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Role of Extracellular Vesicle-Derived Noncoding RNAs in Diabetic Kidney Disease

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Keywords
Extracellular vesicles · Noncoding RNA · Diabetic kidney disease · Diagnostic biomarkers · Therapeutic target

Abstract

Background: Diabetic kidney disease (DKD), a metabolism-related syndrome characterized by abnormal glomerular filtration rate, proteinuria, and renal microangiopathy, is one of the most common forms of chronic kidney disease, whereas extracellular vesicles (EVs) have been recently evidenced as a novel cell communication player in DKD occurrence and progress via releasing various bioactive molecules, including proteins, lipids, and especially RNA, among which noncoding RNAs (including miRNAs, lncRNAs, and circRNAs) are the major regulators. However, the functional relevance of EV-derived ncRNAs in DKD is to be elucidated. ***Summary:*** Studies have reported that EV-derived ncRNAs regulate gene expression via a diverse range of regulatory mechanisms, contributing to diverse phenotypes related to DKD progression. Furthermore, there are already many potential clinical diagnostic and therapeutic studies based on these ncRNAs, which can be expected to have potential applications in clinical practice for EV-derived ncRNAs. ***Key Messages:*** In the current review, we summarized the mechanistic role of EVs in DKD according to biological function classifications, including inflammation and oxidative stress, epithelial-mesenchymal transition, cell death, and extracellular matrix deposition. In addition, we comprehensively discussed the potential applications of EV-derived ncRNAs as diagnostic biomarkers and therapeutic targets in DKD.

Introduction

Diabetic Kidney Disease

Diabetic kidney disease (DKD), originating from type 1 and type 2 diabetes mellitus (DM) [1], is a major form of chronic kidney disease featuring abnormal glomerular filtration rate, proteinuria, and renal microangiopathy in China and all over the world. It is estimated that approximately 50% of DKD patients will develop end-stage renal disease that requires long-term dialysis [2, 3], and though a stable condition could be maintained with dialysis for a relatively long time period [4], renal failure-related death is an inevitable outcome for most of the DKD patients. According to the statistical data from the International Diabetes Federation (http://www.diabetesatlas.org/), the increased prevalence of DM to 10.5% in 2021 is expected to continue rising up to 11.3% and 12.2% in 2030 and 2045, respectively. In this case, a significant increase in DKD patients will also be foreseen. Although renal replacement treatment provides a management option for DKD patients in current clinical

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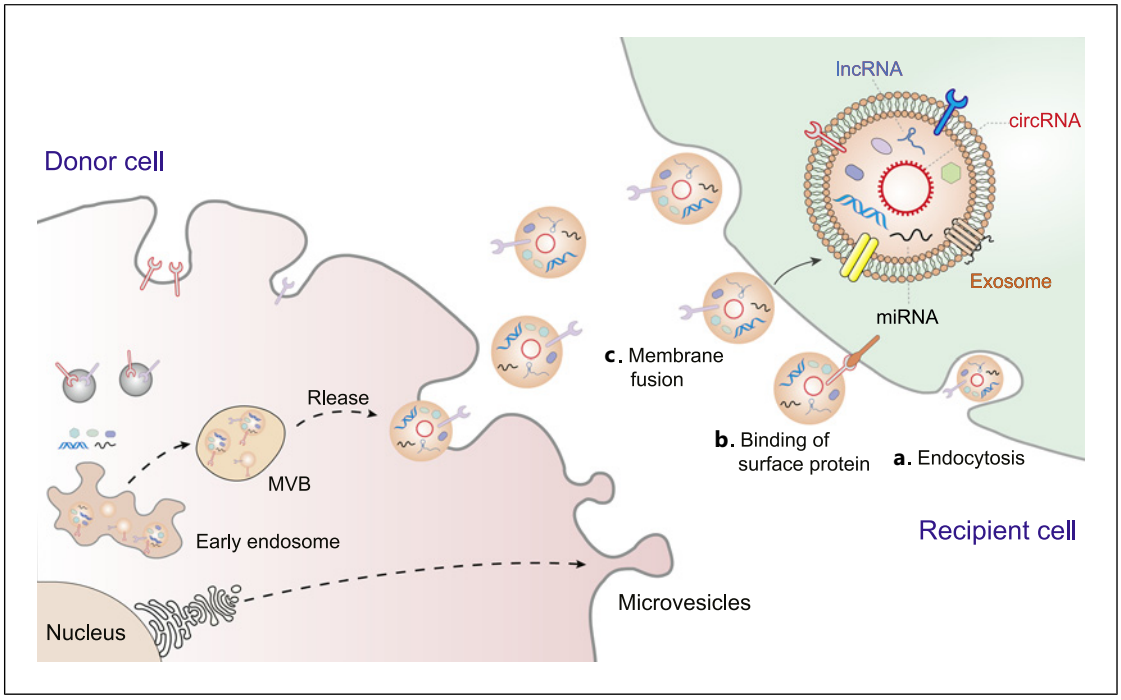

Fig. 1. Biological processes of EV genesis, release, and uptaking. In host cells, firstly, the protein components from the Golgi apparatus or internalized from the cell surface are transported onto the early endosome. Then, the maturation of early endosomes results in the formation of late endosomes and MVBs. Finally, EVs are secreted by host cells. On the side of recipient cells, EVs are uptaken by the recipient cells through the following processes: endocytosis (**a**), binding of surface protein (**b**), and membrane fusion (**c**). Then, multiple biological components, including proteins, lipids, and nucleic acids (e.g., noncoding RNAs), are delivered into the recipient cells. EVs, extracellular vesicles; MVBs, multivesicular bodies.

practice, a certain therapeutic gap is presented between these clinical treatment modalities and cure purposes [5]; therefore, it is particularly important to understand and clarify the mechanisms involved in DKD, and we look forward to finding more suitable treatment options.

Extracellular Vesicles

Cell-released vesicles with membranous structures, a kind of cell-released nanoscale-size microparticles (30–1,000 nm), are widely reported to be involved in cell-cell communication [6, 7]. Extracellular vesicles (EVs) encompass various subtypes classified by their synthesis and release mechanisms, including microvesicles, ectosomes, oncosomes, apoptotic bodies, and exosomes [8]. The two most recognized types are exosomes and microvesicles. In addition, some special types of EVs are released by certain types of cells or under certain conditions, such as apoptotic EVs and autophagic EVs, as well as cancer cell-secreted large oncosomes [9]. Through protecting the impacts from proteases, nucleases, and other environmental factors by their lipid double-layer membranes, EVs may directly act on neighboring or distant recipient cells in various ways, including endocytosis (Fig. 1a), protein binding (Fig. 1b), and membrane fusion (Fig. 1c), thus releasing multiple types of bioactive molecules (proteins, lipids, and RNAs) and orchestrating multiple cellular processes in recipient cells [10]. The effects of EVs on recipient cells reflect the multifactorial consequence of cell- or tissue-specific adsorption and uptake of EVs, the composition and abundance of functional EV cargo, and the degree of adaptability of recipient cells in response to certain EV cargo. Different sets of surface proteins on EVs and recipient cells are involved in different EV uptake pathways, granting a layer of specificity in the targeted delivery of EV cargo. In some other cases, EV-induced signaling in recipient cells does not require internalization of EVs or their luminal cargo but is triggered by molecular interactions at the interfaces of EVs and recipient cell membranes [11].

Noncoding RNAs

MicroRNAs (miRNAs), a type of endogenous small RNA with a length of 20–24 nucleotides (nt), have many essential adjustable functions in cells. By complementarily

binding to the 3′-untranslated region of targeted mRNAs, miRNAs act as regulators of gene expression, thereby inhibiting posttranscriptional gene expression [12]. Increasing evidence has reported that miRNAs are selectively sorted into EVs and participate in intercellular communication in DKD [13]. PIWI-interacting RNAs (piRNAs), a type of small RNA with a length of 21–35 nt, specifically interact with PIWI protein to perform multifaceted functions in germline development and somatic tissues. The piRNA complex inhibits gene expression in two ways: one is by regulating the formation of heterochromatin and mediating DNA methylation modification, thereby regulating the expression of transcription-level genes; another approach is to rely on active catalytic enzymes to silence transposon mRNA, thereby inhibiting gene expression after transcription [14–16]. In addition to small RNAs, large ncRNAs also participate in gene regulation in various biological processes. Long noncoding RNAs (lncRNAs), collectively referred to as transcripts with more than 200 nt, have limited potential to encode proteins [17]. lncRNAs perform functions through multiple molecular and cellular mechanisms, such as interacting with epigenetic factors or TFs to modulate gene transcription, sequestering miRNAs, modifying RNA, splicing and affecting mRNA stability, interacting with proteins, and encoding functional small peptides [18–21]. In addition, lncRNAs can also be selectively sorted into EVs and participate in cell-to-cell communication in the microenvironment [22]. Circular RNAs (circRNAs), generated by a particular form of alternative splicing called back-splicing, regulate gene expression in multiple ways, including recruiting diverse epigenetic factors to orchestrate gene transcription and signal transduction, interaction with transcriptional factors and cofactors or target gene promoters, interacting with miRNAs, splicing factors, and diverse RNA-binding proteins, and orchestrating a broad repertoire of RNA or protein modifications to affect their activation and stability [23–27]. Newly added studies have indicated that circRNAs participate in multiple diseases, including DKD. Increasing evidence has proposed that RNAs, especially noncoding RNAs (ncRNAs) [28, 29], including miRNAs [30], piRNAs [31], lncRNAs [32], and circRNAs [33], are the major cell communication function executors in EVs, and EV-derived ncRNAs have been shown to play a critical role in DKD [34–37] via several ways, including inflammation and oxidative stress (OS), epithelial-mesenchymal transition (EMT), cell death, and extracellular matrix (ECM) deposition. Although several recent reviews emphasized the role of EV-derived ncRNAs in DKD [14, 38–41], most studies only focus on one type of ncRNA and do not summarize their effects based on the mechanistic view. In the current review, we summarized the mechanistic role of EVs in DKD according to biology function classifications, including inflammation and OS, EMT, cell death, and ECM deposition. In addition, there is ongoing or upcoming research on potential clinical diagnosis and treatment based on these ncRNAs, which is expected to have potential applications in clinical practice.

Emerging Mechanistic Paradigms of EV-Derived ncRNAs in DKD

In order to intuitively understand the role of EV-derived ncRNAs in DKD, we have illustrated these mechanistic paradigms in Figure 2 and discussed them in detail in the following table (Table 1).

Regulation of Inflammation and Oxidative Stress

Inflammation is an immune response-related process that plays a vital role not only in host pathogen defense but also in tissue homeostasis [62], including tissue repair, regeneration, and remodeling through recruitment and activation of the cells involved in innate and adaptive immunity [38]. In the current opinion, DM is a chronic inflammation disease; therefore, inflammation is also critical in DM-derived DKD. Accumulating experimental and clinical evidence verified the role of inflammation in DKD [39]. Zhao et al. [40] found that mesenchymal stem cell (MSC)-derived EVs could reduce the inflammation phenotype of podocytes via the miR-15b-5p-PDK4 axis, thereby playing a protective role in DKD. Through in vitro MSC-derived EVs and high glucose (HG)-treated podocyte co-culture and in vivo EV administration into diabetic mice, Wang et al. [41] found that MSC-derived EVs could exert anti-inflammatory activity via targeting the NLRP3 inflammasome by transferring miR-22-3p into podocytes. In addition, Zhuang et al. [58] showed that γ-aminobutyric acid treatment could block podocyte injury aggravation induced by macrophage-derived EVs via regulating the miR-21a-5p-Tnpo1/miR-25-3p-ATXN3 signal axis. In addition to the protective role of EVs in DKD, recent studies have shown the pro-inflammatory role of exosomes in DKD. Jia et al. [62] found that EV-miR-199a-5p derived from human renal cortex proximal tubule epithelial cells (HK-2) induced M1 polarization by targeting the Klotho/TLR4 pathway, further accelerating the progression of DKD. This evidence suggested that EV-derived ncRNAs can influence the development of DKD by regulating inflammation.

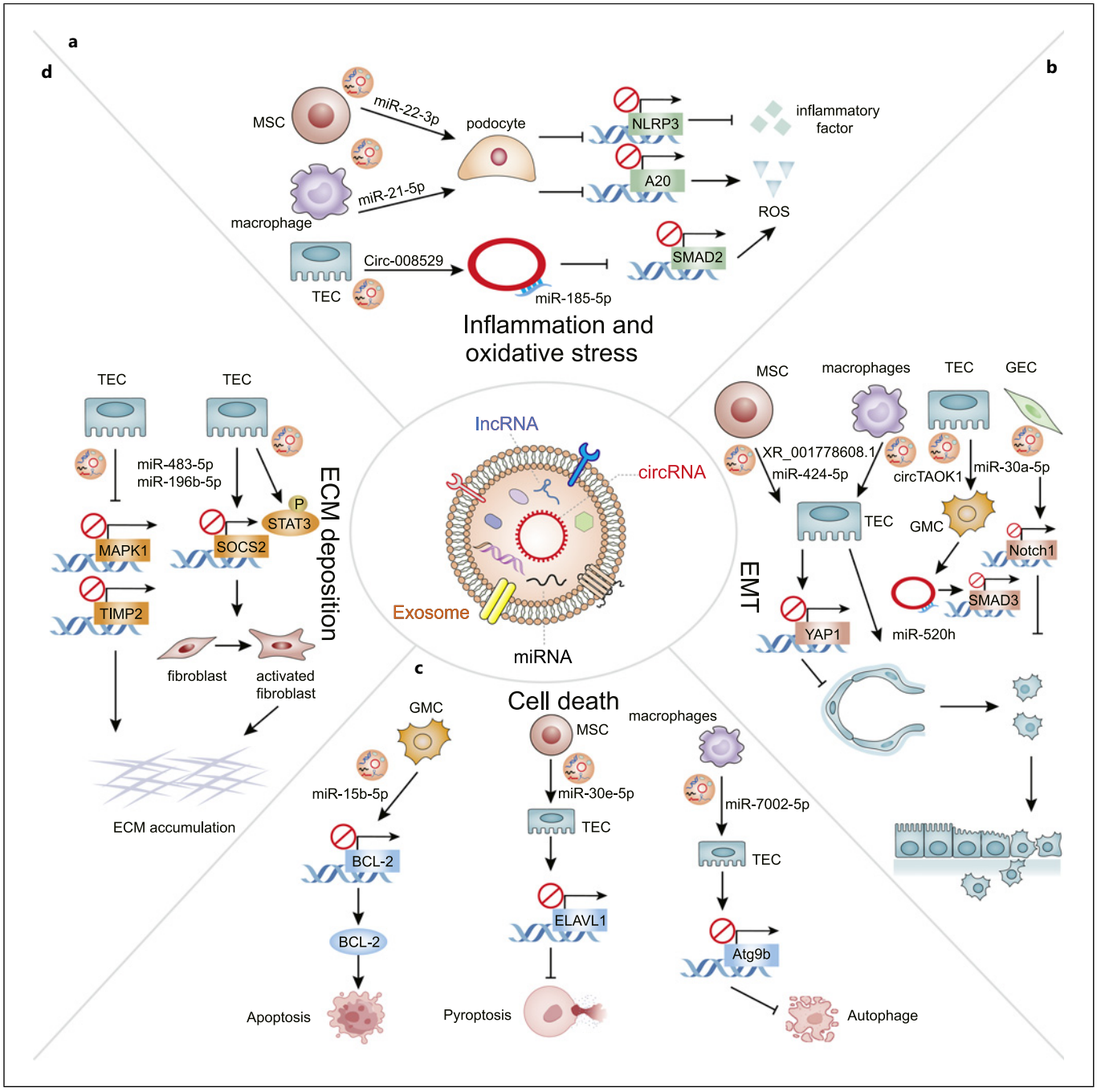

Fig. 2. EV-derived ncRNAs play important roles in regulating DKD development and progression. A view of the cellular interaction pathways involving EV-derived ncRNAs in DKD, including (**a**) inflammation and OS, (**b**) EMT, (**c**) cell death, and (**d**) ECM deposition. ncRNAs, noncoding RNAs; OS, oxidative stress; EMT, epithelial-mesenchymal transition; ECM, extracellular matrix; MSC, mesenchymal stem cell; TEC, tubular epithelial cell; GMC, glomerular mesangial cell; GEC, glomerular endothelial cell.

Reactive oxygen species, such as superoxide or hydroxyl, are natural by-products of oxygen metabolism that can regulate multiple biological processes, including cell proliferation, signaling transduction, and aging [63]. Kidney is particularly vulnerable to early structural and functional damage caused by OS [64]; therefore,

Table 1. The emerging roles of EV-derived ncRNAs in DKD

EV-derived ncRNAs	Source cell	Target cell	Function and mechanism	DKD progression	Reference
miR-15b-5p	GMCs	GMCs	Induces mesangial cell apoptosis by targeting BCL-2	–	[42]
circ_0125310	GMCs	GMCs	Promotes cell proliferation and fibrosis by regulating the miR-422a/IGF1R/p38 axis	Up	[43]
miR-483-5p	TECs	–	Boosts ECM deposition by lessening the restraint of cellular miR-483-5p on MAPK1 and TIMP2 mRNAs	Up	[44]
miR-196b-5p	TECs	Fibroblasts	Increases ECM production by inhibiting SOCS2 expression and enhancing STAT3 phosphorylation	Up	[45]
miR-92a-1-5p	TECs	GMCs	Induces MFT and leads to ER stress by downregulating the expression of RCN3	Up	[46]
circ_0008529	TECs	–	Increases inflammation and apoptosis by regulating the miR-185-5p/SMAD2 pathway	Up	[47]
miR-221	Podocytes	TECs	Induces PTEC dedifferentiation through Wnt/β-catenin signaling	Up	[48]
miR-30a-5p	GECs	GECs	Regulates GEC EMT and angiogenesis by modulating Notch1/VEGF signaling pathway	Down	[49]
circTAOK1	TECs	GMCs	Promotes proliferation, fibrosis, and EMT by regulating the miR-520h/SMAD3 axis	Up	[50]
miR-30e-5p	BMSCs	PTECs	Ameliorates pyroptosis by inhibiting ELAVL1	Down	[51]
miR-22-3p	MSCs	Podocytes	Increases inflammation by activating the NLRP3 signaling pathway	Down	[41]
miR-424-5p	MSCs	PTECs	Decreases cell apoptosis and inhibits EMT by inhibiting YAP1 activation	Down	[52]
miR-26a-5p	ADSCs	Podocytes	Targets TLR4, activates the NF-κB pathway, and downregulates VEGFA	Down	[53]
miR-15b-5p	MSCs	Podocytes	Reduces apoptosis and inflammation by targeting PDK4 and decreasing the VEGFA expression	Down	[40]
miR-let-7a	BMSCs	Renal cells	Suppresses apoptosis of renal cells and OS by targeting USP22	Down	[54]
miR-16-5p	hUSCs	Podocytes	Suppresses podocyte apoptosis by targeting VEGFA	Down	[55]
miR-125a	adMSCs	GMCs	Inhibits HDAC1 and ET-1	Down	[56]
miR-7002-5p	Macrophages	PTECs	Suppresses autophagy by inhibiting the expression of Atg9b	Up	[57]
miR-21a-5p/miR-25-3p	Macrophages	Podocytes	Increases apoptosis by regulating Tnpo1/ATXN3 axis	Down	[58]
miR-93-5p	Macrophages	Podocytes	Induces apoptosis by regulating the miR-93-5p/TLR4 axis	Down	[59]
ENSMUST00000181751.1, XR_001778608.1, and XR_880236.2	Macrophages	TECs	Promotes EMT by regulating the MAPK pathway	–	[60]
miR-21-5p	Macrophages	Podocytes	Promotes ROS production and activates inflammation by inhibiting the A20 expression	Up	[61]

TECs, tubule epithelial cells; GECs, glomerular endothelial cells; BMSCs, bone marrow mesenchymal stem cells; ADSCs, adipose-derived stem cells; hUSCs, human urine-derived stem cells.

increased OS and its related injury could affect DKD development and progression [65]. Recent studies on diabetic animal models have demonstrated that EV-derived ncRNAs can be a main determinant in OS regulation during the pathophysiological process of DKD. Gao et al. [66] demonstrated that the serum of DKD patients rich in EV-miR-4449 facilitates OS by regulating the expression of HIC1. Furthermore, Ding et al. [61] found that miR-21-5p in macrophage-derived EVs promoted podocyte injury by increasing reactive oxygen species levels. These studies indicated the OS regulatory role of EV-derived ncRNA.

Regulation of Epithelial-Mesenchymal Transition

EMT caused by HG is considered an important pathogenic factor for renal injury, disruption of glomerular filtration barrier, and proteinuria, leading to the deterioration of DKD [67]. Li et al. [50] found that exosomal circTAOK1 contributes to DKD progression by boosting proliferation, fibrosis, and EMT of glomerular endothelial cells (GECs). Mechanically, circTAOK1 regulates SMAD3 expression by sponging miR-520h. Exosomal miR-30a-5p suppresses EMT and abnormal angiogenesis of GECs by modulating the Notch1/VEGF signaling pathway [49]. Cui et al. [52] found that MSC-derived EV-miR-424-5p could inhibit HG-induced cell apoptosis and EMT by inhibiting YAP1 activation in HK2 cells. Furthermore, HG-treated macrophage-derived EV-lncRNA, including ENSMUST00000181751.1, XR_001778608.1, and XR_880236.2, could promote EMT by regulating the MAPK pathway in DKD [60]. Therefore, EV-derived ncRNAs can regulate the DKD process by modulating EMT.

Regulation of Cell Death

In DKD, cell death is considered to play a role in the depletion of the renal cells gradually [68], and several types of cell death, such as apoptosis, pyroptosis, and autophagy, have been found to be present in the kidney. Tsai et al. [42] showed that upregulated glomerular mesangial cell (GMC)-derived EV-miR-15b-5p could mediate MC apoptosis through targeting BCL-2 in DKD. Duan et al. [53] found that adipose-derived stem cell (ADSCs)-derived EV-miR-26a-5p could ameliorate the pathological symptoms of DKD in diabetic mice and inhibit HG-induced glomerular podocytes from apoptosis by targeting TLR5. Interestingly, Mao et al. [54] highlighted that bone marrow mesenchymal stem cell (BMSC)-derived EV-miR-let-7a could repress renal cell apoptosis through downregulation of USP22. Moreover, Duan et al. [55] revealed that overexpressed EV-miR-16-5p in human urine-derived stem cells (hUSCs) could suppress podocyte apoptosis. Surprisingly, MSC-derived EV-miR-125a inhibited mesangial hyperplasia and kidney fibrosis in rats through the promotion of cell apoptosis [56]. M2 macrophage-derived EV-miRNA-93-5p could improve lipopolysaccharide-induced podocyte apoptosis by targeting TLR4 in DKD [59]. Pyroptosis is a gasdermin-dependent form of pro-inflammatory necrotic cell death [69] and has been proved to be involved in DKD [70]. Gao et al. [66] demonstrated that enriched EV-miR-4449 in the serum of DKD patients could promote pyroptosis via the miR-4449/HIC1 pathway. In addition, miR-21-5p in macrophage-derived EVs can regulate pyroptosis-mediated podocyte injury by targeting A20 in DKD [61]. Lv et al. [51] found that BMSC-derived EV-miR-30e-5p inhibits caspase-1-mediated pyroptosis by targeting ELAVL1 in HG-induced HK-2 cells. Exosomal miR-7002-5p derived from HG-induced macrophages suppresses autophagy in TECs by targeting Atg9b [57]. Taken together, these studies proved that EV-ncRNAs play important roles in regulating the DKD process via mediating cell death. Numerous cell death regulators are implicated in playing a critical role in DKD, which may provide novel insight into DKD management.

Regulation of ECM Deposition

Fibrosis, defined by the formation and accumulation of ECM mainly by tissue-resident parenchymal cells and interstitial cells, is essential for wound healing, which is a secondary response to tissue injury, providing a scaffold for regeneration after or concomitant to the cessation of the inflammatory response [71]. In the kidney, no virtual data could accurately define the pros or cons of the physiological role of fibrosis. Recently, increasing evidence has indicated that EV-derived ncRNAs can modulate the process of DKD by regulating renal fibrosis. Zhu et al. [43] demonstrated that the HG-induced EV-circ_012531 sponged miR-422a and targeted the IGF1R/p38 axis, thereby leading to ECM deposition in DKD. Moreover, Liu et al. [44] showed that EVs containing lncRNA HNRNPA1 were delivered to urine to lessen the inhibition of miR-483-5p on MAPK1 and TIMP2, eventually boosting ECM deposition and promoting renal interstitial fibrosis in DKD. In addition, EV-circ_0008529 was found to contribute to ECM accumulation via the miR-185-5p/SMAD2 pathway in DKD [47]. The proliferation of myofibroblasts also plays an important role in ECM deposition and renal interstitial fibrosis formation. Tsai et al. [46] found that the exosomal miR-92a-1-5p secreted by HG-stimulated PTECs is absorbed by GMCs, inducing myofibroblast transdifferentiation

in vitro and in vivo, ultimately leading to GMC injury. These studies suggested the influence of ECM deposition and renal fibrosis on DKD occurrence and progression.

Regulation of Signal Transduction Pathway

According to previous studies, several signaling pathways have been found to be involved in the process of DKD, including Wnt/β-catenin, TGF-β, MAPK, PI3K, Notch, and JAK/STAT signal pathway [72–78]. Su et al. [48] found that miR-221 in EVs can regulate Wnt/β-catenin signaling by directly targeting DKK2 to mediate PTEC dedifferentiation, thereby inducing PTEC injury in DKD. Bai et al. [79] illuminated that circ_DLGAP4 in EVs could promote DKD progression by sponging miR-143 and further regulating the ERBB3/NF-κB/MMP-2 axis. Additionally, Hu et al. [45] proved that miR-196b-5p in EVs could modulate the crosstalk between PTECs and fibroblasts during the development of renal fibrosis via regulating the STAT3/SOCO2 signaling pathway. Additional DKD modulating related signaling pathways might be identified in the future. Nevertheless, more studies are required to elucidate the precise molecular mechanisms involved in EV-derived ncRNA-regulated signal pathways in DKD, thereby offering possible intervention modalities via targeting these pathways for DKD management.

Potential Clinical Applications of EV ncRNAs in DKD

Mounting evidence suggested that EV-derived ncRNAs have the potential to serve as diagnostic biomarkers based on their high specificity and sensitivity and their easy accessibility via noninvasive collection [80, 81]. Kim et al. [82] found that 7 EV-derived miRNAs (miR-1246, miR-642a-3p, let-7c-5p, miR-1255b-5p, let-7i-3p, miR-5010-5p, and miR-150-3p) were specifically increased in DKD patients compared to healthy volunteers, among which miR-4449 was remarkably upregulated in DKD patients. Compared with healthy controls and DM patients, the expression of 14 urine EV-derived miRNAs (miR-4491, miR-2117, miR-4507, miR-5088-5P, miR-1587, miR-219a-3p, miR-5091, miR-498, miR-4687-3p, miR-516b-5p, miR-4534, miR-1275, miR-5007-3p, and miR-4516) was upregulated (>2-fold) in DKD patients according to the study by Zhao et al. [83] Further ROC analysis revealed that miR-4534 had a relatively high area under the curve (AUC) of 0.786 (95% confidence interval [CI]: 0.607–0.965), which indicated that the quantification of miRNAs in urinary EVs can be utilized as a primary or at least an auxiliary diagnostic criterion of DKD. Zang et al. [84] further identified differential expression of EV-derived miR-21-5p and miR-30b-5p in patients with DKD and renal dysfunction. The AUC reached as high as 0.830 (CI: 0.673–0.986; $p = 0.004$) when taking the miR-21-5p into consideration and was slightly decreased when using miR-30b-5p (AUC: 0.813; 95% CI: 0.652–0.974; $p = 0.006$), which represent potential biomarkers related to the pathogenesis of DKD [84]. Our previous study has found that miRNA-615-3p in the urinary exosomes is significantly upregulated in DKD patients and positively correlated with the expression of inflammation and fibrosis molecules associated with DKD, making it a novel biomarker for evaluating the progression of DKD [85]. Besides diagnostic value, EV-derived miR-155, miR-424, miRNA-451-5p, and miR-99a-5p have been also proved to hold prognostic value as an early and sensitive noninvasive indicator of renal disease [86–88]. Taken together, these studies suggested that EV-derived ncRNAs in biofluids have exhibited tremendous potential in the development of noninvasive biomarkers, and their clinical applications deserve further research. In addition to serving as diagnostic and prognostic biomarkers, EVs also have therapeutic potential. Some preclinical studies have shown that EVs from stem cells can protect DKD by transferring renal protective ncRNAs to damaged MCs (miR-125a and miR-222) [56, 89], podocytes (miR-26a-5p and miR-215-5p) [53, 90], and renal TECs (miR-125b and miR-let7c) [91, 92]. Considering the crucial biological functions of EV-derived ncRNAs in DKD, the strategies on specifically targeting EVs or their cargoes, such as the ncRNAs, can be prospective therapeutic choices for DKD. Additionally, the research of Luo et al. [93] revealed the transcriptome characteristics and heterogeneity of EVs at the single EV level through high-throughput methods for the first time, providing an important basis for the functional research and modification application of EVs.

Conclusions and Prospects

This review summarized the mechanisms of EV-derived ncRNAs in DKD occurrence and progression and their potential as diagnostic biomarkers and therapeutic targets. To date, studies have indicated that EV-derived ncRNAs play a versatile role in DKD by modulating inflammation and OS, EMT, cell death, ECM deposition, and the signal transduction pathway. However, only a small fraction of EV-derived ncRNAs have

been identified, and systematic recognition of the role of EV-derived ncRNAs in DKD initiation and progression should be performed. Recently, Luo et al. [93] reported the single EV profiling method via single-cell RNA sequencing, which may help to better understand the specific mechanisms of EV-ncRNA-related DKD phenotype regulation, thereby providing novel insights that link EV biology and DKD diagnosis, prognosis, and treatment. Currently, tremendous advances have emerged in identifying possible candidate biomarkers in DKD early diagnosis, whereas more large-scale, multicenter clinical trials should be well designed to verify their utility. Furthermore, there are still some considerable obstacles, such as therapeutic-scale EV production and high-efficacy recipient cell recognition, hindering the clinical application of EV-derived ncRNAs in DKD. Therefore, certain efforts should be made to fulfill the basic mechanism of understanding and possible clinical translation.

Conflict of Interest Statement

The authors report no declarations of interest.

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Author Contributions

Miao Hu and Ling Zhou conceived the review. Xiahong Shen and Ling Zhou designed the review and provided supervision. Miao Hu drafted the manuscript and prepared the figures. Xiahong Shen and Ling Zhou helped to modify the figures and revise the manuscript. All authors read and approved the final manuscript.

References

1 Molitch ME, Adler AI, Flyvbjerg A, Nelson RG, So WY, Wanner C, et al. Diabetic kidney disease: a clinical update from kidney disease: improving global outcomes. Kidney Int. 2015;87(1):20–30. https://doi.org/10.1038/ki.2014.128
2 Guo J, Liu Z, Gong R. Long noncoding RNA: an emerging player in diabetes and diabetic kidney disease. Clin Sci. 2019;133(12):1321–39. https://doi.org/10.1042/CS20190372
3 Tang SCW, Yiu WH. Innate immunity in diabetic kidney disease. Nat Rev Nephrol. 2020;16(4):206–22. https://doi.org/10.1038/s41581-019-0234-4
4 Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, et al. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American heart association councils on kidney in cardiovascular disease, high blood pressure research, clinical cardiology, and epidemiology and prevention. Circulation. 2003;108(17):2154–69. https://doi.org/10.1161/01.CIR.0000095676.90936.80
5 Tuttle KR, Bakris GL, Bilous RW, Chiang JL, de Boer IH, Goldstein-Fuchs J, et al. Diabetic kidney disease: a report from an ADA Consensus Conference. Am J Kidney Dis. 2014;64(4):510–33. https://doi.org/10.1053/j.ajkd.2014.08.001
6 Tkach M, Théry C. Communication by extracellular vesicles: where we are and where we need to go. Cell. 2016;164(6):1226–32. https://doi.org/10.1016/j.cell.2016.01.043
7 Raposo G, Stahl PD. Extracellular vesicles: a new communication paradigm? Nat Rev Mol Cell Biol. 2019;20(9):509–10. https://doi.org/10.1038/s41580-019-0158-7
8 Shah R, Patel T, Freedman JE. Circulating extracellular vesicles in human disease. N Engl J Med. 2018;379(10):958–66. https://doi.org/10.1056/NEJMra1704286
9 Minciacchi VR, Freeman MR, Di Vizio D. Extracellular vesicles in cancer: exosomes, microvesicles and the emerging role of large oncosomes. Semin Cell Dev Biol. 2015;40:41–51. https://doi.org/10.1016/j.semcdb.2015.02.010
10 Kalluri R, LeBleu VS. The biology, function, and biomedical applications of exosomes. Science. 2020;367(6478). https://doi.org/10.1126/science.aau6977
11 Wang SE. Extracellular vesicles in cancer therapy. Semin Cancer Biol. 2022;86(Pt 2):296–309. https://doi.org/10.1016/j.semcancer.2022.06.001
12 Trionfini P, Benigni A. MicroRNAs as master regulators of glomerular function in health and disease. J Am Soc Nephrol. 2017;28(6):1686–96. https://doi.org/10.1681/ASN.2016101117
13 Kato M, Natarajan R. MicroRNAs in diabetic nephropathy: functions, biomarkers, and therapeutic targets. Ann N Y Acad Sci. 2015;1353(1):72–88. https://doi.org/10.1111/nyas.12758
14 Grimson A, Srivastava M, Fahey B, Woodcroft BJ, Chiang HR, King N, et al. Early origins and evolution of microRNAs and Piwi-interacting RNAs in animals. Nature. 2008;455(7217):1193–7. https://doi.org/10.1038/nature07415
15 Ozata DM, Gainetdinov I, Zoch A, O'Carroll D, Zamore PD. PIWI-interacting RNAs: small RNAs with big functions. Nat Rev Genet. 2019;20(2):89–108. https://doi.org/10.1038/s41576-018-0073-3
16 Peng Q, Chiu PK, Wong CY, Cheng CK, Teoh JY, Ng CF. Identification of piRNA targets in urinary extracellular vesicles for the diagnosis of prostate cancer. Diagnostics. 2021;11(10):1828. https://doi.org/10.3390/diagnostics11101828
17 Soutschek M, Schratt G. Non-coding RNA in the wiring and remodeling of neural circuits. Neuron. 2023;111(14):2140–54. https://doi.org/10.1016/j.neuron.2023.04.031
18 Wang P, Xue Y, Han Y, Lin L, Wu C, Xu S, et al. The STAT3-binding long noncoding RNA lnc-DC controls human dendritic cell differentiation. Science. 2014;344(6181):310–3. https://doi.org/10.1126/science.1251456
19 Zhang S, Zhao BS, Zhou A, Lin K, Zheng S, Lu Z, et al. m(6)A demethylase ALKBH5 maintains tumorigenicity of glioblastoma stem-like cells by sustaining FOXM1 expression and cell proliferation program. Cancer Cell. 2017;31(4):591–606.e6. https://doi.org/10.1016/j.ccell.2017.02.013
20 Han JDJ. LncRNAs: the missing link to senescence nuclear architecture. Trends Biochem Sci. 2023;48(7):618–28. https://doi.org/10.1016/j.tibs.2023.03.007
21 Mattick JS, Amaral PP, Carninci P, Carpenter S, Chang HY, Chen LL, et al. Long non-coding RNAs: definitions, functions, challenges and recommendations. Nat Rev Mol Cell Biol. 2023;24(6):430–47. https://doi.org/10.1038/s41580-022-00566-8
22 Xu Z, Chen Y, Ma L, Chen Y, Liu J, Guo Y, et al. Role of exosomal non-coding RNAs from tumor cells and tumor-associated macrophages in the tumor microenvironment. Mol Ther. 2022;30(10):3133–54. https://doi.org/10.1016/j.ymthe.2022.01.046

23 Sanger HL, Klotz G, Riesner D, Gross HJ, Kleinschmidt AK. Viroids are single-stranded covalently closed circular RNA molecules existing as highly base-paired rod-like structures. Proc Natl Acad Sci USA. 1976;73(11):3852–6. https://doi.org/10.1073/pnas.73.11.3852
24 Li Z, Huang C, Bao C, Chen L, Lin M, Wang X, et al. Exon-intron circular RNAs regulate transcription in the nucleus. Nat Struct Mol Biol. 2015;22(3):256–64. https://doi.org/10.1038/nsmb.2959
25 Yang Y, Fan X, Mao M, Song X, Wu P, Zhang Y, et al. Extensive translation of circular RNAs driven by N(6)-methyladenosine. Cell Res. 2017;27(5):626–41. https://doi.org/10.1038/cr.2017.31
26 Chen N, Zhao G, Yan X, Lv Z, Yin H, Zhang S, et al. A novel FLI1 exonic circular RNA promotes metastasis in breast cancer by coordinately regulating TET1 and DNMT1. Genome Biol. 2018;19(1):218. https://doi.org/10.1186/s13059-018-1594-y
27 Chen LL. The expanding regulatory mechanisms and cellular functions of circular RNAs. Nat Rev Mol Cell Biol. 2020;21(8):475–90. https://doi.org/10.1038/s41580-020-0243-y
28 Kung JT, Colognori D, Lee JT. Long noncoding RNAs: past, present, and future. Genetics. 2013;193(3):651–69. https://doi.org/10.1534/genetics.112.146704
29 Kashi K, Henderson L, Bonetti A, Carninci P. Discovery and functional analysis of lncRNAs: methodologies to investigate an uncharacterized transcriptome. Biochim Biophys Acta. 2016;1859(1):3–15. https://doi.org/10.1016/j.bbagrm.2015.10.010
30 Bracken CP, Scott HS, Goodall GJ. A network-biology perspective of microRNA function and dysfunction in cancer. Nat Rev Genet. 2016;17(12):719–32. https://doi.org/10.1038/nrg.2016.134
31 Batista PJ, Chang HY. Long noncoding RNAs: cellular address codes in development and disease. Cell. 2013;152(6):1298–307. https://doi.org/10.1016/j.cell.2013.02.012
32 Patop IL, Wust S, Kadener S. Past, present, and future of circRNAs. EMBO J. 2019;38(16):e100836. https://doi.org/10.15252/embj.2018100836
33 Lin H, Yu J, Gu X, Ge S, Fan X. Novel insights into exosomal circular RNAs: redefining intercellular communication in cancer biology. Clin Transl Med. 2021;11(12):e636. https://doi.org/10.1002/ctm2.636
34 Zhu L, Liu X, Pu W, Peng Y. tRNA-derived small non-coding RNAs in human disease. Cancer Lett. 2018;419:1–7. https://doi.org/10.1016/j.canlet.2018.01.015
35 Li B, Hong J, Hong M, Wang Y, Yu T, Zang S, et al. piRNA-823 delivered by multiple myeloma-derived extracellular vesicles promoted tumorigenesis through re-educating endothelial cells in the tumor environment. Oncogene. 2019;38(26):5227–38. https://doi.org/10.1038/s41388-019-0788-4
36 Nie JH, Li TX, Zhang XQ, Liu J. Roles of noncoding RNAs in normal human brain development, brain tumor, and neuropsychiatric disorders. Noncoding RNA. 2019;5(2):36. https://doi.org/10.3390/ncrna5020036
37 Zhu L, Li J, Gong Y, Wu Q, Tan S, Sun D, et al. Exosomal tRNA-derived small RNA as a promising biomarker for cancer diagnosis. Mol Cancer. 2019;18(1):74. https://doi.org/10.1186/s12943-019-1000-8
38 Sun L, Wang X, Saredy J, Yuan Z, Yang X, Wang H. Innate-adaptive immunity interplay and redox regulation in immune response. Redox Biol. 2020;37:101759. https://doi.org/10.1016/j.redox.2020.101759
39 Navarro-Gonzalez JF, Mora-Fernandez C, Muros de Fuentes M, Garcia-Perez J. Inflammatory molecules and pathways in the pathogenesis of diabetic nephropathy. Nat Rev Nephrol. 2011;7(6):327–40. https://doi.org/10.1038/nrneph.2011.51
40 Zhao T, Jin Q, Kong L, Zhang D, Teng Y, Lin L, et al. microRNA-15b-5p shuttled by mesenchymal stem cell-derived extracellular vesicles protects podocytes from diabetic nephropathy via downregulation of VEGF/PDK4 axis. J Bioenerg Biomembr. 2022;54(1):17–30. https://doi.org/10.1007/s10863-021-09919-y
41 Wang Y, Liu J, Wang H, Lv S, Liu Q, Li S, et al. Mesenchymal stem cell-derived exosomes ameliorate diabetic kidney disease through the NLRP3 signaling pathway. Stem cells. 2023;41(4):368–83. https://doi.org/10.1093/stmcls/sxad010
42 Tsai YC, Kuo MC, Hung WW, Wu LY, Wu PH, Chang WA, et al. High glucose induces mesangial cell apoptosis through miR-15b-5p and promotes diabetic nephropathy by extracellular vesicle delivery. Mol Ther. 2020;28(3):963–74. https://doi.org/10.1016/j.ymthe.2020.01.014
43 Zhu Y, Zha F, Tang B, Ji TT, Li XY, Feng L, et al. Exosomal hsa_circ_0125310 promotes cell proliferation and fibrosis in diabetic nephropathy via sponging miR-422a and targeting the IGF1R/p38 axis. J Cell Mol Med. 2022;26(1):151–62. https://doi.org/10.1111/jcmm.17065
44 Liu D, Liu F, Li Z, Pan S, Xie J, Zhao Z, et al. HNRNPA1-mediated exosomal sorting of miR-483-5p out of renal tubular epithelial cells promotes the progression of diabetic nephropathy-induced renal interstitial fibrosis. Cell Death Dis. 2021;12(3):255. https://doi.org/10.1038/s41419-021-03460-x
45 Hu R, Li X, Peng C, Gao R, Ma L, Hu J, et al. miR-196b-5p-enriched extracellular vesicles from tubular epithelial cells mediated aldosterone-induced renal fibrosis in mice with diabetes. BMJ Open Diabetes Res Care. 2020;8(1):e001101. https://doi.org/10.1136/bmjdrc-2019-001101
46 Tsai YC, Kuo MC, Hung WW, Wu PH, Chang WA, Wu LY, et al. Proximal tubule-derived exosomes contribute to mesangial cell injury in diabetic nephropathy via miR-92a-1-5p transfer. Cell Commun Signal. 2023;21(1):10. https://doi.org/10.1186/s12964-022-00997-y
47 Niu Z, Ren G, Huang L, Mu L. Circ_0008529 contributes to renal tubular cell dysfunction in high glucose stress via miR-185-5p/SMAD2 pathway in diabetic nephropathy. Biochem Genet. 2023;61(3):963–78. https://doi.org/10.1007/s10528-022-10296-3
48 Su H, Qiao J, Hu J, Li Y, Lin J, Yu Q, et al. Podocyte-derived extracellular vesicles mediate renal proximal tubule cells dedifferentiation via microRNA-221 in diabetic nephropathy. Mol Cell Endocrinol. 2020;518:111034. https://doi.org/10.1016/j.mce.2020.111034
49 Ning Y, Zhou X, Wang G, Zhang L, Wang J. Exosome miR-30a-5p regulates glomerular endothelial cells' EndMT and angiogenesis by modulating Notch1/VEGF signaling pathway. Curr Gene Ther. 2024;24(2):159–77. https://doi.org/10.2174/0115665232258527230919071328
50 Li B, Sun G, Yu H, Meng J, Wei F. Exosomal circTAOK1 contributes to diabetic kidney disease progression through regulating SMAD3 expression by sponging miR-520h. Int Urol Nephrol. 2022;54(9):2343–54. https://doi.org/10.1007/s11255-022-03139-y
51 Lv J, Hao YN, Wang XP, Lu WH, Xie LY, Niu D. Bone marrow mesenchymal stem cell-derived exosomal miR-30e-5p ameliorates high-glucose induced renal proximal tubular cell pyroptosis by inhibiting ELAVL1. Ren Fail. 2023;45(1):2177082. https://doi.org/10.1080/0886022X.2023.2177082
52 Cui C, Zang N, Song J, Guo X, He Q, Hu H, et al. Exosomes derived from mesenchymal stem cells attenuate diabetic kidney disease by inhibiting cell apoptosis and epithelial-to-mesenchymal transition via miR-424-5p. FASEB J. 2022;36(10):e22517. https://doi.org/10.1096/fj.202200488R
53 Duan Y, Luo Q, Wang Y, Ma Y, Chen F, Zhu X, et al. Adipose mesenchymal stem cell-derived extracellular vesicles containing microRNA-26a-5p target TLR4 and protect against diabetic nephropathy. J Biol Chem. 2020;295(37):12868–84. https://doi.org/10.1074/jbc.RA120.012522
54 Mao R, Shen J, Hu X. RETRACTED: BMSCs-derived exosomal microRNA-let-7a plays a protective role in diabetic nephropathy via inhibition of USP22 expression. Life Sci. 2021;268:118937. https://doi.org/10.1016/j.lfs.2020.118937
55 Duan YR, Chen BP, Chen F, Yang SX, Zhu CY, Ma YL, et al. Exosomal microRNA-16-5p from human urine-derived stem cells ameliorates diabetic nephropathy through protection of podocyte. J Cell Mol Med. 2021;25(23):10798–813. https://doi.org/10.1111/jcmm.14558
56 Hao Y, Miao J, Liu W, Cai K, Huang X, Peng L. Mesenchymal stem cell-derived exosomes carry MicroRNA-125a to protect against diabetic nephropathy by targeting histone deacetylase 1 and downregulating endothelin-1. Diabetes Metab Syndr Obes. 2021;14:1405–18. https://doi.org/10.2147/DMSO.S286191
57 Zhao J, Chen J, Zhu W, Qi XM, Wu YG. Exosomal miR-7002-5p derived from highglucose-induced macrophages suppresses autophagy in tubular epithelial cells by targeting Atg9b. FASEB J. 2022;36(9):e22501. https://doi.org/10.1096/fj.202200550RR

58 Zhuang Y, Zheng H, Yang Y, Ni H. GABA alleviates high glucose-induced podocyte injury through dynamically altering the expression of macrophage M1/M2-derived exosomal miR-21a-5p/miR-25-3p. Biochem Biophys Res Commun. 2022;618:38–45. https://doi.org/10.1016/j.bbrc.2022.06.019
59 Wang Z, Sun W, Li R, Liu Y. miRNA-93-5p in exosomes derived from M2 macrophages improves lipopolysaccharide-induced podocyte apoptosis by targeting Toll-like receptor 4. Bioengineered. 2022;13(3):7683–96. https://doi.org/10.1080/21655979.2021.2023794
60 Yang H, Bai Y, Fu C, Liu W, Diao Z. Exosomes from high glucose-treated macrophages promote epithelial-mesenchymal transition of renal tubular epithelial cells via long noncoding RNAs. BMC Nephrol. 2023;24(1):24. https://doi.org/10.1186/s12882-023-03065-w
61 Ding X, Jing N, Shen A, Guo F, Song Y, Pan M, et al. MiR-21-5p in macrophage-derived extracellular vesicles affects podocyte pyroptosis in diabetic nephropathy by regulating A20. J Endocrinol Invest. 2021;44(6):1175–84. https://doi.org/10.1007/s40618-020-01401-7
62 Jia Y, Zheng Z, Xue M, Zhang S, Hu F, Li Y, et al. Extracellular vesicles from albumin-induced tubular epithelial cells promote the M1 macrophage phenotype by targeting Klotho. Mol Ther. 2019;27(8):1452–66. https://doi.org/10.1016/j.ymthe.2019.05.019
63 Brownlee M. Biochemistry and molecular cell biology of diabetic complications. Nature. 2001;414(6865):813–20. https://doi.org/10.1038/414813a
64 Singh DK, Winocour P, Farrington K. Oxidative stress in early diabetic nephropathy: fueling the fire. Nat Rev Endocrinol. 2011;7(3):176–84. https://doi.org/10.1038/nrendo.2010.212
65 Brownlee M. The pathobiology of diabetic complications: a unifying mechanism. Diabetes. 2005;54(6):1615–25. https://doi.org/10.2337/diabetes.54.6.1615
66 Gao C, Wang B, Chen Q, Wang M, Fei X, Zhao N. Serum exosomes from diabetic kidney disease patients promote pyroptosis and oxidative stress through the miR-4449/HIC1 pathway. Nutr Diabetes. 2021;11(1):33. https://doi.org/10.1038/s41387-021-00175-y
67 Ying Q, Wu G. Molecular mechanisms involved in podocyte EMT and concomitant diabetic kidney diseases: an update. Ren Fail. 2017;39(1):474–83. https://doi.org/10.1080/0886022X.2017.1313164
68 Priante G, Gianesello L, Ceol M, Del Prete D, Anglani F. Cell death in the kidney. Int J Mol Sci. 2019;20(14):3598. https://doi.org/10.3390/ijms20143598
69 Galluzzi L, Vitale I, Aaronson SA, Abrams JM, Adam D, Agostinis P, et al. Molecular mechanisms of cell death: recommendations of the nomenclature committee on cell death 2018. Cell Death Differ. 2018;25(3):486–541. https://doi.org/10.1038/s41418-017-0012-4
70 Zhang KJ, Wu Q, Jiang SM, Ding L, Liu CX, Xu M, et al. Pyroptosis: a new frontier in kidney diseases. Oxid Med Cel Longev. 2021; 2021:6686617. https://doi.org/10.1155/2021/6686617
71 Djudjaj S, Boor P. Cellular and molecular mechanisms of kidney fibrosis. Mol Aspects Med. 2019;65:16–36. https://doi.org/10.1016/j.mam.2018.06.002
72 Kawakami T, Ren S, Duffield JS. Wnt signalling in kidney diseases: dual roles in renal injury and repair. J Pathol. 2013;229(2):221–31. https://doi.org/10.1002/path.4121
73 Liu M, Liang K, Zhen J, Zhou M, Wang X, Wang Z, et al. Sirt6 deficiency exacerbates podocyte injury and proteinuria through targeting Notch signaling. Nat Commun. 2017;8(1):413. https://doi.org/10.1038/s41467-017-00498-4
74 Zhang LY, Wang Y, Yang YR, Shao JJ, Liang B. MiR-135a regulates renal fibrosis in rats with diabetic kidney disease through the Notch pathway. Eur Rev Med Pharmacol Sci. 2020;24(4):1979–87. https://doi.org/10.26355/eurrev_202002_20375
75 Ma L, Wu F, Shao Q, Chen G, Xu L, Lu F. Baicalin alleviates oxidative stress and inflammation in diabetic nephropathy via Nrf2 and MAPK signaling pathway. Drug Des Devel Ther. 2021;15:3207–21. https://doi.org/10.2147/DDDT.S319260
76 Kong Z, Xiao M, Wang B, Zhang W, Che K, Lv W, et al. Renoprotective effect of isoorientin in diabetic nephropathy via activating autophagy and inhibiting the PI3-K-AKT-TSC2-mTOR pathway. Am J Chin Med. 2023;51(5):1269–91. https://doi.org/10.1142/S0192415X23500581
77 Liu Y, Wang W, Zhang J, Gao S, Xu T, Yin Y. JAK/STAT signaling in diabetic kidney disease. Front Cell Dev Biol. 2023;11:1233259. https://doi.org/10.3389/fcell.2023.1233259
78 Xu P, Zhan H, Zhang R, Xu XJ, Zhang Y, Le Y, et al. Early growth response factor 1 upregulates pro-fibrotic genes through activation of TGF-β1/Smad pathway via transcriptional regulation of PAR1 in high-glucose treated HK-2 cells. Mol Cel Endocrinol. 2023;572:111953. https://doi.org/10.1016/j.mce.2023.111953
79 Bai S, Xiong X, Tang B, Ji T, Li X, Qu X, et al. Exosomal circ_DLGAP4 promotes diabetic kidney disease progression by sponging miR-143 and targeting ERBB3/NF-κB/MMP-2 axis. Cell Death Dis. 2020;11(11):1008. https://doi.org/10.1038/s41419-020-03169-3
80 Jiang L, Gu Y, Du Y, Liu J. Exosomes: diagnostic biomarkers and therapeutic delivery vehicles for cancer. Mol Pharm. 2019;16(8):3333–49. https://doi.org/10.1021/acs.molpharmaceut.9b00409
81 Zhang W, Su X, Li S, Liu Z, Wang Q, Zeng H. Low serum exosomal miR-484 expression predicts unfavorable prognosis in ovarian cancer. Cancer Biomark. 2020;27(4):485–91. https://doi.org/10.3233/CBM-191123
82 Kim H, Bae YU, Jeon JS, Noh H, Park HK, Byun DW, et al. The circulating exosomal microRNAs related to albuminuria in patients with diabetic nephropathy. J Transl Med. 2019;17(1):236. https://doi.org/10.1186/s12967-019-1983-3
83 Zhao Y, Shen A, Guo F, Song Y, Jing N, Ding X, et al. Urinary exosomal MiRNA-4534 as a novel diagnostic biomarker for diabetic kidney disease. Front Endocrinol. 2020;11:590. https://doi.org/10.3389/fendo.2020.00590
84 Zang J, Maxwell AP, Simpson DA, McKay GJ. Differential expression of urinary exosomal MicroRNAs miR-21-5p and miR-30b-5p in individuals with diabetic kidney disease. Sci Rep. 2019;9(1):10900. https://doi.org/10.1038/s41598-019-47504-x
85 Wang J, Tao Y, Zhao F, Liu T, Shen X, Zhou L. Expression of urinary exosomal miRNA-615-3p and miRNA-3147 in diabetic kidney disease and their association with inflammation and fibrosis. Ren Fail. 2023;45(1):2121929. https://doi.org/10.1080/0886022X.2022.2121929
86 Barutta F, Tricarico M, Corbelli A, Annaratone L, Pinach S, Grimaldi S, et al. Urinary exosomal microRNAs in incipient diabetic nephropathy. PLoS One. 2013;8(11):e73798. https://doi.org/10.1371/journal.pone.0073798
87 Mohan A, Singh RS, Kumari M, Garg D, Upadhyay A, Ecelbarger CM, et al. Urinary exosomal microRNA-451-5p is a potential early biomarker of diabetic nephropathy in rats. PLoS One. 2016;11(4):e0154055. https://doi.org/10.1371/journal.pone.0154055
88 Uil M, Hau CM, Ahdi M, Mills JD, Kers J, Saleem MA, et al. Cellular origin and microRNA profiles of circulating extracellular vesicles in different stages of diabetic nephropathy. Clin Kidney J. 2021;14(1):358–65. https://doi.org/10.1093/ckj/sfz145
89 Gallo S, Gili M, Lombardo G, Rossetti A, Rosso A, Dentelli P, et al. Stem cell-derived, microRNA-carrying extracellular vesicles: a novel approach to interfering with mesangial cell collagen production in a hyperglycaemic setting. PLoS One. 2016;11(9):e0162417. https://doi.org/10.1371/journal.pone.0162417
90 Jin J, Wang Y, Zhao L, Zou W, Tan M, He Q. Exosomal miRNA-215-5p derived from adipose-derived stem cells attenuates epithelial-mesenchymal transition of podocytes by inhibiting ZEB2. BioMed Res Int. 2020;2020:2685305. https://doi.org/10.1155/2020/2685305
91 Wang B, Yao K, Huuskes BM, Shen HH, Zhuang J, Godson C, et al. Mesenchymal stem cells deliver exogenous MicroRNA-let7c via exosomes to attenuate renal fibrosis. Mol Ther. 2016;24(7):1290–301. https://doi.org/10.1038/mt.2016.90
92 Cai X, Zou F, Xuan R, Lai XY. Exosomes from mesenchymal stem cells expressing microribonucleic acid-125b inhibit the progression of diabetic nephropathy via the tumour necrosis factor receptor-associated factor 6/Akt axis. Endocr J. 2021;68(7):817–28. https://doi.org/10.1507/endocrj.EJ20-0619
93 Luo T, Chen SY, Qiu ZX, Miao YR, Ding Y, Pan XY, et al. Transcriptomic features in a single extracellular vesicle via single-cell RNA sequencing. Small methods. 2022;6(11):e2200881. https://doi.org/10.1002/smtd.202200881