yanji, Jilin, 133000, People's Republic of China, Tel +86 433 273 2352, Email zhenhuacui684@gmail.com

Abstract: Extracellular vesicles (EVs) are released into body fluids, including blood, urine, saliva, pleural and peritoneal fluid, by various cell types through different mechanisms. Various types of EVs differ in structure and function; but, their common characteristic is carrying a variety of bioactive molecules such as RNA, proteins, and lipids. EVs can regulate the function of target cells through interaction with them. Acute kidney injury (AKI) is a common and potentially serious clinical condition characterized by a rapid decline in renal function, manifested as abnormal classic indicators such as serum creatinine and decreased urine output. AKI not only affects the renal function of patients, but it is also closely related to dysfunction in other organs, including the lung, heart, brain, liver, intestine, and immune system. EVs by carrying bioactive molecules (eg, proteins, RNA, lipids) and mediating intercellular communication can play critical roles in inflammation, apoptosis, tubular injury, and fibrosis during AKI. Some key mechanisms of EVs in AKI pathophysiology include promoting tubular cell proliferation, enriching HMGB1/HSP70, leading to NF-Kβ/MAPK activation, and carrying pro-inflammatory molecules (eg, TNF-α, IL-1β, IL-6). In the context of renal fibrosis, EVs can directly participate in its pathogenesis by carrying pro-fibrotic factors and regulating fibroblast activity, accelerating the progression of fibrosis. Besides being involved in the pathogenesis, EVs can also serve as potential diagnostic tools and therapeutic agents against AKI and renal fibrosis. This narrative review summarizes the biogenesis, composition, and functional mechanisms of EVs in AKI as well as renal fibrosis pathogenesis, along with highlighting their potential as diagnostic biomarkers and therapeutic targets.

Keywords: extracellular vesicles, exosomes, acute kidney injury, biomarkers

Introduction

Acute Kidney Injury (AKI) is a clinical syndrome characterized by a rapid decline in renal function caused by various etiologies. It is marked by a rapid decrease in glomerular filtration rate, leading to elevated serum creatinine and possibly decreased urine output. AKI has a high incidence and mortality rate in clinical settings, especially among patients in the Intensive Care Unit (ICU), posing a life-threatening condition.[1] Accordingly, it occurs in about 10–15% of hospitalized and more than 50% of ICU patients.[2] The main causes of AKI include prolonged renal ischemia, toxic drugs, and sepsis.[3] Despite continuous advancements in medical technology, there is currently no standard therapeutic measure for AKI and its mortality rate is still high.[4] Therefore, affected patients may face long-term complications without full recovery, like chronic kidney disease (CKD) or even end-stage kidney disease (ESKD).[5]

Through in-depth study of intercellular communication mechanisms, extracellular vesicles (EVs) have gradually attracted attention as a novel form of intercellular communication. EVs are membrane-bound vesicles released by cells into the extracellular space through active or passive mechanisms, with diameters ranging from 30 nm to several micrometers. Depending on their size and formation mechanism, EVs can be classified into exosomes, microparticles, and apoptotic bodies. EVs play an important role in both physiological and pathological processes. They can carry a variety of bioactive molecules, including proteins, nucleic acids (such as mRNA, miRNA, lncRNA), and lipids. By

Received: 24 June 2025
Accepted: 15 October 2025
Published: 11 November 2025

binding to the cell membrane, endocytosis, or molecular transfer, EVs transmit information between cells and regulate the function of target cells.[6]

In the pathological process of AKI, EVs, as an important regulatory factor, are widely involved in various pathological processes such as inflammation, apoptosis, renal tubular injury and repair, and renal fibrosis.[7] For example, following ischemia-reperfusion injury, renal tubular epithelial cells can release a large number of EVs. These EVs can promote the recruitment and activation of immune cells by carrying inflammatory factors or regulating miRNAs, thereby exacerbating the local inflammatory response.[8] EVs also play a pivotal role in the repair process of renal tubular cells. Accordingly, they can help damaged renal tubular epithelial cells recover their function by carrying anti-apoptotic signaling molecules or proteins that promote cell proliferation.[9] In addition, urinary EVs can also serve as a valuable and non-invasive diagnostic tool in various kidney conditions like AKI, glomerular diseases (eg, focal segmental glomerulosclerosis, IgA nephropathy), tubular disease (eg, Gitelman's and Bartter syndromes), renovascular disease, and renal transplantation (eg, delayed graft function, acute cellular rejection, antibody-mediated rejection).[10]

The specific role of EVs in kidney diseases, including AKI, has been the subject of a few review articles published so far.[7,8,11–13] This narrative mini review tries to update and summarize the biogenesis, composition, and functional mechanisms of EVs in AKI as well as renal fibrosis pathogenesis. It also highlights EVs' potential functions as diagnostic biomarkers and therapeutic targets for AKI and renal fibrosis.

Origin and Composition

Source

EVs are membrane-bound vesicles released into the extracellular environment by various cells through active or passive mechanisms. According on their size, formation mechanism, and biological function, EVs are generally divided into exosomes, microparticles (or microvesicles), and apoptotic bodies. By fusing with the membrane of target cells, EVs transfer their contents (such as proteins, RNA, lipids), playing a crucial role in immune regulation and inflammatory responses.[14] EVs also participate in regulating cell death, particularly in acute and chronic kidney injuries, where they contribute to improving the therapeutic outcomes of kidney diseases by modulating cell death pathways.[15] Furthermore, EVs provide new perspectives for regulating various physiological and pathological processes due to their unique stability, effective information transmission capability, and precise targeted uptake mechanism.[14–19] As carriers, EVs possess unique advantages in delivering drugs and genetic materials without eliciting immune responses.[6] EVs can also be used as effective drug delivery carriers, especially in the field of targeted therapy, where they can achieve precise treatment goals by specifically recognizing target cells. In addition to effectively transporting drugs, EVs can also reduce the side effects of drugs in the body through their natural biocompatibility, low immunogenicity, and targeted delivery.[20]

Exosomes are small vesicles with a diameter ranging from 30 to 150 nm. They are formed through the endocytic pathway and released into the extracellular space after the fusion of multivesicular bodies (MVBs) with the cell membrane. The formation of exosomes is mediated by the endosomal sorting complex required for transport (ESCRT) protein family, involving four main complexes (ESCRT-0, ESCRT-I, ESCRT-II, and ESCRT-III). These complexes complete the assembly and shedding of vesicles by recognizing specific membrane proteins and lipids. The fate of organic and inorganic nanoparticles is dependent on the function of microglial extracellular vesicles, which play a crucial role in the clearance and transport of nanoparticles.[21] There are also non-ESCRT-dependent formation mechanisms, such as the promotion of vesicle formation through lysophosphatidylcholine (LPC) and its metabolites. Exosomes facilitate intercellular gene communication by transferring exosomal shuttling RNAs (esRNA), providing a previously undescribed complex mechanism for mammalian cell communication.[22]

In the context of AKI, renal tubular epithelial cells are the main source of EVs. The exosomes released by these cells carry damage markers (such as miR-21 and miR-29c), which can be potential biomarkers for AKI in urine. Immune cells in the kidney, such as macrophages, T cells, and B cells, can all release exosomes. Exosomes are involved in inflammation regulation by modifying the secretion of cytokines and chemokines. Exosomes secreted by macrophages are rich in miR-155, which can activate the NF-κB signaling pathway and promote inflammatory responses. Exosomes released from glomerular endothelial cells are closely associated with glomerular inflammation and increased capillary

permeability. These exosomes are enriched in vascular endothelial growth factor (VEGF) and endothelin-1, exerting a significant impact on the glomerular microenvironment. There are considerable differences in biological functions and mechanisms of action between extracellular and extracellular vesicles bound to the extracellular matrix.[23]

Microvesicles typically have a diameter ranging from 100 to 1000 nm and are formed by budding directly from the cell membrane. The formation process of microvesicles is primarily associated with membrane remodeling and phospholipid asymmetry, regulated by phospholipase C as well as actin-myosin complexes. Compared to exosomes, microvesicles exhibit larger particle sizes and more diverse compositions.[24] In renal ischemia-reperfusion injury (IRI), the release of microvesicles from renal endothelial cells significantly increases. These microvesicles carry high levels of High Mobility Group Box 1 (HMGB1) and Heat Shock Protein 70 (HSP70), serving as drivers of inflammatory responses. Platelet microvesicles constitute the majority of circulating microvesicles, and their release is often associated with the activation of the coagulation system. Microvesicles derived from mesenchymal stem cells (MSCs) exhibit potent repair capabilities, particularly in ischemic AKI. The pH-mediated selection system provides a novel method for efficient analysis of circulating RNA, enhancing the diagnostic accuracy of exosomal and lipoprotein RNA.[25] Embryonic stem cell microvesicles (ESMVs) mediate novel paracrine signaling through the transfer of miRNAs, potentially regulating gene expression in neighboring cells within the stem cell microenvironment. This discovery offers a new mechanism for stem cell-cell communication and provides potential tools for miRNA/siRNA therapy and virus-free gene delivery.[26]

Apoptotic bodies are the largest extracellular vesicles (500–5000 nm in diameter). They bud from the cell membrane of apoptotic cells and may contain organelle fragments and a large amount of DNA. Although apoptotic bodies are rarely released under physiological conditions, in pathological circumstances like AKI, the number of apoptotic bodies increases significantly due to the intensification of the apoptosis process.[27] Accordingly, in an AKI model, a large number of renal tubular epithelial cells undergo apoptosis due to oxidative stress or toxic injury and release a large number of apoptotic bodies. These apoptotic bodies can be phagocytosed by macrophages, further stimulating the release of inflammatory factors.[28] Moreover, in a septic AKI model induced by cecal ligation and puncture in mice, platelet-derived EVs containing lipopolysaccharide promoted inflammation, apoptosis, oxidative stress (eg, MDA), and mitochondrial dysfunction. The underlying mechanism of these detrimental consequences was partially the activation of the ERK/Smad3/p53 pathway by ADP-ribosylation factor 6 (ARF6).[29] In severe inflammatory responses, the release of apoptotic bodies from macrophages themselves also increases. These apoptotic bodies contain a large amount of phosphatidylserine (PS), which is the main signal for immune cell clearance.[28]

Composition

Proteins are the most predominant functional molecules in EVs, categorized into membrane and luminal proteins. Membrane proteins play a pivotal role in the formation of EVs and cellular targeted recognition.[30] The tetraspanin family, including CD9, CD63, and CD81, are hallmark proteins of exosomes. These proteins bind to lipid rafts, facilitating vesicle formation and targeted delivery functions.[31]

AKI is associated with altered expression of specific miRNAs, and targeting specific miRNAs may provide renal protection in AKI. Specific miRNAs in body fluids are expected to become the next generation of disease biomarkers.[32] miRNAs play a pivotal role in the occurrence and development of kidney diseases, possessing both diagnostic and therapeutic potential, and are an important direction in current kidney disease research.[33] The types of nucleic acids in exosomes include mRNA, microRNAs (miRNAs), circular RNA (circRNA), long non-coding RNA (lncRNA), and mitochondrial DNA (mtDNA). mRNA in exosomes can be translated into functional proteins in target cells. miRNA is the most widely studied type of nucleic acid in exosomes. During renal IRI, the release of microRNAs (exo-miRs) from urinary exosomes is closely linked to the transforming growth factor-β (TGF-β) signaling pathway. This mainly involves the regulation of exo-miR changes at different stages by the TGF-β signaling pathway, as well as their joint participation in orchestrating renal pathological processes. In a rat model of AKI due to IRI, under injury conditions, the levels of miR-16, miR-24, and miR-200c in the urine increased. While, during the recovery phase, exo-miRs (miR-9a, miR-141, miR-200a, miR-200c, miR-429) that target Zeb1/2 mRNA are upregulated collectively. Zeb1/2 is a key regulator of the TGF-β1 signaling pathway, indicating that changes in these exo-miRs reflect the renal fibrosis process mediated by the TGF-β signaling pathway.[34] In a cisplatin-induced acute kidney injury model, it was demonstrated that mesenchymal

stromal cells (MSCs) and the microvesicles (MVs) can promote renal tissue repair by regulating a specific miRNA-mRNA network.[35]

The composition of EVs is complex and diverse, with molecules such as proteins, nucleic acids, and lipids playing significant roles in their biological functions and clinical applications. Lipids constitute the primary component of the EV membrane, primarily including phospholipids, cholesterol, and sphingolipids, which offer stability and specific biological functions to the vesicles.[27] Changes in these molecules can reflect the pathological state of cells, providing a rich source of information for the diagnosis and treatment of AKI.[11]

The Pathogenesis of Acute Kidney Injury

Mediating Inflammatory Response

EVs serve as crucial mediators of inflammatory factor transmission, capable of carrying pro-inflammatory molecules such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6) to target cells. These inflammatory factors, by activating downstream signaling pathways (such as the NF-κB and MAPK pathways), promote the release of more inflammatory mediators from target cells, thereby expanding the inflammatory response spectrum. Monocyte chemoattractant protein-1 (MCP-1), as an adhesion molecule, recruits inflammatory cells during IRI, causing tubular damage and also interstitial fibrosis. Activating transcription factor 3 (ATF3) is a transcriptional repressor that can be induced by various stress stimuli and has anti-apoptotic and anti-inflammatory effects on the kidney. Studies have found that during IRI, exosomal ATF3 RNA can inhibit the transcription of the pro-inflammatory gene MCP-1, exerting a protective effect on the kidney.[36] In an inflammatory microenvironment, three significantly upregulated miRNAs (miR-146a-5p, miR-147b, and miR-155-5p) in tubular cell-derived exosomes (PTCs) and their EVs are enriched in the Toll-like receptor signaling pathway. Specifically, miR-146a-5p targets TRAF6 and IRAK1, negatively regulating NF-κB activity and inhibiting excessive inflammation; while, miR-155-5p targets key molecules in the NF-κB pathway (such as IKKβ) to promote the expression of pro-inflammatory factors. Regarding miR-147b, it may participate in inflammatory signal transmission by regulating genes related to the Toll-like receptor signaling pathway (such as COL4A2).[37] In a study utilizing male C57BL/6 mice to establish a renal IRI model, hypoxia/reoxygenation (H/R) induced endoplasmic reticulum stress (ER stress) in renal tubular epithelial cells, which was transmitted to macrophages via exosomes and promoted their M1 polarization. The expression level of miR-106b-5p in exosomes derived from renal tubular epithelial cells experiencing ER stress was significantly elevated. ATL3 is a potential target protein of miR-106b-5p, involved in the ER stress and M1 polarization processes of macrophages. Inhibiting the expression of miR-106b-5p can alleviate renal damage in AKI mice.[38] Human neutrophils are capable of generating EVs and regulating their functional responses through these vesicles. Neutrophil-derived EVs may play a significant role in immune responses and inflammation regulation.[39]

Regulating Cell Apoptosis

The role of EVs in AKI extends beyond inflammatory responses, profoundly influencing the survival and function of renal tubular epithelial cells through their dual anti-apoptotic and pro-apoptotic functions. As delivery vehicles, EVs are transforming existing treatment paradigms in clinical applications.[40] Many EVs exhibit anti-apoptotic properties; yet, in certain scenarios, EVs can accelerate the apoptosis of renal tubular epithelial cells by delivering pro-apoptotic factors such as Bax, Caspase family proteins, and TNF-α. The pro-apoptotic and anti-apoptotic effects of EVs are not entirely contradictory, but are dynamically regulated according to different pathological environments and cell sources.[41]

Promoting Renal Tubular Epithelial Cell Injury and Repair

EVs play a dual role in AKI, both exacerbating the damage to renal tubular epithelial cells and, on the other hand, participating in their repair process under specific conditions. Damaged renal tubular epithelial cells release a large number of EVs, which carry damage-associated molecular patterns (DAMPs) and further exacerbate local cellular damage and inflammatory responses. Related research on the biomedical applications of functional cargo in EVs, including drug delivery and disease biomarker discovery, has analyzed the diverse applications of exosomes in the

biomedical field, such as cancer treatment and immunotherapy.[42] Similar to cell apoptosis, the role of EVs in injury and repair is influenced by both the type of source cells and environmental conditions. EVs released by mesenchymal stem cells (MSCs) and renal proximal tubular cells (RPCs) primarily promote repair, while EVs released by damaged renal tubular epithelial cells tend to exacerbate injury.[43]

Participation in Renal Fibrosis

Renal fibrosis is one of the key pathological characteristics of AKI progressing to CKD.[44] EVs play a crucial regulatory role in the occurrence and progression of renal fibrosis. Accordingly, transforming growth factor-β1 (TGF-β1)-induced epithelial-mesenchymal transition (EMT) is a key step in renal fibrosis.[45] Bone marrow mesenchymal stem cell-derived microvesicles (BM-MSC-MVs) and the MVs they secrete play a role in renal tissue repair.[46] Studies have found that in elderly rats, the expression of miR-344a, miR-133b-3p, miR-294, miR-423-3p, and miR-872-3p is downregulated in BM-MSCs, and a similar trend is also observed in serum. BM-MSC-MVs from young rats significantly inhibit TGF-β1-mediated EMT in HK2 cells, while the inhibitory effect is weaker in elderly rats. Notably, miR-133b-3p and miR-294 significantly inhibit TGF-β1-mediated EMT in HK2 cells.[47] EVs can directly participate in the formation of renal fibrosis by carrying pro-fibrotic factors and regulating fibroblast activity, accelerating the progression of fibrosis. By constructing a unilateral ischemic reperfusion injury (UIRI) mouse model and a hypoxia-treated NRK-52E cell model, it was found that the content of miR-150-5p in exosomes secreted by renal tubular epithelial cells after hypoxia treatment increased. When miR-150-5p binds to the 3'-untranslated region (3-UTR) of cytokine signaling inhibitor 1 (SOCS1), it inhibits the expression of SOCS1. Since SOCS1 negatively regulates the activation of the JAK/STAT pathway, affecting the activation process of various cells, miR-150-5p activates the JAK/STAT pathway by downregulating the expression of SOCS1, ultimately promoting the activation and proliferation of fibroblasts and advancing the process of renal fibrosis.[48] Among exosomal miRNAs, miR-133b and miR-199b promote TGF-β1-induced EMT and renal fibrosis by targeting and inhibiting SIRT1.[49]

Besides nucleic acid, protein biomarkers also serve as a potential index of renal fibrosis in both animal and human models.[50] For instance, two proteins, α-1-antitrypsin and ceruloplasmin, could act as biomarkers of IgA nephropathy because their level increased in urinary exosomes in humans.[51] Another example is activator of G-protein signaling 3 in urinary exosomes, which was demonstrated to be a promising biomarker in polycystic kidney disease.[52]

Potential Application as Diagnostic Markers and Therapeutic Targets for AKI

Diagnostic Markers

In patients with AKI, significant changes occur in the content and types of miRNAs in urine or blood. Through research on the rat model of renal IRI, it was found that miRNAs in urinary exosomes (exo-miRs) can reflect the progression of AKI, providing potential biomarkers for noninvasive detection of AKI.[53] By constructing a rat model of sepsis-induced AKI, among 84 detected miRNAs, miR-181a-5p and miR-23b-3p showed differential expression before the increase in serum creatinine, potentially serving as important tools for early diagnosis and also as therapeutic targets. Furthermore, lipopolysaccharide (LPS) affects the release and size of serum exosomes.[54] In an inflammatory microenvironment, miRNAs such as miR-146a-5p, miR-147b, and miR-155-5p in PTCs and EVs participate in renal inflammatory responses by regulating the Toll-like receptor signaling pathway. These findings provide new targets for understanding the molecular mechanisms of renal inflammation and support the potential application of EV-encapsulated miRNAs as noninvasive biomarkers, laying the foundation for early diagnosis and therapeutic intervention in AKI in the future.[55] The level of urinary exosomal miR-106b-5p is correlated with the severity of AKI and can be used as a diagnostic marker.[56] On the other hand, miR-29c in urinary exosomes is significantly correlated with renal function index (eGFR) and the degree of renal fibrosis. Therefore, it can serve as a novel noninvasive biomarker for evaluating the severity and disease progression of renal fibrosis.[57] Microvesicles isolated from human urine contain RNA, with an integrity similar to that of kidney tissue, including 18S and 28S rRNA. RNA is better preserved in microvesicles compared to whole-cell urine,[58] indicating that urinary microvesicles can serve as a novel noninvasive source of nucleic acids for biomarkers in kidney diseases.

Proteins in EVs also have diagnostic value. Kidney injury molecule-1 (KIM-1) is significantly enriched in EVs from AKI patients, and its level is positively correlated with the severity of kidney injury. The average particle size of EVs in the urine of AKI patients is significantly smaller than that of the healthy control group, and their concentration is significantly elevated. Western blot can be used for quantitative analysis of the expression levels of specific proteins in EVs. In the urine EVs of AKI patients, the expression level of KIM-1 and HSP70 is significantly enhanced. Compared with traditional markers of kidney function (such as serum creatinine and blood urea nitrogen), miRNAs and proteins in EVs exhibit higher sensitivity and specificity. Additionally, exosomes may have significant potential in the diagnosis and treatment of lysosomal storage diseases, especially in the discovery of disease markers and drug delivery.[59]

Therapeutic Targets

The incidence rate and mortality of AKI are high, and effective treatment modalities are lacking.[60] Mitochondrial dysfunction plays a crucial role in the pathogenesis of AKI, and miRNA may become a potential target for the treatment of AKI.[61] For example, in a cisplatin-induced mouse model of AKI, miR-709 is upregulated in the renal tubules after AKI, mediating mitochondrial dysfunction and apoptosis by inhibiting the expression of mitochondrial transcription factor A (TFAM). Targeting miR-709 is expected to become a new method for protecting mitochondrial function and preventing cell death in AKI.[62] Interfering with the miR-150-5p/SOCS1 axis, such as inhibiting exosomal miR-150-5p or upregulating SOCS1, may become a new strategy for delaying the progression of UIRI to renal fibrosis.[63] By regulating the production, release, or uptake of EVs, new paradigms can be introduced for the treatment of AKI. Inhibiting the production of MVBs or suppressing related signaling pathways can effectively reduce the release of pro-inflammatory EVs and alleviate the inflammatory response in AKI. Blocking this process can effectively reduce the release of pro-inflammatory EVs. Studies have found that the release of EVs can be reduced by using lysosomal inhibitors or certain drugs, such as paclitaxel, thereby inhibiting the further exacerbation of inflammatory responses. Exosomes can serve as ideal drug carriers, targeting precisely and reducing side effects.[64] In the context of sepsis-associated AKI, fibroblastic reticular cell-derived EVs are promising drug-delivery vehicles (recombinant CD5L) by promoting mitochondrial autophagy and restricting inflammasome activation, leading to improved kidney function.[65] In addition, exosomes may also serve as gene therapy vectors, with advantages over viral vectors in terms of non-immunogenicity, allowing for remote delivery of nucleic acids to regulate cellular function.[66]

Despite being heterogeneous, EVs obtained from MSCs have myriad and unique properties for AKI treatment. These include having anti-inflammatory, anti-fibrotic, as well as proangiogenic activities, low immunogenicity, high biocompatibility, ease of penetrating the barriers, and mitigating cell apoptosis/necrosis/oxidative stress.[67] In this regard, for example, an experimental study in a rat ischemia-reperfusion model demonstrated that small EVs derived from MSCs significantly improved indexes of renal function (serum creatinine and urea), increased anti-inflammatory cytokine levels (interleukin-10), and attenuated the complement activation (C3 and C4 levels) compared to the placebo.[68] Exosomes derived from MSCs have also been shown to attenuate kidney injury and fibrosis in an unilateral ureteric obstruction mouse model via the inhibition of the extracellular matrix protein accumulation and epithelial-to-mesenchymal transition process secondary to the delivery of miR-186-5p.[69] The role of small EVs derived from MSCs in the treatment of different kidney diseases, including AKI, drug-induced nephropathy (eg, cisplatin, glycerol, gentamicin), CKD, renal fibrosis, renal cell carcinoma, and kidney transplantation, has been comprehensively addressed and discussed elsewhere.[70]

Table 1 lists and summarizes the potential therapeutic indications and related mechanisms of different types of EV for different pathogenic processes of AKI. In addition, the role of EV in the pathophysiology, diagnosis, and treatment of AKI and renal fibrosis has been schematically depicted in Figure 1.

New Scientific Contributions

The current review is not a mere repetition of existing studies; instead, it supplements the field of EVs and kidney diseases with three core novel values through deepened mechanisms, integrated evidence, and clear directions:

Table 1 Types and Key Mechanisms of Different Types of Extracellular Vesicles for Pathogenic Process of Acute Kidney Injury/Renal Fibrosis and Their Potential Outcomes

Pathogenic Process	EV Type	Key Mechanisms [References]	Functional Outcome
Inflammatory Response	Exosomes/ Microvesicles	• Carrying pro-inflammatory Molecules (TNF-α, IL-1β,IL-6)[53] • Transferring miR-106b-5p, leading to macrophage M1 polarization[58] • Enriching HMGB1/HSP70, leading to NF-Kβ/MAPK activation[63]	Augmenting inflammation and immune cell recruitment[53,58,63]
Cell Apoptosis	All EV types	• Delivering pro-apoptotic factors (eg, Bax, Caspases)[6] • Transferring anti-apoptotic signals (eg, MSC-EVs)[26]	Having dual role by either promoting or inhibiting tubular cell Death[6,26]
Tubular Injury & Repair	Exosomes/ Microvesicles	• Releasing DAMPs from damaged cells, leading to inflammation[33] • Delivering MSC-EVs with anti-apoptotic miRNAs/ proteins[54] • Promoting tubular cell proliferation[54]	Exacerbating injury or enhancing tissue repair[33,54]
Renal Fibrosis	Exosomes/ Microvesicles	• Carrying miR-150, leading to SOCS1 inhibition and JAK/STAT activation[47] • Transferring miR-133b/ miR-199b, targeting SIRT1, and promoting EMT[48] • Delivering TGF-β1, leading to fibroblast activation[56]	Inducing fibroblast proliferation and ECM deposition[47,48,56]

Abbreviations: EVs, Extracellular vesicles; HMGB1/HSP70, High Mobility Group Box 1/Heat Shock Protein 70; MSC-EVs, Mesenchymal stem cell-derived extracellular vesicles; DAMPs, damage-associated molecular patterns; SOCS1, cytokine signaling inhibitor 1; EMT, epithelial-mesenchymal transition; TGF-β1, transforming growth factor-β1; SIRT1, silent information regulator; ECM, extracellular matrix.

1) This review pioneers the systematic integration of the differential roles of distinct EV subtypes across the entire pathological trajectory of AKI, addressing the longstanding fragmentation gap in mechanistic research.
2) The present review refines the etiology-specificity of EVs as diagnostic biomarkers, markedly enhancing their clinical translational potential.
3) Our review concretely articulates actionable EV-based therapeutic strategies and delineates current research limitations, providing a clear roadmap for future investigations.

Future Perspective

EVs, as crucial mediators of intercellular communication, have gained increasing attention in recent years regarding their role in AKI and renal fibrosis. EVs classified into exosomes, microparticles, and apoptotic bodies transmit a diverse array of bioactive molecules, including miRNA, proteins, lipids, and lncRNA. They can also serve as a carrier of nephroprotective agents and genes. They not only play a pivotal role in the onset and progression of AKI, but also offer novel potential avenues for its early diagnosis and targeted therapy of this serious and potentially life-threatening condition. These encouraging findings have also been demonstrated for renal fibrosis. In preclinical investigations, findings of small EVs derived from MSCs in the treatment of different kidney diseases, such as AKI and renal fibrosis, have been promising.

Although remarkable progress has been made in EV research about AKI, revealing their significant role in pathogenesis, diagnosis, and treatment, there are still many limitations and challenges in current research, necessitating further in-depth exploration. The isolation, purification, and characterization techniques of EVs have not been unified and harmonized. Meanwhile, existing methods, such as ultracentrifugation, and size exclusion chromatography suffer from issues like low purity and insufficient efficiency, which may adversely affect the reliability of research results.

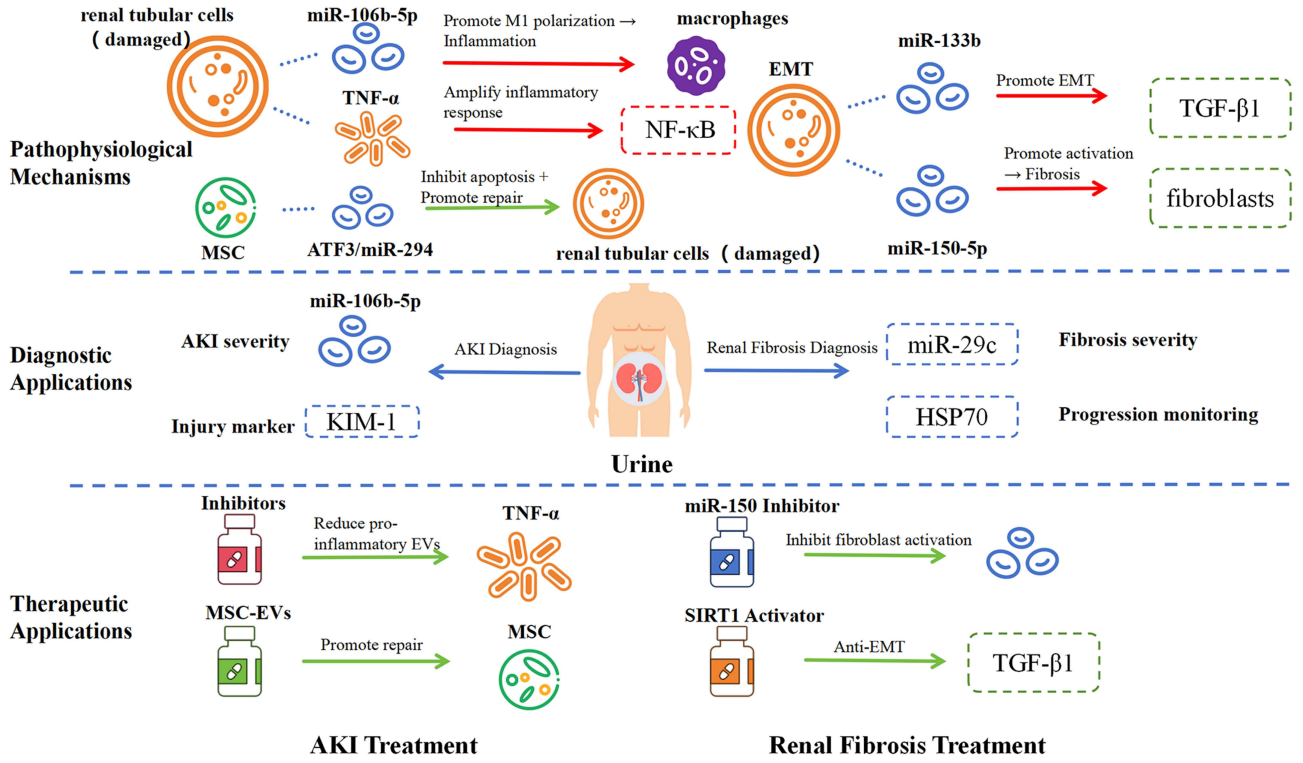

Figure 1 The core role of extracellular vesicles in the pathophysiology, diagnosis, and treatment of acute kidney injury and renal fibrosis.

Developing highly specific separation techniques such as microfluidic chips and antibody capture and standardized operating procedures, is crucial to promote the clinical translation of EVs. Furthermore, it is necessary to improve EV tracing techniques both in vitro and in vivo to monitor their biodistribution and targeting efficiency in real time. Meanwhile, the safety of EVs as therapeutic vectors or targets (such as immunogenicity, off-target effects) needs to be rigorously evaluated in pre-clinical and clinical studies. Finally, existing research mostly focuses on the analysis of single factors, lacking systematic exploration. The differences in sources, sizes, and molecular compositions of EVs may lead to significant variations in their functions during different stages or etiologies of AKI. Therefore, more research is needed in the future to delve into the molecular mechanisms and animal models to clarify the specific role of extracellular vesicles in AKI and their potential clinical application value.

Research on EVs in the field of AKI is currently at a pivotal stage, transitioning from mechanism exploration to clinical translation. Serving as diagnostic markers and therapeutic targets for AKI and renal fibrosis, EVs hold immense clinical application potential. Through technological innovation, interdisciplinary collaboration, and clinical validation, EVs are poised to emerge as a novel breakthrough in early diagnosis, prevention, and treatment of AKI and renal fibrosis.

Author Contributions

R.X.: Literature collection, content synthesis, and initial manuscript preparation. S.L.: Critical review of content, reference organization, and manuscript revision. Z.C.: Topic conceptualization, final manuscript approval, and academic supervision. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

There is no funding to report.

Disclosure

No potential financial and non-financial conflict of interest relevant to this article was reported.

References

1. Ronco C, Bellomo R, Kellum JA. Acute kidney injury. *Lancet*. 2019;394(10212):1949–1964. doi:10.1016/S0140-6736(19)32563-2
2. Karimzadeh I, Barreto EF, Kellum JA, et al. Moving toward a contemporary classification of drug-induced kidney disease. *Crit Care*. 2023;27(1):435. doi:10.1186/s13054-023-04720-2
3. Goyal A, Daneshpajouhnejad P, Hashmi MF, et al. Acute Kidney Injury. In: *StatPearls [Internet]*. Treasure Island (FL): StatPearls Publishing; 2025.
4. An JN, Kim SG, Song YR. When and why to start continuous renal replacement therapy in critically ill patients with acute kidney injury. *Kidney Res Clin Pract*. 2021;40(4):566–577. doi:10.23876/j.krcp.21.043
5. Chawla LS, Eggers PW, Star RA, Kimmel PL. Acute kidney injury and chronic kidney disease as interconnected syndromes. *N Engl J Med*. 2014;371(1):58–66. doi:10.1056/NEJMra1214243
6. Al-Jipouri A, Eritja À, Bozic M. Unraveling the multifaceted roles of extracellular vesicles: insights into biology, pharmacology, and pharmaceutical applications for drug delivery. *Int J Mol Sci*. 2023;25(1):485. doi:10.3390/ijms25010485
7. Kosanović M, Milutinovic B, Glamočlija S, Morlans IM, Ortiz A, Bozic M. Extracellular vesicles and acute kidney injury: potential therapeutic avenue for renal repair and regeneration. *Int J Mol Sci*. 2022;23(7):3792. doi:10.3390/ijms23073792
8. Zhao X, Li Y, Wu S, et al. Role of extracellular vesicles in pathogenesis and therapy of renal ischemia-reperfusion injury. *Biomed Pharmacother*. 2023;165. 115229. doi:10.1016/j.biopha.2023.115229
9. Wei J, Xie Z, Kuang X. Extracellular vesicles in renal inflammatory diseases: revealing mechanisms of extracellular vesicle-mediated macrophage regulation. *Int J Mol Sci*. 2025;26(8):3646. doi:10.3390/ijms26083646
10. Sun IO, Lerman LO. Urinary extracellular vesicles as biomarkers of kidney disease: from diagnostics to therapeutics. *Diagnostics*. 2020;10(5):311. doi:10.3390/diagnostics10050311
11. Yan Q, Liu M, Mao J, Zhao Z, Wang B. Extracellular vesicles in acute kidney injury: mechanisms, biomarkers, and therapeutic potential. *Int J Nanomed*. 2025;20:6271–6288. doi:10.2147/IJN.S519345
12. Li S, Zhou L, Huang Y, Tang S. Emerging frontiers in acute kidney injury: the role of extracellular vesicles. *Bioact Mater*. 2025;48:149–170. doi:10.1016/j.bioactmat.2025.02.018
13. Quaglia M, Merlotti G, Colombatto A, et al. Stem cell-derived extracellular vesicles as potential therapeutic approach for acute kidney injury. *Front Immunol*. 2022;13. 849891. doi:10.3389/fimmu.2022.849891
14. Wang Z, Qin Z, Wang J, et al. Engineering extracellular vesicles with macrophage membrane fusion for ameliorating imiquimod-induced psoriatic skin inflammation. *J DermatolTreat* 2023;34(1):2220445. doi:10.1080/09546634.2023.2220445
15. Zhou Z, Shi L, Chen B, Qian H. Regulation of regulated cell death by extracellular vesicles in acute kidney injury and chronic kidney disease. *Cytokine Growth Factor Rev*. 2024;76:99–111. doi:10.1016/j.cytogfr.2023.12.006
16. Al-Omar MT, Alnajjar MT, Ahmed ZT, Salaas FMI, Alrefaei TSM, Haider KH. Endothelial progenitor cell-derived small extracellular vesicles for myocardial angiogenesis and revascularization. *J Clin Trans Res*. 2022;8(6):476–487.
17. Huang L, Xiong J, Fu J, et al. Bone marrow mesenchymal stem cell-derived exosomal LINC00847 inhibits the proliferation, migration, and invasion of Ewing sarcoma. *J Clin Trans Res*. 2022;8(6):563–576.
18. Desai PP, Narra K, James JD, Jones HP, Tripathi AK, Vishwanatha JK. Combination of small extracellular vesicle-derived annexin A2 protein and mRNA as a potential predictive biomarker for chemotherapy responsiveness in aggressive triple-negative breast cancer. *Cancers*. 2022;15(1):212. doi:10.3390/cancers15010212
19. Wei G, Li C, Jia X, et al. Extracellular vesicle-derived CircWhsc1 promotes cardiomyocyte proliferation and heart repair by activating TRIM59/STAT3/Cyclin B2 pathway. *J Adv Res*. 2023;53:199–218. doi:10.1016/j.jare.2022.12.014
20. Chen K, Si Y, Guan JS, et al. Targeted extracellular vesicles delivered verrucarin a to treat glioblastoma. *Biomedicines*. 2022;10(1):130. doi:10.3390/biomedicines10010130
21. Gao J, Song Q, Gu X, et al. Intracerebral fate of organic and inorganic nanoparticles is dependent on microglial extracellular vesicle function. *Nat Nanotechnol*. 2024;19(3):376–386. doi:10.1038/s41565-023-01551-8
22. Chimal-Vega B, Maldonado-Arvizu JE, Hernández Avalos AD, Díaz-Villanueva JF, Avila-Barrientos LP, García González VG. Inter-tissue communication mechanisms via exosomes and their implications in metabolic diseases: opportunities for pharmacological regulation. *Future Pharmacol*. 2025;5(1):11.
23. Mebarek S, Buchet R, Pikula S, et al. Do media extracellular vesicles and extracellular vesicles bound to the extracellular matrix represent distinct types of vesicles? *Biomolecules*. 2023;14(1):42. doi:10.3390/biom14010042
24. Wang X, Li H, Wang Z, et al. Site- and structure-specific glycosylation signatures of bovine, caprine, porcine, and human milk-derived extracellular vesicles. *J Agric Food Chem*. 2023;71(51):20826–20837. doi:10.1021/acs.jafc.3c06439
25. Yang R, Lou D, Xia K, Sun L, Zhu Q. A pH-mediated highly selective system enabling simultaneous analysis of circulating RNAs carried by extracellular vesicles and lipoproteins. *Anal Chem*. 2023;95(51):18803–18813. doi:10.1021/acs.analchem.3c03924
26. Wang AYL, Kao HK, Liu YY, Loh CYY. Engineered extracellular vesicles derived from pluripotent stem cells: a cell-free approach to regenerative medicine. *Burns Trauma*. 2025;13:tkaf013. doi:10.1093/burnst/tkaf013
27. Doyle LM, Wang MZ. Overview of extracellular vesicles, their origin, composition, purpose, and methods for exosome isolation and analysis. *Cells*. 2019;8(7):727. doi:10.3390/cells8070727
28. Li ZL, Li XY, Zhou Y, Wang B, Lv LL, Liu BC. Renal tubular epithelial cells response to injury in acute kidney injury. *EBioMedicine*. 2024;107:105294. doi:10.1016/j.ebiom.2024.105294
29. Lu X, Jiang G, Gao Y, et al. Platelet-derived extracellular vesicles aggravate septic acute kidney injury via delivering ARF6. *Int J Biol Sci*. 2023;19(16):5055–5073. doi:10.7150/ijbs.87165

30. Kumar MA, Baba SK, Sadida HQ, et al. Extracellular vesicles as tools and targets in therapy for diseases. *Signal Transduct Target Ther*. 2024;9(1):27. doi:10.1038/s41392-024-01735-1
31. Jankovičová J, Sečová P, Michalková K, Antalíková J. Tetraspanins, more than markers of extracellular vesicles in reproduction. *Int J Mol Sci*. 2020;21(20):7568. doi:10.3390/ijms21207568
32. Bakinowska E, Kiełbowski K, Pawlik A. The role of MicroRNA in the pathogenesis of acute kidney injury. *Cells*. 2024;13(18):1559. doi:10.3390/cells13181559
33. Bravo-Vázquez LA, Paul S, Colín-Jurado MG, et al. Exploring the therapeutic significance of microRNAs and lncRNAs in kidney diseases. *Genes*. 2024;15(1):123. doi:10.3390/genes15010123
34. Sonoda H, Lee BR, Park KH, et al. miRNA profiling of urinary exosomes to assess the progression of acute kidney injury. *Sci Rep*. 2019;9(1):4692. doi:10.1038/s41598-019-40747-8
35. de Almeida DC, Êj B, Azevedo H, et al. A regulatory miRNA-mRNA network is associated with tissue repair induced by mesenchymal stromal cells in acute kidney injury. *Front Immunol*. 2017;(7):645. doi:10.3389/fimmu.2016.00645
36. Chen HH, Lai PF, Lan YF, et al. Exosomal ATF3 RNA attenuates pro-inflammatory gene MCP-1 transcription in renal ischemia-reperfusion. *J Cell Physiol*. 2014;229(9):1202–1211. doi:10.1002/jcp.24554
37. Baer PC, Neuhoff AK, Schubert R. microRNA expression of renal proximal tubular epithelial cells and their extracellular vesicles in an inflammatory microenvironment in vitro. *Int J Mol Sci*. 2023;24(13):11069. doi:10.3390/ijms241311069
38. Li X, Zhong Y, Yue R, et al. Inhibition of MiR-106b-5p mediated by exosomes mitigates acute kidney injury by modulating transmissible endoplasmic reticulum stress and M1 macrophage polarization. *J Cell Mol Med*. 2023;27(19):2876–2889. doi:10.1111/jcmm.17848
39. Hurtado Gutiérrez MJ, Allard FL, Mosha HT, Dubois CM, McDonald PP. Human neutrophils generate extracellular vesicles that modulate their functional responses. *Cells*. 2022;12(1):136. doi:10.3390/cells12010136
40. Okamura A, Yoshioka Y, Saito Y, Ochiya T. Can extracellular vesicles as drug delivery systems be a game changer in cardiac disease? *Pharm Res*. 2023;40(4):889–908. doi:10.1007/s11095-022-03463-z
41. Montanari M, Guescini M, Gundogdu O, et al. Extracellular vesicles from campylobacter jejuni CDT-treated caco-2 cells inhibit proliferation of tumour intestinal caco-2 cells and myeloid U937 cells: detailing the global cell response for potential application in anti-tumour strategies. *Int J Mol Sci*. 2022;24(1):487. doi:10.3390/ijms24010487
42. Qian F, Huang Z, Zhong H, et al. Analysis and biomedical applications of functional cargo in extracellular vesicles. *ACS Nano*. 2022;16(12):19980–20001. doi:10.1021/acsnano.2c11298
43. Ceccotti E, Quaglia M, Camussi G, Bruno S. Mesenchymal stem cells derived extracellular vesicles for chronic kidney disease: pleiotropic mechanisms of actions of a versatile therapy. *Front Bioeng Biotechnol*. 2025;13:1612193. doi:10.3389/fbioe.2025.1612193
44. Gao C, He J, Wang Y, et al. The role of FAK in renal collecting duct in the progression from acute kidney injury to chronic kidney disease. *Transl Res*. 2025;282:41–55. doi:10.1016/j.trsl.2025.06.002
45. Liang L, Mi Y, Zhou S, Yang A, Wei C, Dai E. Advances in the study of key cells and signaling pathways in renal fibrosis and the interventional role of Chinese medicines. *Front Pharmacol*. 2024;15:1403227. doi:10.3389/fphar.2024.1403227
46. Wu T, Liu Y, Wang S, Shi C. MSC-derived extracellular vesicles: roles and molecular mechanisms for tissue repair. *Int J Nanomed*. 2025;20:7953–7974. doi:10.2147/IJN.S525394
47. Wang Y, Fu B, Sun X, et al. Differentially expressed microRNAs in bone marrow mesenchymal stem cell-derived microvesicles in young and older rats and their effect on tumor growth factor-β1-mediated epithelial-mesenchymal transition in HK2 cells. *Stem Cell Res Ther*. 2015;6:185. doi:10.1186/s13287-015-0179-x
48. Zhou X, Zhao S, Li W, et al. Tubular cell-derived exosomal miR-150-5p contributes to renal fibrosis following unilateral ischemia-reperfusion injury by activating fibroblast in vitro and in vivo. *Int J Biol Sci*. 2021;17(14):4021–4033. doi:10.7150/ijbs.62478
49. Sun Z, Ma Y, Chen F, Wang S, Chen B, Shi J. miR-133b and miR-199b knockdown attenuate TGF-β1-induced epithelial to mesenchymal transition and renal fibrosis by targeting SIRT1 in diabetic nephropathy. *Eur J Pharmacol*. 2018;837:96–104. doi:10.1016/j.ejphar.2018.08.022
50. Jing H, Tang S, Lin S, Liao M, Chen H, Zhou J. The role of extracellular vesicles in renal fibrosis. *Cell Death Dis*. 2019;10(5):367. doi:10.1038/s41419-019-1605-2
51. Moon PG, Lee JE, You S, et al. Proteomic analysis of urinary exosomes from patients of early IgA nephropathy and thin basement membrane nephropathy. *Proteomics*. 2011;11(12):2459–2475. doi:10.1002/pmic.201000443
52. Keri KC, Regner KR, Dall AT, Park F. Urinary exosomal expression of activator of G protein signaling 3 in polycystic kidney disease. *BMC Res Notes*. 2018;11(1):359. doi:10.1186/s13104-018-3467-6
53. Clementi A, Virzì GM, Ronco C, Monciino P, Zanella M. Urinary and plasma miRNAs in the early detection of acute kidney injury and their possible role as therapeutic targets. *J Clin Med*. 2025;14(7):2306. doi:10.3390/jcm14072306
54. Da-silva CCS, Anauate AC, Guirao TP, Novaes ADS, Maquigussa E, Boim MA. Analysis of exosome-derived microRNAs as early biomarkers of lipopolysaccharide-induced acute kidney injury in rats. *Front Physiol*. 2022;13:944864. doi:10.3389/fphys.2022.944864
55. Oh S, Lee CM, Kwon SH. Extracellular vesicle MicroRNA in the kidney. *Compr Physiol*. 2023;13(3):4833–4850. doi:10.1002/cphy.c220023
56. Kalluri R, LeBleu VS. The biology, function, and biomedical applications of exosomes. *Science*. 2020;367(6478):eaau6977. doi:10.1126/science.aau6977
57. Lv LL, Cao YH, Ni HF, et al. MicroRNA-29c in urinary exosome/microvesicle as a biomarker of renal fibrosis. *Am J Physiol Renal Physiol*. 2013;305(8):F1220–7. doi:10.1152/ajprenal.00148.2013
58. Miranda KC, Bond DT, McKee M, et al. Nucleic acids within urinary exosomes/microvesicles are potential biomarkers for renal disease. *Kidney Int*. 2010;78(2):191–199. doi:10.1038/ki.2010.106
59. Hegeman CV, de Jong OG, Lorenowicz MJ. A kaleidoscopic view of extracellular vesicles in lysosomal storage disorders. *Extracell Vesicles Circ Nucl Acids*. 2022;3(4):393–421. doi:10.20517/evcna.2022.41
60. Gameiro J, Fonseca JA, Outerelo C, Lopes JA. Acute kidney injury: from diagnosis to prevention and treatment strategies. *J Clin Med*. 2020;9(6):1704. doi:10.3390/jcm9061704
61. Yao C, Li Z, Sun K, Zhang Y, Shou S, Jin H. Mitochondrial dysfunction in acute kidney injury. *Ren Fail*. 2024;46(2):2393262. doi:10.1080/0886022X.2024.2393262

62. Guo Y, Ni J, Chen S, et al. MicroRNA-709 mediates acute tubular injury through effects on mitochondrial function. *J Am Soc Nephrol*. 2018;29 (2):449–461. doi:10.1681/ASN.2017040381
63. Guo C, Cui Y, Jiao M, et al. Crosstalk between proximal tubular epithelial cells and other interstitial cells in tubulointerstitial fibrosis after renal injury. *Front Endocrinol*. 2024;14. 1256375. doi:10.3389/fendo.2023.1256375
64. Akbari A, Nazari-Khanamiri F, Ahmadi M, Shoaran M, Rezaie J. Engineered exosomes for tumor-targeted drug delivery: a focus on genetic and chemical functionalization. *Pharmaceutics*. 2022;15(1):66. doi:10.3390/pharmaceutics15010066
65. Li Y, Hu C, Zhai P, et al. Fibroblastic reticular cell-derived exosomes are a promising therapeutic approach for septic acute kidney injury. *Kidney Int*. 2024;105(3):508–523. doi:10.1016/j.kint.2023.12.007
66. Chen J, Tang TT, Cao JY, et al. KIM-1 augments hypoxia-induced tubulointerstitial inflammation through uptake of small extracellular vesicles by tubular epithelial cells. *Mol Ther*. 2023;31(5):1437–1450. doi:10.1016/j.ymthe.2022.08.013
67. Kraińska MM, Pietrzkowska N, Turlej E, Zongjin L, Marycz K. Extracellular vesicles derived from mesenchymal stem cells as a potential therapeutic agent in acute kidney injury (AKI) in felines: review and perspectives. *Stem Cell Res Ther*. 2021;12(1):504. doi:10.1186/s13287-021-02573-6
68. Zilberman Itskovich S, Sova M, Abu-Hamad R, et al. Effects of small extracellular vesicles derived from mesenchymal stromal cells on acute kidney injury: a rat ischemia-reperfusion model. *Cureus*. 2025;17(5):e84411. doi:10.7759/cureus.84411
69. Yang Y, Wang J, Zhang Y, Hu X, Li L, Chen P. Exosomes derived from mesenchymal stem cells ameliorate renal fibrosis via delivery of miR-186-5p. *Hum Cell*. 2022;35(1):83–97. doi:10.1007/s13577-021-00617-w
70. Lu Y, Wang L, Zhang M, Chen Z. Mesenchymal stem cell-derived small extracellular vesicles: a novel approach for kidney disease treatment. *Int J Nanomed*. 2022;17:3603–3618. doi:10.2147/IJN.S372254