Proceedings of ICBioMed 2026 Symposium: Biomedical Engineering and Public Health: Real-Time Wearables for Disease Detection
DOI: 10.54254/2753-8818/2026.ES37853

Exosome-Mediated Cellular Injury in Diabetic Nephropathy: Mechanisms and Research Progress

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Abstract. Diabetic nephropathy (DN) is the major microvascular complication of diabetes and is still an important source of progressive renal disease and renal failure worldwide. Exosomes represent an efficient form of cellular extracellular communication in which cells exchange regulatory elements, such as microRNAs, proteins and lipids. There is evidence accumulating that alterations of exosome biosynthesis, components and cellular uptake are associated with renal damage in diabetic conditions. In particular, exosome components regulate cellular dysfunction of podocytes and tubular epithelium, inflammation, oxidative imbalance, autophagy, apoptosis and fibrotic remodeling. This review integrates current evidence concerning the contribution of exosomes to DN, with emphasis on exosomal miRNAs, their downstream molecular networks, and their involvement in different forms of renal cellular damage. The potential utility of exosome-derived molecules for noninvasive disease assessment and targeted intervention is also discussed. Analysis of exosome-dependent intercellular signaling will lead to a clearer understanding of the biological processes of DN, and new biomarkers and therapeutic targets will be developed for DN.

Keywords: diabetic nephropathy, exosome, cell injury, miRNA, signaling pathway

1. Introduction

Diabetic nephropathy (DN) is characterized by chronic proteinuria and a progressive deterioration of kidney function. DN affects 25% to 40% of patients with diabetes and causes a large economic burden. The International Diabetes Federation forecast the diabetic population to reach 784 million by 2045 and will increase the prevalence of DN [1]. DN is one of the main causes of end-stage renal disease (ESRD) all over the world [2]. In China, DN is the leading cause of ESRD in middle-aged and old people, indicative of the increase in incidence of diabetes in that population [3]. DN is caused by the interaction of hemodynamic and metabolic factors (hyperglycemia, proteinuria, lipid overload). Histologically, DN is characterized by significant structural alterations of the glomerular and the tubulointerstitial compartments. Glomerular change shows as the enlargement of glomerular

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DOI: 10.54254/2753-8818/2026.ES37853

size, over-secretion of mesangial matrix, thickening of basement membrane, and disturbance of normal foot process in podocyte, while tubular lesion shows as epithelial cell enlargement and proliferation, basal membrane regeneration. Chronic high blood sugar activates the effect pathways that promote deposition of extracellular protein, leading to renal fibrosis and functional loss. Hyperglycemia-induced microvascular injury speeds up the deterioration of DN. With the increase in its incidence, diabetic nephropathy will exert a heavy impact on China's health care and public health [4]. Understanding the pathogenesis of DN facilitates exploration of new targets for the treatment of DN.

Exosomes consist of a heterogeneous population of membrane-closed extracellular particles with a diameter within the range of 30–150 nm. They are formed when multivesicular bodies protrude their interior into the extracellular space during endocytosis and they are usually round in shape by electron microscopy. Their surfaces are loaded with transmembrane proteins and provide specific recognition and capture of the receptor cells [5]. Within these vesicles, a heterogeneous repertoire of bioactive molecules is loaded and delivered to the recipient cells thereby affecting cellular function and signaling. Their main biological function is the transport of bioactive molecules and transmission of intercellular information through ligand–receptor contacts and direct content delivery to target cells. Besides their physiological roles, exosomes have promise for antigen presentation, drug delivery and disease diagnosis [6]. Pathological conditions change the secretion, molecular composition and function of exosomes, which may promote or reflect the adaptations of the cells to disease. As in DN, several factors also interfere with exosome secretion. For example, high glucose levels and oxidative stress significantly alter the levels of exosomes in renal tubular epithelial cells and their miRNA and protein content. These exosomes subsequently induce pathological processes such as podocyte damage, renal interstitial fibrosis and inflammatory pathways through cell-cell communications [7, 8].

Recent studies have broadened our knowledge of the role of exosomes in DN. In type 2 diabetes, exosomes contribute to renal injury by activating certain molecular pathways in renal cells. Exosomal miRNAs have been identified as regulators of apoptosis in renal cells, executors of oxidative stress and modulators of epithelial–mesenchymal transition [9, 10], some exosomes targets critical pathways such as TGF-β1/Smad3, which is implicated in extracellular matrix accumulation and fibrosis, Wnt/β-catenin, which mediates epithelial-mesenchymal transition and podocyte damage [11, 12]. Exosomes in human blood (serum), urine and other biological fluids are suggested to be biomarkers for evaluating risk of diabetic nephropathy and contribute valuable information for timely timely management of diabetes-related chronic kidney disease [13]. Exosomal signaling is playing an increasingly important role in driving cellular alterations that initiate or promote DN. This review covers how exosomes mediate cellular injury in DN in a comprehensive way, indicating strategies for therapeutic intervention and provides new directions for treatment of DN.

2. Roles of exosomal mirnas in DN-associated cellular injury

2.1. Exosomal miRNAs in DN-associated cellular injury

Exosomal miRNAs act as mediators of intercellular communication in DN by regulating target gene expression and influencing multiple pathological mechanisms such as apoptosis, pyroptosis, oxidative stress, fibrosis, inflammation and autophagy. Owing to their stability and effective delivery potential, exosomal miRNAs can be transferred to the recipient cells and induce functional changes during DN [14]. Some studies have shown that exosomal miRNAs originated from different cells have protective or pathogenic effects depending on cargo content and target cells. For instance,

DOI: 10.54254/2753-8818/2026.ES37853

miR-30e-5p alleviated renal injury by targeting ELAVL1 and inhibiting pyroptosis-related pathways [15]. Similarly, exosomal miR-424-5p derived from MSCs could inhibit epithelial mesenchymal transition by targeting YAP1, leading to less renal fibrosis [16].

Macrophage-derived exosomal miRNAs also participate in the progression of DN. With high-glucose exposure, M2 macrophage-derived exosomal miR-25-3p can inhibit podocyte apoptosis and EMT and promote podocyte autophagy, thereby alleviating cell injury [17]. Conversely, hyperglycemia results in an alteration of macrophage-derived exosomal cargo, increased miR-7002-5p detrimentally influences the autophagic machinery by negative regulation of Atg9b and thus aggravates renal damage [18]. In addition, exosomal miR-92a-1-5p promotes mesangial cell injury by regulation of RCN3-related signaling pathways [19]. Some other exosomal miRNAs including miR-16-5p, miR-215-5p and miR-204 also participate in the regulation of podocyte protection, EMT and tubular injury through VEGFA, ZEB2, METTL7A/CIDEC signaling [20, 21]. Overall, exosomal miRNAs are the critical factors influencing the progression of DN-related cell injury through the regulation of various pathways. The regulatory effects of exosomal miRNAs on cell injury in DN-associated renal injury are summarized in Figure 1.

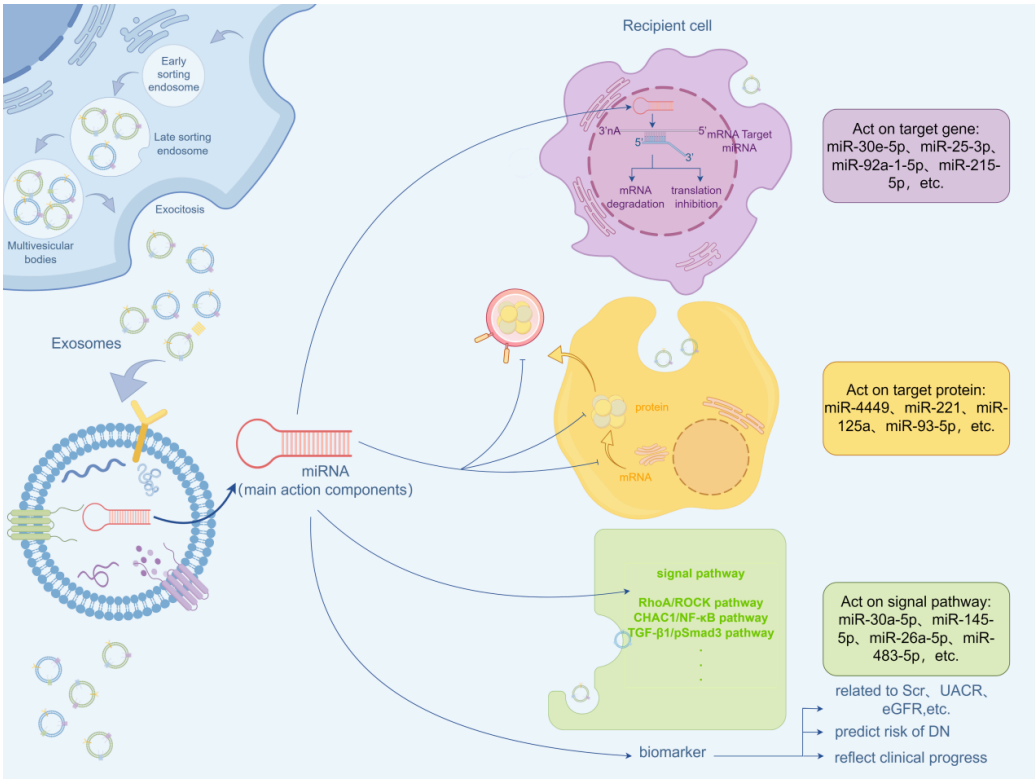

Figure 1. Exosomes regulate cell injury through miRNAs

2.2. Mechanisms of exosomal miRNAs in DN-associated cellular injury

Exosomal miRNAs regulate DN-associated cellular injury by targeting genes and downstream pathways. Once delivered into the recipient cells, exosomal miRNAs bind to the 3′ untranslated sequences of target mRNAs and impact some pathological processes. Inflammation and pyroptosis are important mechanisms causing exosome-induced renal injury. In serum-origin exosomes enriched with miR-4449, exosomes are taken up by renal proximal tubular cells, and the miR-4449 suppresses the expression of anti-inflammatory regulator HIC-1 to activate NLRP3 inflammasome,

DOI: 10.54254/2753-8818/2026.ES37853

ROS accumulation, and pyroptotic cell death [9]. By contrast, macrophage M2-derived exosomes convey miR-93-5p to podocytes, which negatively regulates TLR4, thereby inhibiting the NF-κB- and JNK/SAPK-mediated responses and maintaining podocyte integrity [22].

Exosomal miRNAs also play roles in renal fibrosis and dedifferentiation of cells. Podocyte-originated exosomal miR-221 facilitates the dedifferentiation of cells by targeting the DKK2 gene, contributing to renal impairment [23]. Exosomal miR-483-5p also promoted extracellular matrix accumulation and renal interstitial fibrosis by regulating the TIMP2 expression and enhancing activation of the TGF-β1/Smad3 pathway [24]. In addition, exosomal miR-125a attenuates DN progression by targeting HDAC1 and reducing endothelin-1-mediated renal injury [25]. Besides inflammation and fibrosis, exosomal miRNAs also regulate apoptosis and endothelial dysfunction in DN. Urinary exosomal miR-145-5p induced the activation of the RhoA/ROCK pathway by promoting the phosphorylation of MYPT1 protein, which promotes podocyte apoptosis [26]. Urinary exosomal miR-30a-5p protects from glomerular endothelial cells by targeting Notch1 and VEGF, protecting high glucose-induced endothelial-mesenchymal transition of glomerular endothelial cells and pathological angiogenesis [27]. Exosomal miRNAs play a major role in DN as molecular conveyors in regulating diverse target genes and signaling pathways. By reshaping multiple injury-related cellular processes, these miRNAs hold useful molecular information for disease diagnosis as well as opportunity for mechanism-based therapies for DN.

2.3. Exosomal miRNAs as diagnostic biomarkers in DN

Recent studies on urinary exosomes, which are noninvasively obtained, have shown that the miRNAs contained in these urinary exosomes can be used as biomarkers to predict and diagnose DN. Han and Zang et al. [28, 29] used molecular techniques, such as qPCR and correlation analysis, to demonstrate that exosomal miR-145-5p are positively correlated with serum creatinine and the urinary albumin-to-creatinine ratio. Moreover, the abundance of miR-27a-3p and miR-30b-5p was correlated with metabolic parameters related to glucose and lipid homeostasis, providing a molecular bridge between metabolic disturbances and renal damage. ROC curve analysis further showed that exosomal miRNAs were possible diagnostic biomarkers of DN. Ali et al. [30] proved that urinary exosomes can successfully distinguish diabetic patients with renal injury from those without. Wang et al. [31] showed that urinary exosomal miRNA-615-3p increased with the DN progression and there were significant differences in levels between DN stages. Clinical analysis showed the value of miRNA-615-3p for diagnosis of DN progress surpassed that of a traditional ACR indicator, thus serving as an important marker for advanced DN.

3. Signaling pathways regulated by exosomes in DN

DN progression through transfer of bioactive cargos (proteins and miRNAs) that regulate different signaling pathways involved in inflammation, oxidative stress, fibrosis, apoptosis and autophagy. Among these signaling pathways, MAPK signaling pathway is an important one that contributes to exosome-induced renal injury. Exosomes derived from renal cells under high-glucose conditions induce MAPK signaling pathways, including ERK, p38MAPK, JNK signaling [32, 33]. Activation of ERK promotes extracellular matrix accumulation by inducing fibronectin and collagen expressions, and contributes to glomerulosclerosis [34]. Meanwhile, the activity of p38MAPK and JNK can lead to inflammatory and oxidative injury by increasing cytokine production, with subsequent aggravation of renal cell injury [33]. Besides MAPK signaling pathways, exosomal miRNA regulates the epigenetic and fibrotic pathways in DN. For example, high-glucose-induced

DOI: 10.54254/2753-8818/2026.ES37853

exosomal miR-21 inhibits KDM6A expression and disrupts the KDM6A/KLF10 regulatory axis, resulting in promotion of RAAS activity and TGF-β1/Smad signal pathway, increased ECM deposition and renal fibrosis [35].

Exosomes also regulate cellular metabolism and autophagy. MSC-derived exosomes inhibit the excessive activation of mTOR, enhance autophagic activity and decrease lipid accumulation [36, 37]. Exosomes can also inhibit NF-κB-induced inflammatory responses and regulate pathways involved in apoptosis, which mitigate the progression of renal inflammation collectively. In summary, such findings indicate that exosomes regulate the progression of DN by multiple signaling mechanisms, particularly MAPK pathways, highlighting their potential as therapeutic targets for DN.

4. Additional mechanisms underlying exosome-mediated renal injury

Exosomes can lead to cell injury by having certain biomolecules that can be transported by exosomes, including proteins, lipids and metabolites, through different regulating mechanisms such as signals, immune response or metabolic intervention. The origin of the specific cells enables exosome proteins secreted by the cells to trigger the cell death and cell injury. For example, in high glucose environment, exosomes from the tubular epithelial cells increase the expression of Epsin1 and DLL4/N1ICD, leading to the activation of M1 macrophages and resulting in tubular injury [11]. Exosomes from adipose mesenchymal stem cells promote autophagy flux and alleviate the renal podocyte injury by inhibiting activation of MPC5, thereby alleviating renal fibrosis [37]. Moreover, exosomes are also crucial for delivering targeted peptides and immunomodulatory molecules. The exosomal membrane containing CD47 weakens the removal of exosomes by phagocytosis, thereby favouring increased systemic persistence, and increase efficiency for delivery to target sites. Additionally, MSC derived exosomes ameliorate hyperglycemia stimulated inflammatory response of tubular epithelial cells and glomerular endothelial cells by inducing reduced expression of IL-6, IL-1β and TNF-α, and decreased renal inflammation and glomerular fibrosis [38].

Exosome secretion is regulated by different physiological mechanisms that affect cellular injury onset, repair and aggravation. Exosomal communication therefore provides a pathway for connective immunity-cell activation to environmental shifts in the inflammatory milieu. Exosomes of activated macrophages, neutrophils and T lymphocytes can carry inflammation-associated molecules such as TNF-α, IL-6, miR-155 and others that could be used to transmit inflammatory messages to recipient cells. After local or systemic dissemination, these exosomes may enter renal tissue and modify the activity of mesangial and tubular epithelial cells, favouring a proinflammatory environment that induces cell death and renal fibrotic remodeling. Finally, anti-inflammatory exosomes derived from Tregs or bone marrow derived MSCs secrete elements such as IL-10 and miR-146a , thereby decreasing renal inflammation and facilitating protection from cell death and injury [39]. The vascular system can also regulate endothelial function and vasculature remodeling through the secretion of exosomes. Hyperglycaemia-induced endothelial dysfunction causes exosomes that contain adhesion molecules and pro-coagulant factors, such as tissue factor, to be released and induce platelet aggregation and infiltration of monocytes, aggravating renal vascular inflammation and thrombosis [40]. Exosomes from vascular smooth muscle cells can also deliver microRNAs to promote mesangial cell proliferation and extracellular matrix formation, accelerating glomerulosclerosis. Exosomes from the endocrine-related organs also participate in insulin resistance and in regulating metabolism. Exosomes from insulin-resistant adipocytes or hepatocytes may contain miRNAs that impair renal insulin function through a systemic supply and make renal oxidative stress and hyperglycemia-induced apoptosis [41]. In addition, exosomes from adrenal

DOI: 10.54254/2753-8818/2026.ES37853

glands may convey glucocorticoids or catecholamines, impacting on inflammation-related gene expression and thereby directly affecting renal injury. An overview of the mechanisms involved in exosome-caused cellular injury in diabetic nephropathy, for example, cargo transfer, function regulation, immune impact, regulation of metabolism and so on, is summarized in Figure 2.

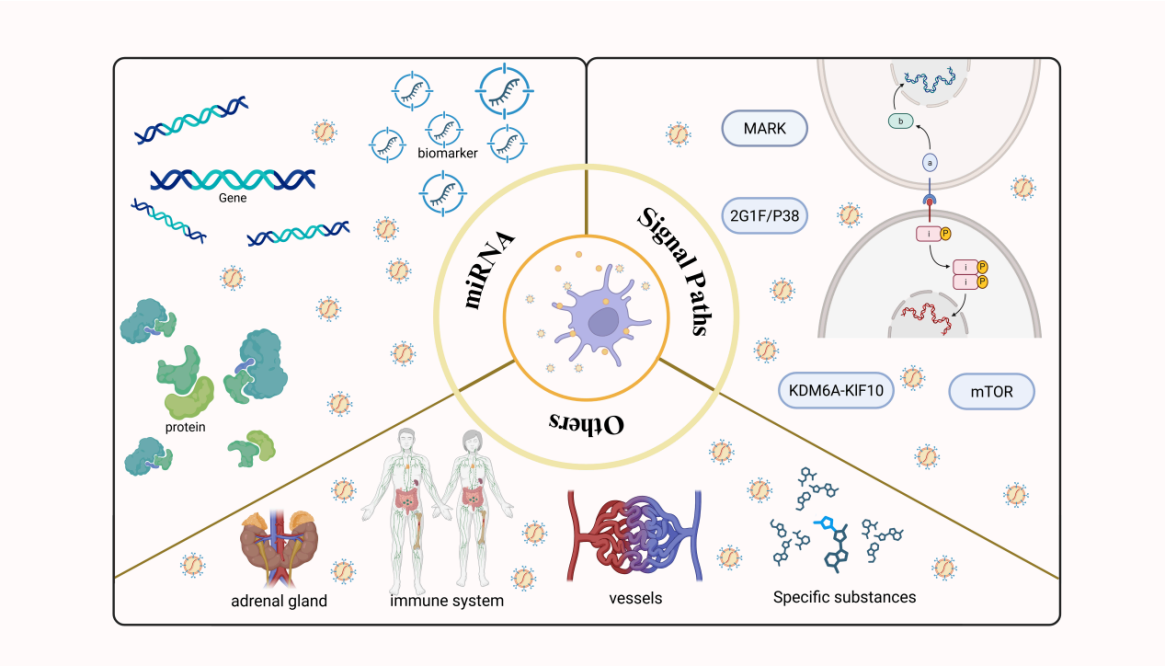

Figure 2. Overview of exosome-mediated cellular injury mechanisms in DN

5. Conclusion

Exosomes play critical roles in intercellular communication in DN, leading to initiation and progression of renal injury by transferring their bioactive cargos, including miRNAs, proteins and lipids. Accumulating evidence shows that exosomes modulate various pathological processes associated with DN, such as inflammation, oxidative stress, apoptosis, autophagy defects and renal fibrosis, leading to cellular injury and development of disease. Exosome-derived molecules contained in various biological fluids possess strong potential as noninvasive biomarkers for the early diagnosis and monitoring of DN. The clinical use of exosomes for DN is still limited by considerable biological and technical ambiguities. Variations in vesicle populations, poorly understood molecular sorting processes, unpredictable cell tropism, and varying clinical techniques are major limitations. Combining systems-level molecular profiling with improved visualization techniques and programmable vesicle engineering may provide a route to translating the present experimental results into clinical applications to diagnose and treat disease.

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