Journal of Nanobiotechnology

REVIEW

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Future embracing: exosomes driving a revolutionary approach to the diagnosis and treatment of idiopathic membranous nephropathy

Lin Wang[1,2†], Jinxiang Wang[3†], Ao Xu[1,2†], Lijuan Wei[1†], Ming Pei[1], Tuwei Shen[1,2], Xian Xian[1,2], Kang Yang[4], Lingyan Fei[5*], Yihang Pan[3*], Hongtao Yang[1,2*] and Xianwen Wang[6*]

Abstract

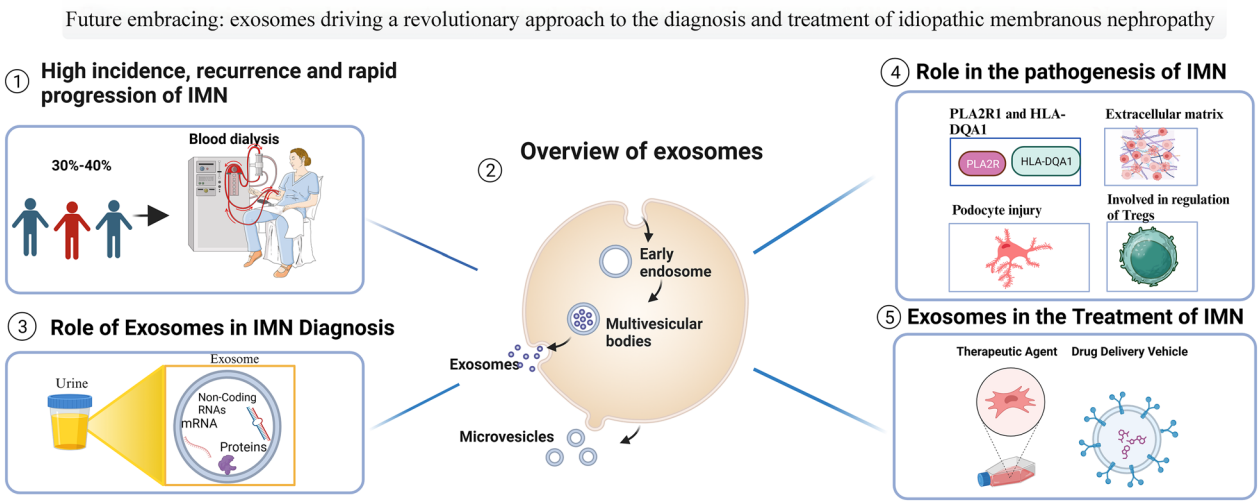
Membranous nephropathy (MN) is a leading cause of nephrotic syndrome in adults and is associated with high rates of end-stage renal disease. Early detection and precise interventions are crucial for improving patient prognosis and quality of life. However, the current diagnosis primarily relies on renal biopsies and traditional biomarkers, which have limitations. Additionally, targeted therapeutic strategies are lacking. Exosomes, small vesicles that facilitate intercellular communication, have emerged as potential noninvasive diagnostic markers due to their stability, diverse cargo, and rapid detectability. They also hold promise as carriers for gene and drug delivery, presenting innovative opportunities in renal disease prognosis and treatment. However, research on exosomes in the context of idiopathic membranous nephropathy (IMN) remains limited, with a focus on exploring urinary exosomes as IMN markers. In this review, we summarize the current status of MN diagnosis and treatment, highlight the fundamental characteristics of exosomes, and discuss recent advancements in their application to IMN diagnosis and therapy. We provide insights into the clinical prospects of exosomes in IMN and acknowledge potential challenges. This article aims to offer forward-looking insights into the future of exosome-mediated IMN diagnosis and treatment, indicating a revolutionary transformation in this field.

Keywords Membranous nephropathy, Exosomes, Biomarkers, Cellular communication, Gene therapy

†Lin Wang, Jinxiang Wang, Ao Xu, and Lijuan Wei have contributed equally to this work.

*Correspondence:
Lingyan Fei
Lingyanfei2022@163.com
Yihang Pan
panyih@mail.sysu.edu.cn
Hongtao Yang
tjtcmht@126.com
Xianwen Wang
xianwenwang@ahmu.edu.cn
[1]Nephrology Department, First Teaching Hospital of Tianjin University of Traditional Chinese Medicine, Tianjin 300381, China
[2]Graduate School, Tianjin University of Traditional Chinese Medicine, Tianjin 301617, China
[3]Guangdong Provincial Key Laboratory of Digestive Cancer Research, Digestive Diseases Center, Scientific Research Center, The Seventh Affiliated Hospital of Sun Yat-Sen University, Guangdong 518107, China
[4]Nephrology Department, The First Affiliated Hospital of Henan University of Chinese Medicine, Henan 450099, China
[5]Department of Nephrology, Kidney and Urology Center, The Seventh Affiliated Hospital of Sun Yat-Sen University, Shenzhen 518107, China
[6]School of Biomedical Engineering, Research and Engineering Center of Biomedical Materials, Anhui Medical University, Hefei 230032, People's Republic of China

Graphical Abstract



Introduction

Idiopathic membranous nephropathy (IMN) is an autoimmune glomerular podocytosis syndrome [1]. Its clinical features mainly include proteinuria or nephrotic syndrome with insidious onset, which is a common cause of adult nephrotic syndrome in China. In recent years, both domestic and international studies have demonstrated a progressively increasing incidence of IMN [2–7]. In Caucasians, IMN accounts for approximately 30–40% of primary nephrotic syndrome cases [8]. In China, the prevalence of IMN has increased significantly in recent renal biopsy cases. According to data from a retrospective study covering 10 years and 6049 cases of renal pathology from Peking University First Hospital in 2015 [9], the incidence of IMN increased from 16.8% in 2003–2007 to 29.35% in 2008–2012. Moreover, another study led by academician Hou Fanfan in 2016, which included data from nearly 70,000 patient renal biopsies across 938 hospitals in 282 cities throughout China, revealed that while the incidences of other glomerular diseases remained stable, the incidence of MN doubled from 12.2% in 2004 to 24.9% in 2014, positioning it as the second most common cause of primary glomerulopathy [5]. In the same year, after calibrating data on kidney disease types across 11 years in the Chinese population, Xu and colleagues reported an annual increase of 13% in MN patients, demonstrating a trend toward surpassing IgA nephropathy [5]. Research has suggested that in the northeastern region of China, the incidence of IMN has exceeded that of IgA nephropathy, suggesting that IMN is the leading cause of primary glomerulopathies [10, 11] and poses a serious threat to human health.

The natural course of MN exhibits significant variability. Approximately 30% of patients experience spontaneous remission, while approximately 70% manifest persistent proteinuria. Within 5–20 years, 40–60% of patients progress to end-stage renal disease (ESRD) [3], making it a significant contributor to ESRD. Due to the high incidence and recurrence rates of this disease, early detection and preventive treatment are essential for improving patient prognosis and quality of life. Currently, the diagnosis of IMN still relies on invasive renal biopsies, which carry potential risks of complications such as bleeding and infections and are not suitable for repeated evaluations of renal changes. However, traditional IMN biomarkers, such as the serum creatinine concentration, estimated glomerular filtration rate (eGFR), serum albumin (ALB) concentration, and urine protein concentration, all have limitations in terms of sensitivity and specificity [12]. Moreover, novel biomarkers, including autoantibodies against intrinsic podocyte antigens such as anti-PLA2R and anti-THSD7A, exhibit increased sensitivity and specificity. However, they still do not encompass all IMN patients. For instance, there is a possibility of underdiagnosing anti-PLA2R- and/or anti-THSD7A-negative IMN patients. Therefore, in-depth research into the pathogenesis of IMN and the exploration of new biomarkers are pressing challenges in the current field of kidney disease research. Currently, specific drugs capable of halting or reversing the progression of MN are lacking. Although the International Kidney Disease

Guidelines (KDIGO) have issued guidelines for the treatment of MN, recommending medications that provide varying degrees of therapeutic effects for MN, corresponding biologics and low-dose steroids combined with immunosuppressive regimens exhibit unstable efficacy. These approaches can cause potential immune-related side effects, increased rates of relapse, and increased economic burdens [13–15], preventing patients from fully meeting the treatment needs of MN patients. As a result, there is an urgent need to identify noninvasive diagnostic markers and specific therapeutic targets for IMN.

Moreover, related studies have reported that almost all intrinsic renal cells, such as endothelial cells, podocytes, and tubular epithelial cells, can secrete exosomes and mediate crosstalk between different types of cells in the kidney [16, 17]. There is a characteristic change in exosome content in renal diseases such as acute kidney injury [18], IgA nephropathy [19], diabetic nephropathy [20], renal tubular acidosis [21], and polycystic kidney disease [22]. In addition, exosomal miRNAs are more stable than circulating miRNAs, and they are protected from degradation by rRNA enzymes [23]. Based on these features, exosomes have great potential as biomarkers and therapeutic agents for the early diagnosis of IMN. Currently, exosomes have been widely studied as biomarkers for the diagnosis of renal diseases and as therapeutic means for renal diseases, but there is a relative lack of application of exosomes in the diagnosis and treatment of idiopathic membranous nephropathy (IMN). In this paper, we hope to systematically review the progress in the use of exosomes in the diagnosis and treatment of IMN and provide a reference for the future diagnosis and treatment of IMN. This review first describes the generation and origin of exosomes, their composition and contents, and their biological properties and functions and then explores the application of exosomes in IMN diagnosis, pathogenesis and therapy. Finally, we look ahead to current limitations and challenges, as well as potential directions for future research and clinical translation of exosomes.

Overview of exosomes

Generation and origins of exosomes

The biogenesis of exosomes begins with the maturation of early endosomes to late endosomes or multivesicular bodies (MVBs) containing intraluminal vesicles (ILVs). Endosomes are the focal point of the endocytosis pathway and determine whether internalized proteins and lipids are degraded or recycled [24]. Endosomes are categorized as early endosomes, late endosomes, or recycling endosomes. The biogenesis of exosomes involves double invagination of the plasma membrane, with the initial inward bending of the plasma membrane forming a cup-shaped structure that includes cell surface proteins and extracellular components such as soluble proteins, lipids, metabolites, small molecules, and ions. These components can be internalized through endocytosis and membrane invagination along with cell surface proteins. The de novo formation of early-sorting endosomes (ESEs) is initiated. Sometimes, it may be directly fused with pre-ESE, which is preformed from components of the endoplasmic reticulum (ER), the trans-Golgi network (TGN), and the mitochondrion. Early-sorting endosomes (marked by Rab5) mature through acidification and substance exchange to become late-sorting endosomes (LSEs) (marked by Rab7). Ultimately, the second internalization of LSEs results in the formation of MVBs. These MVBs contain ILVs with diameters ranging from 40 to 150 nm, which are formed by inward budding of the MVB membrane. ILVs can be directly fused with lysosomes or autophagic lysosomes to undergo degradation, and the degradation products can be recycled by the cell. The other pathway is plasma membrane fusion, in which the contents are released into the extracellular space in the form of exosomes [25, 26]. This process is referred to as exosome biogenesis and distinguishes it from other forms of vesicle release, such as budding from the plasma membrane, apoptotic body formation, or membrane rupture (Fig. 1). There are two distinct mechanisms involved in the formation of ILVs: ESCRT-independent and ESCRT-dependent mechanisms required for cargo sorting into endosomes. ESCRT consists of four complexes and auxiliary proteins: ESCRT-0, ESCRT-I, ESCRT-II, and ESCRT-III. These complexes collaborate in an orderly manner, recognizing ubiquitinated proteins on the endosomal membrane and inducing inward budding to form ILVs. Another mechanism, which is ESCRT-independent, relies on lipid raft microdomains enriched in sphingomyelinase and microdomains enriched in tetraspanins [27–29].

Composition and contents of exosomes

Exosomes are lipid bilayer cup-shaped vesicles with sizes ranging from 30 to 200 nm [30]. Embedded within their phospholipid bilayer membrane are numerous proteins and lipids believed to have evolved from parent cells [31]. The lipid composition of these exosome bilayers includes phosphatidylcholines, phosphatidylethanolamine, phosphatidylinositol, phosphatidylserine, and sphingomyelin [32]. These components are more balanced in the exosome when their proportions are 26:26:19:19:20 and 43:23:12:12:9, respectively [33]. Elevated levels of sphingomyelin and phosphatidylinositol ensure their stability in biological fluids with varying pH levels, guarding against lipid or protein hydrolysis that might occur during systemic circulation [34]. In addition, exosome

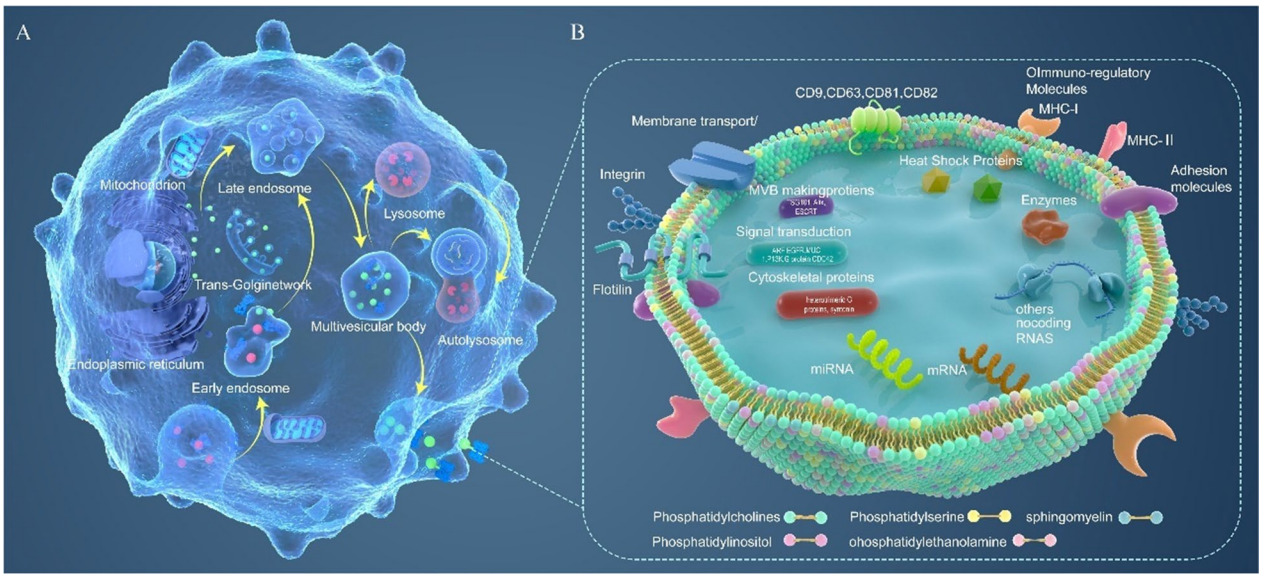


Fig. 1 Exosome production and contents. **A** The process of exosome generation. **B** The contents of exosomes

membranes are enriched with lipid rafts of various proteins, such as tyrosine kinase Src and glycosylphosphatidylinositol-owned proteins [35]. The proteins contained in exosomes can be categorized into two groups: nonspecific and specific. Among them, nonspecific proteins are widely present in all types of exosomes, regardless of their cell of origin. These proteins include tetraspanins (such as CD9, CD63, CD81, and CD82) serving as exosomal surface markers, proteins involved in exosome trafficking and binding to target cells (such as GTPases, annexins, and flotillin) [36], proteins participating in the biogenesis of MVBs like TSG101, Alix, ESCRT complexes, heat shock proteins (Hsc70, Hsp90), GTPases, and membrane-associated proteins [37], as well as cytoskeletal proteins (such as heterotrimeric G proteins, 14-3-3, syntenin). On the other hand, specific proteins within exosomes encompass tissue-specific proteins, such as the major histocompatibility complex class II (MHC-II), present on the surface of nearly all dendritic cells (DC) and B lymphocytes [38], and proteins unique to specific cell types. These specific proteins do not exist independently from nonspecific proteins. For instance, the shell of tetraspanin proteins is composed of various cell-specific transmembrane proteins, including α and β integrin chains (such as αM found on T cells and dendritic cells, α4β1 present on reticular cells, and β2 located on the apex of dendritic cells), cholesterol, and flotillin as lipid raft components. Additionally, certain members of the immunoglobulin family (such as A33 antigen on intestinal cells, intercellular adhesion molecule 1 (ICAM-1)/CD54 on B cells, and P-selectin on platelets) as well as cell surface peptidases (such as aminopeptidase N/CD13 on M cells and dipeptidyl peptidase IV/CD26 on intestinal cells) are also included [31]. Exosomes also encompass molecules involved in signaling pathways, such as β-catenin, ADP-ribosylation factor 1 (ARF1), epidermal growth factor receptor (EGFR), mucin 1 (MUC1), phosphoinositide 3-kinase (PI3K), G-proteins, cytoskeletal proteins, and cell division control protein 42 (CDC42) [35]. Simultaneously, exosomes harbor a diverse array of RNA types, including mRNA and noncoding RNAs such as miRNA, lncRNA, and tRNA. These RNAs exhibit functional roles, capable of influencing the transcriptome of recipient cells [39–42]. Among them, miRNA represents the most abundant RNA species in exosomes [43, 44].

Biological characteristics and functions of exosomes

The functions of exosomes are contingent upon their originating cells [45]. They participate in immune responses, inflammation, angiogenesis, coagulation, intercellular communication, as well as the dissemination of pathogens such as prions and viruses [17]. The attributes of exosomes underscore their significant role in disease diagnosis, noncellular therapies, and the delivery of proteins, genes, and chemical substances [46–48]. First, the composition of exosomes varies due to the cell type, stimuli, stress, transformation, and differentiation functions of the source cells, rendering their detection and characterization in bodily fluids promising as diagnostic markers and prognostic indicators of diseases [49–55]; Second, exosomes are of natural origin and are inherently highly biocompatible and less immunogenic, and can be used as endogenous carriers [44]. At the same

time, because of their nanoscale [33], exosomes are capable of crossing biological barriers, evading the mononuclear phagocytic system (MPS), and other advantages, and are easy to deliver drugs to the target organs [44, 56]. In addition, exosomes can be isolated from a variety of body fluids and can be stored at −80 °C for long periods of time and have a relatively long lifespan in vivo [17, 45, 57]. Finally, exosomes contain bioactive substances and proteins, and their lipid bilayer structure protects them from enzymatic degradation [58, 59]. Based on the above characteristics such as endogenous, biocompatible and multifunctional properties, exosomes are expected to be a new means of drug delivery system, immunotherapy, and precision therapy.

The application of exosomes in the diagnosis and treatment of IMN

Role of exosomes in IMN diagnosis

The optimization of treatment for kidney diseases relies on the availability of diagnostic and prognostic biomarkers. Early diagnosis and treatment of IMN present significant challenges in the field of kidney disease [60]. Currently, diagnosing IMN requires the exclusion of secondary factors such as hepatitis B infection, systemic lupus erythematosus, cancer, or drug-related effects that can cause IMN [1]. Although renal biopsy remains the gold standard for diagnosing IMN [61], it poses the risk of potential severe postoperative complications such as bleeding and infection, and it is inconvenient for repetitive procedures to assess and evaluate kidney damage. Moreover, inappropriate sampling or lack of representativeness can affect the credibility of renal biopsy results [62]. The anti-PLA2R antibody is currently the best noninvasive biomarker, yet its positivity rate ranges from 50 to 72% in different ethnicities within the IMN population [62, 63], leaving some patients unsatisfied. Additionally, traditional biomarkers such as the serum creatinine concentration, eGFR, and urinary protein concentration exhibit low sensitivity, particularly in the early stages of kidney damage [12, 64]. Therefore, the search for novel noninvasive diagnostic biomarkers capable of identifying IMN has emerged as a vibrant area of research within the current landscape of glomerular disease studies [65, 66].

Exosomes, as potential biomarkers, were recognized by the Massachusetts Institute of Technology Technology Review as one of the "Top 10 Breakthroughs of 2015" [60, 64]. Unlike renal biopsies, exosomal biomarkers are not only exempt from the limitations of potentially nonrepresentative sampling but also sidestep the traumatic nature and potential complications associated with tissue biopsies [64]. The encapsulation of exosomes shields their cargo from RNA enzymes and repeated freeze–thaw cycles in both intracellular and extracellular environments, ensuring the integrity and stability of the biomolecular information they carry [21, 67]. Furthermore, exosomes express origin-specific markers, allowing for the monitoring of changes in specific cellular compartments within tissues, thereby enabling the tracking of lesion locations [64]. For instance, the presence of podocyte proteins like podocin [68], nephrin, and podocalyxin [69, 70] determines the increased in podocyte or endothelial-origin exosomes, potentially implying podocyte damage. Analysis of urinary exosomes may be useful in the diagnostic classification of other disease processes involving the renal tubules, such as polycystic kidneys [71], lysosomal storage diseases like Niemann-Pick disease and cystinosis, and transporter mutations like Gitelman and Bartter syndromes. Similarly, elevated levels of endothelial proteins in urinary exosomes, such as PL-VAP, CD31, and CD144 [72], indicate endothelial damage. Of particular interest, urinary exosomal miR-200b is associated with renal fibrosis in chronic kidney disease (CKD) only when measured in CD13 + exosomes (those not derived from proximal tubules) [73]. This suggests that exosomal biomarkers associated with this cellular subset might possess unique advantages. Previous research has also shown characteristic changes in exosome content in various kidney diseases, such as acute kidney injury [18], IgA nephropathy [19], diabetic nephropathy (DN) [20], renal tubular acidosis [21], and polycystic kidney disease [22]. This indicates the potential and substantial promise of exosomes as biomarkers in the field of kidney diseases.

Urinary exosomes in diagnosing IMN

Normal urine contains exosomes from each type of epithelial cell in the urinary space, including podocytes, endothelial cells, mesangial cells of the glomerulus, tubular cells of the nephron, and transitional epithelial cells of the urinary excretion system, and isolation of urinary exosomes allows identification of their sources [74, 75]. Thus, through urine collection and analysis, changes in the function of the entire renal, prostate, and bladder urinary systems can be monitored [67, 76–78]. This finding aligns with the findings of Miranda et al., who reported that exosomes isolated from human urine exhibited a comprehensive RNA profile similar to that of the kidneys [21]. Additionally, urinary exosomes offer advantages, such as large volume, rich content, and noninvasive collection [79–81]. Compared to the original urine metabolic pattern, the exosome metabolic pattern holds greater potential for MN diagnostics [79] and demonstrates increased stability [82–84]. Currently, urinary exosomes have been established as biomarkers for numerous kidney disorders, including CKD [85], DN [86, 87], autosomal dominant polycystic kidney disease

[88], renal cell carcinoma [89], and renal fibrosis [73, 90]. These exosomal markers in urine can be detected in quantities as low as 0.5 mL, suggesting high sensitivity [91]. With further research, urinary exosomes have also been found to be useful for assessing the severity of kidney diseases.

(1) Urinary exosomal proteins as IMN biomarkers

Under normal circumstances, approximately 3% of the total protein content in urine originates from urinary exosomes, with 70% originating from the urinary system and 30% from the circulatory system [76]. During the formation of urinary exosomes, various components undergo selective enrichment, and changes in their protein composition may reflect pathological processes in the urinary system or systemic diseases [21, 92]. Moreover, proteins in urinary exosomes more accurately reflect changes in kidney tissue compared to urinary proteins [93], underscoring the significant potential of urinary exosomes proteins as biomarkers for both the urinary system and systemic conditions [76, 94]. For instance, urinary exosomal ceruloplasmin (CP) is significantly elevated by 10–20 times in CKD patients compared to healthy controls and increases significantly before the onset of proteinuria [95]. Urinary exosomal transcription factor Elf3 protein is exclusively detected in DN and can reflect irreversible podocyte damage, serving as an early noninvasive biomarker for DN podocyte injury [96]. Urinary exosomal fibroblast-specific protein 1 (FSP1) correlates with the diagnosed glomerular crescent formation rate and total crescent formation rate in kidney biopsies, reflecting ongoing glomerular injury activity (crescent formation) [97]. Polycystin-1 (PC-1), the protein product of the autosomal dominant polycystic kidney disease gene, is readily detectable in urinary exosomes, despite its lower abundance in renal tissue [75]. Other proteins in urinary exosomes, such as Fetuin-A [98], activating transcription factor 3 (ATF3) [99, 100] and aquaporin-1 [101], show significant changes in the early stages of AKI and may be potential markers for early detection of AKI. In certain hereditary kidney diseases, the production of pathological proteins regulated by defective genes in exosomes may be reduced (PKD1 in polycystic kidney disease) [102] or completely absent (SLC12A1 in Bartter syndrome type 1) [67] (see Table 1). These studies collectively indicate the widespread utility of urinary exosomal proteins as biomarkers in the field of kidney diseases, revealing a certain feasibility of urinary exocytosis in the diagnosis of IMN, although it has not been directly elucidated.

In patients with IMN, the urinary exosomal marker proteins (Alix, CD63, and TSG101) were significantly greater than those in the control group, exhibiting a positive correlation with proteinuria [103]. This can reflect the active pathological changes in renal tissue associated with IMN and holds the potential to become a noninvasive biomarker for IMN diagnosis, disease assessment, and prognosis prediction [103]. Urinary exosomal ceruloplasmin is notably elevated in patients with CKDs, including MN [92, 95], and further investigation using the rat Heymann nephritis model revealed that this elevation occurred prior to the onset of proteinuria. Additionally, studies have indicated a positive correlation between the urinary exosomal proteins Nrf2 and NLRP3 and serum anti-PLA2R antibodies. Lower levels of Nrf2 or NLRP3 are suggestive of better treatment outcomes, suggesting their potential as prospective biomarkers for prognosis assessment [104].

(2) Urinary exosomal mRNA as biomarkers for IMN.

Urine presents a potential source of nucleic acids, although these may arise from apoptotic cells and potentially not accurately reflect the functional state of viable cells [21]. Furthermore, urine's intricate composition, coupled with a lack of specificity in its components, may introduce interference into component detection [21]. However, urinary exosomes selectively encapsulate mRNA and miRNA, overcoming these drawbacks by enriching for relatively specific components [21]. Moreover, the bilayer membrane structure of exosomes shields against degradation by both intracellular and extracellular RNases, rendering exosomal RNA more stable than total urine RNA [21]. Recent research, as indicated in Table 2, underscores the practicality of urinary exosomal mRNA as biomarkers for various kidney diseases, including IMN, DN, FSGS, IgA nephropathy, renal fibrosis, and CKD. For example, in IMN patients, CCL2 mRNA expression was significantly elevated compared to healthy controls [118]. Similarly, in patients with renal fibrosis, urinary exosomal CD2AP mRNA downregulation correlated negatively with renal function, proteinuria levels, severity of fibrosis, and glomerular sclerosis [119]. Among DN, those with proteinuria displayed notably elevated levels of urinary exosomal WT1 mRNA expression compared to nonproteinuric patients. WT1 levels were indicative of the extent of diabetic glomerular injury [68, 106]. These findings collectively underscore the critical role of urinary exosomal vesicle mRNA as essential diagnostic and prognostic tools for various kidney diseases, including IMN. This methodology capitalizes on the enrichment of specific mRNA types and the inherent stability of exosomal RNA, ultimately amplifying the potential for early detection and management of renal pathologies [68, 118, 120].

Table 1 Potential biomarkers of IMN from urinary exosomal proteins

Kidney disease	Urinary exosome protein	Isolation method of urinary exosomes	Number ernrolled/animal model	Results	References
IMN	Alix	Ultracentrifugation	IMN (n = 49) and healthy controls (n = 21)	The urinary exosome marker protein Alix is significantly elevated compared to the control group, positively correlated with proteinuria, reflecting active renal histopathological changes in IMN	[103]
	CD63	Ultracentrifugation	IMN (n = 49) and healthy controls (n = 21)	The urinary exosome marker protein CD63 is significantly elevated compared to the control group, positively correlated with proteinuria, reflecting active renal histopathological changes in IMN	[103]
	TSG101	Ultracentrifugation	IMN (n = 49) and healthy controls (n = 21)	The urinary exosome marker protein TSG101 is significantly elevated compared to the control group, positively correlated with proteinuria, reflecting active renal histopathological changes in IMN	[92, 103]
	Ceruloplasmin	Ultracentrifugation	IMN (n = 9) and healthy controls (n = 15)	Urinary exosomal ceruloplasmin is markedly elevated in MN patients, and further investigation using the Heymann nephritis rat model revealed its elevation prior to the onset of proteinuria	[95]
	Nrf2	Ultracentrifugation	IMN (n = 49) and healthy controls (n = 21)	The urinary exosomal protein Nrf2 is positively correlated with serum anti-PLA2R antibodies. Lower levels of Nrf2 are indicative of better treatment outcomes and may serve as a potential biomarker for prognostic assessment in IMN	[104]
	NLRP3	Ultracentrifugation	IMN (n = 49) and healthy controls (n = 21)	The urinary exosomal protein NLRP3 is positively correlated with serum anti-PLA2R antibodies. Lower levels of NLRP3 are indicative of better treatment outcomes and may serve as a potential biomarker for prognostic assessment in IMN	[104]

Table 1 (continued)

Kidney disease	Urinary exosome protein	Isolation method of urinary exosomes	Number ernrolled/animal model	Results	References
CKD	Ceruloplasmin	Ultracentrifugation	CKD (n = 15) and Controls (n = 15)	Elevated urinary exosomal ceruloplasmin observed prior to proteinuria makes it a potential urinary biomarker for early-stage kidney disease diagnosis	[95]
	Osteoprotegerin	Ultracentrifugation	CKD (n = 14) and healthy controls (n = 4)	Urinary exosomal protein Osteoprotegerin levels are higher in patients with CKD than in healthy volunteers	[105]
DN	ELF3	Ultracentrifugation	DN (n = 25) and minimal change nephrotic syndrome (MCNS, n = 25)	ELF3 can only be detected in UE of DN and can reflect podocyte damage, serving as an early noninvasive marker for podocyte injury in DN	[96]
	AMBP	Ultracentrifugation-based and Exoquick® reagent-based	DN (n = 5) and healthy controls (n = 5)	Elevated levels of AMBP found in UE of DN patients	[93]
	MLL3	Ultracentrifugation-based and Exoquick® reagent-based	DN (n = 5) and healthy controls (n = 5)	MLL3 is exclusively detected in UE of DN patients, with no observation in exosomes from control subjects	[93]
	VDAC1	Ultracentrifugation-based and Exoquick® reagent-based	DN (n = 5) and healthy controls (n = 5)	Reduced levels of VDAC1 observed in UE of DN patients	[93]
	WT1	Ultracentrifugation	type-1 diabetes mellitus patients (n = 48) patients and healthy controls (n = 25)	The WT1 protein is predominantly present in UE of diabetic patients, with its expression levels increasing as kidney function declines. This suggests its potential as an early noninvasive marker for DN	[68, 106]
	PEPD and MUP1	Ultracentrifugation	Diabetic fatty rats	Compared with the control group, DN rats showed increased expression of the urinary exosomal protein PEPD and decreased expression of MUP	[107]
	Ceruloplasmin	Ultracentrifugation	Diabetic patients (classified as normoproteinuria, microalbuminuria, and proteinuria) (n = 82), with healthy controls (n = 1)	Urinary exosomal protein Ceruloplasmin shows elevated levels in microalbuminuric diabetic nephropathy(DN), indicating its potential as an early marker for diabetic kidney disease	[92]
	AQP5 and AQP2	Ultracentrifugation	DN (n = 35) and healthy controls (n = 7)	Upregulation of AQP5 and AQP2 expression in DN patients	[108]
	CD63	Total exosome isolation reagent	Microalbuminuria-stage DN patients (n = 62) and controls (n = 29)	During the early stages of diabetic kidney injury, urinary levels of CD63-positive exosomes are significantly elevated	[109]

Table 1 (continued)

Kidney disease	Urinary exosome protein	Isolation method of urinary exosomes	Number ernrolled/animal model	Results	References
	Regucalcin	Ultracentrifugation	CKD patients (n = 7) and controls (n = 4)/STZ	Reduced expression of Regucalcin protein in DN kidney tissue	[110]
IgA	Aminopeptidase N	Ultracentrifugation	Healthy volunteers without hematuria (n = 7), early IgA nephropathy (IgAN) (n = 5) and thin basement membrane nephropathy (TBMN) (n = 7)	Four proteins (aminopeptidase N, vasorin precursor, alpha-1-antitrypsin, and ceruloplasmin) have been selected as candidate biomarkers for distinguishing early IgAn from TBMN	[111]
	Angiotensin receptor	Ultracentrifugation	Healthy volunteers without hematuria (n = 7), early IgA nephropathy (IgAN) (n = 5) and thin basement membrane nephropathy (TBMN) (n = 7)	Four proteins (aminopeptidase N, vasorin precursor, alpha-1-antitrypsin, and ceruloplasmin) have been selected as candidate biomarkers for distinguishing early IgAn from TBMN	[111]
	Al-antitrypsin and CP	Ultracentrifugation	Healthy volunteers without hematuria (n = 7), early IgA nephropathy (IgAN) (n = 5) and thin basement membrane nephropathy (TBMN) (n = 7)	Four proteins (aminopeptidase N, vasorin precursor, alpha-1-antitrypsin, and ceruloplasmin) have been selected as candidate biomarkers for distinguishing early IgAn from TBMN	[111]
AKI	Fetuin-A	Ultracentrifugation	3 healthy volunteers, 3 ICU patients with AKI,and 3 ICU patients without AKI/Cisplatin	Compared to healthy volunteers or ICU patients without AKI, patients with AKI in the ICU exhibit a significant increase in Fetuin-A levels in their UE	[98]
	ATF3	Ultracentrifugation	Septic AKI patients (n = 8) and healthy controls (n = 8)	①Compared to healthy volunteers, septic AKI patients have higher levels of uATF3, which is negative in all healthy volunteers. ②Persistent presence of ATF3 is observed in UE of the acute injury rat model, occurring earlier in time than the elevation of serum creatinine	[99]
		Ultracentrifugation	2 healthy volunteers, 2 ICU patients with AKI, and 4 patients with CKD/Cisplatin and I/R	ATF3 in UE increases during the early stages of AKI, whereas it remains unchanged in CKD patients	[100]
	Fetal globulin-A	Ultracentrifugation	AKI patients (n = 3) and health volunteers (n = 3)	Elevated urinary exosomal Fetuin-A in AKI may serve as an early indicator of AKI, but Fetuin-A does not increase in renal azotemia	[98]

Table 1 (continued)

Kidney disease	Urinary exosome protein	Isolation method of urinary exosomes	Number ernrolled/animal model	Results	References
	Aquaporin 1(AQP1)	Ultracentrifugation	5 patients with proteinuria and 2 healthy volunteers/I/R	Urinary exosomal AQP1 can be employed for early-to-late stage monitoring of renal cell status following kidney I/R, encompassing I/R-induced cellular injury and early-phase regeneration, while also predicting posttransplant AKI due to I/R (delayed graft dysfunction)	[101]
	AQP2	Improved ultracentrifugation	Gentamicin	Urinary exosomal AQP2 serves as a biomarker for detecting gentamicin-induced dysfunction in collecting duct cells. Additionally, urinary exosomal AQP2 can be used for early detection of gentamicin-induced kidney injury beyond collecting duct damage	[112]
	NGAL	Ultracentrifugation	15 kidney allograft recipients	Neutrophil gelatinase-associated lipocalin (NGAL), produced by distal renal tubules, emerges as a promising novel biomarker for both AKI and CKD	[113]
	CD26	Ultracentrifugation	AKI (n = 133) and non-AKI patients (n = 68)	CD26 is significantly lower in the AKI group compared to the control group	[114]
	WT1	Ultracentrifugation	2 ICU patients with AKI (n = 2) and healthy volunteers (n = 2)/Cisplatin and I/R	Urinary WT-1 is present in animal models prior to severe glomerulosclerosis and in patients with 9/10 segmental glomerulosclerosis, but absent in 8 control subjects. WT-1 may serve as an indicator of early podocyte injury	[100]
Polycystic kidney/ADPKD	Polycystin-1	Ultracentrifugation	Unkown	Polycystin-1, the gene product of autosomal dominant polycystic kidney disease, is minimally abundant in renal tissue but readily detectable in UE	[75]
	PKD1	Sucrose density gradient centrifugation	Individuals with PKD1 mutations (n = 13) and healthy controls (n = 18)	PKD1 and PKD2 encode polycystin-1 (PC1) and polycystin-2 (PC2), respectively. Measuring urinary exosomal PC1/TMEM2 or PC2/TMEM2 ratios may hold practical value in the diagnosis and monitoring of polycystic kidney disease	[22]

Table 1 (continued)

Kidney disease	Urinary exosome protein	Isolation method of urinary exosomes	Number ernrolled/animal model	Results	References
Bartter syndrome	SLC12A1	Ultracentrifugation	Unkown	Immunoblot of Bartter syndrome type 1 patients, associated with mutations in the SLC12A1 gene, which encodes the sodium–potassium-chloride cotransporter 2	[67]
Renal ischemia—reperfusion injury	Aquaporin -1	Ultracentrifugation	Renal ischemia—reperfusion rat model	In renal ischemia—reperfusion injury, urinary exosomal aquaporin-1 abundance reduction emerges as a novel urine biomarker for kidney ischemia—reperfusion damage	[101]
Renal fibrosis	E-cadherin	Ultracentrifugation	27 prevalent case-patients with posterior urethral valves and 20 age-matched controls	The case patients excreted significantly less E-cadherin than both the normal and nonnormal control group	[115]
	TGF-B1	Ultracentrifugation	Prevalent case-patients with posterior urethral valves (n = 27) and 20 controls (n = 20)	Case patients excrete significantly higher levels of TGF-B1 compared to both normal control and nonnormal control groups.。	[115]
	N-adherin	Ultracentrifugation	27 prevalent case-patients with posterior urethral valves and 20 age-matched controls	Case patients excrete significantly lower levels of N-cadherin compared to both normal control and nonnormal control groups	[115]
	L1CAM	Ultracentrifugation	27 prevalent case-patients with posterior urethral valves and 20 age-matched controls	Case patients excrete significantly higher levels of L1CAM compared to both normal control and nonnormal control groups	[115]
FSGS	WT1	Ultracentrifugation	FSGS (n = 25) and healthy volunteers (n = 5) or SSNS/podocin/rTTAX TRE/Vpr double transgenic mice	In human subjects, urinary exosomal WT-1 is significantly elevated in FSGS patients compared to healthy volunteers or SSNS patients	[116, 117]

IMN idiopathic membranous nephropathy, *CKD* chronic kidney disease, *AKI* acute kidney injury, *DN* diabetic nephropathy, *IgAN* IgA nephropathy, *MCNS* minimal change nephrotic syndrome, *TBMN* Thin basement membrane nephropathy, *NGAL* neutrophil gelatinase-associated lipocalin, *SSNS* steroid-sensitive nephrotic syndrome, *UE* urinary exosome

Table 2 Potential biomarkers of IMN from urinary exosomal mRNAs

Kidney disease	Urinary exosome mRNA	Isolation method of urinary exosomes	Number ernrolled/animal model	Result	References
MN	CCL2	Ultracentrifugation	IgAN patients (n = 55) and normal individuals (n = 24)	Compared to the healthy control group, CCL2 is significantly upregulated in membranous nephropathy (MN) patients	[118]
Renal fibrosis	CD2AP	Ultracentrifugation	CKD patients (n = 32) and controls (n = 7)	Compared to the healthy control group, renal disease patients exhibit downregulated CD2AP mRNA expression in UE, which is negatively correlated with kidney function, proteinuria levels, and the severity of renal fibrosis and glomerulosclerosis	[119]
DN	WT1	Ultracentrifugation	DN (n = 20) and healthy subjects (n = 5)	①In DN patients, the expression of WT1 in UE is significantly higher in those with proteinuria compared to those without. ②Among podocyte-derived signal transduction factors in UE, the level of WT1 reflects the extent of diabetic glomerular damage in patients	[68, 106]
FSGS	WT1	Ultracentrifugation	Healthy volunteers (n = 5) and FSGS patients (n = 7)	In focal segmental glomerulosclerosis (FSGS) patients, urinary exosomal WT-1 is significantly higher than in healthy volunteers or steroid-sensitive nephrotic syndrome (SSNS) patients. WT1 expression correlates with disease activity and can serve as a noninvasive biomarker for early progression of podocyte injury and treatment-induced remission in FSGS or SSNS	[116]
IgA	CCL2	Ultracentrifugation	IgAN (n = 55) and normal individuals (n = 24)	Compared to the healthy control group, CCL2 is significantly upregulated in IgA nephropathy patients, as well as in patients with minimal change nephrosis (MCN) and MN	[118]
CKD	Cystatin C	Ultracentrifugation	The puromycin aminonucleoside (PAN) model in rats simulates a animal model of podocyte injury resembling minimal change glomerulopathy	①The mRNA content of exosomal cystatin C is correlated with the disease activity of puromycin aminonucleoside-induced nephropathy in rats (PAN).②In clinical studies, free urinary cystatin C has been identified as a diagnostic marker for acute kidney injury (AKI) induced by sepsis, cardiac surgery, or drug toxicity	[120–122]
MCN	CCL2	Ultracentrifugation	IgAN patients (n = 55) and normal individuals (n = 24)	Compared to the healthy control group, CCL2 is significantly upregulated in patients with MCN	[118]

MN membranous nephropathy, *MCN* minimal change nephrosis, *FSGS* focal segmental glomerulosclerosis, *SSNS* steroid-sensitive nephrotic syndrome, *UE* urinary exosomes

(3) Urinary Exosomal Non-Coding RNAs as Biomarkers for IMN.

MicroRNAs (miRNAs) are a class of noncoding RNAs that play a crucial role in the regulation of gene expression. Typically, they interact with the 3' UTR of target mRNAs to suppress gene expression [123], influencing various biological processes [124]. Aberrant expression of miRNAs has been linked to numerous human diseases [125, 126], suggesting that they could be potential biomarkers for a variety of kidney disorders [127–129] (Table 3). Moreover, urinary exosomes contain abundant miRNAs, rendering them potential biomarkers for diverse diseases [21, 130, 131]. They can also reflect kidney dysfunction and structural damage [21, 127–129, 131]. For instance, in CKD, the overexpression of the urinary exosomes miR-181a-5p [85] and miR-451 [132] individually contributes to CKD pathogenesis through lipid metabolism modulation, renal fibrosis, and mesangial hypertrophy [132]. Renal fibrosis serves as an indicator of permanent CKD-related damage, and correlations between elevated miR-200b [73] and decreased miR-29c [90, 119] levels and CKD-related fibrosis have been established. In DN patients, urinary exosomal miR-21-5p [133], miR-15b, miR-34a, miR-636 [134], and miR-30b-5p [133] hold promise as potential biomarkers. In lupus nephritis (LN) patients, urinary exosomal miR-21, miR-29c, and miR-150 are potential predictive biomarkers for disease progression [135]. Notably, reduced levels of urinary exosomal miR-29a and miR-29c are associated with disease severity, tubulointerstitial fibrosis, and glomerulosclerosis in DN, focal segmental glomerulosclerosis, IgA nephropathy, MN, and membranoproliferative glomerulonephritis [90, 119]. These findings underscore the invaluable diagnostic advantage of urinary extracellular vesicle miRNAs in early-stage kidney diseases. In patients with IMN, Ma et al. [16] identified MUC3A in blood and urinary exosomes as a potential diagnostic biomarker for IMN. The implication is that the MUC3A gene encodes amino acids pertinent to IMN pathogenesis, possibly involving the lectin pathway via mannose binding.

Role of exosomes in the pathogenesis of IMN

Elucidating the pathogenic mechanisms underlying IMN through the use of exosomes is imperative for improving the diagnosis and treatment of this disease. Exosomes are not only cellular entities but also pivotal players within the framework of disease mechanisms [159]. Previously, it was widely believed that the primary physiological role of urinary exosomes was the disposal of senescent proteins from cells, possibly through a more effective protein elimination method than proteasomal and lysosomal degradation [76]. This process is akin to the shedding of outdated membrane proteins and subsequent membrane remodeling by mature reticulocytes via the exosomal route [160]. However, an increasing body of evidence suggests that the role of urinary exosomes extends beyond the elimination of extracellular cellular waste [161, 162]. Another potential role of miRNAs is their ability to impact recipient cell mRNAs and miRNAs by secreting and reabsorbing their contents, thus regulating collaborative functions among various parts of the kidney [74]. Songjia Guo, Jinshi Zhang, and their colleagues employed high-throughput sequencing to analyze urinary exosomal miRNA expression profiles in healthy controls and IMN patients. These authors revealed significant downregulation of miRNAs, including miR-532-3p, miR-9-5p, miR-30b-5p, miR-129-5p, miR-125b, and miR-338-5p, in IMN patients [163, 164]. These findings suggest the potential involvement of these miRNAs in the pathogenesis of IMN.

(1) Associated with PLA2R1 and HLA-DQA1.

PLA2R1 and HLA-DQA1 have been confirmed to be risk factors for IMN [165]. Currently, anti-PLA2R antibodies serve as crucial diagnostic markers for IMN, with approximately 70% of IMN patients exhibiting their presence via kidney biopsies. A search of the TargetScanHuman8.0 database (https://www.targetscan.org/vert_80] revealed that differentially expressed genes, such as miR-30b-5p and miR-9-5p, in the urinary exosomes of IMN patients potentially regulate PLA2R1. Additionally, other members of the miR-30 family (miR-30 s) are associated with HLA-DQA1. Further Spearman correlation analysis indicated a significant negative correlation between miR-30b-5p and anti-PLA2R antibodies [164]. Hence, we postulate that urinary exosomes may participate in the pathogenesis of IMN by potentially modulating anti-PLA2R antibodies and/or HLA-DQA1 (Fig. 2).

(2) Regulating extracellular matrix and combating renal fibrosis.

It is well known that both MNs and DNs are associated with varying degrees of excessive accumulation of extracellular matrix, leading to gradual glomerular sclerosis and renal fibrosis. Renal fibrosis is the ultimate outcome of CKD development and a major contributor to ESRD. Research has indicated that miR-30b-5p and miR-9-5p may be involved in the process of renal fibrosis [166, 167]. In DN mouse models and human kidney tissues, miR-30b-5p is significantly downregulated, thereby promoting epithelial–mesenchymal transition (EMT) in

Table 3 Potential biomarkers of IMN from urinary exosomal noncoding RNA

Kidney disease	Urinary exosomal noncoding RNA	Isolation method of UE	Number ernrolled/animal model	Result	References
IMN	MUC3A	ExoQuick reagent precipitation kit	IMN patients (n = 10) and normal controls (n = 10)	MUC3A could be regarded as a potential diagnostic biomarker for IMN. It is hypothesized that the MUC3A gene may encode relevant amino acids, thereby participating in the pathogenesis of IMN through the galectin pathway	[136]
CKD	miR-181a-5p	Sucrose density gradient centrifugation	Different stages of CKD (n = 15) and healthy controls (n = 10)	Expression of the urinary exosome miR-181a-5p is upregulated in CKD, and it may be involved in the pathogenesis of CKD by mediating lipid metabolism	[85]
	miR-451	Ultracentrifugation	CKD subjects (n = 48), healthy controls (n = 23)	Compared with healthy volunteers, miR-451 was significantly lower in urine but higher in plasma in CKD patients (stages 3 and 5)	[132]
	miR-200b/miR-200c	Urine exosome purification kit	CKD patients with different degrees of renal fibrosis (n = 8) and normal individuals (n = 12)/I/R	In the injury state, miR-200c were increased in UEs	[73, 137]
	miR-21	Total exosome isolation reagent	Scrub typhus patients with AKI (n = 25) and patients without AKI (n = 25)	①miR-21 levels correlated directly with the total leukocyte counts and inversely with the estimated glomerular filtration rate (eGFR).②Upregulated miR-21 in UE may serve as a noninvasive prognostic marker for CKD	[138]
	miR-29c	Ultracentrifugation	CKD patients (n = 32) and controls (n = 7)	Reduced levels of miR-29 in UE of CKD patients may play a distinct role in kidney diseases by potentially mitigating renal fibrosis. Urinary miR-29c levels exhibit a positive correlation with EGFR	[90, 119]
	miR-16	Urine exosome purification kit	I/R	In the context of CKD patient's compromised condition, there is an elevation in the expression of miR-16 in UE	[137]
	miR-24	Urine exosome purification kit	I/R	In the context of CKD patient's compromised condition, there is an elevation in the expression of miR-24 in UE	[137]
DN	miR-21-5p	miRCURY™ exosomes isolation kit	Sequencing in type 2 diabetic DKD patients (T2DKD; n = 14) and controls with type 2 diabetes and normal renal function (T2DNRF; n = 15); T2DKD (n = 22) was validated against two controls, T2DNRF (n = 15) and controls without diabetic hyperalgesia (n = 18)	Compared to individuals with well-functioning kidneys and type 2 diabetes, there is a notable increase in the expression of UE miR-21-5p in patients with T2DKD and CKD. This expression is significantly correlated with blood creatinine levels, indicating its potential as a biomarker for DKD	[133]

Table 3 (continued)

Kidney disease	Urinary exosomal noncoding RNA	Isolation method of UE	Number ernrolled/animal model	Result	References
	miR-15a-5p	Ultracentrifugation	40 patients with type 2 diabetes mellitus (T2DM) patients, 20 patients with normoalbuminuria and 20 patients with macroalbuminuria	miR-15a-5p was downregulated in DKD patients compared to T2DM patients	[139]
	miR-15b	Ultracentrifugation	136 patients with T2DM and 44 healthy controls	Upregulated (UE)	[134]
	miR-15b-5p	miRCURY™ exosome isolation kit/ultracentrifugation	The entire study group included subjects (n = 40 each) with normal glucose tolerance (NGT), patients with T2DM and normoalbuminuria (T2DM-NA), T2DM- Microalbuminuria (MIC) patients and T2DM patients with macroalbuminuria (T2DM-MAC)/15 healthy control patients, 20 type I diabetic patients without DN and 28 type I diabetic patients with DN	In comparison to T2DM-NA patients, there is a reduction in the expression of miR-15b-5p in extracellular vesicles of T2DM-MIC patients, offering a potential identifier for T2DM-MIC individuals	[140, 141]
	miR-16	Ultracentrifugation	STZ	Upregulated	[142]
	miR-19b-3p	Ultracentrifugation	T2DM (n = 15) and DN patients (n = 28)/LPS	Clinically, elevated levels of miR-19b-3p have been identified in UE, and these levels are correlated with the severity of tubulointerstitial inflammation in DKD patients	[143]
	miR-23c	Unknown	15 diabetic patients with nephrotic range proteinuria	Upregulation	[144]
	miR-24-3p	miRCURY™ exosome isolation kit	40NGT, 40 T2DN, 40 T2DN(with microalbumininuria,MIC), 40 T2DN(with macroalbuminuria, MAC)	Compared to T2DM-NA patients, there is an increase in the expression of miR-24-3p in EV of T2DM-MIC patients. This expression is linked to metabolic parameters associated with renal dysfunction and can also serve as an identifier for T2DM-MIC individuals	[140]
	miR-27b-3p	miRCURY™ exosome isolation kit	40NGT, 40 T2DN, 40 T2DN(with MIC),40 T2DN(with MAC)	In comparison to T2DM-NA patients, there is an elevation in the expression of miR-27b-3p in EV of T2DM-MIC patients. This expression is associated with metabolic parameters linked to renal dysfunction and can also serve as an identifier for T2DM-MIC individuals	[140]
	miR-29c-5p	Ultracentrifugation	15 healthy control patients, 20 type I diabetic patients without DN and 28 type I diabetic patients with DN	miR-29c-5p predicted DN (AUC = 0.774)	[141]

Table 3 (continued)

Kidney disease	Urinary exosomal noncoding RNA	Isolation method of UE	Number ernrolled/animal model	Result	References
	miR-30a	Ultracentrifugation	T2DN patients (n = 156) and controls (n = 210)	Upregulated (UE)	[87]
	miR-34a	Ultracentrifugation	T2DN patients (n = 136) and healthy controls (n = 44)	Upregulated (UE)	[134]
	miR-636	Ultracentrifugation	T2DN patients (n = 136) and healthy controls (n = 44)	Upregulated (UE)	[134]
	MiR-30b-5p	miRCURY™ exosome isolation kit	Sequencing in type 2 diabetic DKD patients (T2DKD; n = 14) and controls with type 2 diabetes and normal renal function (T2DNRF; n = 15); T2DKD (n = 22) was validated against two controls, T2DNRF (n = 15) and controls without diabetic hyperalgesia (n = 18)	Compared to individuals with well-functioning kidneys and type 2 diabetes, there is a notable decrease in the expression of UE miR-30b-5p in T2DKD and CKD patients. Both of these miRNAs are significantly correlated with blood creatinine levels. In DKD patients, UE MiR-30b-5p can serve as a potential biomarker	[133, 145]
	miR-29a/29c	Ultracentrifugation	DN patients (n = 3) and controls (n = 7)	Reduced levels of miR-29 in UE of DN patients may play a specific role in kidney disease by reducing renal fibrosis	[90]
	miR-133b/miR-133a-3p	Ultracentrifugation/unknown	210 T2DN patients/15 diabetic patients with nephrotic range proteinuria	The expression level of UE mir -133b was significantly higher compared to normal T2DN patients ($P < 0.001$)./In comparison with the control group, miR-133a-3p expression was decreased in patients with DN	[87, 144]
	miR-145	Ultracentrifugation	12 normoalbuminuric type 1 diabetic patients (DM1) and 12 microalbuminurie DMI/STZ	①Urinary exosomal miR-145 levels were significantly elevated in the microalbuminurieDMI group compared with normoalbuminuric DM1 patients and control nondiabetic subjects, miR-145 may be a new candidate biomarker; ② Elevated levels of miR-145 were also found in both urinary EVS and glomeruli in an early animal model of experimental DN	[146]
	miR-150-5p/miR-150-3p	Ultracentrifugation/unknown	40 patients with T2DM patients, 20 patients with normoalbuminuria and 20 patients with macroalbuminuria/15 diabetic patients with nephrotic range proteinuria	miR-150-5p was upregulated in DKD patients compared to T2DM patients	[139, 144]
	miR-153-3p	Unknown	Fifteen patients with DN ranging from proteinuria on renal biopsy were followed prospectively for one year in six of these patients	Upregulation	[144]

Table 3 (continued)

Kidney disease	Urinary exosomal noncoding RNA	Isolation method of UE	Number ernrolled/animal model	Result	References
	miR-188-5p	Unknown	Fifteen patients with DN ranging from proteinuria on renal biopsy were followed prospectively for one year in six of these patients	Upregulation	[144]
	miR-320c/miR-320e	Exosome precipitation reagent ExoQuick-TC/unknown	8 healthy controls, 8 patients with type II diabetes and 8 patients with type II DN/Fifteen patients with DN ranging from proteinuria on renal biopsy were followed prospectively for one year in six of these patients	Upregulation	[144, 147]
	miR-342	Ultracentrifugation	T2DN patients (n = 156) and controls (n = 210)	Upregulated	[87]
	miR-362-3p	Ultracentrifugation	40 patients with T2DM patients, 20 patients with normoalbuminuria and 20 patients with macroalbuminuria	miR-362-3p was upregulated in DKD patients compared to T2D patients	[139]
	miR-877-3p	Ultracentrifugation	40 patients with T2DM patients, 20 patients with normoalbuminuria and 20 patients with macroalbuminuria	miR-877-3p was upregulated in DKD patients compared to T2D patients	[139]
	miR-451-5p	Ultracentrifugation	Diabetic (n = 20), healthy control (n = 23)/diabetic rats	An increase in miR-451–5p was observed by miRNA sequencing of DN UEs./Elevated miR-451 in UE of diabetic rats appeared earlier than any significant renal pathology and elevation of ACR, and miR-451/miR-451-5p was identified as a potential biomarker for early detection of renal dysfunction in experimental models of DN	[142, 148]
	let-7i-5p	miRCURY™ exosome isolation kit	Normal glucose tolerance (NGT) (n = 40),Type 2 diabetes mellitus (T2DM-NA) (n = 40),T2DM with microalbuminuria (MIC) (n = 40),T2DM with macroalbuminuria (MAC) (n = 40)	Deposit let-7i-3p was increased in the EV of patients with T2 DM-MIC compared to patients with T2 DM-NA and correlated with metabolic parameters associated with renal dysfunction.Target genes of let-7I-5p are significantly involved in proteoglycan metabolism and are involved in the pathogenesis of DN	[140]
	let-7c-5p	Ultracentrifugation	15 healthy control patients, 20 type I diabetic patients without DN and 28 type I diabetic patients with DN	Compared with controls, let-7c-5p was significantly upregulated in the UE of DN patients	[141]
	miR-548ah-3p	Unknown	Fifteen patients with DN ranging from proteinuria on renal biopsy were followed prospectively for one year in six of these patients	Upregulation	[144]

Table 3 (continued)

Kidney disease	Urinary exosomal noncoding RNA	Isolation method of UE	Number ernrolled/animal model	Result	References
	miR-548p	Unknown	Fifteen patients with DN ranging from proteinuria on renal biopsy were followed prospectively for one year in six of these patients	Upregulation	[144]
	miR-760	Unknown	Fifteen patients with DN ranging from proteinuria on renal biopsy were followed prospectively for one year in six of these patients	Upregulation	[144]
	miR-3677-3p	Unknown	Fifteen patients with DN ranging from proteinuria on renal biopsy were followed prospectively for one year in six of these patients	Upregulation	[144]
	VDAC1	Ultracentrifugation (with or without the addition of DTT) and commercial reagents Exoquick®	Advanced DN (n = 5) and healthy controls (n = 5)	In DN, urinary exosomal VDAC1 levels are reduced/Expression of VDAC1 and VDAC2 was upregulated in the kidney of streptozotocin-induced diabetic rats	[93, 149]
	ELF3	Ultracentrifugation	DN (n = 48), healthy controls (n = 5)	Urinary exosomal Elf3 protein can only be detected in the UEs of patients with DN.The presence of urinary exosomal Elf3 protein in patients with DN suggests irreversible damage to podocytes	[96]
	AMBP	Ultracentrifugation (with or without the addition of DTT) and commercial reagents Exoquick®	Advanced DN (n = 5) and healthy controls (n = 5)	Patients with DN have elevated levels of AMBP in UE and decreased levels of urinary AMBP	[93]
	MLL3	Ultracentrifugation (with or without the addition of DTT) and commercial reagents Exoquick®	Advanced DN (n = 5) and healthy controls (n = 5)	MLL3 was exclusively detected in UE of DN, with increased gene expression observed in peripheral blood cells of DN	[93]
LN	let-7a	miRCURY™ exosome isolation kit	13 LN patients with renal flare and18 remission stage	Compared with inactive LN, let-7a was significantly downregulated in patients with active LN	[150]
	miR-21	miRCURY™ exosome isolation kit	13 LN patients with renal flare and18 remission stage/45 LN patients and 20 healthy	①miR-21 was significantly downregulated in patients with active LN compared to inactive disease.②In patients with LN, urinary exosomal miR-21 may serve as a potential biomarker for predicting disease progression.③The LN chronicity index correlates with the urinary exosome miR-21	[135, 150]

Table 3 (continued)

Kidney disease	Urinary exosomal noncoding RNA	Isolation method of UE	Number ernrolled/animal model	Result	References
	miR-29c	Ultracentrifugation/miRCURYM exosome isolation kit	45 LN patients and 20 healthy/LN (n = 32), nonlupus CKD patients (n = 15) and healthy controls (n = 20)	①In patients with LN, urinary exosomal miR-29c may serve as a potential biomarker for predicting disease progression. ②miR-29c levels in UE were negatively correlated with histologic chronicity index and glomerulosclerosis	[135, 151]
	miR-31	miRCURY™ exosomes isolation kit	In 14 patients with proliferative lupus glomerulonephritis, renal outcomes after treatment were clinical response (n = 7) and no response (n = 7)	Responding patients expressed significantly higher levels of miR-31 in UE compared to nonresponding patients	[152]
	miR-107	miRCURY™ exosomes isolation kit	In 14 patients with proliferative lupus glomerulonephritis, renal outcomes after treatment were clinical response (n = 7) and no response (n = 7)	Responding patients expressed significantly higher levels of miR-107 in UE compared to nonresponding patients	[152]
	miR-135b-5p	miRCURY™ exosomes isolation kit	In 14 patients with proliferative lupus glomerulonephritis, renal outcomes after treatment were clinical response (n = 7) and no response (n = 7)	Responding patients expressed significantly higher levels of miR-135b-5p in UE compared to nonresponding patients	[152]
	miR-146a/miR-146a-5p	Ultracentrifugation	38 patients with SLE and 12 healthy controls/34 LN patients (15 active LN IV, 14 inactive LNIV, 15 active LN IV-CC) and 13 healthy volunteers	①Patients with active LN had the greatest increase in miR-146a compared with controls or SLE patients withoutLN. ②The expression level of miR146a-5p was significantly higher compared to the control group	[153, 154]
	miR-150	miRCURY™ exosomes isolation kit	LN patients (n = 45) and healthy controls (n = 20)	LN UEs miR-150 correlates with renal chronicity index and miR-150 can be used as a noninvasive biomarker for predicting LN/ESRD disease progression with better predictive value than conventional biomarkers	[135]
	miR-654-5p	Ultracentrifugation	34 LN patients (15 active LN IV, 14 inactive LNIV, 15 active LN IV-CC) and 13 healthy volunteers	The expression level of miR-654-5p was significantly higher compared to the control group	[154]
	miR-3135b	Ultracentrifugation	34 LN patients (15 active LN IV, 14 inactive LNIV, 15 active LN IV-CC) and 13 healthy volunteers	The expression level of miR-3135b was significantly higher compared to the control group	[154]
FSGS	miR-193a	ExoQuick exosome precipitation	Primary FSGS (n = 8) and minimal change disease (MCD, n = 5)	Urinary exosomal miR-193a levels were significantly higher in children with primary FSGS than in children with MCD	[155]

Table 3 (continued)

Kidney disease	Urinary exosomal noncoding RNA	Isolation method of UE	Number ernrolled/animal model	Result	References
Renal fibrosis	miR-200b/miR-200	Ultracentrifugation	38 CKD patients with different degrees of renal fibrosis and in 12 normal individuals/32 CKD patients and 7 controls	In the CKD group, the level of miR-200b was lower than that in the normal group, which was negatively correlated with renal fibrosis./Compared with the control group, miR-200 expression levels were reduced	[156]
	miR-29c/miR-29	Ultracentrifugation	32 patients with renal interstitial fibrosis and 20 patients without/32 CKD patients and 7 controls	Compared with the control group, miR-29 expression levels were reduced and significantly negatively correlated with tubulointerstitial fibrosis. miR-29a and miR29c could distinguish the severity of fibrosis	[90, 157]
AKI	miR-16	Urine exosome purification kit	Rat renal ischemia—reperfusion injury as a model of acute kidney injury	miR-16 b expression was increased in UEs in the CKD injury state	[137]
	miR-21	Total exosome isolation reagent	25 scrub typhus patients with AKI and 25 age and sex matched patients without AKI	miR-21 levels were directly correlated with total leukocyte count and inversely correlated with eGFR	[158]
	miR-24	Urine exosome purification kit	Rat renal ischemia—reperfusion injury as a model of AKI	Increased miR-24 expression in UEs in the CKD injury state	[137]
	miR200C	Urine exosome purification kit	Rat renal ischemia—reperfusion injury as a model of AKI	In the CKD injury state, miR-200c expression was increased in UEs	[137]
	miR-29c	Ultracentrifugation	IgAN patients (n = 12) and healthy controls (n = 12)	Urinary exosomal miR-29c expression was significantly downregulated in IgAN patients compared to normal controls and could be used as a biomarker for IgAN	[131]
	miR-205-5p/miR-205	Ultracentrifugation	IgAN patients (n = 12) and healthy controls (n = 12)	Urinary exosomal miR205 expression was significantly downregulated in IgAN patients compared to normal controls and could serve as a biomarker for IgAN	[131]
	miR- 146a	Ultracentrifugation	IgAN patients (n = 12) and healthy controls (n = 12)	Urinary exosomal miR-146a expression was significantly upregulated in IgAN patients compared to normal controls and can be used as a biomarker for IgAN	[131]

IMN idiopathic membranous nephropathy, *CKD* chronic kidney disease, *ESRD* end-stage renal disease, *AKI* acute kidney injury, *DKD* diabetic kidney disease, *EV* exosomal vesicle, *LN* lupus nephritis, *MAC* macroalbuminuria, *MIC* microalbuminuria, *NGT* normal glucose tolerance, *T2DNRF* type 2 diabetes and normal renal function, *T2DKD* type 2 diabetic diabetic kidney disease, *T2DM* type 2 diabetes mellitus, *MCD* minimal change disease, *T2DM-NA* T2DM and normoalbuminuria, *T2DM-MAC* T2DM patients with macroalbuminuria, *eGFR* estimated glomerular filtration rate

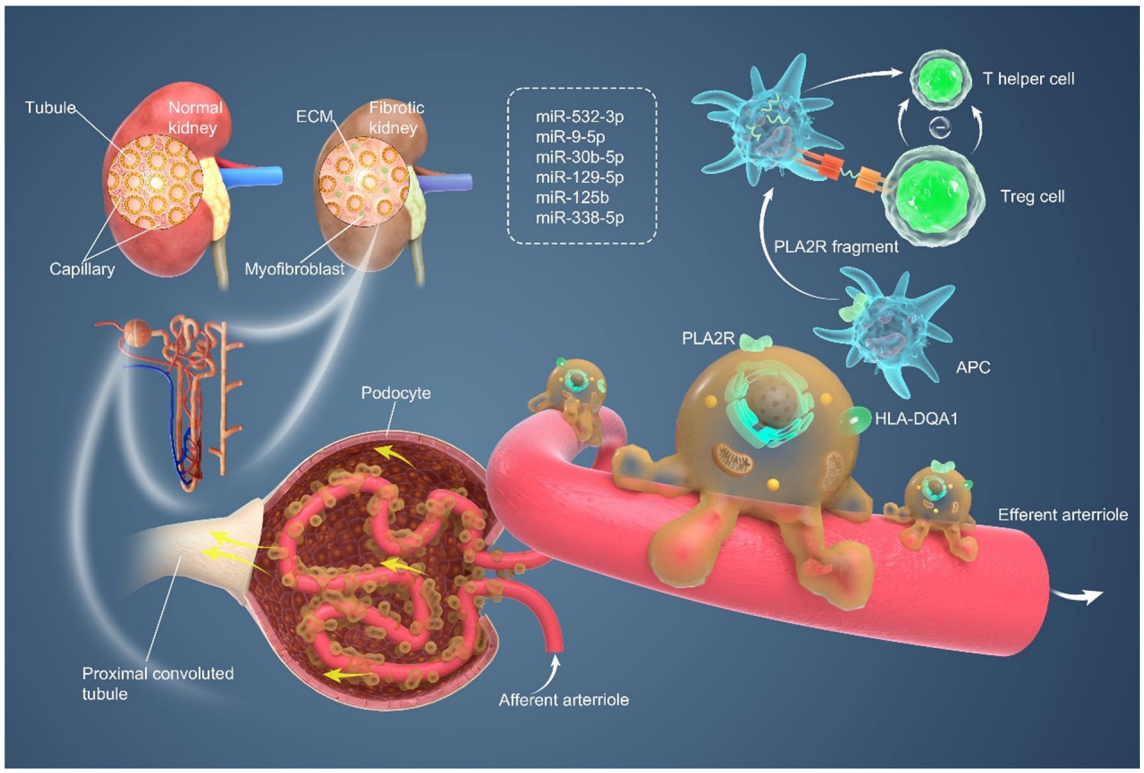


Fig. 2 The role of exosomes in the pathogenesis of IMN. The role of exosomes in the pathogenesis of IMN. The five miRNAs in the figure are the differential miRNAs identified by miRNA flux sequencing in IMN patients compared with healthy controls, and they are involved in the pathogenesis of IMN through four main aspects, namely, the regulation of anti-PLA2R antibody and/or HLA-DQA1, renal fibrosis, podocyte injury, and immune homeostasis of Tregs

DN. Moreover, overexpression of miR-30b-5p can mitigate high glucose-induced EMT [166]. This effect is likely achieved by targeting the key EMT activator SNAI1. In unilateral ureteral obstruction (UUO) mice, miR-9-5p protects against renal fibrosis by inhibiting the downregulation of genes associated with key metabolic pathways, including mitochondrial function, oxidative phosphorylation, fatty acid oxidation (FAO), and glycolysis [167]. In IMN patients, there are differences in the expression of urinary exosomal miR-30b-5p and miR-9-5p. The downregulation of urinary exosomal miR-9-5p in IMN patients may reflect the active metabolism of pathways related to kidney fibrosis. Based on the above findings, it can be inferred that miR-30b-5p and miR-9-5p might also play a role in the renal fibrosis process in IMN [164] (Fig. 2).

(3) Associated with podocyte injury.

Podocytes are terminally differentiated visceral epithelial cells of the glomerulus in the kidney; together with the basement membrane and endothelial cells, these cells form the glomerular filtration barrier [168]. Podocyte injury leads to proteinuria, and reduced podocyte numbers are considered a relative risk factor for progressive kidney damage [169]. The primary pathological change in IMN is kidney glomerular podocyte injury caused by immune complex deposition. MiRNAs are essential for maintaining podocyte homeostasis. Studies have shown that differentially expressed miR-9-5p and miR-30 s in IMN urinary exosomes may be involved in maintaining podocyte stability [164]. Wu et al. reported that downregulation of miR-30 induces proteinuria and podocyte injury [145]. Further confirmation in a rat model demonstrated that miR-30 exerts a protective effect by directly inhibiting Notch1 and p53, which mediate podocyte injury [137]. Moreover, recent research has suggested that miR-30 may enhance mouse podocyte injury and proteinuria improvement by potentially regulating calcium/calcineurin signaling and disrupting urokinase-type plasminogen activator receptor-integrin β3 (uPAR-ITGB3) signal transduction [170]. In addition, miR-9-5p, regulated by tumor susceptibility candidate gene 2 (CASC2), targets PPARγ and can alleviate podocyte injury [171]. Furthermore, relevant literature indicates that differentially expressed genes associated with urinary exosomal miRNAs, such as miR-532-3p [172],

miR-429 [173], miR-129-5p [174], miR-107 [172], miR-25-3p [175], and miR-206 [176, 177], are associated with glomerular podocyte injury, and miR-532 and miR-107 have been confirmed to participate in podocyte injury in MN [178] (Fig. 2).

(4) Tregs are involved in the regulation and modulation of the immune response.

Currently, antigen–antibody reactions are considered the primary immunopathogenic mechanism of MN [179], and CD4 + T cells are recognized as key cellular participants in immune responses [180]. CD4 + T cells consist of helper T cells (Th) and regulatory T cells (Tregs), with the former playing a pivotal role in the immune response by secreting cytokines that mediate inflammatory reactions and pathogen clearance [180]. Treg cells primarily regulate the intensity of Th cell responses to prevent excessive immune reactions, causing self-repair damage [180]. Clinically, MN is also characterized by evident Th cell subset imbalances. Multiple studies have indicated that Th17 cell expression is enhanced in MN patients, along with upregulated IL-17 and other cytokines [181–183], while the proportion of Treg cells is reduced [183]. In the urine of IMN patients, differentially expressed miRNAs, including miR-532-3p [184], miR-9-5p [185], miR-30b-5p [186], miR-129-5p [186], miR-125b [187], and miR-338-5p [188], have been found to participate in the regulation of Tregs across various diseases. Therefore, it is inferred that in IMN, the differential expression of miRNAs, including miR-532-3p, miR-9-5p, miR-30b-5p, miR-129-5p, miR-125b, and miR-338-5p, in urine exosomes might also be involved in Treg regulation to prevent kidney damage potentially caused by excessive immune reactions [184]. However, these assumptions await further experimental validation [164] (Fig. 2).

The role of exosomes in the treatment of IMN

Treatment for IMN primarily involves the use of steroids in combination with alkylating agents in modern medicine. The latest 2021 guidelines from KDIGO [189] included rituximab as a first-line treatment for IMN. However, challenges persist, such as inconsistent efficacy, substantial side effects, and a high relapse rate, which fail to fully meet the therapeutic needs of MN patients [190]. Consequently, exploring safer and more effective treatment approaches is imperative. Exosomes have demonstrated potential as cellular therapy alternatives in preclinical and clinical studies, with data indicating the feasibility and safety of exosome-based treatments. For instance, exosomes derived from dendritic cells (DCs), which contain major histocompatibility complex/peptide complexes and promote T-cell immune responses, have been tested in clinical trials as vaccines against metastatic melanoma and non-small cell lung cancer [191–193]. Furthermore, exosomes sourced from stem cells have been developed for applications in cardiovascular disease, diabetes, graft-versus-host disease, and neurological and orthopedic disorders [194–196]. Clinical trials have also explored the use of plant-derived exosomes for curcumin delivery [197, 198]. In the field of kidney diseases, multiple preclinical, clinical, and in vitro models have been used to investigate the potential therapeutic applications of exosomes in conditions such as DN [199], hypertension-related cardiorenal syndrome [200], acute kidney injury [201, 202], IgA nephropathy [203], cadmium nephropathy [204], obstructive kidney diseases [205], and ischemia/reperfusion injury [206]. Exosomes, which can act as therapeutic agents or drug delivery vehicles, exhibit significant potential to mitigate systemic consequences in patients with CKD [207], suggesting that they are promising candidates for treatment [208–210]. Moreover, the discovery of mRNAs and miRNAs in exosomes and their role in cell-to-cell communication signify a novel direction for utilizing exosomes as delivery vehicles for therapeutic drugs [76].

(1) Therapeutic agents: exosomes with inherent healing activity.

Exosomes carrying RNA can selectively deliver their contents to specific target cells, temporarily correcting dysfunctional processes [76]. This endows exosomes with immense potential as therapeutic delivery vehicles. Exosomes have found widespread application in kidney diseases, such as modulating kidney transplant rejection, rectifying metabolic defects, and fostering renal regeneration. These therapeutic extracellular vesicles (EVs) seem to primarily derive from various sources of mesenchymal stem cells [211]. Mesenchymal stem cells (MSCs), recognized as among the most effective stem cell types for inducing kidney regeneration and having diverse differentiation potential [212], predominantly treat kidney ailments through the paracrine release of EVs [213, 214]. For instance, they have demonstrated the ability to reverse acute and chronic kidney injuries in various experimental models [215]. These effects are partly driven by paracrine enhancement of recovery [215–217] and are strongly mediated by the cargo of RNA within exosomes and/or microvesicles [218, 219]. Injection of exosomes derived from bone marrow mesenchymal stem cells (BMSCs) into DN rats significantly improves renal tissue oxidative stress damage, reduces urinary protein excretion, and safeguards renal function [220]. Injection of exosomes isolated from urine-derived stem cells (SCs)

into DN rats decreases cellular apoptosis and urinary ALB while enhancing glomerular endothelial cell growth [221]. Moreover, urinary stem cells have been shown to repair podocyte injury through exosome-mediated mechanisms [222] (see Fig. 3 for details). Additionally, exosomes from cultured epithelial cells also exhibit some effects in vitro [223].

For many kidney-related diseases, the primary targets for potential exosome-based therapies are endothelial cells, which play important roles in regulating blood pressure, locally regulating blood flow, modulating blood coagulation, and removing plasma lipids and are readily accessible to exosomes from the circulation [94]. Dysregulation of these processes constitutes a significant factor contributing to common CKDs. Endothelial cells face the bloodstream, positioning them as "low-hanging fruits" for exosome-based therapies and largely circumventing targeting issues [76]. Although current research lacks the application of exosomes as therapeutic agents for IMN, the future may involve utilizing mesenchymal stem cells or epithelial cells as sources, with endothelial cells as targets, potentially ushering in a new paradigm for treating IMN.

(2) Drug delivery vehicles: exosomes as therapeutic carriers.

Currently, various drug delivery vehicles, such as liposomes, micelles, nanoparticles, and hydrogels, are being extensively investigated. However, many of these materials face significant challenges, such as low bioavailability and high systemic toxicity [33]. Recently, exosomes and microvesicles have garnered substantial attention as novel drug delivery vehicles due to the following attributes: (a) Safety: Exosomes, which are endogenous carriers, exhibit excellent biocompatibility, low immunogenicity, and good tolerability, thereby establishing safer and more effective drug delivery systems (DDSs) [224–229]. (b) Barrier penetration: Exosomes and microvesicles, owing to their small size and flexibility, can traverse major biological barriers, including the blood–brain barrier (BBB) [230–233]. Zhuang et al.

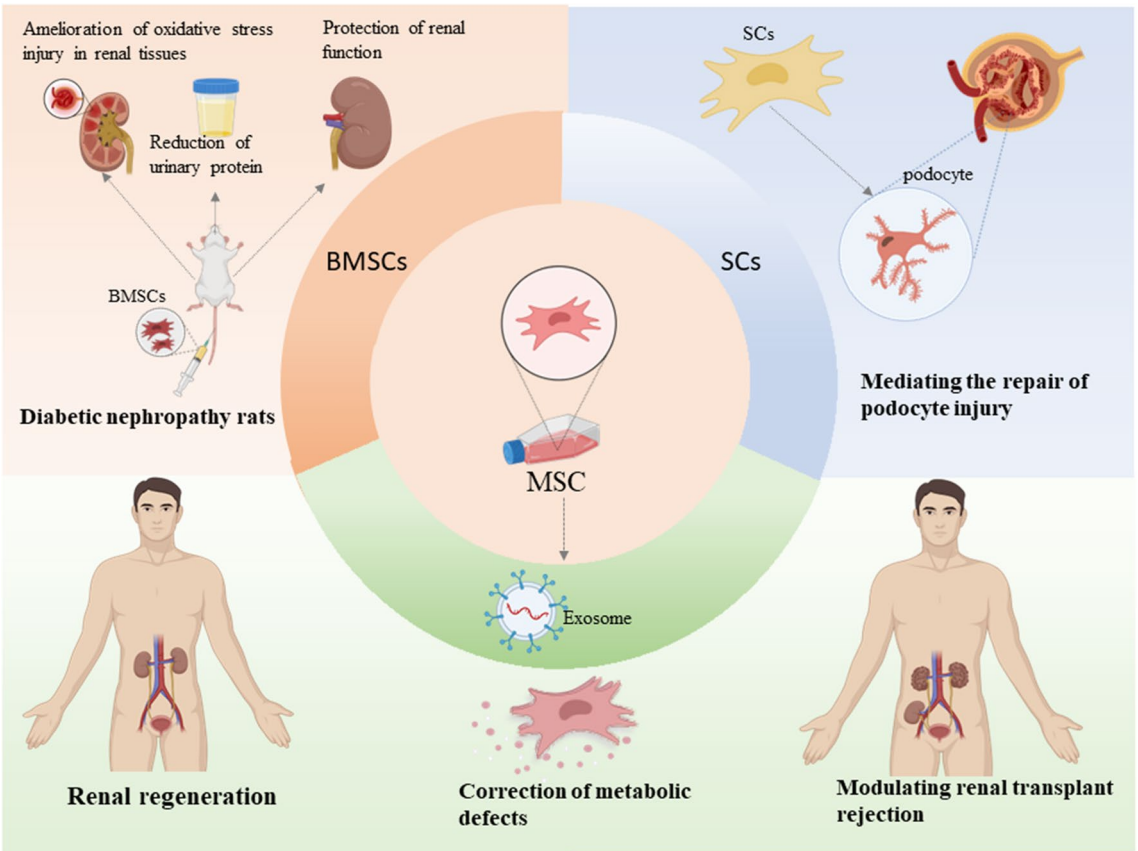


Fig. 3 Exosomes as therapeutic agents for IMN. Exosomes as therapeutic agents for IMN. Exosomes used as therapeutic agents for IMN are mainly derived from mesenchymal stem cells (MSCs), which can be subdivided into bone marrow mesenchymal stem cells (BMSCs) and urothelial stem cells (SCs). Each of the three pathways shown in the figure treats IMN through different pathways

discovered that exosomes effectively transport curcumin to the brain to treat neuroinflammation-related diseases without side effects [227]. (c) Specificity: Analysis of the proteins on the surface of exosome membranes aids in developing drug delivery systems for targeted cell-specific delivery [234]. (d) Stability: The bilayer structure of exosomes shields their cargo from RNases and proteases, enhancing drug stability and efficacy [94]; see Fig. 4 for details. Additionally, research suggests that the bioavailability of exosome delivery systems surpasses that of other systems. For instance, doxorubicin loaded into exosomes has been shown to be more effective than other delivery systems and to cause fewer adverse effects on major organ systems, especially the heart [235]. In the future, exosomes hold promise for delivering drugs or traditional Chinese medicine monomers for treating IMN to target organs, enhancing treatment precision and effectiveness.

Future outlook and challenges

As novel biological signaling molecules and therapeutic carriers, exosomes have unique advantages in the field of kidney disease diagnosis and treatment. Compared with other renal diseases, there are relatively few studies on the use of exosomes in the treatment of IMN, which also means that exosome development in IMN will help revolutionize the diagnosis and treatment of IMN. Inevitably, there are some challenges to overcome.

(1) Extension of clinical applications: exosomes face the challenges of standardization and standardized methods in the clinical treatment of IMN. Ensuring consistency and accuracy in the exosome collection, purification and assay process is critical to ensure the efficacy and reproducibility of the results. Large-scale multicenter clinical trials are necessary to extensively validate the efficacy and safety of exosomes in patients with IMN and to develop relevant guidelines and standards.
(2) In-depth mechanistic exploration of exosomes: although exosomes play an important role in the pathogenesis of IMN, their specific regulatory mechanisms and targets of action are not yet fully understood. Future studies should further explore the relationship between exosomes and IMN and

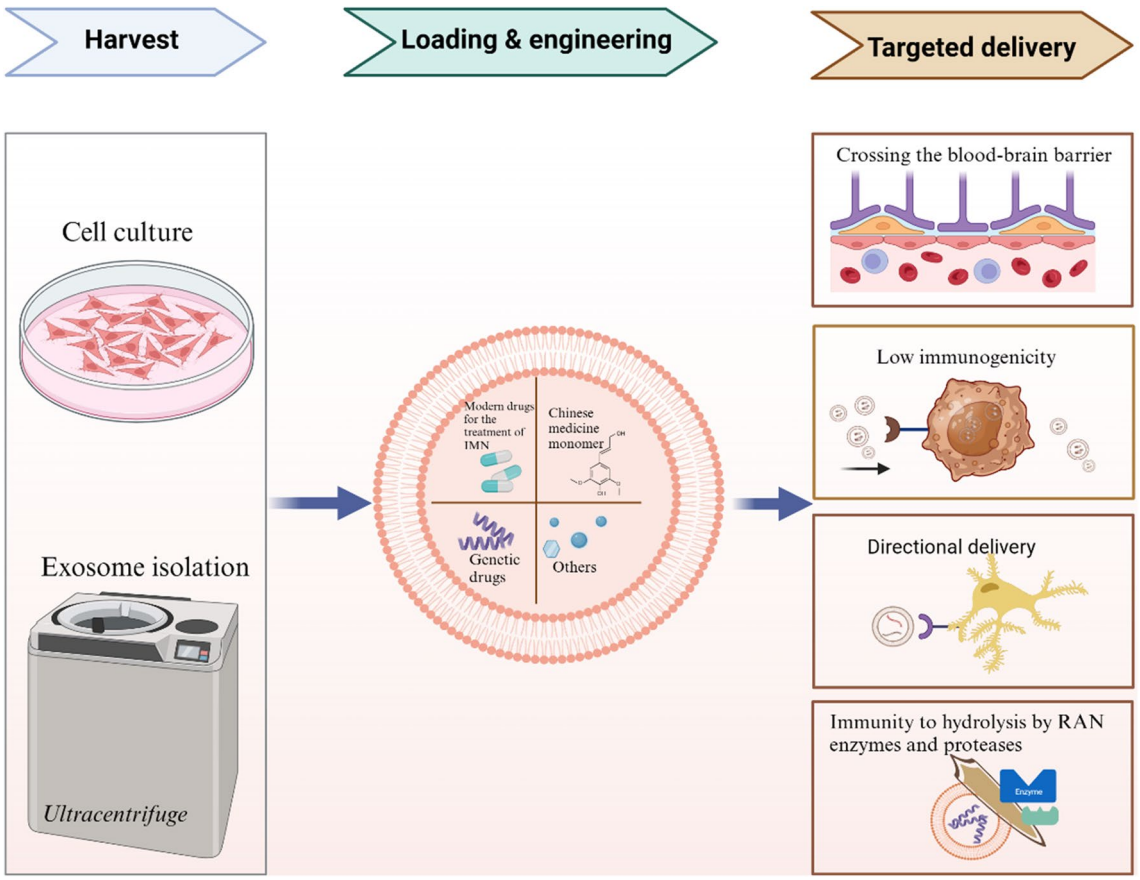


Fig. 4 Exosomes as drug delivery carriers. Exosomes, as drug delivery carriers, consist of three main components: harvesting, loading engineering and targeted delivery

reveal their regulatory networks and signaling pathways to better understand the occurrence and progression of IMN.

(3) The development of individualized therapeutic strategies: IMN is a heterogeneous disease with significant clinical variability. As potential biomarkers and therapeutic targets, exosomes hold promise for individualized diagnosis and treatment. Future research should focus on the transition from discovery to application. Exosomes can be used for early diagnosis, patient staging and severity prediction, as well as for more accurate identification of underlying etiologies, improved patient categorization, and stratification of patients with IMN. Appropriate exosome-targeted therapies should be selected based on individual patient characteristics. After specific therapeutic strategies have been defined, continuous monitoring of therapeutic efficacy allows for close individualization of diagnosis and treatment.

(4) Optimization of drug delivery vehicles and associated techniques: the foremost challenges of using exosomes as drug delivery vehicles include imperfect extraction and separation techniques, which can lead to low yields and low encapsulation and loading efficiencies. Functionalizing exosomes is needed for encapsulating hydrophilic macromolecules. Concurrently, advancing and optimizing exosome delivery systems and technologies is crucial for enhancing exosome stability and targeting within the body. Additionally, additional pharmacological studies are needed to validate the safety and efficacy of exosome-targeted therapies for eventual clinical translation.

(5) Interdisciplinary Collaboration and Data Sharing: exosome research demands interdisciplinary collaboration involving experts from fields such as nephrology, molecular biology, and bioinformatics. Future efforts should strengthen collaboration and communication between different domains, facilitating data and resource sharing to expedite research progress and promote exosome applications in IMNs.

In conclusion, exosomes hold immense potential for the diagnosis and treatment of IMN. Future research and clinical practices should further refine the techniques and methods, explore their mechanisms comprehensively, develop personalized treatment strategies, intensify drug development, and foster interdisciplinary collaboration to realize the widespread application of exosomes in IMN. These findings could lead to more precise and effective diagnostic and therapeutic tools for IMN patients, significantly improving disease management and prognosis.

Abbreviations

ARF1	ADP-ribosylation factor 1
ATF3	Activating transcription factor 3
CDC42	Cell division control protein 42
CP	Cerulo plasmin
DCs	Dendritic cells
eGFR	Estimated glomerular filtration rate
EMT	Epithelial–mesenchymal transition
ER	Endoplasmic reticulum
ESE	Early-sorting endosome
Evs	Extracellular vesicles
FSP1	Fibroblast-specific protein1
MSCs	Mesenchymal stem cells
NGAL	Neutrophil gelatinase-associated lipocalin
PI3K	Phosphoinos itide 3-kinase
SCs	Stem cells
Th	Helper T cells
Treg	Regulatory Tcells
UUO	Unilateral ureteral obstruction
AKI	Acute kidney injury
BMSCs	Bone marrowmesenchymal stem cells
CKD	Chronic kidney disease
DN	Diabetic nephropathy
ESRD	End-stage renal disease
FSGS	Focal segmental glomerulo sclerosis
IgAN	IgA nephropathy
ILVs	Intra luminal vesicles
IMN	Idiopathic membranous nephropathy
KDIGO	International Kidney Disease Guidelines
LSEs	Late-sorting endosomes
MCN	Minimal change nephrosis
MCNS	Minimal change nephrotic syndrome
MHC-II	Major histocompatibility complex class II
MN	Membranous nephropathy
MPS	Mononuclear phagocyte system
MUC1	Mucin1
MVBs	Multi vesicula rbodies
NGAL	Neutrophil gelatinase-associated lipocalin
SSNS	Steroid-sensitive nephrotic syndrome
TBMN	Thin basement membrane nephropathy
TGN	Trans-Golgi network
UE	Urinary exosomes

Acknowledgements

This work was supported by the National Natural Science Foundation of China (No. 2019YFC1709401, 82372552), the Tianjin Municipal Health Commission (No. 2021012), the Guangdong Basic and Applied Basic Research Foundation (No. 2023A1515111044), the Shenzhen Science and Technology Program (grant no. RCBS20231211090733052; RCBS20231211090701008), the Excellent Youth of Natural Science Research Projects in Anhui Province Universities (2023AH030060), the Research Fund of Anhui Institute of Translational Medicine (2022zhyx-C01), the Basic and Clinical Cooperative Research and Promotion Program of Anhui Medical University (2021xkT028), and the Postdoctoral Fellowship Program of CPSF (No. GZC20233233). All the authors contributed to the article and approved the submitted version.

Author contributions

LW, JW, KY: writing, review and editing and designed the manuscript. LW, TS, MP, AX and XX: modified the tables and figures and revised the manuscript. LF: writing, review and editing. PY: writing, review, editing, and supervision. HY and XW: writing-review & editing, supervision, resources, conceptualization.

Availability of data and materials

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Competing interests
The authors declare that there are no competing interests.

Received: 9 March 2024 Accepted: 13 June 2024
Published online: 08 August 2024

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