The key role of miR-378 in kidney diseases (Review)

YANGYANG LIU[1], SHUQING SHI[2], TAO CHENG[2], HAOSHUO WANG[3], HUAN WANG[2] and YUANHUI HU[2]

[1]Department of Cardiovascular Diseases, Sanming Integrated Medicine Hospital, Sanming, Fujian 365000, P.R. China;
[2]Department of Cardiovascular Diseases, Guang'anmen Hospital, China Academy of Chinese Medical Sciences, Beijing 100053, P.R. China;
[3]Department of Endocrinology, Guang'anmen Hospital, China Academy of Chinese Medical Sciences, Beijing 100053, P.R. China

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Abstract. MicroRNAs (miRNAs/miRs) are endogenous, small non-coding RNAs conserved across species that post-transcriptionally regulate gene expression by both suppressing translation and inducing mRNA degradation. miRNAs are found in various tissues, exhibit variable expression and their dysregulation is implicated in numerous disease processes. Furthermore, miRNA expression levels have a key role in the normal development of kidney tissue and are key regulators of kidney function, modulating diverse biological processes across renal cell lineages. miR-378 participates in pathological processes associated with kidney diseases, including kidney cancer, kidney transplantation and diabetic nephropathy. Despite its considerable effects on these conditions, a comprehensive summary of the roles of miR-378 is unavailable. In the present review, the existing literature on miR-378 in kidney diseases is consolidated, and its validated gene targets and biological effects in both malignant and non-malignant conditions are highlighted, thereby providing a foundation for future research.

Contents

1. Introduction

The kidneys are vital metabolic organs that maintain homeostasis, regulate water-electrolyte and acid-base balance, and carry out endocrine functions. Chronic kidney disease (CKD) is a long-term and irreversible condition caused by factors such as hypertension, diabetes, infections, medications, autoimmunity and genetic metabolic disorders (1). CKD can result in both acute and chronic renal impairment, structural and functional impairment, renal fibrosis and ultimately end-stage renal disease (ESRD), which impose considerable burdens on patients and society (2). By 2030, CKD-related renal failure and cardiac complications are projected to become the 13th leading cause of mortality worldwide, rising to the 5th leading cause by 2040 (3). The histopathological characteristics of CKD include persistent renal tissue inflammation, and renal tubulointerstitial and glomerular fibrosis, characterized by excessive extracellular matrix (ECM) deposition (4). Despite advances in understanding its pathophysiology, the complex mechanisms underlying CKD remain incompletely understood and effective treatments are limited. Therefore, exploring new therapeutic targets and strategies is needed for delaying CKD progression and improving the quality of life of patients.

MicroRNAs (miRNAs/miRs) are non-coding RNAs comprising 19-22 nucleotides that stably exist in the blood and regulate post-transcriptional gene expression by binding to target mRNAs (5). miRNAs exhibit organ- and tissue-specific expression in target cells and tissues, and have key roles in fundamental cellular processes, including development, differentiation, proliferation, apoptosis, immune regulation and organogenesis (6,7). The characteristics of miRNAs are similar in men and women, and are unaffected by age, highlighting their potential as candidate biomarkers for various diseases (8). Notably, increasing evidence has implicated the role of miRNAs in human diseases such as liver, neurodevelopmental and cardiovascular diseases (9-11).

Abnormal expression of kidney-related miRNAs, which regulate protein translation or stability, impacts various biological processes (12). This can affect the normal function of glomerular mesangial cells, podocytes, renal tubular epithelial cells and renal interstitial fibrosis (13,14), thereby contributing to CKD development (15). Renal miRNAs, such as miRNA-302b-3p, have been shown to promote renal tissue fibrosis by disrupting tissue inhibitor of matrix metalloproteinase-3, SOX6, JAK/STAT and PTEN/AKT signaling, or by impairing autophagy (16-20). They can also induce inflammation by modulating the NF-κB signaling pathway (21,22).

miR-378 generally refers to a miRNA family and miR-378a is a specific member of this family (8); notably, miR-378a-5p

Correspondence to: Professor Yuanhui Hu or Professor Huan Wang, Department of Cardiovascular Diseases, Guang'anmen Hospital, China Academy of Chinese Medical Sciences, 5 Beixiange, Xicheng, Beijing 100053, P.R. China
E-mail: huyuanhui2841@gamyy.cn
E-mail: wanghuan3772@gamyy.cn

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and miR-378-3p may differ in sequence and expression patterns. miR-378a undergoes further processing to produce two mature miRNAs: miR-378a-5p and miR-378a-3p; originating from the same precursor but located on different arms, they possess unique sequences, and thus recognize and bind to different target mRNAs, carrying out distinct biological functions. For example, miR-378a-5p is associated with tumor metabolism, while miR-378a-3p is involved in processes such as mitochondrial oxidative metabolism and cellular differentiation. These differences make them noteworthy in the pathogenesis of kidney diseases and potential therapeutic targets. The present review systematically elaborates on research associated with the miR-378 family in the context of kidney diseases.

A previous study investigated the anti-fibrotic effects of different concentrations of gypenosides (GPs) on an *in vitro* model using NRK-49F renal normal rat kidney fibroblast cells stimulated by TGF-β1. The experimental methods involved stimulating NRK-49F cells with TGF-β1 to induce fibrosis and treating them with various concentrations of GPs. The anti-fibrotic activity was assessed using multiple assays, including reverse transcription-quantitative-PCR (RT-qPCR) and western blotting. TGF-β1 stimulation was shown to considerably alter the expression levels of 151 miRNAs, whereas GPs could counteract these changes by modulating the expression levels of 18 miRNAs. Notably, TGF-β1 was able to downregulate miR-378a-5p expression. Bioinformatics analysis predicted that miR-378a-5p targets were predominantly enriched in mRNAs encoding proteins in the PI3K/AKT signaling pathway. Notably, overexpression of miR-378a-5p suppressed the upregulation of α-smooth muscle actin (α-SMA), collagen type I (COL1), PI3K and AKT induced by TGF-β1. Furthermore, GPs inhibited the PI3K/AKT signaling pathway by upregulating miR-378a-5p in NRK-49F cells stimulated by TGF-β1, thereby reducing the excessive secretion of ECM components. These findings suggested that GPs may target miR-378a-5p through the PI3K/AKT signaling pathway to inhibit renal NRK-49F cell fibrosis (23). Additionally, miR-378 has been reported to be involved in the pathological processes underlying kidney diseases, including kidney cancer, kidney transplantation and diabetic nephropathy [diabetic kidney disease (DKD)]; these processes include renal tubulointerstitial fibrosis and angiogenesis (24,25).

To the best of our knowledge, a limited number of studies have comprehensively examined the functions of miR-378 in kidney diseases. The present review provides a detailed analysis of the role of miR-378 in different pathological states of the kidney, and highlights its targets and the biological pathways it influences. Additionally, the potential of miR-378 in diagnosing and treating kidney diseases is discussed.

2. Regulation of miR-378 in kidney diseases

Acute kidney injury (AKI). An overview of the role of miR-378 in AKI is provided in Table I. Cisplatin is a commonly used drug for the treatment of various malignant tumors (26). It is an effective drug, however, it is also associated with various side effects, including nephrotoxicity (27) and AKI, which occurs in over half of patients treated with cisplatin, making it the primary manifestation (28). The underlying pathological mechanism mainly involves excessive oxidative stress and inflammation in the proximal tubular epithelial cells, leading to apoptosis and necrosis and, ultimately, acute renal failure.

Wolenski *et al* (29) examined miRNA profiles in the urine of rats with cisplatin-induced renal injury by RNA sequencing of kidney tissues and found a considerable increase in the expression levels of miR-378 (29). The central inflammatory process and apoptosis mediated by miR-378 has been reported to involve regulation of the Fos/AP-1 pathway, thus, contributing to the development of AKI (30). As multifunctional progenitor cells with self-renewal and multi-differentiation abilities, mesenchymal stem cells (MSCs) can differentiate into a variety of cell types, including proximal tubular epithelial cells (31). Previous studies have shown that miRNAs, such as miR-709 and miR-449, have an important role in the process of cisplatin-induced AKI (32,33). Furthermore, MSCs can treat cisplatin-induced AKI by downregulating the expression levels of miR-378 (30). Additionally, differentially expressed genes (e.g., Lingo4, Sytl3, Rnf125 and Arntl) integrated into the AKI and Connectivity Map database have indicated that gliclazide (with negative enrichment scores <-0.9) is a potential drug for treating cisplatin-induced AKI due to its functions being similar to those of MSCs (30). The primary mechanism involves inhibiting the endoplasmic reticulum response or oxidative stress (34,35). Moreover, gliclazide can reduce serum creatinine, blood urea nitrogen and microalbuminuria levels in diabetic rats, thereby reducing DKD (35). Therefore, MSCs and gliclazide may modulate the miR-378/Fos-mediated inflammatory response to treat cisplatin-induced AKI.

miR-378a-3p has previously been confirmed as a target of long noncoding RNA (lncRNA)136131 through dual-luciferase reporter assays, fluorescence *in situ* hybridization colocalization and RT-qPCR analysis. Notably, lncRNA136131 can increase expression of Rab10 and inhibit tubular epithelial cell apoptosis in AKI by targeting miR-378a-3p. Furthermore, after intervention with lncRNA136131 small interfering RNA, ischemia-reperfusion (I/R)-induced AKI has been shown to be aggravated, leading to renal tubular injury, tubular cell apoptosis and the upregulation of cleaved caspase-3. Notably, lncRNA136131 may suppress the apoptosis of renal tubular epithelial cells and prevent the progression of I/R-induced AKI by targeting the miR-378a-3p/Rab10 axis, and may serve as a novel target for AKI treatment (36).

Tubular cell death is a key factor in the occurrence of I/R renal injury. Previous studies have established a rat model of renal injury and have conducted hypoxia/reoxygenation (H/R)-induced HK-2 cell injury *in vitro*, and have revealed that the expression of miR-378a-3p is upregulated in models of renal injury. miR-378a-3p can directly bind to the 3'UTR of glutathione peroxidase 4 (GPX4) and solute carrier family 7 member 11 (SLC7A11) mRNA, negatively regulating their expression, whereas silencing miR-378a-3p has been reported to alleviate I/R-induced renal injury in rats. In an *in vitro* H/R-induced injury model in HK-2 cells, miR-378a-3p was revealed to induce ferroptosis (iron-dependent cell death). These findings indicated that I/R induces the upregulation of miR-378a-3p, leading to the activation of ferroptosis in renal injury by downregulating GPX4 and SLC7A11, suggesting that miR-378a-3p regulates ferroptosis in I/R-induced renal injury (37).

Table I. miR-378 roles and levels in kidney disease.

First author, year	Disease	Main aspects of the study	Type of miR-378	Trend	Model	Condition	Pathway/Targets	(Refs.)
Wolenski, 2017	AKI	Improves inflammation and cell apoptosis	miR-378	Upregulated	AKI	Cisplatin-induced renal injury	Fos/AP-1	(29)
Wu, 2022	AKI	Improves cell apoptosis	miR-378-3p	Upregulated	BUMPT cells and AKI	I/R	lncRNA136131/ miR-378a-3p/Rab10 axis	(36)
Ding, 2020	AKI	Improves ferroptosis	miR-378-3p	Upregulated	Tubular cell death	I/R	-	(37)
Lei, 2018; Wang, 2017	DKD	-	miR-378	Downregulated	DKD	Streptozotocin-induced DKD	-	(51,52)
Assmann, 2019	Severe DKD	-	miR-378-3p	Upregulated	-	-	-	(53)
Wang, 2019	MsPGN	Inhibits the abnormal proliferation of RMCs, and improves mesangial hyperplasia and fibrosis	miR-378	Downregulated	MsPGN rat model	ucMSC-EVs	TGF-β1/Smad2/3	(61)
Xiong, 2020	Kidney transplantation	Improves interstitial fibrosis and progressive tubular atrophy	miR-378	Downregulated	Renal allotransplantation	-	-	(64)

AKI, acute kidney injury; lncRNA, long noncoding RNA; DKD, diabetic nephropathy; STZ, streptozotocin; ucMSC-EVs, umbilical cord mesenchymal stem cell-released extracellular vesicles; MsPGN, mesangial proliferative glomerulonephritis; I/R, ischemia-reperfusion; RMCs, renal mesangial cells; miR, microRNA.

Kidney cancer. A brief overview of the role of miR-378 in kidney cancer is provided in Table II. Renal cell carcinoma (RCC) is a common malignant tumor of the adult kidney, with a global mortality rate exceeding 100,000 annually; in addition, both the incidence and mortality rates of RCC are steadily increasing (38). Current treatments for RCC primarily include targeted therapy and surgical resection; however, targeted therapy is ineffective for some patients (39), and surgical resection is associated with a high rate of recurrence (40).

Numerous studies investigating the genetic mechanism underlying RCC have made considerable progress, although the results show some differences. Redova *et al* (41) and Hauser *et al* (42) compared serum miRNA levels in patients with clear-cell RCC with those in healthy individuals, and revealed that the expression levels of miR-378 were considerably increased in patients with clear-cell RCC. These studies also collected samples from patients with clear-cell, papillary and chromophobe RCC for miRNA verification. Redova *et al* (41) concluded that miR-378 expression was increased in patients with clear cell RCC compared with healthy controls, and the combination of miR-378 and miR-451 provided improved identification of RCC. However, Hauser *et al* (42) did not observe similar trends for miR-378. Furthermore, neither study revealed an association between miR-378 expression and pathological tumor staging, lymph node/distant metastasis, vascular invasion or Fuhrman grade.

Fedorko *et al* (43) analyzed and compared 195 individuals with RCC, including clear-cell, papillary and chromophobe RCC with 110 healthy controls using RT-qPCR, and detected elevated levels of miR-378 in patients with RCC. Additionally, this previous study observed an association between miR-378 and the stage of RCC. Moreover, the combination of miR-378 and miR-210 demonstrated good sensitivity and specificity for identifying RCC. The researchers of this study also analyzed serum miR-378 levels in patients with RCC before and after surgery (at 1 week and 3 months). A significant reduction in miR-378 levels was observed 3 months post-surgery, indicating its strong diagnostic and prognostic potential for RCC (43).

In a study examining miRNA levels in renal tissue from 100 patients with renal malignancies, of which 65 survived and 35 succumbed, the expression levels of miR-378a-5p were revealed to be considerably increased in the survival group ($P<0.05$). Furthermore, Cox regression analysis showed that a high expression level of miR-378a-5p was positively associated with the survival rate of RCC, indicating that increased miR-378a-5p levels may be associated with longer overall survival. Additionally, a combination of three miRNA groups (miR-378a-5p, miR-642a-5p and miR-23a-5p) was identified, with an area under the curve (AUC) value of 0.712 ($P<0.05$), thereby showing moderate prediction accuracy. This combination was considered to have potential as a biomarker for evaluating the prognosis of RCC. However, no significant association was observed between clinical features and the relative expression levels of these miRNAs ($P>0.05$) (44).

A previous systematic review and meta-analysis investigated the diagnostic significance of miR-378 as a potential biomarker for human RCC. The combined sensitivity and specificity of miR-378 in diagnosing RCC were revealed to be high, with values of 0.78 and 0.79, respectively. The positive and negative likelihood ratios were 3.7 and 0.28, respectively,

Table II. miR-378 roles and levels in renal cell carcinoma.

	Exploration		Validation			
First author, year	Patients vs. controls	Trend of miR-378	Patients vs. controls	Trend of miR-378	Findings	(Refs.)
Redova, 2012	Clear-cell RCC vs. healthy individuals	Upregulated	Clear-cell RCC, papillary RCC and chromophobe RCC vs. healthy individuals	Elevated	No associations among miR-378, pathological tumor staging, lymph node/distant metastasis, vascular invasion and Fuhrman grade	(41)
Hauser, 2012	Clear-cell RCC vs. healthy individuals	Upregulated	Clear-cell RCC, papillary RCC and chromophobe RCC vs. healthy individuals	No differences		(42)
Fedorko, 2015	Clear-cell RCC vs. healthy individuals	Upregulated	Before operation vs. after operation	Elevated	miR-378 level is associated with stage of RCC	(43)
Chen, 2024	Survival group (n=65) vs. mortality group (n=35)	Upregulated	-	-	miR-378a-5p, miR-642a-5p and miR-23a-5p, are associated with the prognosis of RCC	(44)

RCC, renal cell carcinoma; miR, microRNA.

indicating its potential diagnostic accuracy. The AUC value of 0.85 further supported its diagnostic value. This study suggested that miR-378 could be a useful biomarker for the early detection and diagnosis of RCC (45).

DKD. A brief overview of the role of miR-378 in DKD is provided in Table I. DKD is a common microvascular complication in patients with diabetes. The pathological changes of DKD mainly involve thickening of the glomerular basement membrane, mesangial hypertrophy, glomerular sclerosis and tubular interstitial fibrosis, which eventually lead to ESRD (46,47). The main clinical features are proteinuria and a decreased glomerular filtration rate (48). Additionally, podocyte apoptosis is closely related to the development of diabetes (49).

Previous studies have investigated the relationship between circulating or urinary miRNAs and the occurrence of DKD in patients with diabetes (17). High blood glucose has been shown to induce abnormal expression of miRNAs, such as miR-192, miR-216a and miR-204, in kidney cells, thereby promoting renal cell fibrosis and glomerular dysfunction (50).

Various studies have examined the expression levels of miR-378 in DKD; however, the findings are inconsistent. Lei *et al* (51) and Wang *et al* (52) established a model of DKD based on streptozotocin-induced DKD to assess miR-378 expression in kidney tissue. The results revealed that miR-378 expression levels were decreased (51,52). However, Assmann *et al* (53) reported that nine out of 48 miRNAs had considerably different expression levels in patients with type 1 diabetes with and without nephropathy, and this study confirmed that miR-378-3p expression was significantly increased in patients with severe DKD. These differences may due to the types of cases included and the different testing methods used.

Studies on the pathological mechanism of miR-378 in DKD have shown that miR-378-mediated MAPK signaling pathways alleviate mesangial hypertrophy and tubular fibrosis in DKD (52,54). Traditional Chinese medicine offers notable advantages in treating DKD. Astragaloside IV, the primary active component of *Astragalus*, may delay DKD progression through multiple mechanisms: i) Regulating the TGF-β/SMADs signaling pathway to downregulate TGF-β1, SMAD2/3 and α-SMA expression levels in the renal interstitium (55); ii) enhancing the activity of muscle/endoplasmic reticulum Ca^{2+}ATPase (SERCA) and increasing SERCA2 expression in mice with DKD, thereby inhibiting podocyte apoptosis and reducing diabetes-induced kidney damage (56); iii) targeting miR-378 to modulate the miR-378/TRAF5 signaling pathway to inhibit podocyte apoptosis and delay further deterioration of DKD (51).

Mesangial proliferative glomerulonephritis (MsPGN). An overview of the role of miR-378 in MsPGN is provided in Table I. MsPGN is characterized by the diffuse proliferation of mesangial cells and mesangial matrix deposition, which can lead to renal interstitial fibrosis, irreversible progressive glomerulosclerosis and ESRD (57,58). MsPGN accounts for ~60% of all primary glomerulonephritis cases in China, and is the main cause of CKD, chronic renal failure and uremia (2). miRNAs can affect the proliferation and ECM accumulation of glomerular mesangial cells (59).

In a previous study, a rat model of MsPGN was induced using anti-Thy-1.1 and the rats were treated with different doses of umbilical cord MSC-derived extracellular vesicles (ucMSC-EVs) (60). EV intervention in the MsPGN model inhibited the abnormal proliferation of renal mesangial cells, and alleviated mesangial hyperplasia and fibrosis in rat kidney tissue. *In vitro* experiments revealed that miR-378 directly targeted PSMD14, a deubiquitinating enzyme that stabilizes TGF-β1 through deubiquitination, leading to TGF-β1/Smad2/3 activation. Knockdown of miR-378 or overexpression of PSMD14 reduced the protective effects of ucMSC-EVs by activating the TGF-β1/Smad2/3 signaling pathway. Additionally, miR-378 targets were revealed to be enriched in ubiquitinated protein degradation-related pathways. These findings indicated that PSMD14 may contribute to triggering deubiquitination to maintain TGF-β1 stability (61).

Kidney transplantation. A brief overview of the role of miR-378 in kidney transplantation is provided in Table I. The most effective treatment for ESRD is kidney transplantation; however, chronic allograft dysfunction (CAD), characterized primarily by interstitial fibrosis and progressive tubular atrophy (IF/TA), frequently occurs (62). CAD may result from I/R injury (IRI) during kidney transplantation. The roles of miRNAs in transplantation-related kidney diseases have gained significant attention and warrant investigation (63).

miR-378 is associated with various kidney diseases and CAD. The expression levels of miR-378 have been shown to be decreased in the renal tissue of patients undergoing renal allotransplantation (64). In addition, significant variability in miR-378 expression has been observed across different kidney transplantation-related pathological biopsies, with optimal biopsy protocols, allograft function and morphology being identified (65). Deep sequencing data have revealed nucleotide differences in miR-378 between interstitial IF/TA and normal biopsies (66). Notably, miR-378 may be associated with transplant-related kidney disease and has potential value in assessing and managing kidney allografts.

In vivo (mouse model of kidney unilateral IRI) and *in vitro* (NRK-52E cells undergoing H/R) experiments have shown that renal I/R can cause a considerable decrease in miR-378 expression and an increase in renal interstitial fibrosis (64). In addition, increasing miR-378 levels have been shown to target caspase 3 expression, thereby inhibiting apoptosis, and to reduce the TGF-β1-induced levels of COL1, COL4 and α-SMA levels, thereby inhibiting renal interstitial fibrosis (52). Therefore, the protective role of miR-378 in renal transplantation, IRI and renal interstitial fibrosis may be a therapeutic target for the treatment of CAD.

3. Conclusions

miR-378, has also been implicated in the regulation of the occurrence and progression of various kidney diseases. Notably, miR-378 has a role in numerous pathological processes, including renal tubulointerstitial fibrosis and angiogenesis, with additional functions likely to be elucidated in the future. These findings suggest that miR-378 may act as a key regulator in kidney disease pathology.

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Authors' contributions

YL chose the title, retrieved the literature and drafted the manuscript. SS, TC and HaW retrieved, collated, categorized and analyzed information. YH and HuW governed the whole process, completed the conception, were responsible for the acquisition of key data, in-depth analysis and interpretation of results and ensuring the scientific nature of the article. Data authentication is not applicable. All authors contributed to the article, and read and approved the final version of the manuscript.

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Not applicable.

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Competing interests

The authors declare that they have no competing interests.

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