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Frontier role of extracellular vesicles in kidney disease

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Abstract
Kidney diseases represent a diverse range of conditions that compromise renal function and structure which characterized by a progressive deterioration of kidney function, may ultimately necessitate dialysis or kidney transplantation as end-stage treatment options. This review explores the complex landscape of kidney diseases, highlighting the limitations of existing treatments and the pressing need for innovative strategies. The paper delves into the role of extracellular vesicles (EVs) as emerging biomarkers and therapeutic agents in the context of kidney pathophysiology. Urinary extracellular vesicles (uEVs), in particular, offer a non-invasive means of assessing renal injury and monitoring disease progression. Additionally, mesenchymal stem cell-derived EVs (MSC-EVs) are examined for their immunomodulatory and tissue repair capabilities, presenting a promising avenue for novel therapeutic interventions. And discusses the potential of engineering EVs to enhance their targeting and therapeutic efficacy. This paper systematically integrates the latest research findings and aims to provide a comprehensive overview of the role of EVs in kidney disease, providing cutting-edge insights into their potential as a diagnostic and therapeutic tool.

Keywords Extracellular vesicles, Kidney disease, Pathogenesis, Biomarker, Targeted therapy

Introduction

Kidney diseases pose a significant challenge to public health departments worldwide, directly impacting global morbidity and mortality rates [1, 2]. Research statistics indicate that approximately 10–15% of adults globally are affected by kidney diseases of varying severity [3, 4].The early symptoms of kidney disease are often inconspicuous, but as the disease progresses, patients may experience a reduction in urine output, frothy urine, hematuria, edema, anemia, and other symptoms. Prolonged illness can have a profound impact on patients' quality of life and lead to a range of serious complications, including cardiovascular diseases, diabetes, and hypertension [5]. If not treated promptly, the disease may advance to renal failure, requiring alternative treatments such as dialysis or kidney transplantation [6]. While dialysis and kidney transplantation are effective for treating renal failure, they demand long-term patient commitment and carry certain risks and complications [7].

Extracellular vesicles (EVs) are nanoscale lipid-membrane-enclosed structures secreted by a variety of cell types and serve as pivotal agents in intercellular communication [8]. The EVs are primarily categorized into two major classes: exosomes and ectosomes [9]. Ectosomes

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arise from the outward budding of the cell membrane, encompassing a size spectrum from 50 nanometers to 1 micrometer, which includes microvesicles, microparticles, and larger vesicles [8, 9]. In contrast, exosomes are a subset of EVs that are derived from the endosomal compartment, typically exhibiting diameters ranging from 40 to 160 nanometers, with an average size of approximately 100 nanometers [8, 9]. EVs are capable of encapsulating a diverse array of cellular constituents, such as DNA, RNA, lipids, metabolites, and proteins, which are sourced from both the cytoplasm and the cell membrane (Fig. 1). This cargo reflects the specific physiological state and functional profile of the originating cell [10]. As natural transporters in the biological milieu, EVs exhibit several advantageous characteristics, including stability, biocompatibility, low immunogenicity, low toxicity, and the capacity to traverse biological barriers [11]. These attributes render EVs highly promising in the realm of drug delivery. Their inherent biocompatibility is complemented by an appropriate size distribution and intrinsic cellular targeting capabilities, which confer unique benefits for the delivery of therapeutic agents [12, 13].

In recent years, the role of EVs in nephrology has garnered considerable attention [14–16]. In the context of kidney injury, extracellular vesicles originating from different parts of the kidney play a propelling role in the progression of disease by mediating intercellular communication among different cell types within the nephron [17, 18]. Concurrently, EVs possess unique compositions specific to their origins, and significant changes in their quantity and components can reflect the physiological or pathological state of their source, thus endowing them with the value of being disease biomarkers [19, 20]. Moreover, in-depth research on EVs, especially MSC-EVs, and the bioactive molecules they carry, has unveiled their immense potential in the treatment of kidney diseases [21, 22]. Therefore, the thorough investigation of the mechanisms of EVs in kidney diseases aids in deepening our understanding of the pathogenesis of these conditions. Moreover, it holds significant research importance and practical value for the improvement of diagnostic techniques and the development of novel therapeutic approaches.

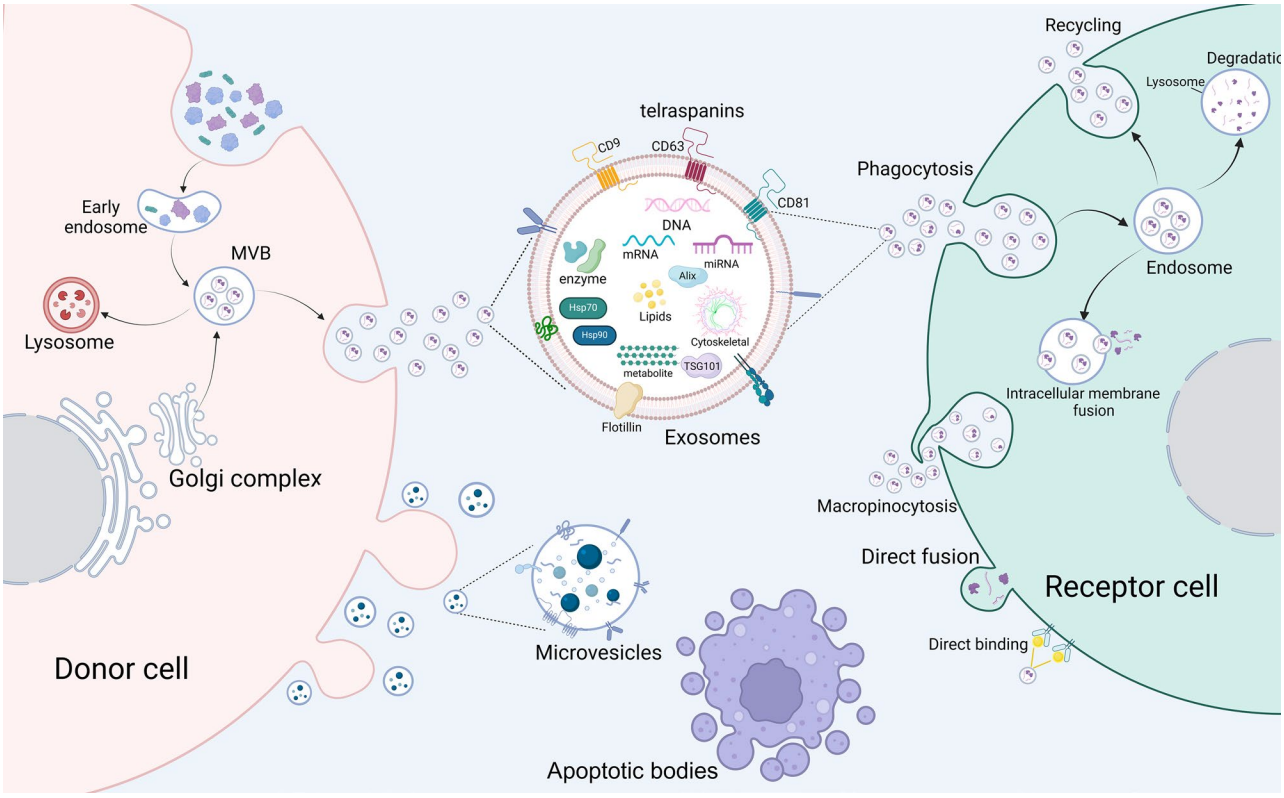

Fig. 1 EVs classification, biogenesis, and uptake. Based on their biogenesis and size, EVs are typically divided into two categories: exosomes and ectosomes. Exosomes are a subset of EVs that originate from the endosomal compartment, while ectosomes arise from budding of the cell membrane, including microvesicles, microparticles, and larger vesicles. EVs possess a phospholipid bilayer that can encapsulate a variety of cellular components, such as DNA, RNA, lipids, metabolites, and proteins. EVs can be internalized by recipient cells through mechanisms such as membrane fusion, phagocytosis, pinocytosis, and clathrin-mediated endocytosis

EVs in the pathology and diagnosis of kidney disease

Development and pathological changes of renal disease

Extracellular vesicles play a crucial role in renal pathology, being involved in the development process from the initial stages of kidney disease. The progression of kidney disease is a multifaceted process characterized by dynamic shifts in renal function. Acute kidney injury (AKI) and chronic kidney disease (CKD) represent the two principal stages of this continuum [23]. AKI typically arises from abrupt injury or illness, precipitating a swift deterioration in kidney function, common inciting factors include infections [24], sepsis [25], ischemia [26], and exposure to nephrotoxic drugs [27].Rapid decline in renal function, electrolyte disturbance and acid-base imbalance are considered typical symptoms of AKI [28]. Conversely, CKD is distinguished by a gradual and sustained deterioration of renal function attributable to enduring or recurrent kidney damage or pathology. Notably, among the prevalent etiologies are diabetes, hypertension, and glomerulonephritis, with IgA nephropathy being particularly significant [4, 29].

From a pathological standpoint, the hallmarks of AKI and CKD diverge. AKI is primarily associated with tubular necrosis, interstitial edema, inflammation, and vascular alterations [30], which are often reversible with prompt intervention, thus offering the potential for renal function recovery. In contrast, the pathological features of CKD are more intricate, encompassing glomerulosclerosis, tubular atrophy, interstitial fibrosis, renal ischemia, and capillary loss [31], which are generally irreversible and contribute to a progressive decline in renal function.

It is crucial to recognize that there is not an absolute dichotomy between AKI and CKD, there exists a degree of overlap and the potential for interconversion [32, 33]. Patients with AKI, if not treated promptly and effectively, may evolve into CKD; likewise, individuals with CKD may manifest AKI characteristics under certain conditions [28]. A profound investigation into the mechanisms driving the progression and pathological changes of kidney disease is of paramount importance for unraveling the complexities of these conditions and for informing diagnostic and therapeutic strategies.

Pathological effects of EVs in kidney disease

EVs secreted by damaged kidney cells play an indispensable role in the complex multi-dimensional pathological processes associated with kidney diseases [34, 35]. Data shows that under damaged or stressed conditions, extracellular vesicle-mediated long-distance communication between different regions and different cells in the kidney can amplify kidney damage [36]. This process involves key aspects such as inflammatory response, oxidative stress, apoptosis, and tissue fibrosis in the kidney (Fig. 2). These factors can interfere with normal cellular signaling pathways, leading to the disruption of intracellular homeostasis and increased sensitivity to damage [37, 38]. At the same time, these factors not only participate in the initial stage of kidney damage through interaction but may also continuously exacerbate the damage through a variety of mechanisms, thereby affecting the long-term health of the kidney [39, 40].

The role of EVs in inflammation and immune modulation

Kidney disease involves a complex, multistage inflammatory process orchestrated by a complex network of cytokines/chemokines, growth factors, adhesion molecules and signal transduction pathways [41]. The injury to renal tubular epithelial cells (TECs) and macrophage infiltration remain the pivotal mechanisms determining the extent of inflammatory damage [42]. There is a complex interplay between macrophages and TECs, for example, the infiltration of macrophages can exacerbate TECs injury, oxidative stress, and apoptosis [43]. Studies have indicated that in cisplatin-induced acute kidney injury (CP-AKI), macrophage-derived EVs (Mϕ-EVs) facilitate communication between autophagy-deficient macrophages and TECs by transferring miR-195a-5p. This transfer leads to mitochondrial damage in TECs and the activation of inflammatory cells in the kidney [42]. In diabetic kidney disease(DKD), Mϕ-EVs induced by high glucose levels, carrying miR-7002-5p, target autophagy-related gene 9B (Atg9b) to suppress autophagy in renal tubular epithelial cells, inducing dysfunction, autophagy inhibition, and inflammation [44].

TECs-EVs also have a powerful role in driving persistent inflammation. Research has found that the secretion of TEC-EVs induced by bovine serum albumin (BSA) has been proven to promote the expression of miR-26a-5p. This upregulation of miR-26a-5p targets the cationic amino acid transporter regulator homolog 1/the nuclear factor kappa B (CHAC1/NF-κB) pathway, exacerbating TEC inflammatory injury [45]. TECs-EVs containing miR-19b-3p [46] and miR-374b-5p [47], as well as Mϕ-EVs containing miR-155 [48], can target the NF-κB/suppressor of cytokine signaling-1 (SOCS-1) pathway to participate in the interaction between renal tubular epithelial cells and macrophages. This interaction significantly activates M1-type macrophages, thereby exacerbating renal tubular interstitial inflammation. Furthermore, it has been discovered that miR-199a-5p within exosomes from human serum albumin (HSA)-stimulated HK-2 cells promotes M1 polarization by targeting the Klotho/toll-like receptor 4 (TLR4) signaling pathway, potentially accelerating the progression of DKD [49]. Proteinuria is a widely recognized indicator of renal dysfunction and plays a key role in renal tubular interstitial inflammation [50]. Studies have shown that

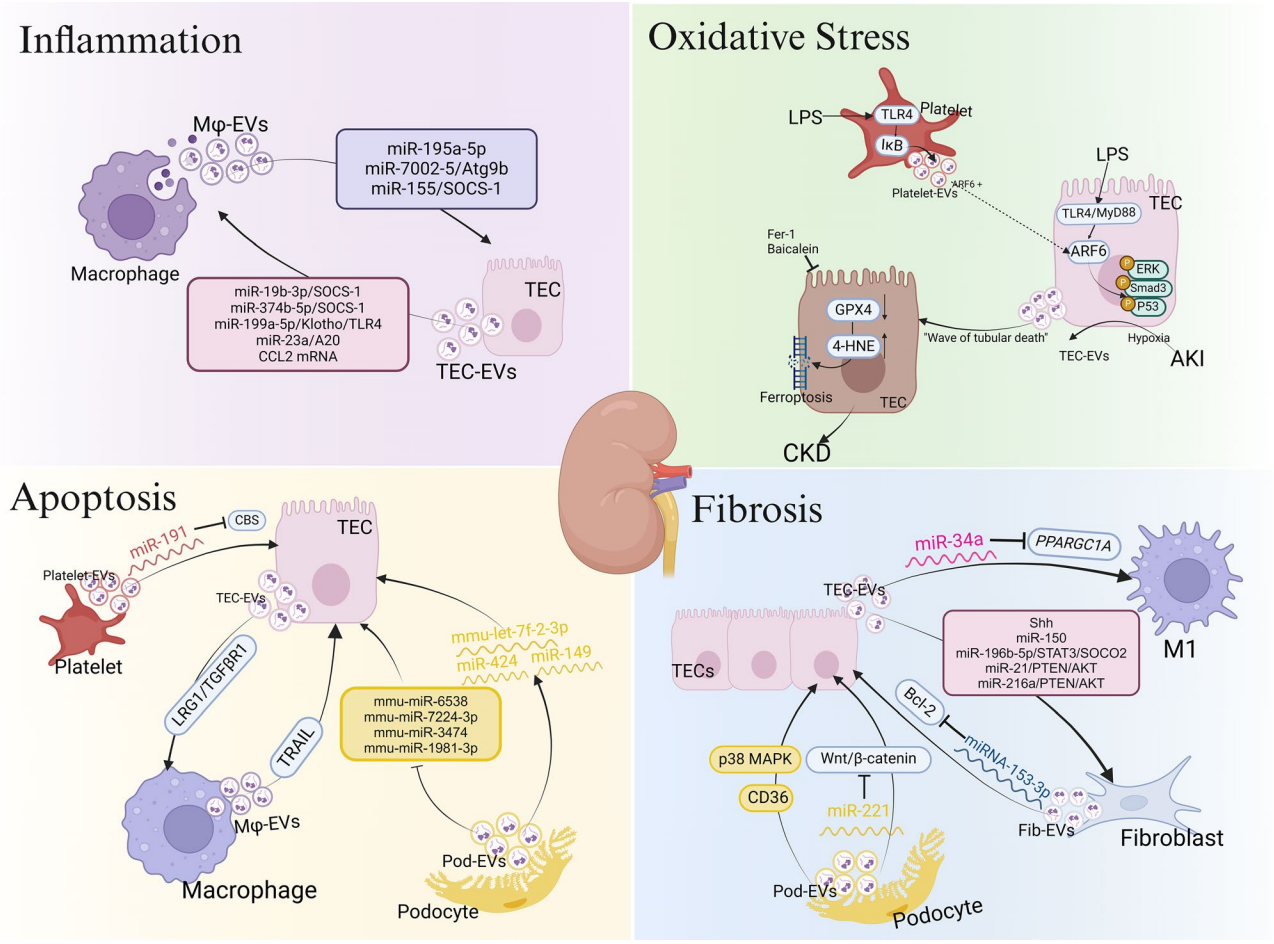

Fig. 2 EVs-mediated intercellular communication in the pathology of kidney disease. Under conditions of injury or stress, extracellular vesicle-mediated long-distance communication between different regions of the kidney and various kidney cells can exacerbate kidney damage by inducing key aspects such as inflammatory responses, oxidative stress, apoptosis and tissue fibrosis of kidney cells

in proteinuric kidney disease, TECs-EVs rich in chemokine ligand 2(CCL2) mRNA. These mRNAs are transferred to macrophages via EVs, activating their function and exacerbating albumin-induced renal tubular interstitial inflammation [51]. Furthermore, in patients with DKD exhibiting significant albuminuria, researchers have found that TEC-EVs treated with HSA can promote macrophage glycolytic activation by stabilizing hypoxia-inducible factor 1α(HIF-1α), thereby inducing renal fibrosis and inflammation [52]. Hypoxia is a potent inducer of inflammation within the tubulointerstitial inflammation. HIF-1α serves as the central regulator of the hypoxic response. The HIF-1α-driven release of these miRNA-23a-enriched EVs from hypoxic TECs can be internalized by recipient macrophages. Consequently, this internalization leads to the suppression of the ubiquitin editor A20 expression and the promotion of tubulointerstitial inflammation [53].

Additionally, research has demonstrated that kidney injury molecule-1(KIM-1), a protein expressed by injured renal tubules, can recognize phosphatidylserine (PS) exposed on the surface of apoptotic cells. The interaction between KIM-1 and PS facilitates the uptake of EVs, thereby enhancing hypoxia-induced tubulointerstitial inflammation [54].Recent studies have also revealed that the disruption of gut microbiota and its derived outer membrane vesicles (OMVs) play a significant role in tubulointerstitial inflammation of DKD. An increase in OMVs due to gut microbiota dysbiosis is transferred to the tubulointerstitial inflammation via the intestinal barrier. This transfer induces cell inflammation and renal tubular interstitial injury by activating the caspase-11 pathway triggered by lipopolysaccharide [55]. These findings enhance our understanding of the influence of gut microbiota and its released OMVs on the development and progression of kidney disease.

The role of EVs in the formation of oxidative stress

EVs related to oxidative stress can have beneficial or detrimental effects. They have the capacity to transport a

range of molecules, including antioxidants, enzymes, and oxidized species that can generate reactive oxygen species (ROS) [56]. In a study conducted at the Royal Brisbane and Women's Hospital in Australia, researchers observed that hypoxic TEC-derived EVs, through the transfer of specific miRNAs and other bioactive molecules, intensify oxidative stress and tissue damage in the kidney [57]. This process potentially drives the transition from AKI to CKD. Furthermore, an increase in platelet-derived EVs during sepsis has been shown to aggravate septic AKI via the release of ADP-ribosylation factor 6(ARF6), which in turn, stimulates inflammation, apoptosis, and oxidative stress [58]. The proposed mechanism involves the activation of the extracellular signal-regulated kinase (ERK)/Smad3/p53 signaling pathway by ARF6. Our findings may offer potential therapeutic targets for the management of septic AKI.

The role of EVs in the formation of regulating apoptosis

Apoptosis is a form of programmed cell death that plays a crucial role in maintaining the balance of cell numbers and the normal development and renewal of tissues under normal physiological conditions [59]. However, in kidney diseases, abnormal apoptosis may accelerate the progression of the disease [60]. Apoptosis of TECs plays a significant role in kidney diseases [61]. Excessive apoptosis can disrupt the structure and function of the renal tubules, leading to impaired reabsorption and secretion functions, which further exacerbates kidney damage. For instance, in DKD, TECs release lipotoxic exosomes rich in leucine-rich α-2-glycoprotein 1 (LRG1). And the LRG1/TGFβR1 signaling pathway enhances the expression of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) in macrophages and TRAIL-positive macrophage-derived exosomes, promoting TECs apoptosis and establishing a feedback loop in DKD [62]. Additionally, platelet microvesicles secrete miR-191, which induces TECs apoptosis by targeting Cystathionine-β-synthase (CBS) [63]. After high glucose (HG) stimulation, podocyte-derived EVs undergo specific changes, with downregulation of mmu-miR-1981-3p, mmu-miR-3474, mmu-miR-7224-3p, and mmu-miR-6538, and upregulation of mmu-let-7f-2-3p, also promoting apoptosis of TECs [64]. The crosstalk pathways between the glomeruli and renal tubules have also been carefully studied. Results confirming that endothelial cells damaged by podocytes release EVs containing specific microRNAs, especially miR-424 and miR-149, which may activate the p38 MARK signaling pathway, inducing apoptosis in renal tubular epithelial cells [65].

Furthermore, mesangial cells (MCs) maintain the structure and function of the glomerulus, and increased apoptosis of MCs can lead to impaired glomerular filtration function, affecting the normal filtering and excretory functions of the kidney. Studies have found that HG upregulates urinary EVs miR-15b-5p, which directly binds to the target BCL-2 in DKD, causing MCs apoptosis [66].

The role of EVs in the formation of fibrosis

Renal fibrosis, with a particular focus on tubulointerstitial fibrosis, represents a prevalent terminal pathway for the majority of progressive chronic kidney diseases [67, 68]. The pathogenesis of this fibrotic process is exceedingly intricate, implicating a broad spectrum of both resident and infiltrating renal cell populations. The morphological characteristics of renal fibrosis include glomerulosclerosis, tubular atrophy, interstitial chronic inflammation, fibrosis itself, and vascular rarefaction [69].

Intercellular communication is pivotal in the development of renal fibrosis, with injured renal tubular cells participating in disease progression through extensive communication with interstitial fibroblasts. Research indicates that TEC-EVs carrying the sonic hedgehog (Shh) signaling ligand are upregulated during renal injury. The Shh ligand is then transported to interstitial fibroblasts via exosomes, facilitating their transition into myofibroblasts and perpetuating the fibrotic cascade [70].Similarly, TECs directly regulate the activation and proliferation of fibroblasts through exosome-mediated miR-150 [71]. Furthermore, miR-196b-5p [72] and miR-21 [73], miR-216a [74] derived from TEC-EVs mediate crosstalk between TECs and fibroblasts during the development of renal fibrosis. Respectively, they target the signal transducer and activator of transcription 3/SOCS2(STAT3/SOCS2) and phosphatase and tensin homolog (PTEN)/AKT signaling pathways. In fibroblast-derived EVs(Fibro-EVs), studies have shown that miR-153-3p contained within microvesicles (MVs) released by renal interstitial fibroblasts is transferred to proximal renal tubular epithelial cells through the damaged tubular basement membrane [75]. This transfer induces apoptosis in TECs by suppressing B-cell lymphoma-2(Bcl-2) levels, thereby exacerbating renal interstitial fibrosis (RIF). It has been reported that macrophages, in addition to participating in the inflammatory response of kidney disease, are also involved in the process of fibrosis formation. For example, exosomal miRNA-34a from TECs has been shown to target and inhibit the PPARGC1A gene, promoting the activation of M1 macrophages and the fibrosis of renal tubular cells [76].

In the context of DKD, the HNRNPA1-mediated exosome sorting mechanism transports miR-483-5p from TECs to urine. This process diminishes the inhibitory effect of miR-483-5p on mitogen-activated protein kinase 1(MAPK1) and tissue Inhibitor of metalloproteinases 2(TIMP2) mRNAs, and accelerating the progression of DKD-induced renal interstitial fibrosis

[77]. Podocyte-derived EVs have also been shown to be involved in the fibrotic development of kidney disease. In the pathogenesis of DKD, podocyte-derived EVs containing miR-221 exacerbate renal cell injury through the Wnt/β-catenin signaling pathway, thereby further promoting the progression of renal cell injury and fibrosis [78].Additionally, a new study has elucidated the mechanism of interaction between podocyte microparticles and CD36 on TECs, activating the p38MAPK/transforming growth factor-β receptor signaling pathway, thereby promoting fibrotic responses [79].

EVs as diagnostic biomarkers for kidney diseases

Accurate diagnostic markers are essential for the early detection and precise treatment of kidney diseases, which have a complex and dynamic pathological progression. Renal biopsy is a powerful tool for diagnosing and classifying glomerular diseases, but it is limited by sampling errors and the difficulty of obtaining subsequent renal biopsies to track the progress of treatment. Considerable effort is being expended to discover non-invasive biomarkers for both acute and chronic kidney injury. Urinary extracellular vesicles (uEVs) are a rich source of biomarkers because they are released from every part of the nephron [80], are easily accessible. It can comprehensively and directly reflect the real-time status of tissue inflammation and kidney injury [81, 82],making them an ideal non-invasive source of potential biomarkers for kidney diseases (Fig. 3).

Protein cargos of EVs for the diagnosis of kidney diseases

Ischemia/reperfusion AKI (I/R-AKI)

Studies have demonstrated that uEVs AQP1 levels decrease within 6 h post-injury and remain low for up to 96 h, without a significant increase in plasma creatinine levels [83]. This suggests that uEVs AQP1 may serve as a sensitive biomarker for detecting renal cell status throughout the I/R injury timeline, indicating its potential for early I/R injury detection. Additionally, researchers have identified potential biomarker candidates for the diagnosis of AKI through proteomic analysis of uEVs. Simultaneously, they have detected that uEVs Fetuin-A may serve as a biomarker for the detection of I/R-AKI [84].In I/R-AKI, the level of uEVs Na/H exchanger isoform 3 (NHE3) protein is elevated compared to the control group, a result that has also been confirmed in four

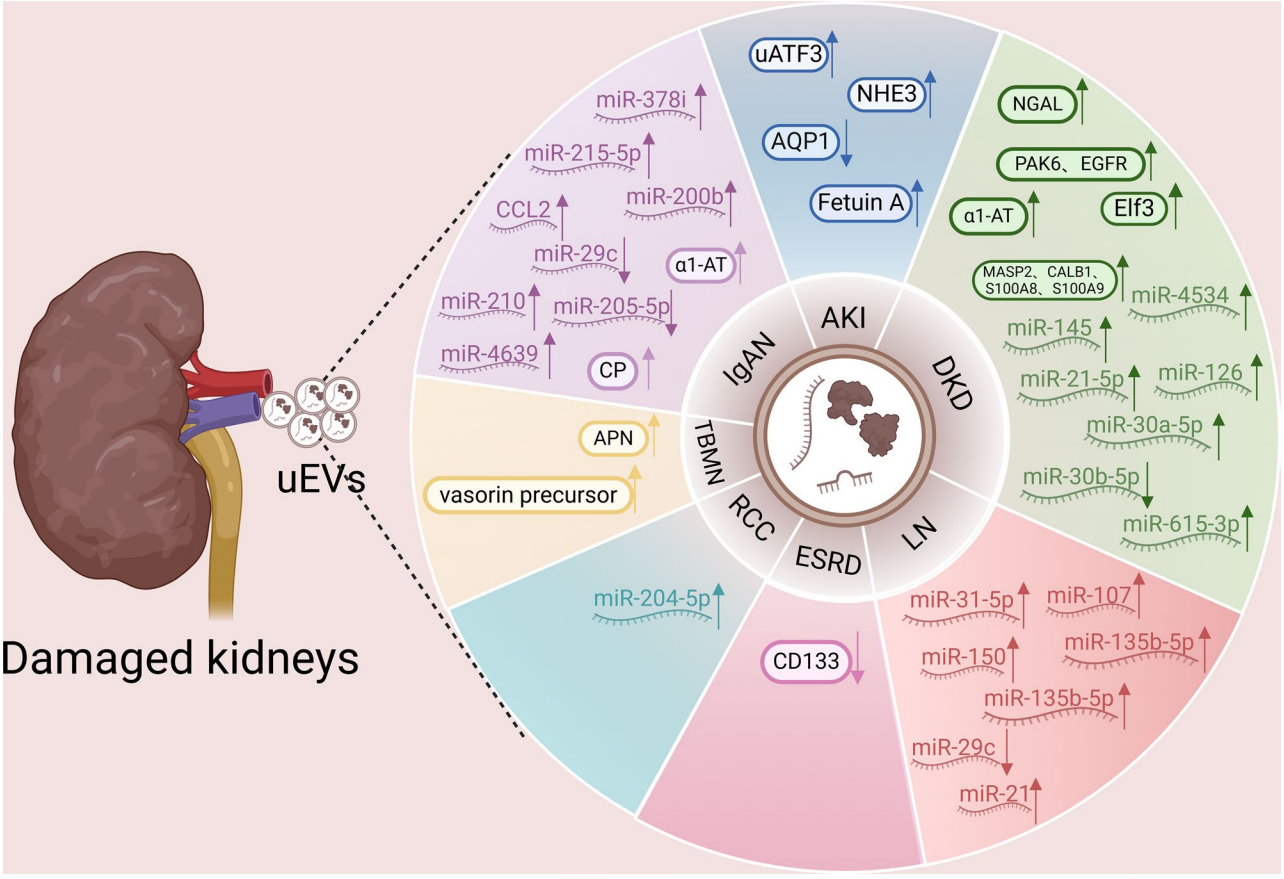

Fig. 3 Urinary extracellular vesicles (uEVs) serve as biomarkers for kidney diseases. Proteins and nucleic acids derived from uEVs hold promise as potential biomarkers for various types of kidney diseases. Abundant in source and easily accessible, they are ideal non-invasive biomarkers

other AKI models. This suggests that uEVs NHE3 could serve as a diagnostic biomarker for AKI [85].

Sepsis-AKI (S-AKI)

uATF3 [86], typically undetectable in sepsis without AKI, may qualify as a qualitative indicator for sepsis-AKI diagnosis. In contrast, the role of neutrophil gelatinase-associated lipocalin (NGAL) in sepsis-AKI remains debated, particularly regarding its critical value and baseline levels. The presence of transcription factor uATF3 in uEVs is emerging as a potential biomarker for sepsis-associated AKI.

Diabetic kidney disease (DKD

Researchers have meticulously examined the proteomic changes within EVs at different stages of DKD. Utilizing proteomic approaches, key proteins MASP2, CALB1, S100A8, and S100A9 were identified as potential biomarkers for the diagnosis and monitoring of DKD [87]. In diabetic patients with normal albuminuria, uEVs containing alpha-1-antitrypsin (α1-AT) were significantly increased and elevated with the progression of DKD, indicating their potential as biomarkers for early diagnosis of DKD [88]. Similarly, another study found that NGAL within exosomes is an early biomarker for DKD, and it outperforms free NGAL in the DKD evaluation in children and adolescents with type 1 diabetes mellitus [89].Additionally, researchers investigated the differential expression of actin cytoskeleton regulatory factors in uEVs, and the upregulation of uEVs proteins PAK6 and EGFR suggests that they may become new biomarkers for the diagnosis of DKD [90].It has been reported that pathological changes in podocytes play a key role in the development of DKD. Studies have found that the presence of Elf3 protein in the uEVs of patients with DKD indicates irreversible damage in podocytes. This suggests that Elf3-positive urinary extracellular vesicles ($Elf3^{+}$uEVs) can serve as a new biomarker for podocyte injury in patients with type 2 diabetes mellitus (T2DM), especially in those with significant proteinuria [91]. Additionally, Wilms' tumor protein (WT1) in uEVs is predominantly found in the exosomes of diabetic patients. Detection has revealed that its expression levels increase with the decline of renal function, making it another potential biomarker for podocyte injury [92].

End-stage renal disease (ESRD)

In ESRD patients, the absence of uEVs expressing the CD133 marker contrasts sharply with healthy subjects, where such EVs are readily detectable [93]. The presence of urinary CD133 EV may reflect ongoing nephron homeostatic processes, suggesting a potential role in ESRD diagnosis.

IgA nephropathy (IgAN)and thin basement membrane nephropathy (TBMN)

Urinary exosome proteomic analysis has identified several proteins, such as aminopeptidase N, vasorin precursor, α-1-antitrypsin, and ceruloplasmin. These proteins differentiate early IgA nephropathy from tubulointerstitial nephritis and normal conditions, indicating their potential as biomarkers [94].

Lupus nephritis (LN)

Urinary podocyte-derived microparticles (MPS) levels are positively correlated with clinical indicators of SLE activity [95], including the SLE disease activity index (SLEDAI) score and anti-dsDNA antibody titer, suggesting their potential as non-invasive biomarkers for lupus nephritis diagnosis and monitoring.

Others

In essential hypertension (EH), increased levels of urinary podocyte-specific EVs and peritubular capillary (PTC) endothelial microparticles(EMPs) may indicate renal microcirculation damage [96], suggesting their potential as new biomarkers for renal capillary loss. Urinary PTC-EMP levels are directly related to renal histological PTC counts and fibrosis [97], further supporting their role as a novel biomarker for renal intracapillary loss.

RNA cargos of EVs for the diagnosis of kidney diseases

Diabetic kidney disease (DKD)

A study involving 103 patients with diabetic kidney disease (DKD), 100 patients with diabetes without kidney disease, and 53 healthy controls. Results showed that the levels of WT1 mRNA and ACE mRNA in circulating EVs were elevated in DKD patients, suggesting that they may serve as potential early diagnostic markers for DKD [98]. Another study found that the enriched expression of uEVs miRNA-4534, which targets BCL2 interacting protein 3(BNIP3) and is involved in the forkhead box O(FOXO) signaling pathway, may become a new biomarker for the progression of DKD in type 2 diabetes [99]. Additionally, research has found that the progression of proteinuria is paralleled by an increase in the levels of miR145 and miR126 in uEVs. And they are simultaneously elevated in renal epithelial cells undergoing epithelial-mesenchymal transition (EMT), highlighting their potential as biomarkers for the progression of diabetic nephropathy and the occurrence of proteinuria [100]. Analysis of miRNA in uEVs from patients with T2DM revealed that in patients with microalbuminuria (MIC), the levels of let-7i-3p, miR-24-3p, and miR-27b-3p were increased, while the level of miR-15b-5p was decreased. In patients with macroalbuminuria (MAC), the concentration of miR-30a-5p in uEVs was specifically modified, but not in MIC patients, indicating that

miR-30a-5p may be associated with severe renal damage [101].Additionally, it has been found that in type 2 diabetic patients with kidney damage, the enrichment of uEVs miR-21-5p and the reduction of miR-30b-5p may represent candidate biomarkers for renal injury in type 2 diabetes [102].Furthermore, data indicate that uEVs miR-615-3p is positively correlated with various renal injury markers. And the diagnostic efficacy of miRNA-615-3p in combination with albumin-to-creatinine Ratio(ACR) is higher than that of ACR alone, suggesting that it can serve as a more stable and sensitive diagnostic biomarker for DKD [103].

IgA nephropathy (IgAN)

In the context of IgAN, EV-associated CCL2 has been found to be correlated with the estimated glomerular filtration rate (eGFR) and associated with kidney inflammation and C3 deposition. Elevated CCL2 levels are also linked to the progression of renal dysfunction, implying that uEVs and exosomal CCL2 mRNA could serve as biomarkers reflecting IgAN activity and the deterioration of renal function [104]. In patients with IgAN and DKD, researchers have observed a decrease in the expression of miR-200b in uEVs as fibrosis progresses [105], suggesting its potential as a diagnostic biomarker. Furthermore, researchers have explored the differences in the uEVs microRNA expression profiles between patients with IgAN and healthy controls. The significant upregulation of uEVs miRNAs, such as miR-215-5p and miR-378i [106], miR-4639 and miR-210 [107], and the significant downregulation of miR-29c and miR-205-5p [106] may represent new non-invasive biomarkers for IgAN. These findings may aid in diagnosis, assessment of severity, and evaluation of disease progression in IgAN.

Lupus nephritis (LN)

In lupus nephritis (LN), the regulatory effects of uEVs miRNAs, including miR-135b-5p, miR-107, and miR-31-5p, have been demonstrated to be potential early biomarkers for the disease [108]. In the study of LN renal fibrosis, researchers have found that miR-29c is correlated with the chronicity of kidney disease [109]. Moreover, this level of variation is independent of renal function, indicating that it can serve as a non-invasive biomarker for the early progression to fibrotic processes in LN patients. In recent years, due to the insufficiency of a single biomarker in achieving adequate sensitivity and specificity in clinical diagnosis. Another study has demonstrated that a multi-biomarker panel composed of uEVs miRNAs, including miR-29c, miR-150, and miR-21, can be used to detect early renal fibrosis and predict the progression of LN [110].

Renal cell carcinoma(RCC)

In mice with the transgenic PrCC-TFE3 gene, uEVs miR-204-5p levels surge during precancerous and tumor development stages, indicating its potential as a diagnostic biomarker for xp11 translocation renal cell carcinoma [111].In clear cell renal cell carcinoma (ccRCC), researchers have detected that the expression levels of exosomal miR-210 and miR-1233 in ccRCC patients are significantly higher than those in healthy individuals. Circulating microRNAs, miR-210 and miR-1233, may potentially serve as biomarkers for the future diagnosis and monitoring of ccRCC [112].

Early renal injury in hypertension

In hypertensive patients, increased levels of uEVs miR-146a are significantly correlated with urinary albumin excretion, with a decrease observed in patients with proteinuria [113], indicating its potential as a non-invasive biomarker for early renal injury in hypertension.

BKV nephropathy (BKVN)

The BK virus (BKV) is an important pathogen causing nephropathy in renal transplant recipients. Recent studies have shown that BKV-associated microRNAs are significantly enriched in the uEVs fraction of patients with BKV nephropathy (BKVN). The diagnostic role of specific microRNAs such as BKV-miR-B1-5p, which has been found to be consistent with the assessment of blood and urine BK viral loads, suggests that uEVs microRNAs may become valuable biomarkers for the diagnosis and monitoring of BKVN [114].

In conclusion, the exploration of EVs as biomarkers in kidney diseases is a rapidly evolving field, presenting new opportunities for early diagnosis, disease monitoring, and personalized therapeutic strategies. Future research is warranted to validate the clinical potential of these biomarkers and to elucidate their mechanisms of action in the context of various kidney diseases.

EVs-based therapy in kidney diseases

The treatment of kidney diseases has always faced many challenges. Existing therapeutic methods, such as drug therapy and dialysis, can control the condition to a certain extent, but find it difficult to completely reverse the damage. Drug therapy often only targets specific aspects, and struggles to address all pathological issues comprehensively. Moreover, the self-repair capacity of kidney tissue is relatively weak. Once severe damage occurs, it is extremely challenging to restore its normal structure and function. Although dialysis can temporarily replace some of the kidney's functions, long-term dialysis may lead to cardiovascular complications, malnutrition, and psychological issues for patients.

In the realm of kidney disease research and therapeutics, EVs have emerged as a promising avenue, exhibiting distinct properties and therapeutic potential based on their cellular origins. Notably, EVs derived from mesenchymal stem cells (MSC-EVs), renal tubular epithelial cells (TEC-EVs), and other sources have each demonstrated unique contributions to the field. The following sections will delve into the advancements and applications of these diverse EVs in the treatment of renal pathologies.

Stem cell- derived extracellular vesicles

MSCs possess unique abilities for self-renewal and differentiation, and they have a rich variety of sources, including umbilical cord, placenta, bone marrow, adipose tissue, and Urinary stem cells, among others. In recent years, MSC-EVs have been extensively studied as therapeutic molecules for kidney diseases in both in vitro cellular models and preclinical animal models (Fig. 4).

HucMSC-EVs

Ischemia/Reperfusion AKI (I/R-AKI) Studies have found that human umbilical cord mesenchymal stem cell-derived extracellular vesicles (hucMSC-EVs) can improve the outcomes of I/R-AKI and promote the repair and regeneration of renal tubular cells [115]. In AKI, exosomes derived from mesenchymal stem cells, specifically miR-125b-5p, adhere to TECs via very late antigen-4(VLA-4) and lymphocyte function-associated antigen-1(LFA-1), targeting the miR-125b-5p/p53 signaling pathway in TECs. This targeting induces cell cycle arrest and apoptosis, and mediates kidney repair in AKI [116]. Similarly, exosomal miR-148b-3p from hucMSCs can suppress apoptosis in I/R injury by downregulating the expression of pyruvate dehydrogenase kinase 4(PDK4), activating the activating transcription factor 6(ATF-6) pathway, and inducing endoplasmic reticulum stress [117]. Research has also demonstrated that pyroptosis is associated with AKI, and hucMSC-Exos can improve AKI by inhibiting pyroptosis and reducing kidney damage [118]. These studies further elucidate the mechanisms by which protective cells hucMSC-EVs resist acute kidney injury.

Cisplatin-induced AKI (CP-AKI) Research indicates that the synergistic effect of pulsed focused ultrasound

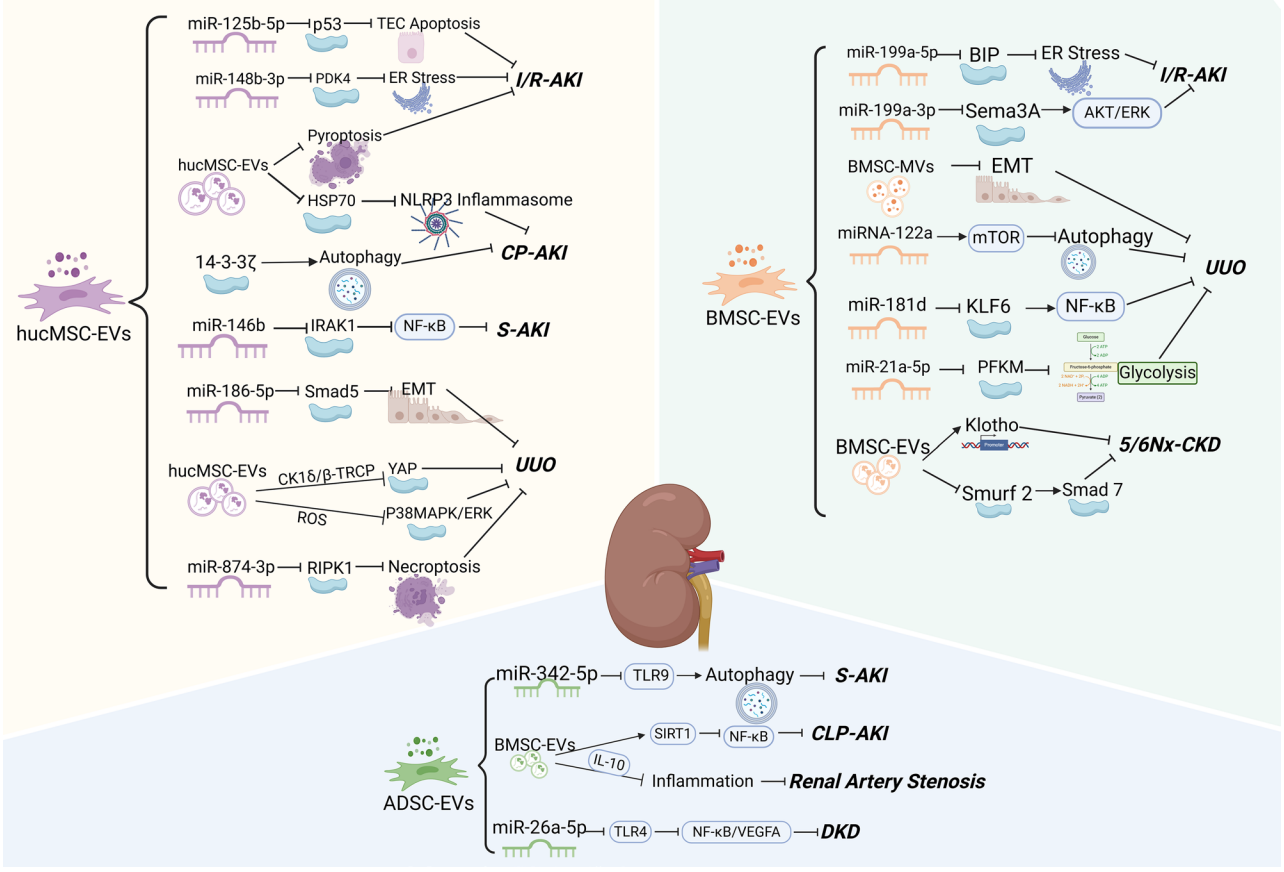

Fig. 4 Therapeutic effect of MSC-EVs on kidney diseases. MSC-EVs, carrying a variety of bioactive molecules, target different molecular mechanisms, alleviating kidney damage by inhibiting inflammatory responses, fibrosis, oxidative stress, and other pathological changes in the kidney

(PFUS) and hucMSC-EVs can inhibit the heat shock protein70/90 (HSP70/90). This inhibition leads to a reduction in the expression of the NLRP3 inflammasome and downstream pro-inflammatory cytokines, ultimately improving renal function [119]. The 14-3-3ζ protein carried by hucMSC-ex can also induce autophagy levels in HK-2 cells, thereby protecting HK-2 cells from the toxic damage of cisplatin [120]. Similarly, pre-incubation with hucMSC-Ex can significantly reduce CP-induced injury in NRK cells, which may be achieved by upregulating Bcl-2 and inhibiting the expression of apoptotic markers, thereby enhancing cell survival and suppressing apoptosis [121].

Glycerin-induced AKI Platelet-rich plasma (PRP) can promote the proliferation of MSCs by inducing the nuclear expression of yes-associated protein (YAP), maintaining and enhancing their stemness. Furthermore, PRP promotes the secretion of hucMCS-EX that inhibit apoptosis of renal tubular cells and repair glycerol-induced AKI through the activation of the AKT/Rab27 pathway in a paracrine manner [122].

Sepsis-AKI(S-AKI) Treatment with hucMSC-Ex upregulates the levels of miR-146b, leading to a reduction in the expression of interleukin-1 receptor-associated Kinase 1 (IRAK1), which in turn suppresses the activity of NF-κB. This ultimately alleviates S-AKI and improves the survival rate of septic mice. This suggests that hucMSC-Ex could serve as a novel therapeutic agent for reducing S-AKI [123].

Unilateral ureteral obstruction (UUO) In CKD, hucMSCs release exosomes carrying miR-186-5p, which reduce the expression of Smad5 by directly binding to its 3'-untranslated region (3'-UTR). This action leads to a decrease in the accumulation of extracellular matrix (ECM) proteins, inhibition of EMT and apoptosis, and alleviation of renal fibrosis [124]. Similarly, hucMSC-Ex can also inhibit the activation of YAP by promoting its ubiquitination and degradation through the delivery of casein kinase 1δ (CK1δ) and β-transducin repeat-containing protein (β-TrCP). This results in reduced collagen deposition and alleviation of mechanical stress-induced renal fibrosis [125]. Furthermore, hucMSC-EVs inhibit apoptosis and promote cell proliferation by suppressing the ROS -activated p38MAPK/ERK signaling pathway. This reduces renal tubular damage and interstitial fibrosis, protecting the UUO kidney from oxidative stress-induced injury [126].Another study has confirmed that the exosomes from hucMSCs carry miR-874-3P, which targets receptor-interacting serine/threonine-protein kinase 1 (RIPK1) to regulate necroptosis, reduces the expression of Phosphoglycerate mutase family member 5 (PGAM5), and promotes the dephosphorylation of the Drp1 gene at the S637 site. This maintains mitochondrial function homeostasis, alleviates renal injury, and promotes repair [127].

BMSC-EVs

Studies have shown that a single injection of bone marrow stem cell (BMSC)-purified MVs at the time of UUO can prevent epithelial-mesenchymal transition (EMT) [128], this protective effect is observed in in vivo experiments using TGF-β1 induced in HK2 cells, indicating that curtailing initial damage can forestall subsequent kidney injury.

Furthermore, recent research has found that BMSC-EVs provides therapeutic approaches for kidney diseases by targeting binding immunoglobulin protein (BIP), semaphorin 3 A(Sema3A), the mammalian target of rapamycin(mTOR) signaling pathway, krüppel-like factor 6(KLF6)/NF-κB, and phosphofructokinase (PFKM) in renal tubular epithelial cells. Specifically, these targets are modulated through miR-199a-5p [129], miR-199a-3p [130],miRNA-122a [131],miR-181d [132], and miR-21a-5p [133], respectively. Exosomes derived from BMSCs can prevent kidney damage and inhibit renal fibrosis both in vitro and in vivo by regulating the klotho protein in rats that have undergone 5/6 nephrectomy [134] and by modulating the Smurf2/Smad7 pathway [135].

ADSC-EVS

Adipose-derived mesenchymal stem cell-derived extracellular vesicles(ADSC-EVs) [136] that have demonstrated efficacy in improving kidney damage within experimental paradigms of chronic metabolic syndrome complicated by renal artery stenosis (MetS+RAS). Furthermore, ADSC-EVs convey miR-26a-5p [137] and miR-342-5p [138], which ameliorate the pathological symptoms of DKD and AKI by aiming at TLR4 and TLR9, respectively. Simultaneously, ADSC-derived EVs manifest protective influences in S-AKI, potentially through the modulation of sirtuin 1(SIRT1) on the NF-κB signaling pathway, thereby diminishing inflammatory responses and apoptosis [139].

Others

HP-MSC-EVs Hepatic MSC-derived extracellular vesicles (HP-MSC-EVs) [140], for instance, concentrate in renal tubules during renal I/R injury. They stimulate the recuperation of kidney function by invoking the kelch-like ECH-associated protein 1(Keap1)-nuclear factor

erythroid 2 related factor 2(Nrf2) signaling pathway and bolstering the mitochondrial function of TECs.

HLSC-EVs Hepatocyte-like stem cell-derived EVs (HLSC-EVs) [141] have evinced reparative traits, forestalling interstitial fibrosis and renal tubular necrosis while advocating kidney regeneration and attenuating the inflow of inflammatory immune cells in a CKD mouse model.

iMSC-EV Induced MSC-derived EVs (iMSC-EV) [142] shield against cisplatin-provoked kidney injury by curbing apoptosis, immune cell infiltration, and inflammation.

PSC-EVs Exosomes derived from PSC-MSCs [143], through the upregulation of SIRT6, have been demonstrated to effectively mitigate endothelial cell injury, attenuate inflammatory responses, preserve renal function, and decelerate the progression of renal fibrosis.

USC-EVs Urinary stem cells (USCs) [144] are capable of averting kidney IRI through exosomal miR-146a-5p, which homes in on the 3'UTR of IRAK1, subsequently suppressing the ignition of the NF-κB pathway and the encroachment of inflammatory cells, thus nurturing kidney function.

hWJMSC-EVs Human Wharton's jelly MSC-derived EVs (hWJMSC-EV) can amplify the expression of miR-30b/c/d in renal tubular cells, alleviate the activation of dynamin-related protein 1(DRP1) and mitochondrial fragmentation, thus assuming an anti-apoptotic role [145]. Furthermore, hWJ-MSC-EV can rehabilitate AKI induced by I/R and assist in balancing the oxidative stress/antioxidant equilibrium by invigorating Nrf2/antioxidant response element(ARE) activation, offering new vistas into the therapeutic mechanisms of MSC-EVs in renal regenerative medicine [146].

Non-stem cell- derived extracellular vesicles

TEC-EVs

Ischemia/Reperfusion AKI (I/R-AKI) TEC-EVs have emerged as significant contributors to the renal repair process following ischemia-reperfusion injury (IRI). Evidence suggests that the systemic administration of EVs from preconditioned renal tubular cells, particularly those subjected to hypoxic preconditioning, can substantially ameliorate severe I/R-AKI. The therapeutic infusion of these EVs within a critical 24 to 48-hour window post-IRI has been shown to enhance renal function, mitigate renal tubular damage, oxidative stress, inflammatory infiltration, fibrosis, and microvascular structural alterations [147].EVs derived from hypoxia-preconditioned renal tubular epithelial cells ameliorate renal IRI via the HIF-1α/Rab22 pathway, while hypoxia-preconditioned hepatocyte EVs may offer renal protection through differential expression of EV-miRNAs [148].Furthermore, miR-590-3p is transferred between renal tubular epithelial cells via exosomes, modulating autophagy by targeting TRAF6. This paracrine miRNA transfer suggests that augmenting miR-590-3p levels in exosomes may bolster autophagy and protect against renal IRI [149].

Cisplatin-induced AKI (CP-AKI) Exosomal miR-122 derived from cisplatin-treated HK2 cells has been demonstrated to inhibit pyroptosis in surrounding cells, with miR-122 targeting embryonic lethal abnormal vision (ELAVL1) to suppress pyroptosis and AKI, offering a potential therapeutic target for AKI [150].

Antimycin A-induced AKI(AMA-AKI) Intrinsic renal scattered tubular cells (STC-like cells) have demonstrated protective effects on AMA-impaired TECs in vitro, with exosomes potentially transferring mitochondria or mitochondrial fragments to rejuvenate the mitochondrial function of recipient cells. Systemic delivery of mitochondria-laden exosomes may integrate into ischemic renal tubules, improving mitochondrial function and mitigating chronic kidney injury [151].

IgA nephropathy (IgAN) The combined therapy of artemisinin and hydroxychloroquine has shown renoprotective effects in IgAN by inhibiting exosomal NF-κB signaling and NLRP3 inflammasome activation, presenting a novel therapeutic strategy for IgAN by modulating exosome release and NF-κB/NLRP3 signaling [152].

Endothelial progenitor cell-EVs (EPC-EVs)

Investigations have uncovered that miR-21-5p, contained within endothelial progenitor cell (EPC)-derived exosomes, possesses the potential to mitigate S-AKI. This is achieved by downregulating the expression of runt-related transcription factor 1(RUNX1), thereby introducing a fresh strategy for renal endothelial preservation in the context of S-AKI [153].

Circulating extracellular vesicles

Circulating exosomal miR-1-3p, identified in the aftermath of myocardial infarction, has been demonstrated to suppress cardiomyocyte (CM)-induced apoptosis and autophagy of renal tubular epithelial cells. It achieves this by targeting autophagy-related protein 13(ATG13) and activating the AKT signaling pathway, thereby enhancing renal function. Post-cardiac injury, these exosomal miR-1-3p are swiftly released into the kidney, where they exert

a positive influence on renal function by directly targeting ATG13 [154].

Others

Human amniotic epithelial cells-EVs (hAEC-EVs) Recent research outcomes highlight human amniotic epithelial cells (hAECs) and their derived exosomes can markedly alleviate cisplatin-induced nephrotoxicity. They reduce mortality and serum creatinine levels and decrease renal tubular damage. The renal protective mechanism involves the inhibition of the TNF-α/MAPK and caspase signaling pathways [155].

Macrophage-derived EVs(Mϕ-EVs) A study's data indicate that exosomal miR-25-3p derived from M2 macrophages protects podocytes from HG-induced injury by activating autophagy in podocytes through the inhibition of dual specificity phosphatase 1(DUSP1) expression [156]. This confirms the importance of paracrine communication via exosomes between M2 macrophages and HG-induced podocytes, and identifies a new potential target for the treatment of diabetic nephropathy.

In summary, different extracellular vesicles (including hucMSC-EVs, BMSC-EVs, ADSC-EVs, TEC-EVs, EPC-EVs, Mϕ-EVs, and Circulating EVs) play a diversified role in the treatment of kidney diseases through the bioactive substances they carry and the signals they transmit. EVs can deliver survival signals to injured kidney cells, inhibiting apoptosis. They promote the proliferation and differentiation of damaged cells, accelerating tissue repair and regeneration. For instance, EVs derived from specific cell types, such as MSC-EVs, can carry miR125b-5p, which promotes renal tubular repair and inhibits apoptosis, thus playing a role in the treatment of AKI [116]. Additionally, extracellular vesicles can transfer molecules with anti-inflammatory effects. For example, IL-10-loaded EVs (IL-10 EVs) produced by engineered macrophages can enhance the stability of IL-10 and its targeting to damaged kidneys. A large number of IL-10 EVs located in the renal tubular interstitial macrophages induce a significant shift in the polarization of renal macrophages from the M1 to the M2 phenotype, ultimately significantly improving renal tubular damage and inflammation caused by ischemia/reperfusion injury [157]. Furthermore, EVs can inhibit the activation and proliferation of fibroblasts, reducing the excessive deposition of extracellular matrix. They modulate fibrotic-related signaling pathways and reverse the fibrotic process. For example, fibrosis-related macrophages promote the differentiation of mesangial cells into myofibroblasts by activating the TGF-β1/Smad2/3/YAP axis, while MSC-EVs antagonize the fibrotic niche in DKD by mediating the degradation of YAP through CK1δ/β-TRCP, alleviating the progression of DKD. These collectively illustrate that the precise regulation of EVs' biosynthesis and function may pave the way for innovative therapeutic interventions in kidney diseases [158] (Table 1).

Engineered extracellular vesicles of kidney diseases

Given the preliminary achievements of EVs in the treatment of kidney diseases, researchers are committed to overcoming their limitations through engineering approaches to achieve more optimized therapeutic strategies. Engineered EVs are gradually becoming the focus of research due to their great potential as multifunctional drug delivery systems in the field of biomedicine.

The design of engineered EVs focuses on improving their delivery capabilities by means of strategic surface modifications or the inclusion of functional ligands. These modifications enable the conjugation of a variety of molecules, such as endogenous and exogenous substances, drugs, proteins, or nucleic acids, to either the surface or the interior of the vesicles [159]. Furthermore, this engineering facilitates the precise targeting of specific cell types or tissues, which is essential for directed therapeutic interventions [160].This approach not only expands the therapeutic potential of EVs, but also introduces a multifaceted enhancement of their capabilities. The ability to selectively deliver cargo to intended sites while minimizing off-target effects is particularly beneficial [161]. The implications of these advancements are significant, as they open the door for a new generation of clinical applications of EVs, providing tailored treatments with enhanced efficacy and safety profiles.

Engineering strategies for EVs can be categorized into three main approaches: cargo loading, surface modification, and genetic engineering. Each engineering strategy has its unique strengths and limitations. In practical applications, it may be necessary to consider the appropriate engineering strategy based on the specific type of kidney disease, therapeutic objectives, and the individual patient's condition. Combining multiple strategies may be required to achieve the best therapeutic outcomes.

Cargo loading

Cargo loading involves incorporating therapeutic agents, such as small molecule drugs, proteins, nucleic acids, etc., into EVs through methods like electroporation, extrusion, sonication, and incubation, to achieve the purpose of drug delivery. Strategies for cargo loading include endogenous loading and exogenous loading. Endogenous loading is an engineering loading method based on the parental cells, which involves modifying the source cells to introduce the target molecules, allowing them to be incorporated into the vesicles during the production of EVs. Exogenous loading, on the other hand, involves

Table 1 Therapeutic role of non-stem cell-derived extracellular vesicles in kidney diseases

Origin	Model	Effective molecules	Therapeutic schedule	Treatment outcome	Ref.
TEC-EVs	IRI, female SD rats, AKI/CKD	undefined	100 μg, two doses (24 and 48 h after surgery), tail vein	improved renal tubular damage, 4-hydroxynanoneal adduct formation, neutrophil infiltration, fibrosis, and microvascular pruning.	[147]
TEC-EVs	IRI, C57BL/6 mice, AKI	HIF-1α/Rab22	50 μg, single dose (24 h before the operation), injected intravenously	Serum creatinine is reduced, and the damage to the renal tubules is alleviated	[148]
TEC-EVs	H/R, HK-2, AKI	miR-590-3p	undefined	increases in the expression of autophagy marker proteins, including Beclin-1 and microtubule associated protein 1 light chain 3 beta (LC3II), and prolonged the autophagic response	[149]
TEC-EVs	Cisplatin, male C57BL/6mice, AKI	miR-122/ELAVL1	undefined	Inhibited pyroptosis	[150]
TEC-EVs	AMA, Male 129-S1 mice, *AKI*	undefined	30ug, single dose, injected caudally	improve mitochondrial pathways and alleviate chronic kidney injury in vivo	[151]
TEC-EVs	BSA and castor oil, SPF male SD rats, IgAN	NF-κB/NLRP3	7.5 mg/kg, tail vein	ameliorated kidney function of IgAN rats and inhibited the expansion of mesangial matrix and proliferation of mesangial cell	[152]
EPO-EVs	CLP, SD rats, AKI	miR-21-5p/RUNX1	tail vein before CLP operation	reduced Serum creatinine and BUN levels, renal tubular injury score, apoptosis rate, inflammatory factors levels, and oxidative stress response as well as increased the proportion of endothelial glycocalyx area in glomerulus	[153]
Circulating-EVs	iodixano, SD rats, CIN	miR-1-3p/ATG13/AKT	tail vein	inhibiting the CM-induced apoptosis and autophagy of renal tubular epithelial cells, and improving the renal function of rats.	[154]
hAEC-EVs	Cisplatin, male C57BL/6J mice, AKI	the TNF-α/MAPK and the caspase signaling pathways	1×10^{8}, single dose, injected intravenously	reduce the mortality rate and attenuate renal dysfunction and pathological damage	[155]
Mφ-EVs	HG, podocytes, DKD	miR-25-3p/DUSP1	200 μg, co-culture	protected podocytes against HG-induced injury through activation the autophagy in podocytes	[156]

using membrane penetration or other loading strategies to directly load the cargo into the isolated EVs [8, 162].

The extrusion method is a commonly used strategy for engineering EVs. For example, by mixing purified neutrophil membranes with recombinant human IL-37 protein and then preparing N-MV@IL-37 through the extrusion method. This approach not only enhances the stability of IL-37 but also enables it to be targeted to injured renal endothelial cells via PSGL-1 on the neutrophil membrane. This enhances the therapeutic effect of IL-37 on renal IRI [163]. Electroporation loading technology primarily involves encapsulating small RNA molecules into the interior of EVs. Studies have shown that by using electroporation to load exogenous microRNA from Caenorhabditis elegans (cel-miR-39) into MSC-EVs, one can protect podocytes from damage, reduce cell death, and decrease albumin permeability [164].

To enhance the efficacy of EVs, various stimuli can be used to bioengineer the originating cells. For instance, exosomes derived from melatonin-stimulated mesenchymal stem cells (Exocue) can reduce the gene expression of miRNAs associated with the severity of CKD, increase the levels of aquaporins AQP2 and AQP5, and decrease blood urea nitrogen (BUN) and creatinine levels. Thereby alleviating the severity of CKD and modulating chronic inflammation and fibrosis [165]. Integrins are a type of protein found on the surface of EVs, and the RGD peptide has a strong binding affinity for integrins. Research indicates that supramolecular nanofibers containing the arginine-glycine-aspartic acid (RGD) peptide can enhance MSC-EVs carrying let-7a-5p miRNA. By

targeting the CASP3 and RragD genes, these nanofibers can reduce apoptosis and activate autophagy [166].

Klotho is a single-pass transmembrane protein that is essential for renal tissue regeneration. By using the Exo-Fect exosome transfection reagent to load recombinant Klotho protein into EVs, it has been found that in an AKI mouse model, engineered EVs expressing recombinant human Klotho exhibit stronger renal protective effects compared to the same dosage of soluble Klotho [167]. In another study, by transfecting MSCs with let-7i-5p antagomir, which is an antagonist targeting let-7i-5p, it is possible to suppress the levels of let-7i-5p in MSC-EVs. This suppression increases the anti-fibrotic activity, reduces the deposition of extracellular matrix, and mitigates epithelial-mesenchymal transition [168].

The advantage of cargo loading is that the type and dose of therapeutic substances (e.g., drugs, nucleic acids, etc.) encapsulated in EVs can be precisely controlled, thus facilitating targeted therapy. It can load some large molecule drugs to improve their stability and bioavailability. However, the loading efficiency of this method may be affected by various factors, such as the nature of the cargo and the loading method.

Surface modification

The surface of EVs is enriched with various proteins and polysaccharides, which can influence the targeting, stability, and immunogenicity of EVs. By modifying the surface molecules of EVs, one can confer cell and tissue targeting specificity, thereby enhancing their targeting efficiency and therapeutic efficacy. Methods for surface modification include chemical modification, bio-fusion expression, and liposome fusion, among others [169]. Chemical modification is key in ensuring that the biological activity and stability of EVs are not compromised while achieving the desired engineered characteristics. For instance, by using copper-free click chemistry, the LTH peptide can be conjugated to the surface of red blood cell-derived extracellular vesicles (REVs) through a reaction between azadibenzocyclooctyne (DBCO) and an azide. The targeting effect of the Kim-1 binding peptide LTH effectively reduces the expression of P-P65 and Snail1 in injured renal tubular cells, inhibiting ischemia/reperfusion injury and unilateral ureteral obstruction-induced kidney inflammation and fibrosis in mice, thus delaying the progression from acute kidney injury (AKI) to chronic kidney disease (CKD) [170].In another study, researchers covalently linked a P-selectin binding peptide (PBP) to a polyethylene glycol-derivatized phospholipid (DMPE-PEG) and then anchored this complex to the surface of EVs. It was found that these PBP-EVs could competitively bind to P-selectin on damaged endothelial cells, inhibiting the invasion of inflammatory cells and thereby reversing the pro-fibrotic renal microenvironment [171].

Furthermore, after achieving efficient expression of the CHIP protein by transducing MSCs with the CHIP gene using lentiviral transduction technology, the authors surface-modified the isolated MSC-EVs-CHIP with superparamagnetic iron oxide nanoparticles (SPION). The results indicated that SPION-EVS-CHIP had a good targeting effect on kidney injury in rats with unilateral ureteral obstruction (UUO). Compared to traditional MSC-EVs, SPION-EVS-CHIP significantly reversed collagen deposition and inhibited the inflammatory response mediated by renal tubular injury by inducing ubiquitination of renal tubular cells and degradation of Smad2/3169 [172].

Surface modification offers the advantage of significantly improving the targeting of EVs to kidney lesion tissues or cells by conjugating targeting ligands or specific molecules on the EV surface, thereby enhancing therapeutic effects. It can improve the stability and bioavailability of EVs. However, the process of surface modification can be quite complex, requiring precise chemical or biological reaction conditions. Modification might alter the natural characteristics of EVs, potentially triggering immune responses or other adverse effects.

Genetic engineering

The gene engineering strategy in engineered EVs refers to the modification of the genes of EVs to express specific proteins or RNAs to achieve particular functions. This process typically involves the specific insertion, deletion, or modification of target genes in the genome, followed by the isolation of EVs containing engineered genetic material or therapeutic agents [173]. Transfection of plasmids can achieve the effect of engineered EVs by introducing plasmids containing specific genes into cells, causing the cells to express the gene and package it into EVs. For example, transfecting RAW 264.7 macrophages with a plasmid encoding mouse IL-10 to produce EVs loaded with interleukin-10 (IL-10-EV). This process can promote mitochondrial autophagy and the polarization of renal tubular interstitial macrophages towards an anti-inflammatory M2 phenotype, effectively treating ischemic acute kidney injury (AKI) [157]. In another study, the authors transfected mouse renal tubular epithelial cells (TEC) with a plasmid encoding mouse VEGF-A to prepare EVs expressing high levels of VEGF-A (sEV-VEGF-A). It was found that these vesicles could treat ischemic renal injury by promoting the repair of the peritubular capillary (PTC) [174].

Lentiviral transduction is a commonly used method for gene delivery, utilizing a modified lentivirus vector to effectively integrate the gene of interest (such as reporter genes, functional genes, or gene-editing tools) into the host cell's genome. In a study, the authors transduced mesenchymal stem cells (MSCs) with an expression

plasmid of miR-let7c via a lentiviral vector. The genetically engineered mesenchymal stem cells with high expression of miR-let7c (miR-let7c-MSCs) could selectively deliver to the damaged kidneys, reducing fibrosis in vivo and alleviating the injury to renal cells stimulated by transforming growth factor-β1 [175].Additionally, by using the lentiviral transfection system to transduce the GDNF gene into human adipose-derived mesenchymal stem cells (ADSCs), one can obtain GDNF-modified exosomes from human adipose-derived mesenchymal stem cells (GDNF-AMSC-exos). Research findings have shown that GDNF-AMSC-exos can enhance the preservation of peritubular capillaries and activate the post-injury angiogenesis program to improve renal fibrosis by activating the SIRT1/eNOS signaling pathway [176]. In addition, the use of an inducible lentiviral vector containing the FOXP3 gene to transduce $CD4^+$ T cells allows for the construction of engineered T cells (Foe-Th). From these T cells, genetically engineered EVs containing specific FOXP3 transcripts are isolated, known as FOE-TEV. These vesicles can improve the inhibition coefficient under secondary lymphatic drainage by suppressing Th1 cell polarization, inhibiting the production of donor-specific antibodies (DSA). And obstructing complement activation, effectively alleviating allograft rejection after renal transplantation [177].Researchers have utilized a lentiviral vector to insert the human EPO gene into Kidney Mesenchymal Stem Cells (KMSCs), resulting in the generation of engineered KMSCs that express EPO ($EPO^{(+)}$–KMSCs). They found that the EVs secreted by these cells can transfer EPO mRNA to target cells, alleviating anemia in rats with chronic kidney disease (CKD) [178]. Additionally, by using a lentiviral vector to transfer the OCT-4 gene into human mesenchymal stem cells, overexpression of OCT-4 was achieved. Subsequently, EVs enriched with Oct-4 mRNA, termed EVs+Oct-4, were isolated. It was found that EVs+Oct-4 exhibited a greater inhibitory effect on the expression of Snail1 and enhanced the anti-apoptotic and proliferative effects on renal cells [179].

Unlike lentiviral transduction, adenoviral transfection is typically used for transient expression of the gene of interest because they do not integrate into the host cell genome but exist in the host cell as free circular DNA. In a study, the authors transfected an adenoviral vector expressing mouse CD26 ($VirusCD26^+$) into a renal tubular epithelial cell line (TCMK-1). And then found that the isolated exosomes with overexpressed CD26 ($Exo\ CD26^+$) could treat ischemia-reperfusion acute kidney injury (IR-AKI) by maintaining cell proliferation and reducing inflammation [180].

Genetic engineering can regulate the production and function of EVs at the genetic level, enabling them to continuously express specific therapeutic gene products. It allows for long-term, stable modification of the intrinsic composition and function of EVs. However, compared to other engineering techniques, genetic engineering is relatively complex to operate, and there are potential risks associated with gene editing and ethical issues. Controlling gene expression is challenging and may result in unpredictable gene expression changes.

In summary, significant strides have been made in the field of kidney disease research through the strategic engineering of EVs. Enhancements in renal targeting and therapeutic efficacy have been achieved by employing techniques such as cargo loading, surface modification, and genetic engineering. These approaches have endowed EVs with the ability to more precisely deliver therapeutic agents and modulate immune responses within the renal microenvironment (Fig. 5). As the field progresses, ongoing research is expected to further elucidate the mechanisms of EVs action in renal pathophysiology and expand their application in the therapeutic arsenal for kidney diseases. The continued development of these nanoscale therapeutics holds promise for the future, potentially offering patients a range of more precise, effective, and personalized diagnostic and treatment options.

Perspectives and challenges

EVs are emerging as promising agents in the advancement of kidney disease diagnostics and therapeutics. However, translating EVs research from the bench to clinical practice is not without its challenges. Researchers are actively engaged in surmounting these hurdles and are exploring innovative approaches to harness the full therapeutic potential of EVs in renal pathologies. In the quest to standardize EVs research, a primary focus is the development of protocols for EVs production, characterization, storage, and clinical assessment. A significant challenge lies in the heterogeneity of EVs [181]; those derived from different cellular origins can exhibit considerable variability in size, composition, and functionality. This diversity complicates processes such as isolation, characterization, and quantification. Current methodologies, including ultracentrifugation, size exclusion chromatography, ultrafiltration, immunocapture, precipitation, and microfluidic technologies, are not without their drawbacks, including low yields and impurities, which can impact subsequent analyses and applications [182]. Establishing standardized methods for EVs isolation and analysis is essential for ensuring the reproducibility and comparability of research outcomes.

Additionally, there is an imperative need to validate techniques for the detection and quantification of specific EVs subpopulations, particularly those from unique cell types or bearing distinct molecular cargo [183]. At present, there are several mature single EV analysis

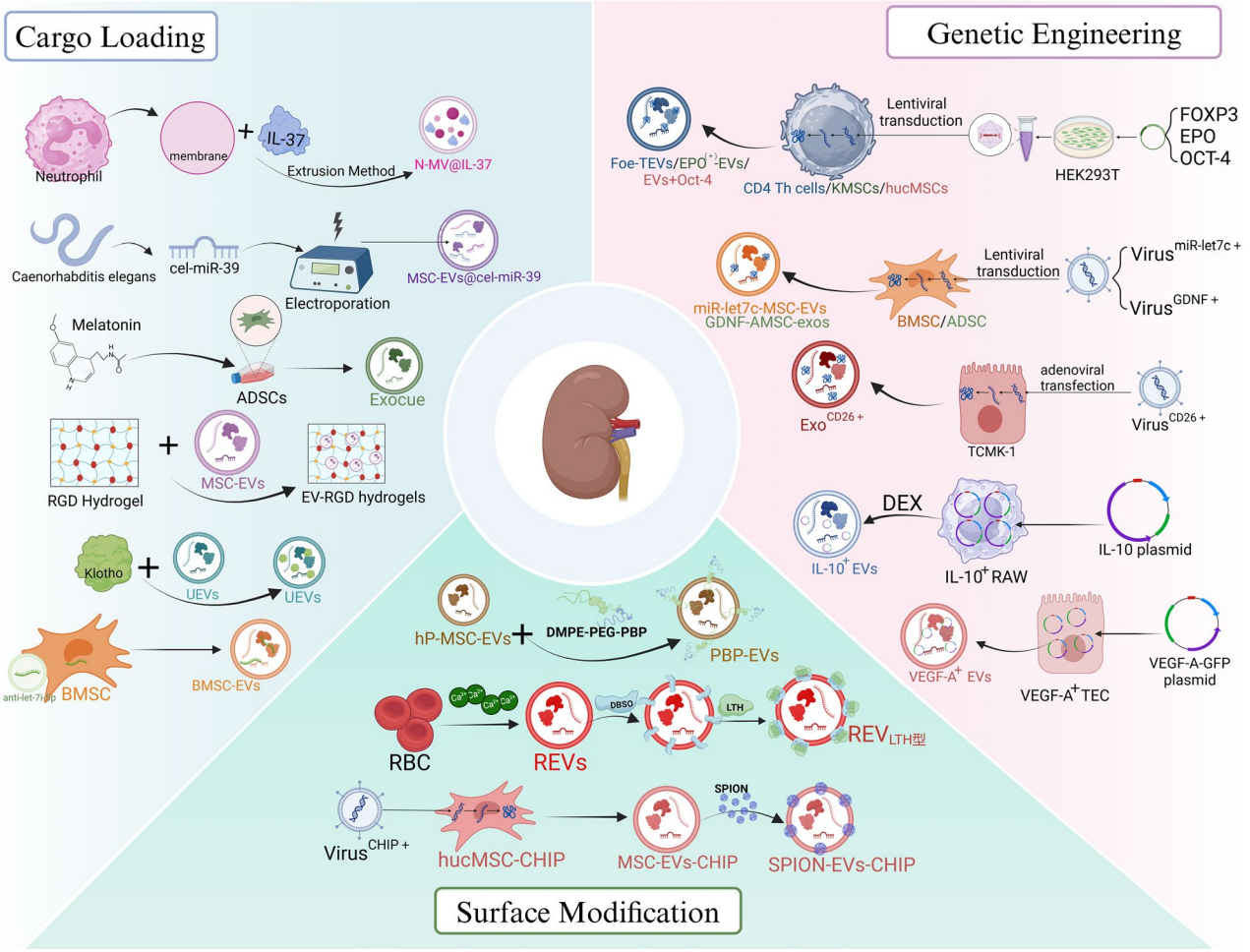

Fig. 5 Engineering strategies for EVs. Three distinct engineering strategies—cargo loading, surface modification, and genetic engineering—are utilized to enhance the therapeutic efficacy and targeting specificity of extracellular vesicles derived from various sources

technologies, including nanoflow cytometry, the ExoView platform, super-resolution fluorescence imaging, surface plasmon resonance (SPR) technology, and single-particle dark-field imaging [184]. In addition, researchers from the University of Gothenburg in Sweden have proposed a method that uses enzymatic treatment, differential centrifugation, and density gradient separation, followed by characterization with electron microscopy and RNA profiling, to directly isolate up to six different EV subpopulations from tissues [185]. The research team from Zhongshan Hospital affiliated with Fudan University in Shanghai has developed HNCIB (High-throughput Nano-bio Chip Integrated System for Liquid Biopsy), a technology capable of simultaneously detecting and analyzing multiple biomarkers on the surface and within EVs [186]. Professor Zheng Lei's team at Nanfang Hospital, Southern Medical University, has respectively constructed a fluorescent aptamer sensor based on aptamer-functionalized metal-organic frameworks and cholesterol-triggered signal amplification-EV-ANCHOR [187], and a single-vesicle membrane protein expression profile analysis technology based on droplet digital immuno-PCR (ddiPCR) [188]. These can be used for the separation and detection of PD-L1EVs and the quantitative detection analysis of specific EV subpopulations, providing a new strategy for the clinical diagnosis of cancer with EV subpopulations. The development of these technologies has provided new avenues and possibilities for the study and application of extracellular vesicles. With the continuous advancement and optimization of technology, it is expected that in the future, more efficient and precise research and applications of extracellular vesicles will be realized.

The biological functions and mechanisms of action of EVs in kidney diseases are not yet fully elucidated. While numerous roles have been identified, the underlying signaling pathways and molecular mechanisms necessitate further exploration [189]. This deeper understanding will be pivotal in revealing the integral roles of EVs in the etiology and progression of renal diseases, thereby

providing a robust theoretical foundation for the development of novel therapeutic interventions. The utilization of EVs as biomarkers also presents its own set of challenges. For example, in studies employing uEVs as biomarkers, the protocols for urine collection and preservation, as well as the methodologies for the isolation of urinary EVs and the elimination of contaminants, are critical [190]. Furthermore, while certain studies suggest that specific molecules within EVs could serve as diagnostic indicators for kidney diseases, the specificity and sensitivity of these biomarkers require additional validation. The establishment of standardized detection methods and reference ranges is imperative to ensure their reliability and reproducibility in clinical settings.

The therapeutic application of EVs is an area that requires further exploration. Although preliminary studies indicate that EVs can function as drug delivery systems or therapeutic agents, their safety and efficacy must be comprehensively evaluated through preclinical and clinical trials. Currently, there is a dearth of extensive clinical trials for EVs. Rigorous clinical trials are indispensable for corroborating existing research findings and for the transformation of EVs into viable clinical therapies [15, 191]. Optimizing the loading and delivery of EVs is another critical challenge. The selection of appropriate loading methods, enhancement of drug or bioactive molecule loading efficiency within EVs, and the optimization of delivery routes and targeting are all focal points of research. Advances in the engineering of EVs offer new opportunities to augment the therapeutic efficacy of EVs in renal diseases [159, 192, 193]. Techniques such as gene editing and synthetic biology provide avenues for modifying EVs to improve their efficacy and targeting specificity. While preclinical studies have demonstrated the potential benefits of EVs in AKI and CKD, the long-term efficacy and durability of EVs therapy remain uncertain. Further research is essential to elucidate the in vivo lifespan of EVs, the duration of drug efficacy, and the safety and efficacy of repeated administrations.

The application of EVs in kidney disease holds great promise but is also confronted with significant challenges, including the development of accurate diagnostic markers, in-depth exploration of therapeutic mechanisms, optimization of targeted delivery systems, long-term safety and efficacy evaluation, translational research and regulatory approval for market launch, etc. To effectively tackle these challenges, it is imperative to sustain ongoing research efforts and to foster technological innovation. Interdisciplinary collaboration is pivotal in propelling the study of EVs in kidney disease. The study of EVs spans fields such as biology, medicine, chemistry, and physics, necessitating a collaborative approach among experts from diverse disciplines to address the issues and challenges effectively. In conclusion, as an emerging field, the study of extracellular vesicles offers novel perspectives and methodologies for the diagnosis and treatment of kidney diseases. Despite the challenges, with ongoing technological advancements and in-depth research, the prospects for the application of EVs in renal medicine are expected to expand significantly (Table 2).

Table 2 Abbreviations

Abbreviation	Full name	Abbreviation	Full name
EVs	Extracellular vesicles	MSC-EVs	Mesenchymal stem cells-EVs
AKI	Acute Kidney Injury	CKD	Chronic Kidney Disease
DKD	Diabetic Kidney Disease	TECs	Renal tubular epithelial cells
Mφ-EVs	Macrophage-derived EVs	CP-AKI	Cisplatin-induced AKI
Atg9b	Autophagy-related gene 9B	BSA	Bovine serum albumin
CHAC1	Cationic amino acid transporter regulator homolog 1	NF-κB	Nuclear Factor kappa B
SOCS-1	Suppressor of cytokine signaling-1	HSA	Human serum albumin
TLR4	Toll-like receptor 4	CCL2	Chemokine Ligand 2
HIF-1α	Hypoxia-inducible factor 1α	KIM-1	Kidney injury molecule-1
PS	Phosphatidylserine	OMVs	Outer membrane vesicles
Shh	Sonic hedgehog	STAT3	Signal transducer and activator of transcription 3
PTEN	Phosphatase and tensin homolog	Fibro-EVs	Fibroblast-derived EVs
MVs	Microvesicles	Bcl-2	B-cell lymphoma-2
RIF	Renal interstitial fibrosis	MAPK1	Mitogen-activated protein kinase 1
TIMP2	Tissue Inhibitor of metalloproteinases 2	LRG1	Leucine-rich α-2-glycoprotein 1
TRAIL	Tumor necrosis factor-related apoptosis-inducing ligand	CBS	Cystathionine-β-synthase
HG	High glucose	MCs	Mesangial cells
ROS	Reactive oxygen species	ERK	Extracellular signal-regulated kinase
ARF6	ADP-Ribosylation Factor 6	**uEVs**	**Urinary extracellular vesicles**
I/R-AKI	Ischemia/Reperfusion AKI	S-AKI	Sepsis-AKI
NHE3	Na/H exchanger isoform 3	NGAL	Neutrophil gelatinase-associated lipocalin
α1-AT	Alpha-1-antitrypsin	T2DM	Type 2 Diabetes Mellitus
WT1	Wilms' tumor protein 1	**ESRD**	**End-Stage Renal Disease**
IgAN	**IgA Nephropathy**	TBMN	Thin basement membrane nephropathy
LN	**Lupus Nephritis**	MPs	Podocyte-derived microparticles
SLEDAI	SLE disease activity index	EH	Essential hypertension
PTC	Peritubular capillary	EMPs	Endothelial microparticles
EMT	Epithelial-mesenchymal transition	MIC	Microalbuminuria
MAC	Macroalbuminuria	ACR	Albumin-to-creatinine ratio
RCC	Renal Cell Carcinoma	BKVN	BK virus nephropathy
VLA-4	Very late antigen-4	LFA-1	Lymphocyte function-associated antigen-1
PDK4	Pyruvate dehydrogenase kinase 4	ATF-6	Activating transcription factor 6
HSP	Heat shock protein	PFUS	Pulsed focused ultrasound
PRP	Platelet-rich plasma	YAP	Yes-associated protein
IRAK1	Interleukin-1 receptor-associated kinase 1	3′-UTR	3′-Untranslated region
ECM	Extracellular matrix	CK1δ	Casein kinase 1δ
β-TrCP	β-transducin repeat-containing protein	UUO	Unilateral ureteral obstruction
RIPK1	Receptor-interacting serine/threonine-protein kinase 1	PGAM5	Phosphoglycerate mutase family member 5
BIP	Binding immunoglobulin protein	Sema3A	Semaphorin 3 A
mTOR	Mammalian target of rapamycin	KLF6	Krüppel-like factor 6
PFKM	Phosphofructokinase	SIRT1	Sirtuin 1
Keap1	Kelch-like ECH-associated protein 1	Nrf2	Nuclear factor erythroid 2 related factor 2
DRP1	Dynamin-related protein 1	ARE	Antioxidant response element
ELAVL1	embryonic lethal abnormal vision	RUNX1	Runt-related transcription factor 1
CM	Cardiomyocyte	ATG13	Autophagy-related protein 13
hAECs	Human amniotic epithelial cells	DUSP1	Dual specificity phosphatase 1
BUN	Blood urea nitrogen	RGD	Arginine-glycine-aspartic
SPIONs	Superparamagnetic iron oxide nanoparticles	DSA	Donor-specific antibodies
KMSCs	Kidney Mesenchymal Stem Cells	BNIP3	BCL2 interacting protein 3
FOXO	Forkhead box O		

Abbreviations

EVs	Extracellular vesicles
AKI	Acute Kidney Injury
DKD	Diabetic Kidney Disease
Mφ-EVs	Macrophage-derived EVs
Atg9b	Autophagy-related gene 9B
CHAC1	Cationic amino acid transporter regulator homolog 1
SOCS-1	Suppressor of cytokine signaling-1
TLR4	Toll-like receptor 4
HIF-1α	Hypoxia-inducible factor 1α
PS	Phosphatidylserine
Shh	Sonic hedgehog
PTEN	Phosphatase and tensin homolog
MVs	Microvesicles
RIF	Renal interstitial fibrosis
TIMP2	Tissue Inhibitor of metalloproteinases 2
TRAIL	Tumor necrosis factor-related apoptosis-inducing ligand
HG	High glucose
ROS	Reactive oxygen species
ARF6	ADP-Ribosylation Factor 6
I/R-AKI	Ischemia/Reperfusion AKI
NHE3	Na/H exchanger isoform 3
α1-AT	Alpha-1-antitrypsin
WT1	Wilms' tumor protein 1
IgAN	IgA Nephropathy
LN	Lupus Nephritis
SLEDAI	SLE disease activity index
PTC	Peritubular capillary
EMT	Epithelial-mesenchymal transition
MAC	Macroalbuminuria
RCC	Renal Cell Carcinoma
VLA-4	Very late antigen-4
PDK4	Pyruvate dehydrogenase kinase 4
HSP	Heat shock protein
PRP	Platelet-rich plasma
IRAK1	Interleukin-1 receptor-associated kinase 1
ECM	Extracellular matrix
β-TrCP	β-transducin repeat-containing protein
RIPK1	Receptor-interacting serine/threonine-protein kinase 1
BIP	Binding immunoglobulin protein
mTOR	Mammalian target of rapamycin
PFKM	Phosphofructokinase
Keap1	Kelch-like ECH-associated protein 1
DRP1	Dynamin-related protein 1
ELAVL1	Embryonic lethal abnormal vision
CM	Cardiomyocyte
hAECs	Human amniotic epithelial cells
BUN	Blood urea nitrogen
SPIONs	Superparamagnetic iron oxide nanoparticles
KMSCs	Kidney Mesenchymal Stem Cells
FOXO	Forkhead box O
MSC-EVs	Mesenchymal stem cells-EVs
CKD	Chronic Kidney Disease
TECs	Renal tubular epithelial cells
CP-AKI	Cisplatin-induced AKI
BSA	Bovine serum albumin
NF-κB	Nuclear Factor kappa B
HSA	Human serum albumin
CCL2	Chemokine Ligand 2
KIM-1	Kidney injury molecule-1
OMVs	Outer membrane vesicles
STAT3	Signal transducer and activator of transcription 3
Fibro-EVs	Fibroblast-derived EVs
Bcl-2	B-cell lymphoma-2
MAPK1	Mitogen-activated protein kinase 1
LRG1	Leucine-rich α-2-glycoprotein 1
CBS	Cystathionine-β-synthase
MCs	Mesangial cells
ERK	Extracellular signal-regulated kinase
uEVs	Urinary extracellular vesicles
S-AKI	Sepsis-AKI
NGAL	Neutrophil gelatinase-associated lipocalin
T2DM	Type 2 Diabetes Mellitus
ESRD	End-Stage Renal Disease
TBMN	Thin basement membrane nephropathy
MPs	Podocyte-derived microparticles
EH	Essential hypertension
EMPs	Endothelial microparticles
MIC	Microalbuminuria
ACR	Albumin-to-creatinine ratio
BKVN	BK virus nephropathy
LFA-1	Lymphocyte function-associated antigen-1
ATF-6	Activating transcription factor 6
PFUS	Pulsed focused ultrasound
YAP	Yes-associated protein
3'-UTR	3'-Untranslated region
CK1δ	Casein kinase 1δ
UUO	Unilateral ureteral obstruction
PGAM5	Phosphoglycerate mutase family member 5
Sema3A	Semaphorin 3 A
KLF6	Krüppel-like factor 6
SIRT1	Sirtuin 1
Nrf2	Nuclear factor erythroid 2 related factor 2
ARE	Antioxidant response element
RUNX1	Runt-related transcription factor 1
ATG13	Autophagy-related protein 13
DUSP1	Dual specificity phosphatase 1
RGD	Arginine-glycine-aspartic
DSA	Donor-specific antibodies
BNIP3	BCL2 interacting protein 3

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Author contributions
L.B. and Q.C. wrote the main manuscript text and design picture, Z.YF, S. LR. and Z.JH.prepared Figs. 1, 2, 3, 4 and 5. J.C and Q.H participated in the overall idea design and text proofreading of the article. All authors reviewed the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

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All of the author has read the journal policies and submit this manuscript in accordance with those policies.

Competing interests
The authors declare no competing interests.

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References

1. Luyckx VA, Tonelli M, Stanifer JW. The global burden of kidney disease and the Sustainable Development Goals. Bull World Health Organ. 2018;96(6):414–22. https://doi.org/10.2471/BLT.17.206441. D.
2. Borg R, Carlson N, Søndergaard J, Persson F. The growing challenge of chronic kidney disease: an overview of current knowledge. Int J Nephrol. 2023;2023(9609266). https://doi.org/10.1155/2023/9609266.
3. Xie Y, Bowe B, Mokdad AH, Xian H, Yan Y, Li T, Maddukuri G, Tsai C-Y, Floyd T, Al-Aly Z. Analysis of the global burden of Disease Study highlights the Global, Regional, and National trends of chronic kidney Disease Epidemiology from 1990 to 2016. Kidney Int. 2018;94(3):567–81. https://doi.org/10.1016/j.kint.2018.04.011.
4. GBD Chronic Kidney Disease Collaboration. Global, Regional, and National Burden of chronic kidney Disease, 1990–2017: a systematic analysis for the global burden of Disease Study 2017. Lancet. 2020;395(10225):709–33. https://doi.org/10.1016/S0140-6736(20)30045-3.
5. Kalantar-Zadeh K, Jafar TH, Nitsch D, Neuen BL, Perkovic V. Chronic kidney disease. Lancet. 2021;398(10302):786–802. https://doi.org/10.1016/S0140-6736(21)00519-5.
6. Fayad AI, Buamscha DG, Ciapponi A. Timing of kidney replacement therapy initiation for acute kidney Injury. Cochrane Database Syst Rev. 2022;11(11):CD010612. https://doi.org/10.1002/14651858.CD010612.pub3.
7. Vijayan A, Abdel-Rahman EM, Liu KD, Goldstein SL, Agarwal A, Okusa MD, Cerda J. AKI!NOW Steering Committee. Recovery after critical illness and acute kidney Injury. Clin J Am Soc Nephrol. 2021;16(10):1601–9. https://doi.org/10.2215/CJN.19601220.
8. Tang T-T, Wang B, Lv L-L, Liu B-C. Extracellular vesicle-based nanotherapeutics: emerging frontiers in anti-inflammatory therapy. Theranostics. 2020;10(18):8111–29. https://doi.org/10.7150/thno.47865.
9. R K, Vs L, The Biology F, Biomedical Applications of Exosomes. Sci (New York N Y). 2020;367(6478). https://doi.org/10.1126/science.aau6977.
10. S G, X S, J W, Al N, Sc A, L M, A Z, M A, Ar I. Technologies and standardization in Research on Extracellular vesicles. Trends Biotechnol. 2020;38(10). https://doi.org/10.1016/j.tibtech.2020.05.012.
11. Chen C, Sun M, Wang J, Su L, Lin J, Yan X. Active Cargo Loading into Extracellular vesicles: highlights the heterogeneous encapsulation Behaviour. J Extracell Vesicles. 2021;10(13):e12163. https://doi.org/10.1002/jev2.12163.
12. Herrmann IK, Wood MJA, Fuhrmann G. Extracellular vesicles as a next-generation drug delivery platform. Nat Nanotechnol. 2021;16(7):748–59. https://doi.org/10.1038/s41565-021-00931-2.
13. Wang J, Chen D, Ho EA. Challenges in the Development and Establishment of Exosome-based drug Delivery systems. J Control Release. 2021;329:894–906. https://doi.org/10.1016/j.jconrel.2020.10.020.
14. 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. https://doi.org/10.1038/s41419-019-1605-2.
15. Grange C, Bussolati B. Extracellular vesicles in kidney disease. Nat Rev Nephrol. 2022;18(8):499–513. https://doi.org/10.1038/s41581-022-00586-9.
16. Kumar MA, Baba SK, Sadida HQ, Marzooqi SA, Jerobin J, Altemani FH, Algehainy N, Alanazi MA, Abou-Samra A-B, Kumar R, Al-Shabeeb Akil AS, Macha MA, Mir R, Bhat AA. Extracellular vesicles as tools and targets in Therapy for diseases. Signal Transduct Target Ther. 2024;9(1):27. https://doi.org/10.1038/s41392-024-01735-1.
17. Bruno S, Porta S, Bussolati B. Extracellular vesicles in renal tissue damage and regeneration. Eur J Pharmacol. 2016;790:83–91. https://doi.org/10.1016/j.ejphar.2016.06.058.
18. Huang J, Wang X, Wang Z, Deng L, Wang Y, Tang Y, Luo L, Leung E. L.-H. Extracellular vesicles as a Novel Mediator of Interkingdom Communication. Cytokine Growth Factor Rev. 2023;73:173–84. https://doi.org/10.1016/j.cytogfr.2023.08.005.
19. Zhu J, Huang J, Sun Y, Xu W, Qian H. Emerging role of Extracellular vesicles in Diabetic Retinopathy. Theranostics. 2024;14(4):1631–46. https://doi.org/10.7150/thno.92463.
20. Jin C, Wu P, Li L, Xu W, Qian H. Exosomes: emerging therapy delivery tools and biomarkers for kidney diseases. Stem Cells Int. 2021;2021(7844455). https://doi.org/10.1155/2021/7844455.
21. Hade MD, Suire CN, Mossell J, Suo Z. Extracellular vesicles: emerging frontiers in Wound Healing. Med Res Rev. 2022;42(6):2102–25. https://doi.org/10.1002/med.21918.
22. Tsuji K, Kitamura S, Wada J. Immunomodulatory and Regenerative effects of Mesenchymal Stem Cell-Derived Extracellular vesicles in Renal diseases. Int J Mol Sci. 2020;21(3):756. https://doi.org/10.3390/ijms21030756.
23. Sato Y, Takahashi M, Yanagita M. Pathophysiology of AKI to CKD progression. Semin Nephrol. 2020;40(2):206–15. https://doi.org/10.1016/j.semnephrol.2020.01.011.
24. Batte A, Shahrin L, Claure-Del Granado R, Luyckx VA, Conroy AL. Infections and acute kidney Injury: A Global Perspective. Semin Nephrol. 2023;43(5):151466. https://doi.org/10.1016/j.semnephrol.2023.151466.
25. Poston JT, Koyner JL. Sepsis Associated Acute Kidney Injury. *BMJ* 2019, *364*, k4891. https://doi.org/10.1136/bmj.k4891
26. Pefanis A, Bongoni AK, McRae JL, Salvaris EJ, Fisicaro N, Murphy JM, Ierino FL, Cowan PJ. Dynamics of Necroptosis in kidney ischemia-reperfusion Injury. Front Immunol. 2023;14:1251452. https://doi.org/10.3389/fimmu.2023.1251452.
27. Perazella MA, Rosner MH. Drug-Induced Acute kidney Injury. Clin J Am Soc Nephrol. 2022;17(8):1220–33. https://doi.org/10.2215/CJN.11290821.
28. Wang Z, Zhang C, From. AKI to CKD: maladaptive repair and the underlying mechanisms. Int J Mol Sci. 2022;23(18):10880. https://doi.org/10.3390/ijms231810880.
29. Ruiz-Ortega M, Rayego-Mateos S, Lamas S, Ortiz A, Rodrigues-Diez RR. Targeting the progression of chronic kidney disease. Nat Rev Nephrol. 2020;16(5):269–88. https://doi.org/10.1038/s41581-019-0248-y.
30. Acute Kidney Injury. Nat Rev Dis Primers. 2021;7(1):51. https://doi.org/10.1038/s41572-021-00291-0.
31. R H, P F, L MK, Fibrosis. From mechanisms to Therapeutic Medicines. Signal Transduct Target Therapy. 2023;8(1). https://doi.org/10.1038/s41392-023-01379-7.
32. Guo R, Duan J, Pan S, Cheng F, Qiao Y, Feng Q, Liu D, Liu Z. The Road from AKI to CKD: Molecular mechanisms and therapeutic targets of Ferroptosis. Cell Death Dis. 2023;14(7):426. https://doi.org/10.1038/s41419-023-05969-9.
33. Ls C, Pl K. Acute kidney Injury and chronic kidney disease: an Integrated Clinical Syndrome. Kidney Int. 2012;82(5). https://doi.org/10.1038/ki.2012.208.
34. Li X-Q, Lerman LO, Meng Y. Potential role of Extracellular vesicles in the pathophysiology of glomerular diseases. Clin Sci (Lond). 2020;134(20):2741–54. https://doi.org/10.1042/CS20200766.
35. 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. https://doi.org/10.1016/j.cytogfr.2023.12.006.
36. Shi L, Zeng H, An Z, Chen W, Shan Y, Ji C, Qian H. Extracellular vesicles: Illuminating Renal pathophysiology and therapeutic frontiers. Eur J Pharmacol. 2024;978:176720. https://doi.org/10.1016/j.ejphar.2024.176720.
37. Thongboonkerd V, Kanlaya R. The divergent roles of exosomes in kidney diseases: Pathogenesis, Diagnostics, Prognostics and therapeutics. Int J Biochem Cell Biol. 2022;149:106262. https://doi.org/10.1016/j.biocel.2022.106262.
38. Karpman D, Tontanahal A. Extracellular vesicles in renal inflammatory and infectious diseases. Free Radic Biol Med. 2021;171:42–54. https://doi.org/10.1016/j.freeradbiomed.2021.04.032.
39. Ginini L, Billan S, Fridman E, Gil Z. Insight into Extracellular vesicle-cell communication: from cell recognition to intracellular fate. Cells. 2022;11(9):1375. https://doi.org/10.3390/cells11091375.
40. Yin S, Zhou Z, Fu P, Jin C, Wu P, Ji C, Shan Y, Shi L, Xu M, Qian H. Roles of Extracellular vesicles in ageing-related chronic kidney disease: Demon or Angel. Pharmacol Res. 2023;193:106795. https://doi.org/10.1016/j.phrs.2023.106795.
41. Fu Y, Xiang Y, Li H, Chen A, Dong Z. Inflammation in kidney repair: mechanism and therapeutic potential. Pharmacol Ther. 2022;237:108240. https://doi.org/10.1016/j.pharmthera.2022.108240.
42. Yuan L, Yang J, Liu F, Li L, Liu J, Chen Y, Cheng J, Lu Y, Yuan Y. Macrophage-derived exosomal miR-195a-5p impairs tubular epithelial cells Mitochondria in Acute kidney Injury mice. FASEB J. 2023;37(1):e22691. https://doi.org/10.1096/fj.202200644R.
43. Jiang W, Xu C, Xu S, Su W, Du C, Dong J, Feng R, Huang C, Li J, Ma T, Macrophage-Derived. LRG1-Enriched extracellular vesicles exacerbate aristolochic acid nephropathy in a TGFβR1-Dependent manner. Cell Biol Toxicol. 2022;38(4):629–48. https://doi.org/10.1007/s10565-021-09666-1.
44. Zhao J, Chen J, Zhu W, Qi X-M, Wu Y-G. Exosomal mir-7002-5p derived from Highglucose-Induced macrophages suppresses autophagy in tubular epithelial cells by targeting Atg9b. FASEB J. 2022;36(9):e22501. https://doi.org/10.1096/fj.202200550RR.
45. Li S, Jia Y, Xue M, Hu F, Zheng Z, Zhang S, Ren S, Yang Y, Si Z, Wang L, Guan M, Xue Y. Inhibiting Rab27a in renal tubular epithelial cells attenuates the inflammation of Diabetic kidney disease through the miR-26a-5p/CHAC1/NF-kB pathway. Life Sci. 2020;261:118347. https://doi.org/10.1016/j.lfs.2020.118347.

46. Lv L-L, Feng Y, Wu M, Wang B, Li Z-L, Zhong X, Wu W-J, Chen J, Ni H-F, Tang T-T, Tang R-N, Lan H-Y, Liu B-C. Exosomal miRNA-19b-3p of tubular epithelial cells promotes M1 Macrophage activation in kidney Injury. Cell Death Differ. 2020;27(1):210–26. https://doi.org/10.1038/s41418-019-0349-y.
47. Ding C, Zheng J, Wang B, Li Y, Xiang H, Dou M, Qiao Y, Tian P, Ding X, Xue W. Exosomal MicroRNA-374b-5p from tubular epithelial cells promoted M1 macrophages activation and worsened renal Ischemia/Reperfusion Injury. Front Cell Dev Biol. 2020;8:587693. https://doi.org/10.3389/fcell.2020.587693.
48. Zhang Z, Chen H, Zhou L, Li C, Lu G, Wang L. Macrophage–derived Exosomal miRNA–155 promotes tubular Injury in ischemia–induced acute kidney Injury. Int J Mol Med. 2022;50(3):116. https://doi.org/10.3892/ijmm.2022.5172.
49. Jia Y, Zheng Z, Xue M, Zhang S, Hu F, Li Y, Yang Y, Zou M, Li S, Wang L, Guan M, Xue Y. Extracellular vesicles from Albumin-Induced tubular epithelial cells promote the M1 macrophage phenotype by Targeting Klotho. Mol Ther. 2019;27(8):1452–66. https://doi.org/10.1016/j.ymthe.2019.05.019.
50. Hung P-H, Hsu Y-C, Chen T-H, Lin C-L. Recent advances in Diabetic kidney diseases: from kidney Injury to kidney fibrosis. Int J Mol Sci. 2021;22(21):11857. https://doi.org/10.3390/ijms222111857.
51. Lv L-L, Feng Y, Wen Y, Wu W-J, Ni H-F, Li Z-L, Zhou L-T, Wang B, Zhang J-D, Crowley SD, Liu B-C. Exosomal CCL2 from tubular epithelial cells is critical for Albumin-Induced Tubulointerstitial inflammation. J Am Soc Nephrol. 2018;29(3):919–35. https://doi.org/10.1681/ASN.2017050523.
52. Jia Y, Chen J, Zheng Z, Tao Y, Zhang S, Zou M, Yang Y, Xue M, Hu F, Li Y, Zhang Q, Xue Y, Zheng Z. Tubular epithelial cell-derived extracellular vesicles induce macrophage glycolysis by stabilizing HIF-1α in Diabetic kidney disease. Mol Med. 2022;28(1):95. https://doi.org/10.1186/s10020-022-00525-1.
53. Li Z-L, Lv L-L, Tang T-T, Wang B, Feng Y, Zhou L-T, Cao J-Y, Tang R-N, Wu M, Liu H, Crowley SD, Liu B-C. HIF-1α Inducing Exosomal microRNA-23a expression mediates the cross-talk between tubular epithelial cells and macrophages in Tubulointerstitial inflammation. Kidney Int. 2019;95(2):388–404. https://doi.org/10.1016/j.kint.2018.09.013.
54. Chen J, Tang T-T, Cao J-Y, Li Z-L, Zhong X, Wen Y, Shen A-R, Liu B-C, Lv L-L. KIM-1 augments Hypoxia-Induced Tubulointerstitial inflammation through Uptake of Small Extracellular vesicles by tubular epithelial cells. Mol Ther. 2023;31(5):1437–50. https://doi.org/10.1016/j.ymthe.2022.08.013.
55. Chen PP, Zhang JX, Li XQ, Li L, Wu QY, Liu L, Wang GH, Ruan XZ, Ma KL. Outer membrane vesicles derived from Gut Microbiota Mediate Tubulointerstitial inflammation: a potential new mechanism for Diabetic kidney disease. Theranostics. 2023;13(12):3988–4003. https://doi.org/10.7150/thno.84650.
56. Chiaradia E, Tancini B, Emiliani C, Delo F, Pellegrino RM, Tognoloni A, Urbanelli L, Buratta S. Extracellular vesicles under oxidative stress conditions: Biological properties and physiological roles. Cells. 2021;10(7):1763. https://doi.org/10.3390/cells10071763.
57. Wang X, Kim CS, Adams BC, Wilkinson R, Hill MM, Shah AK, Mohamed A, Dutt M, Ng MSY, Ungerer JPJ, Healy HG, Kassianos AJ. Human proximal tubular epithelial cell-derived small Extracellular vesicles mediate synchronized tubular ferroptosis in hypoxic kidney Injury. Redox Biol. 2024;70:103042. https://doi.org/10.1016/j.redox.2024.103042.
58. Lu X, Jiang G, Gao Y, Chen Q, Sun S, Mao W, Zhang N, Zhu Z, Wang D, Zhang G, Chen M, Zhang L, Chen S. Platelet-derived extracellular vesicles aggravate septic acute kidney Injury via delivering ARF6. Int J Biol Sci. 2023;19(16):5055–73. https://doi.org/10.7150/ijbs.87165.
59. Xu X, Lai Y, Hua Z-C. Apoptosis and apoptotic body: Disease Message and Therapeutic Target potentials. Biosci Rep. 2019;39(1):BSR20180992. https://doi.org/10.1042/BSR20180992.
60. Zheng Q, Zhang Y, Wang X, Wang F, Zhao H. Isorhapontigenin modulates SOX9/TOLLIP expression to Attenuate Cell apoptosis and oxidative stress in Paraquat-Induced Acute kidney Injury. Oxid Med Cell Longev. 2022;2022(3328623). https://doi.org/10.1155/2022/3328623.
61. Stoian M, Dumitrache AM, Cîrciu F, Stănică R, Stoica V. Apoptosis in Acute kidney Injury. Intern Med. 2020;17(1):45–53. https://doi.org/10.2478/inmed-2020-0101.
62. Jiang W-J, Xu C-T, Du C-L, Dong J-H, Xu S-B, Hu B-F, Feng R, Zang D-D, Meng X-M, Huang C, Li J, Ma T-T. Tubular epithelial cell-to-macrophage communication forms a negative feedback Loop via Extracellular Vesicle transfer to promote renal inflammation and apoptosis in Diabetic Nephropathy. Theranostics. 2022;12(1):324–39. https://doi.org/10.7150/thno.63735.
63. Wu X-Q, Tian X-Y, Wang Z-W, Wu X, Wang J-P, Yan T-Z. miR-191 secreted by platelet-derived microvesicles Induced apoptosis of renal tubular epithelial cells and participated in renal ischemia-reperfusion Injury via inhibiting CBS. Cell Cycle. 2019;18(2):119–29. https://doi.org/10.1080/15384101.2018.1542900.
64. Huang Y, Li R, Zhang L, Chen Y, Dong W, Zhao X, Yang H, Zhang S, Xie Z, Ye Z, Wang W, Li C, Li Z, Liu S, Dong Z, Yu X, Liang X. Extracellular vesicles from high glucose-treated podocytes induce apoptosis of Proximal Tubular Epithelial cells. Front Physiol. 2020;11:579296. https://doi.org/10.3389/fphys.2020.579296.
65. Jeon JS, Kim E, Bae Y-U, Yang WM, Lee H, Kim H, Noh H, Han DC, Ryu S, Kwon SH. microRNA in Extracellular vesicles released by Damaged Podocytes promote apoptosis of renal tubular epithelial cells. Cells. 2020;9(6):1409. https://doi.org/10.3390/cells9061409.
66. Tsai Y-C, Kuo M-C, Hung W-W, Wu L-Y, Wu P-H, Chang W-A, Kuo P-L, Hsu Y-L. High glucose induces Mesangial Cell apoptosis through miR-15b-5p and promotes Diabetic Nephropathy by Extracellular Vesicle Delivery. Mol Ther. 2020;28(3):963–74. https://doi.org/10.1016/j.ymthe.2020.01.014.
67. Humphreys BD. Mechanisms of Renal Fibrosis. Annu Rev Physiol. 2018;80:309–26. https://doi.org/10.1146/annurev-physiol-022516-034227.
68. Djudjaj S, Boor P. Cellular and Molecular mechanisms of kidney fibrosis. Mol Aspects Med. 2019;65:16–36. https://doi.org/10.1016/j.mam.2018.06.002.
69. Yuan Q, Tang B, Zhang C. Signaling pathways of chronic kidney diseases, implications for therapeutics. Signal Transduct Target Ther. 2022;7:182. https://doi.org/10.1038/s41392-022-01036-5.
70. Liu X, Miao J, Wang C, Zhou S, Chen S, Ren Q, Hong X, Wang Y, Hou FF, Zhou L, Liu Y. Tubule-derived exosomes play a Central Role in Fibroblast activation and kidney fibrosis. Kidney Int. 2020;97(6):1181–95. https://doi.org/10.1016/j.kint.2019.11.026.
71. Guan H, Peng R, Mao L, Fang F, Xu B, Chen M. Injured tubular epithelial cells activate fibroblasts to promote kidney fibrosis through mir-150-Containing exosomes. Exp Cell Res. 2020;392(2):112007. https://doi.org/10.1016/j.yexcr.2020.112007.
72. Hu R, Li X, Peng C, Gao R, Ma L, Hu J, Luo T, Qing H, Wang Y, Ge Q, Wang Z, Wu C, Xiao X, Yang J, Young MJ, Li Q, Yang S. miR-196b-5p-Enriched extracellular vesicles from tubular epithelial cells mediated Aldosterone-Induced Renal Fibrosis in mice with diabetes. BMJ Open Diab Res Care. 2020;8(1):e001101. https://doi.org/10.1136/bmjdrc-2019-001101.
73. Zhao S, Li W, Yu W, Rao T, Li H, Ruan Y, Yuan R, Li C, Ning J, Li S, Chen W, Cheng F, Zhou X. Exosomal miR-21 from tubular cells contributes to Renal Fibrosis by activating fibroblasts via Targeting PTEN in obstructed kidneys. Theranostics. 2021;11(18):8660–73. https://doi.org/10.7150/thno.62820.
74. Qu N-Y, Zhang Z-H, Zhang X-X, Xie W-W, Niu X-Q. Microvesicles containing microRNA-216a secreted by tubular epithelial cells participate in renal interstitial fibrosis through activating PTEN/AKT pathway. Eur Rev Med Pharmacol Sci. 2019;23(15):6629–36. https://doi.org/10.26355/eurrev_201908_18552.
75. Zhang X-F, Yang Y, Zhang J, Cao W, Microvesicle-Containing. miRNA-153-3p induces the apoptosis of Proximal Tubular Epithelial cells and participates in renal interstitial fibrosis. Eur Rev Med Pharmacol Sci. 2019;23(22):10065–71. https://doi.org/10.26355/eurrev_201911_19574.
76. Zheng S, Zeng Y, Chu L, Gong T, Li S, Yang M. Renal tissue-derived exosomal miRNA-34a in Diabetic Nephropathy induces renal tubular cell fibrosis by promoting the polarization of M1 macrophages. IET Nanobiotechnol. 2024;2024(5702517). https://doi.org/10.1049/2024/5702517.
77. Liu D, Liu F, Li Z, Pan S, Xie J, Zhao Z, Liu Z, Zhang J, Liu Z. HNRNPA1-Mediated Exosomal sorting of mir-483-5p out of renal tubular epithelial cells promotes the Progression of Diabetic Nephropathy-Induced renal interstitial fibrosis. Cell Death Dis. 2021;12(3):255. https://doi.org/10.1038/s41419-021-03460-x.
78. Su H, Qiao J, Hu J, Li Y, Lin J, Yu Q, Zhen J, Ma Q, Wang Q, Lv Z, Wang R. Podocyte-derived extracellular vesicles mediate renal proximal tubule cells dedifferentiation via microRNA-221 in Diabetic Nephropathy. Mol Cell Endocrinol. 2020;518:111034. https://doi.org/10.1016/j.mce.2020.111034.
79. Munkonda MN, Akbari S, Landry C, Sun S, Xiao F, Turner M, Holterman CE, Nasrallah R, Hébert RL, Kennedy CRJ, Burger D. Podocyte-derived microparticles promote proximal tubule Fibrotic Signaling via P38 MAPK and CD36. J Extracell Vesicles. 2018;7(1):1432206. https://doi.org/10.1080/20013078.2018.1432206.
80. Sun IO, Lerman LO. Urinary extracellular vesicles as biomarkers of kidney disease: from Diagnostics to therapeutics. Diagnostics (Basel). 2020;10(5):311. https://doi.org/10.3390/diagnostics10050311.
81. Erdbrügger U, Blijdorp CJ, Bijnsdorp IV, Borràs FE, Burger D, Bussolati B, Byrd JB, Clayton A, Dear JW, Falcón-Pérez JM, Grange C, Hill AF, Holthöfer H, Hoorn EJ, Jenster G, Jimenez CR, Junker K, Klein J, Knepper MA, Koritzinsky EH, Luther JM, Lenassi M, Leivo J, Mertens I, Musante L, Oeyen E, Puhka M, van Royen ME, Sánchez C, Soekmadji C, Thongboonkerd V, van Steijn V, Verhaegh G, Webber JP, Witwer K, Yuen PST, Zheng L, Llorente A, Martens-Uzunova ES. Urinary extracellular vesicles: a position paper by the Urine Task Force

of the International Society for Extracellular Vesicles. J Extracell Vesicles. 2021;10(7):e12093. https://doi.org/10.1002/jev2.12093.
82. Erdbrügger U, Hoorn EJ, Le TH, Blijdorp CJ, Burger D. Extracellular vesicles in kidney diseases: moving Forward. Kidney360. 2023;4(2):245–57. https://doi.org/10.34067/KID.0001892022.
83. Sonoda H, Yokota-Ikeda N, Oshikawa S, Kanno Y, Yoshinaga K, Uchida K, Ueda Y, Kimiya K, Uezono S, Ueda A, Ito K, Ikeda M. Decreased abundance of urinary exosomal Aquaporin-1 in Renal Ischemia-Reperfusion Injury. Am J Physiol Ren Physiol. 2009;297(4):F1006–1016. https://doi.org/10.1152/ajprenal.00200.2009.
84. Zhou H, Pisitkun T, Aponte A, Yuen PST, Hoffert JD, Yasuda H, Hu X, Chawla L, Shen R-F, Knepper MA, Star RA. Exosomal Fetuin-A identified by proteomics: a novel urinary biomarker for detecting Acute kidney Injury. Kidney Int. 2006;70(10):1847–57. https://doi.org/10.1038/sj.ki.5001874.
85. Y Y, Z R, A X, Y J, Y X, P W, D J, X W. Assessment of urinary exosomal NHE3 as a biomarker of Acute kidney Injury. Diagnostics (Basel Switzerland). 2022;12(11). https://doi.org/10.3390/diagnostics12112634.
86. Panich T, Chancharoenthana W, Somparn P, Issara-Amphorn J, Hirankarn N, Leelahavanichkul A. Urinary exosomal activating Transcriptional factor 3 as the early diagnostic biomarker for Sepsis-Induced Acute kidney Injury. BMC Nephrol. 2017;18:10. https://doi.org/10.1186/s12882-016-0415-3.
87. Gu D, Chen Y, Masucci M, Xiong C, Zou H, Holthofer H. Potential urine biomarkers for the diagnosis of Prediabetes and Early Diabetic Nephropathy based on ISN CKHDP Program. Clin Nephrol. 2020;93(1):129–33. https://doi.org/10.5414/CNP92S123.
88. Ning J, Xiang Z, Xiong C, Zhou Q, Wang X, Zou H. Alpha1-Antitrypsin in urinary extracellular vesicles: a potential biomarker of Diabetic kidney Disease Prior to Microalbuminuria. Diabetes Metab Syndr Obes. 2020;13:2037–48. https://doi.org/10.2147/DMSO.S250347.
89. Ugarte F, Santapau D, Gallardo V, Garfias C, Yizmeyián A, Villanueva S, Sepúlveda C, Rocco J, Pasten C, Urquidi C, Cavada G, San Martin P, Cano F, Irarrázabal CE. Urinary extracellular vesicles as a source of NGAL for Diabetic kidney disease evaluation in children and adolescents with type 1 diabetes Mellitus. Front Endocrinol (Lausanne). 2021;12:654269. https://doi.org/10.3389/fendo.2021.654269.
90. Li T, Liu TC, Liu N, Li MJ, Zhang M. Urinary exosome proteins PAK6 and EGFR as noninvasive diagnostic biomarkers of Diabetic Nephropathy. BMC Nephrol. 2023;24(1):291. https://doi.org/10.1186/s12882-023-03343-7.
91. Sakurai A, Ono H, Ochi A, Matsuura M, Yoshimoto S, Kishi S, Murakami T, Tominaga T, Nagai K, Abe H, Doi T. Involvement of Elf3 on Smad3 activation-dependent injuries in Podocytes and excretion of urinary exosome in Diabetic Nephropathy. PLoS ONE. 2019;14(5):e0216788. https://doi.org/10.1371/journal.pone.0216788.
92. Kalani A, Mohan A, Godbole MM, Bhatia E, Gupta A, Sharma RK, Tiwari S. Wilm's Tumor-1 protein levels in urinary exosomes from Diabetic patients with or without Proteinuria. PLoS ONE. 2013;8(3):e60177. https://doi.org/10.1371/journal.pone.0060177.
93. Dimuccio V, Ranghino A, Praticò Barbato L, Fop F, Biancone L, Camussi G, Bussolati B. Urinary CD133 + extracellular vesicles are decreased in kidney transplanted patients with slow graft function and vascular damage. PLoS ONE. 2014;9(8):e104490. https://doi.org/10.1371/journal.pone.0104490.
94. Moon P-G, Lee J-E, You S, Kim T-K, Cho J-H, Kim I-S, Kwon T-H, Kim C-D, Park S-H, Hwang D, Kim Y-L, Baek M-C. Proteomic analysis of urinary exosomes from patients of early IgA nephropathy and thin basement membrane nephropathy. Proteomics. 2011;11(12):2459–75. https://doi.org/10.1002/pmic.201000443.
95. Lu J, Hu ZB, Chen PP, Lu CC, Zhang JX, Li XQ, Yuan BY, Huang SJ, Ma KL. Urinary podocyte microparticles are Associated with Disease Activity and Renal Injury in systemic Lupus Erythematosus. BMC Nephrol. 2019;20(1):303. https://doi.org/10.1186/s12882-019-1482-z.
96. Kwon SH, Woollard JR, Saad A, Garovic VD, Zand L, Jordan KL, Textor SC, Lerman LO. Elevated urinary podocyte-derived extracellular microvesicles in Renovascular Hypertensive patients. Nephrol Dial Transpl. 2017;32(5):800–7. https://doi.org/10.1093/ndt/gfw077.
97. Sun IO, Santelli A, Abumoawad A, Eirin A, Ferguson CM, Woollard JR, Lerman A, Textor SC, Puranik AS, Lerman LO. Loss of Renal Peritubular Capillaries in Hypertensive Patients Is Detectable by Urinary Endothelial Microparticle Levels. *Hypertension* 2018, *72* (5), 1180–1188. https://doi.org/10.1161/HYPERTENSIONAHA.118.11766
98. Hashemi E, Dehghanbanadaki H, Baharanchi AA, Forouzanfar K, Kakaei A, Mohammadi SM, Zeidi S, Razi F. WT1 and ACE mRNAs of blood extracellular vesicle as biomarkers of Diabetic Nephropathy. J Transl Med. 2021;19(1):299. https://doi.org/10.1186/s12967-021-02964-6.
99. Zhao Y, Shen A, Guo F, Song Y, Jing N, Ding X, Pan M, Zhang H, Wang J, Wu L, Ma X, Feng L, Qin G. Urinary exosomal MiRNA-4534 as a Novel Diagnostic Biomarker for Diabetic kidney disease. Front Endocrinol (Lausanne). 2020;11:590. https://doi.org/10.3389/fendo.2020.00590.
100. Dimuccio V, Bellucci L, Genta M, Grange C, Brizzi MF, Gili M, Gallo S, Centomo ML, Collino F, Bussolati B. Upregulation of miR145 and miR126 in EVs from renal cells undergoing EMT and urine of Diabetic Nephropathy patients. Int J Mol Sci. 2022;23(20):12098. https://doi.org/10.3390/ijms232012098.
101. Prabu P, Rome S, Sathishkumar C, Gastebois C, Meugnier E, Mohan V, Balasubramanyam M. MicroRNAs from urinary extracellular vesicles are non-invasive early biomarkers of Diabetic Nephropathy in type 2 diabetes patients with the Asian Indian phenotype. Diabetes Metab. 2019;45(3):276–85. https://doi.org/10.1016/j.diabet.2018.08.004.
102. Zang J, Maxwell AP, Simpson DA, McKay GJ. Differential expression of urinary exosomal MicroRNAs mir-21-5p and miR-30b-5p in individuals with Diabetic kidney disease. Sci Rep. 2019;9(1):10900. https://doi.org/10.1038/s41598-019-47504-x.
103. Wang J, Tao Y, Zhao F, Liu T, Shen X, Zhou L. Expression of urinary exosomal miRNA-615-3p and miRNA-3147 in Diabetic Kidney Disease and Their Association with inflammation and fibrosis. Ren Fail. 2023;45(1):2121929. https://doi.org/10.1080/0886022X.2022.2121929.
104. Feng Y, Lv L-L, Wu W-J, Li Z-L, Chen J, Ni H-F, Zhou L-T, Tang T-T, Wang F-M, Wang B, Chen P-S, Crowley SD, Liu B-C. Urinary exosomes and Exosomal CCL2 mRNA as biomarkers of active histologic Injury in IgA Nephropathy. Am J Pathol. 2018;188(11):2542–52. https://doi.org/10.1016/j.ajpath.2018.07.017.
105. Yu Y, Bai F, Qin N, Liu W, Sun Q, Zhou Y, Yang J. Non-proximal renal tubule-derived urinary exosomal miR-200b as a biomarker of Renal Fibrosis. Nephron. 2018;139(3):269–82. https://doi.org/10.1159/000487104.
106. Min Q-H, Chen X-M, Zou Y-Q, Zhang J, Li J, Wang Y, Li S-Q, Gao Q-F, Sun F, Liu J, Xu Y-M, Lin J, Huang L-F, Huang B, Wang X-Z. Differential expression of urinary exosomal microRNAs in IgA Nephropathy. J Clin Lab Anal. 2018;32(2):e22226. https://doi.org/10.1002/jcla.22226.
107. Zhao S, Sun Y, Mao Q, Zhou C, Chen Y, Xue D. Exosomal miR-4639 and miR-210 in plasma and urine as biomarkers in IgA Nephropathy. Nephron. 2022;146(6):539–52. https://doi.org/10.1159/000523924.
108. Garcia-Vives E, Solé C, Moliné T, Vidal M, Agraz I, Ordi-Ros J, Cortés-Hernández J. The urinary exosomal miRNA expression Profile is predictive of clinical response in Lupus Nephritis. Int J Mol Sci. 2020;21(4):1372. https://doi.org/10.3390/ijms21041372.
109. Solé C, Cortés-Hernández J, Felip ML, Vidal M, Ordi-Ros J. miR-29c in urinary exosomes as Predictor of early renal fibrosis in Lupus Nephritis. Nephrol Dial Transpl. 2015;30(9):1488–96. https://doi.org/10.1093/ndt/gfv128.
110. Solé C, Moliné T, Vidal M, Ordi-Ros J, Cortés-Hernández J. An exosomal urinary miRNA signature for early diagnosis of Renal Fibrosis in Lupus Nephritis. Cells. 2019;8(8):773. https://doi.org/10.3390/cells8080773.
111. Kurahashi R, Kadomatsu T, Baba M, Hara C, Itoh H, Miyata K, Endo M, Morinaga J, Terada K, Araki K, Eto M, Schmidt LS, Kamba T, Linehan WM, Oike Y. MicroRNA-204-5p: a novel candidate urinary biomarker of Xp11.2 translocation renal cell carcinoma. Cancer Sci. 2019;110(6):1897–908. https://doi.org/10.1111/cas.14026.
112. Zhang W, Ni M, Su Y, Wang H, Zhu S, Zhao A, Li G. MicroRNAs in serum exosomes as potential biomarkers in Clear-Cell Renal Cell Carcinoma. Eur Urol Focus. 2018;4(3):412–9. https://doi.org/10.1016/j.euf.2016.09.007.
113. Perez-Hernandez J, Olivares D, Forner MJ, Ortega A, Solaz E, Martinez F, Chaves FJ, Redon J, Cortes R. Urinary exosome miR-146a is a potential marker of Albuminuria in essential hypertension. J Transl Med. 2018;16(1):228. https://doi.org/10.1186/s12967-018-1604-6.
114. Kim MH, Lee YH, Seo J-W, Moon H, Kim JS, Kim YG, Jeong K-H, Moon J-Y, Lee TW, Ihm C-G, Kim C-D, Park JB, Chung BH, Kim Y-H, Lee S-H. Urinary exosomal viral microRNA as a marker of BK Virus Nephropathy in kidney transplant recipients. PLoS ONE. 2017;12(12):e0190068. https://doi.org/10.1371/journal.pone.0190068.
115. Huang J, Cao H, Cui B, Ma X, Gao L, Yu C, Shen F, Yang X, Liu N, Qiu A, Cai G, Zhuang S. Mesenchymal stem cells-derived Exosomes Ameliorate Ischemia/Reperfusion Induced Acute kidney Injury in a Porcine Model. Front Cell Dev Biol. 2022;10:899869. https://doi.org/10.3389/fcell.2022.899869.
116. Cao J-Y, Wang B, Tang T-T, Wen Y, Li Z-L, Feng S-T, Wu M, Liu D, Yin D, Ma K-L, Tang R-N, Wu Q-L, Lan H-Y, Lv L-L, Liu B-C. Exosomal miR-125b-5p deriving from mesenchymal stem cells promotes tubular repair by suppression of P53

in ischemic acute kidney Injury. Theranostics. 2021;11(11):5248–66. https://doi.org/10.7150/thno.54550.
117. Shi W, Zhou X, Li X, Peng X, Chen G, Li Y, Zhang C, Yu H, Feng Z, Gou X, Fan J. Human umbilical cord mesenchymal stem cells protect against Renal Ischemia-Reperfusion Injury by secreting Extracellular vesicles loaded with miR-148b-3p that target pyruvate dehydrogenase kinase 4 to inhibit endoplasmic reticulum stress at the reperfusion stages. Int J Mol Sci. 2023;24(10):8899. https://doi.org/10.3390/ijms24108899.
118. Wan Y, Yu Y, Yu C, Luo J, Wen S, Shen L, Wei G, Hua Y. Human umbilical cord mesenchymal stem cell exosomes alleviate Acute kidney Injury by inhibiting pyroptosis in rats and NRK-52E cells. Ren Fail. 2023;45(1):2221138. https://doi.org/10.1080/0886022X.2023.2221138.
119. Ullah M, Liu DD, Rai S, Concepcion W, Thakor AS. HSP70-Mediated NLRP3 inflammasome suppression underlies reversal of Acute kidney Injury following extracellular vesicle and focused Ultrasound Combination Therapy. Int J Mol Sci. 2020;21(11):4085. https://doi.org/10.3390/ijms21114085.
120. Wang J, Jia H, Zhang B, Yin L, Mao F, Yu J, Ji C, Xu X, Yan Y, Xu W, Qian H. Huc-MSC Exosome-transported 14-3-3ζ prevents the Injury of Cisplatin to HK-2 cells by inducing Autophagy in Vitro. Cytotherapy. 2018;20(1):29–44. https://doi.org/10.1016/j.jcyt.2017.08.002.
121. Li Z, Cao S. Pre-incubation with human umbilical cord derived mesenchymal stem cells-exosomes prevents Cisplatin-Induced Renal Tubular Epithelial Cell Injury. Aging. 2020;12(18):18008–18. https://doi.org/10.18632/aging.103545.
122. Ji C, Zhang J, Zhou Z, Shi H, Liu W, Sun F, Zhang C, Zhang L, Sun Z, Qian H. Platelet-Rich plasma promotes MSCs exosomes paracrine to repair acute kidney Injury via AKT/Rab27 pathway. Am J Transl Res. 2021;13(3):1445–57.
123. Zhang R, Zhu Y, Li Y, Liu W, Yin L, Yin S, Ji C, Hu Y, Wang Q, Zhou X, Chen J, Xu W, Qian H. Human umbilical cord mesenchymal stem cell exosomes Alleviate Sepsis-Associated Acute kidney Injury via regulating microRNA-146b expression. Biotechnol Lett. 2020;42(4):669–79. https://doi.org/10.1007/s10529-020-02831-2.
124. 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. https://doi.org/10.1007/s13577-021-00617-w.
125. Ji C, Zhang J, Zhu Y, Shi H, Yin S, Sun F, Wang Q, Zhang L, Yan Y, Zhang X, Xu W, Qian H. Exosomes Derived from hucMSC Attenuate Renal Fibrosis through CK1δ/β-TRCP-Mediated YAP degradation. Cell Death Dis. 2020;11(5):327. https://doi.org/10.1038/s41419-020-2510-4.
126. Liu B, Hu D, Zhou Y, Yu Y, Shen L, Long C, Butnaru D, Timashev P, He D, Lin T, Xu T, Zhang D, Wei G. Exosomes released by human umbilical cord mesenchymal stem cells protect against renal interstitial fibrosis through ROS-Mediated P38MAPK/ERK signaling pathway. Am J Transl Res. 2020;12(9):4998–5014.
127. Y Y, M C, Q G, L S, X L, J P, Y Z, T X, D Z, G W. Human umbilical cord mesenchymal stem cell exosome-derived mir-874-3p targeting RIPK1/PGAM5 attenuates kidney tubular epithelial cell damage. Cell Mol Biol Lett. 2023;28(1). https://doi.org/10.1186/s11658-023-00425-0.
128. He J, Wang Y, Lu X, Zhu B, Pei X, Wu J, Zhao W. Micro-vesicles derived from bone marrow stem cells protect the kidney both in Vivo and in Vitro by microRNA-Dependent repairing. Nephrol (Carlton). 2015;20(9):591–600. https://doi.org/10.1111/nep.12490.
129. Wang C, Zhu G, He W, Yin H, Lin F, Gou X, Li X. BMSCs protect against Renal Ischemia-Reperfusion Injury by secreting Exosomes loaded with miR-199a-5p that Target BIP to inhibit endoplasmic reticulum stress at the very early reperfusion stages. FASEB J. 2019;33(4):5440–56. https://doi.org/10.1096/fj.201801821R.
130. Zhu G, Pei L, Lin F, Yin H, Li X, He W, Liu N, Gou X. Exosomes from human-bone-marrow-derived mesenchymal stem cells protect against Renal Ischemia/Reperfusion Injury via transferring miR-199a-3p. J Cell Physiol. 2019;234(12):23736–49. https://doi.org/10.1002/jcp.28941.
131. Li D, Qu J, Yuan X, Zhuang S, Wu H, Chen R, Wu J, Zhang M, Ying L. Mesenchymal stem cells alleviate renal fibrosis and inhibit Autophagy via Exosome transfer of miRNA-122a. Stem Cells Int. 2022;2022(1981798). https://doi.org/10.1155/2022/1981798.
132. Wang S-J, Qiu Z-Z, Chen F-W, Mao A-L, Bai J-C, Hong Y-J, Zhang Z-P, Zhu W-A, Zhang Z-W, Zhou H. Bone marrow mesenchymal stem cell-derived extracellular vesicles containing miR-181d protect rats against Renal Fibrosis by inhibiting KLF6 and the NF-κB signaling pathway. Cell Death Dis. 2022;13(6):535. https://doi.org/10.1038/s41419-022-04875-w.
133. Xu S, Cheuk YC, Jia Y, Chen T, Chen J, Luo Y, Cao Y, Guo J, Dong L, Zhang Y, Shi Y, Rong R. Bone marrow mesenchymal stem cell-derived exosomal miR-21a-5p alleviates renal fibrosis by attenuating glycolysis by Targeting PFKM. Cell Death Dis. 2022;13(10):876. https://doi.org/10.1038/s41419-022-05305-7.
134. Wan F, Yang R-C, Tang Y-W, Tang X-L, Ye T, Zheng J, Zhang H-Q, Lin Y. BMSC-Derived exosomes protect against Kidney Injury through regulating Klotho in 5/6 nephrectomy rats. Eur J Med Res. 2022;27(1):118. https://doi.org/10.1186/s40001-022-00742-8.
135. Liu Y, Guo W, Guo Y, Chen X, Liu W. Bone marrow mesenchymal stem cell-derived exosomes improve renal fibrosis via regulating smurf 2/Smad 7. Front Biosci (Landmark Ed). 2022;27(1):17. https://doi.org/10.31083/j.fbl2701017.
136. Eirin A, Zhu X-Y, Puranik AS, Tang H, McGurren KA, van Wijnen AJ, Lerman A, Lerman LO. Mesenchymal stem cell-derived extracellular vesicles attenuate kidney inflammation. Kidney Int. 2017;92(1):114–24. https://doi.org/10.1016/j.kint.2016.12.023.
137. Duan Y, Luo Q, Wang Y, Ma Y, Chen F, Zhu X, Shi J. Adipose mesenchymal stem cell-derived extracellular vesicles containing microRNA-26a-5p target TLR4 and protect against Diabetic Nephropathy. J Biol Chem. 2020;295(37):12868–84. https://doi.org/10.1074/jbc.RA120.012522.
138. Liu W, Hu C, Zhang B, Li M, Deng F, Zhao S. Exosomal microRNA-342-5p secreted from adipose-derived mesenchymal stem cells mitigates acute kidney Injury in Sepsis mice by inhibiting TLR9. Biol Proced Online. 2023;25(1):10. https://doi.org/10.1186/s12575-023-00198-y.
139. Gao F, Zuo B, Wang Y, Li S, Yang J, Sun D. Protective function of Exosomes from Adipose tissue-derived mesenchymal stem cells in Acute kidney Injury through SIRT1 Pathway. Life Sci. 2020;255:117719. https://doi.org/10.1016/j.lfs.2020.117719.
140. Cao H, Cheng Y, Gao H, Zhuang J, Zhang W, Bian Q, Wang F, Du Y, Li Z, Kong D, Ding D, Wang Y. Function in Renal Ischemia-Reperfusion Injury. ACS Nano. 2020;14(4):4014–26. https://doi.org/10.1021/acsnano.9b08207. Vivo Tracking of Mesenchymal Stem Cell-Derived Extracellular Vesicles Improving Mitochondrial.
141. Kholia S, Herrera Sanchez MB, Cedrino M, Papadimitriou E, Tapparo M, Deregibus MC, Brizzi MF, Tetta C, Camussi G. Human liver stem cell-derived extracellular vesicles prevent Aristolochic Acid-Induced kidney fibrosis. Front Immunol. 2018;9:1639. https://doi.org/10.3389/fimmu.2018.01639.
142. Hong S, Kim H, Kim J, Kim S, Park TS, Kim TM. Extracellular vesicles from Induced Pluripotent Stem cell-derived mesenchymal stem cells enhance the recovery of Acute kidney Injury. Cytotherapy. 2024;26(1):51–62. https://doi.org/10.1016/j.jcyt.2023.09.003.
143. Liu L, Wu Y, Wang P, Shi M, Wang J, Ma H, Sun D. PSC-MSC-Derived exosomes protect against kidney fibrosis in Vivo and in Vitro through the SIRT6/β-Catenin signaling pathway. Int J Stem Cells. 2021;14(3):310–9. https://doi.org/10.15283/ijsc20184.
144. Li X, Liao J, Su X, Li W, Bi Z, Wang J, Su Q, Huang H, Wei Y, Gao Y, Li J, Liu L, Wang C. Human urine-derived stem cells protect against Renal Ischemia/Reperfusion Injury in a rat model via Exosomal miR-146a-5p which targets IRAK1. Theranostics. 2020;10(21):9561–78. https://doi.org/10.7150/thno.42153.
145. Gu D, Zou X, Ju G, Zhang G, Bao E, Zhu Y. Mesenchymal stromal cells derived extracellular vesicles ameliorate Acute Renal Ischemia Reperfusion Injury by Inhibition of mitochondrial fission through miR-30. Stem Cells Int. 2016;2016:2093940. https://doi.org/10.1155/2016/2093940.
146. Zhang G, Zou X, Huang Y, Wang F, Miao S, Liu G, Chen M, Zhu Y. Mesenchymal stromal cell-derived extracellular vesicles protect against acute kidney Injury through Anti-oxidation by enhancing Nrf2/ARE activation in rats. Kidney Blood Press Res. 2016;41(2):119–28. https://doi.org/10.1159/000443413.
147. Dominguez JH, Liu Y, Gao H, Dominguez JM, Xie D, Kelly KJ. Renal tubular cell-derived extracellular vesicles accelerate the recovery of established renal ischemia reperfusion Injury. J Am Soc Nephrol. 2017;28(12):3533–44. https://doi.org/10.1681/ASN.2016121278.
148. Zhang L, Liu H, Xu K, Ling Z, Huang Y, Hu Q, Lu K, Liu C, Wang Y, Liu N, Zhang X, Xu B, Wu J, Chen S, Zhang G, Chen M. Injury mediated by the HIF-1α/Rab22 pathway and potentially affected by microRNAs. Int J Biol Sci. 2019;15(6):1161–76. https://doi.org/10.7150/ijbs.32004. Hypoxia Preconditioned Renal Tubular Epithelial Cell-Derived Extracellular Vesicles Alleviate Renal Ischaemia-Reperfusion.
149. Chen Y, Zhang C, Du Y, Yang X, Liu M, Yang W, Lei G, Wang G. Exosomal transfer of microRNA-590-3p between renal tubular epithelial cells after renal ischemia-reperfusion Injury regulates Autophagy by Targeting TRAF6. Chin Med J (Engl). 2022;135(20):2467–77. https://doi.org/10.1097/CM9.0000000000002377.
150. ZHU B, HE J, YE X, PEI X, BAI Y, GAO F, GUO L, YONG H, ZHAO W. Role of cisplatin in inducing Acute kidney Injury and pyroptosis in mice via the Exosome miR-122/ELAVL1 Regulatory Axis. Physiol Res. 2023;72(6):753–65. https://doi.org/10.33549/physiolres.935129.

151. Zou X, Kwon SH, Jiang K, Ferguson CM, Puranik AS, Zhu X, Lerman LO. Renal scattered tubular-like cells Confer Protective effects in the stenotic murine kidney mediated by release of Extracellular vesicles. Sci Rep. 2018;8(1):1263. https://doi.org/10.1038/s41598-018-19750-y.
152. Bai L, Li J, Li H, Song J, Zhou Y, Lu R, Liu B, Pang Y, Zhang P, Chen J, Liu X, Wu J, Liang C, Zhou J. Renoprotective effects of Artemisinin and Hydroxychloroquine Combination Therapy on IgA Nephropathy via suppressing NF-κB signaling and NLRP3 inflammasome activation by exosomes in rats. Biochem Pharmacol. 2019;169:113619. https://doi.org/10.1016/j.bcp.2019.08.021.
153. Zhang Y, Huang H, Liu W, Liu S, Wang XY, Diao ZL, Zhang AH, Guo W, Han X, Dong X, Katilov O. Endothelial progenitor cells-derived exosomal microRNA-21-5p alleviates Sepsis-Induced Acute kidney Injury by inhibiting RUNX1 expression. Cell Death Dis. 2021;12(4):335. https://doi.org/10.1038/s41419-021-03578-y.
154. Zhao P, Zhu Y, Sun L, Zhu W, Lu Y, Zhang J, Mao Y, Chen Q, Zhang F. Circulating Exosomal Mir-1-3p from rats with myocardial infarction plays a protective effect on contrast-Induced Nephropathy via Targeting ATG13 and activating the AKT Signaling Pathway. Int J Biol Sci. 2021;17(4):972–85. https://doi.org/10.7150/ijbs.55887.
155. Kang X, Chen Y, Xin X, Liu M, Ma Y, Ren Y, Ji J, Yu Q, Qu L, Wang S, Liu G, Xiang C, Yang L. Human amniotic epithelial cells and their derived exosomes protect against Cisplatin-Induced Acute kidney Injury without compromising its Antitumor activity in mice. Front Cell Dev Biol. 2021;9:752053. https://doi.org/10.3389/fcell.2021.752053.
156. Huang H, Liu H, Tang J, Xu W, Gan H, Fan Q, Zhang W. M2 macrophage-derived exosomal mir-25-3p improves high glucose-Induced podocytes Injury through Activation Autophagy via inhibiting DUSP1 expression. IUBMB Life. 2020;72(12):2651–62. https://doi.org/10.1002/iub.2393.
157. Tang T-T, Wang B, Wu M, Li Z-L, Feng Y, Cao J-Y, Yin D, Liu H, Tang R-N, Crowley SD, Lv L-L, Liu B-C. Extracellular vesicle-encapsulated IL-10 as Novel Nanotherapeutics against ischemic AKI. Sci Adv. 2020;6(33):eaaz0748. https://doi.org/10.1126/sciadv.aaz0748.
158. Ji C, Zhang J, Shi H, Chen B, Xu W, Jin J, Qian H. Single-cell RNA transcriptomic reveal the mechanism of MSC Derived Small Extracellular vesicles against DKD Fibrosis. J Nanobiotechnol. 2024;22(1):339. https://doi.org/10.1186/s12951-024-02613-2.
159. Jn Z, C T. Engineered Extracellular vesicles: emerging therapeutic strategies for translational applications. Int J Mol Sci. 2023;24(20). https://doi.org/10.3390/ijms242015206.
160. Opb W, Má B, J L, Xo B, S EA. Advances in therapeutic applications of Extracellular vesicles. Sci Transl Med. 2019;11(492). https://doi.org/10.1126/scitranslmed.aav8521.
161. Z P, W S, Y C, H T, W L, J C, C C. Extracellular vesicles in tissue Engineering: Biology and Engineered Strategy. Adv Healthc Mater. 2022;11(21). https://doi.org/10.1002/adhm.202201384.
162. Y Ak M F. Recent progress in Engineered Extracellular vesicles and their Biomedical Applications. Life Sci. 2024;350. https://doi.org/10.1016/j.lfs.2024.122747.
163. Ma W, Wu D, Long C, Liu J, Xu L, Zhou L, Dou Q, Ge Y, Zhou C, Jia R. Neutrophil-derived nanovesicles deliver IL-37 to mitigate renal ischemia-reperfusion Injury via Endothelial Cell Targeting. J Control Release. 2024;370:66–81. https://doi.org/10.1016/j.jconrel.2024.04.025.
164. Bellucci L, Montini G, Collino F, Bussolati B. Mesenchymal stromal cell-derived extracellular vesicles pass through the Filtration Barrier and protect podocytes in a 3D glomerular model under continuous perfusion. Tissue Eng Regen Med. 2021;18(4):549–60. https://doi.org/10.1007/s13770-021-00374-9.
165. Yea J-H, Yoon YM, Lee JH, Yun CW, Lee SH. Exosomes isolated from melatonin-stimulated mesenchymal stem cells improve kidney function by regulating inflammation and fibrosis in a chronic kidney Disease Mouse Model. J Tissue Eng. 2021;12:20417314211059624. https://doi.org/10.1177/20417314211059624.
166. Zhang C, Shang Y, Chen X, Midgley AC, Wang Z, Zhu D, Wu J, Chen P, Wu L, Wang X, Zhang K, Wang H, Kong D, Yang Z, Li Z, Chen X. (RGD) peptides boost therapeutic efficacy of Extracellular vesicles in kidney repair. ACS Nano. 2020;14(9):12133–47. https://doi.org/10.1021/acsnano.0c05681. Supramolecular Nanofibers Containing Arginine-Glycine-Aspartate.
167. Grange C, Papadimitriou E, Dimuccio V, Pastorino C, Molina J, O'Kelly R, Niedernhofer LJ, Robbins PD, Camussi G, Bussolati B. Urinary extracellular vesicles carrying Klotho improve the recovery of renal function in an Acute Tubular Injury Model. Mol Ther. 2020;28(2):490–502. https://doi.org/10.1016/j.ymthe.2019.11.013.
168. Jin J, Qian F, Zheng D, He W, Gong J, He Q. Mesenchymal stem cells attenuate renal fibrosis via exosomes-mediated delivery of microRNA Let-7i-5p antagomir. Int J Nanomed. 2021;16:3565–78. https://doi.org/10.2147/IJN.S299969.
169. Sadeghi S, Tehrani FR, Tahmasebi S, Shafiee A, Hashemi SM. Exosome Engineering in Cell Therapy and Drug Delivery. *Inflammopharmacology* 2023, *31* (1), 145. https://doi.org/10.1007/s10787-022-01115-7
170. Tang T-T, Wang B, Li Z-L, Wen Y, Feng S-T, Wu M, Liu D, Cao J-Y, Yin Q, Yin D, Fu Y-Q, Gao Y-M, Ding Z-Y, Qian J-Y, Wu Q-L, Lv L-L, Liu B-C. Kim-1 targeted extracellular vesicles: a New Therapeutic platform for RNAi to treat AKI. J Am Soc Nephrol. 2021;32(10):2467–83. https://doi.org/10.1681/ASN.2020111561.
171. Zhang K, Li R, Chen X, Yan H, Li H, Zhao X, Huang H, Chen S, Liu Y, Wang K, Han Z, Han Z-C, Kong D, Chen X-M, Li Z. Renal endothelial cell-targeted extracellular vesicles protect the kidney from ischemic Injury. Adv Sci (Weinh). 2023;10(3):e2204626. https://doi.org/10.1002/advs.202204626.
172. Ji C, Zhang J, Shi L, Shi H, Xu W, Jin J, Qian H. Engineered Extracellular vesicle-encapsulated CHIP as Novel Nanotherapeutics for treatment of Renal Fibrosis. NPJ Regen Med. 2024;9(1):3. https://doi.org/10.1038/s41536-024-00348-0.
173. Yang C, Xue Y, Duan Y, Mao C, Wan M. Extracellular vesicles and their Engineering Strategies, Delivery systems, and Biomedical Applications. J Controlled Release. 2024;365:1089–123. https://doi.org/10.1016/j.jconrel.2023.11.057.
174. Zhong X, Tang T-T, Shen A-R, Cao J-Y, Jing J, Wang C, Zhu X-X, Wen Y, Li Z-L, Wang B, Qin S-F, Liu B-C, Lv L-L. Tubular epithelial cells-derived small Extracellular Vesicle-VEGF-A promotes Peritubular Capillary repair in ischemic kidney Injury. NPJ Regen Med. 2022;7(1):73. https://doi.org/10.1038/s41536-022-00268-x.
175. Wang B, Yao K, Huuskes BM, Shen H-H, Zhuang J, Godson C, Brennan EP, Wilkinson-Berka JL, Wise AF, Ricardo SD. Mesenchymal stem cells deliver exogenous MicroRNA-Let7c via Exosomes to attenuate renal fibrosis. Mol Ther. 2016;24(7):1290–301. https://doi.org/10.1038/mt.2016.90.
176. Chen L, Wang Y, Li S, Zuo B, Zhang X, Wang F, Sun D. Exosomes Derived from GDNF-Modified Human adipose mesenchymal stem cells ameliorate Peritubular Capillary loss in Tubulointerstitial Fibrosis by activating the SIRT1/eNOS signaling pathway. Theranostics. 2020;10(20):9425–42. https://doi.org/10.7150/thno.43315.
177. Lin J, Lv J, Yu S, Chen Y, Wang H, Chen J. Transcript Engineered Extracellular vesicles alleviate Alloreactive Dynamics in Renal Transplantation. Adv Sci (Weinh). 2022;9(31):e2202633. https://doi.org/10.1002/advs.202202633.
178. Choi HY, Kim TY, Lee M, Kim SH, Jhee JH, Lee YK, Kim HJ, Park HC. Kidney mesenchymal stem cell-derived Extracellular vesicles Engineered to Express Erythropoietin improve renal Anemia in mice with chronic kidney disease. Stem Cell Rev Rep. 2022;18(3):980–92. https://doi.org/10.1007/s12015-021-10141-x.
179. Zhang Z-Y, Hou Y-P, Zou X-Y, Xing X-Y, Ju G-Q, Zhong L, Sun J. Oct-4 enhanced the Therapeutic effects of mesenchymal stem cell-derived extracellular vesicles in Acute kidney Injury. Kidney Blood Press Res. 2020;45(1):95–108. https://doi.org/10.1159/000504368.
180. Du J, Sun Q, Wang Z, Wang F, Chen F, Wang H, Shang G, Chen X, Ding S, Li C, Wu D, Zhang W, Zhong M, Li Y. Tubular epithelial cells derived-exosomes containing CD26 protects mice against Renal Ischemia/Reperfusion Injury by maintaining proliferation and dissipating inflammation. Biochem Biophys Res Commun. 2021;553:134–40. https://doi.org/10.1016/j.bbrc.2021.03.057.
181. Bordanaba-Florit G, Royo F, Kruglik SG, Falcón-Pérez JM. Using single-Vesicle technologies to unravel the heterogeneity of Extracellular vesicles. Nat Protoc. 2021;16(7):3163–85. https://doi.org/10.1038/s41596-021-00551-z.
182. Yang D, Zhang W, Zhang H, Zhang F, Chen L, Ma L, Larcher LM, Chen S, Liu N, Zhao Q, Tran PHL, Chen C, Veedu RN, Wang T, Progress. Opportunity, and perspective on Exosome isolation - efforts for efficient exosome-based theranostics. Theranostics. 2020;10(8):3684–707. https://doi.org/10.7150/thno.41580.
183. Zhang H, Freitas D, Kim HS, Fabijanic K, Li Z, Chen H, Mark MT, Molina H, Martin AB, Bojmar L, Fang J, Rampersaud S, Hoshino A, Matei I, Kenific CM, Nakajima M, Mutvei AP, Sansone P, Buehring W, Wang H, Jimenez JP, Cohen-Gould L, Paknejad N, Brendel M, Manova-Todorova K, Magalhães A, Ferreira JA, Osório H, Silva AM, Massey A, Cubillos-Ruiz JR, Galletti G, Giannakakou P, Cuervo AM, Blenis J, Schwartz R, Brady MS, Peinado H, Bromberg J, Matsui H, Reis CA, Lyden D. Identification of distinct nanoparticles and subsets of Extracellular vesicles by asymmetric Flow Field-Flow Fractionation. Nat Cell Biol. 2018;20(3):332–43. https://doi.org/10.1038/s41556-018-0040-4.

184. Wang Z, Zhou X, Kong Q, He H, Sun J, Qiu W, Zhang L, Yang M. Extracellular Vesicle Preparation and Analysis: a state-of-the-art review. Adv Sci (Weinh). 2024;11(30):e2401069. https://doi.org/10.1002/advs.202401069.
185. Crescitelli R, Lässer C, Lötvall J. Isolation and characterization of Extracellular vesicle subpopulations from tissues. Nat Protoc. 2021;16(3):1548–80. https://doi.org/10.1038/s41596-020-00466-1.
186. Zhou J, Wu Z, Hu J, Yang D, Chen X, Wang Q, Liu J, Dou M, Peng W, Wu Y, Wang W, Xie C, Wang M, Song Y, Zeng H, Bai C. High-throughput Single-EV Liquid Biopsy: Rapid, Simultaneous, and multiplexed detection of nucleic acids, proteins, and their combinations. Sci Adv. 2020;6(47):eabc1204. https://doi.org/10.1126/sciadv.abc1204.
187. Feng J, Jia L, Pan W, Fan Y, Guo J, Luo T, Liu C, Wang W, Zheng L, Li B. Rapid and efficient fluorescent aptasensor for PD-L1 positive extracellular vesicles isolation and analysis: EV-ANCHOR. Chem Eng J. 2023;465:142811. https://doi.org/10.1016/j.cej.2023.142811.
188. Liu C, Lin H, Guo J, Yang C, Chen J, Pan W, Cui B, Feng J, Zhang Y, Li B, Yao S, Zheng L. Profiling of single-vesicle surface proteins via Droplet Digital Immuno-PCR for Multi-subpopulation Extracellular vesicles counting towards Cancer Diagnostics. Chem Eng J. 2023;471:144364. https://doi.org/10.1016/j.cej.2023.144364.
189. Dixson AC, Dawson TR, Di Vizio D, Weaver AM. Context-specific regulation of Extracellular Vesicle Biogenesis and Cargo Selection. Nat Rev Mol Cell Biol. 2023;24(7):454–76. https://doi.org/10.1038/s41580-023-00576-0.
190. Droste M, Tertel T, Jeruschke S, Dittrich R, Kontopoulou E, Walkenfort B, Börger V, Hoyer PF, Büscher AK, Thakur BK, Giebel B. Single Extracellular Vesicle Analysis Performed by Imaging Flow Cytometry and Nanoparticle Tracking Analysis evaluate the accuracy of urinary Extracellular Vesicle Preparation techniques differently. Int J Mol Sci. 2021;22(22):12436. https://doi.org/10.3390/ijms222212436.
191. Huang W, Zhu X-Y, Lerman A, Lerman LO. Extracellular vesicles as theranostic tools in kidney disease. Clin J Am Soc Nephrol. 2022;17(9):1418–29. https://doi.org/10.2215/CJN.16751221.
192. Zhang X, Zhang H, Gu J, Zhang J, Shi H, Qian H, Wang D, Xu W, Pan J, Santos HA. Engineered Extracellular vesicles for Cancer Therapy. Adv Mater. 2021;33(14):e2005709. https://doi.org/10.1002/adma.202005709.
193. Ceccotti E, Saccu G, Herrera Sanchez MB, Bruno S. Naïve or Engineered Extracellular vesicles from different cell sources: therapeutic tools for kidney diseases. Pharmaceutics. 2023;15(6):1715. https://doi.org/10.3390/pharmaceutics15061715.

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