Review

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Review

MicroRNAs as Biomarkers and Therapeutic Targets for Acute Kidney Injury

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Abstract: Acute kidney injury (AKI) is a clinical syndrome where a rapid decrease in kidney function and/or urine output is observed, which may result in the imbalance of water, electrolyte and acid base, and is associated with poor prognosis and prolonged hospitalization. Therefore, early diagnosis and treatment to avoid the severe AKI stage is important. While several biomarkers, such as urinary L-FABP and NGAL, can be clinically useful, there is still no gold standard for early detection of AKI and there are limited therapeutic options against AKI. miRNAs are non-coding and single-stranded RNAs that silence their target genes in the post-transcriptional process and are involved in a wide range of biological processes. Recent accumulated evidence has revealed that miRNAs may be potential biomarkers and therapeutic targets for AKI and AKI–CKD transition. In this review article, we summarize the current knowledge about miRNAs as promising biomarkers and potential therapeutic targets for AKI, as well as the challenges in their clinical use.

Keywords: microRNA; acute kidney injury; biomarker; mesenchymal stem cell.

1. Introduction

Acute kidney injury (AKI) is a clinical syndrome where a rapid decrease in kidney function and/or urine output is observed, which may result in the imbalance of water, electrolytes and acid base due to a variety of causes, including sepsis, major surgery, hypovolemia, drug toxicity, urinary tract obstruction and rhabdomyolysis [1]. It is reported that the prevalence of AKI is 23.2% for inpatients [2] and 57.3% in intensive care unit (ICU) patients [3]. The mortality of AKI is 4.9% in all AKI, 3.4% in stage 1, 7.5% in stage 2, 13.2% in stage 3 and 24.1% in dialysis-dependent patients [2]. AKI, which in outpatients is about 70% pre-renal and in inpatients is 55-60% intra-renal, is mostly induced by acute tubular necrosis (ATN) caused by ischemia due to sepsis, or induced by NSAIDs, antibiotics, cisplatin or contrast agents [4]. In addition, anti-cancer agents in current development increase drug-induced AKI. For example, an immune checkpoint inhibitor may cause tubulointerstitial nephritis [5] and a vascular endothelial growth factor (VEGF) inhibitor may cause thrombotic microangiopathy (TMA) [6]. In addition, patients with AKI tend to require extended hospitalization, leading to a significant financial burden. Therefore, early diagnosis and treatment to avoid the severe AKI stage would be important. For the purpose of early diagnosis and establishment of common diagnostic criteria, the concept of AKI was distinguished from acute renal failure (ARF) [7]. Subsequently, several criteria for classifying AKI were developed; risk, injury, failure, loss of kidney function, and end-stage kidney disease (RIFLE), acute kidney injury network (AKIN) and the kidney disease improving global outcomes (KDIGO), where increases in serum creatinine (s-Cr) and/or decreases in urine output were the important criteria [1]. Nevertheless, early diagnosis may

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not always be easy according to the guidelines, partly because s-Cr does not reflect direct tubular injury; thus, biomarkers over s-Cr and urine output would be required as biomarkers for AKI. There are several biomarkers for AKI reported, including neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule 1 (KIM-1), L-type fatty acid-binding protein (L-FABP), cystatin C, Clusterin, interleukin-18 (IL-18), Proenkephalin A 119–159 (Penkid), the product of insulin like growth factor binding protein 7 (IGFBP-7) and tissue inhibitor of metalloproteinase 2 (TIMP-2). However, there is still no gold standard for early detection of AKI [8,9].

The long-term outcome is also problematic since patients who develop AKI do not necessarily experience complete recovery of renal function; it may instead lead either to the development of chronic kidney disease (CKD) or to exacerbation of the rate of progression of preexisting CKD or irreversible ESRD [10]. Kidneys have the potential to regenerate after AKI [11]. The replacements of detached tubular cells has been analyzed for decades. There are three candidate cell types for regeneration; mesenchymal stem cells (MSCs), kidney stem cells and remaining tubular cells. It is reported that bone-marrow-derived MSCs transfer to the injured kidneys, differentiate into tubular cells and become replacements [12], but recent gene-tracking systems reveal that replacements by MSCs are less than 1%. Instead, MSCs have an important role in regeneration due to their paracrine effects [13,14]. Adult kidney stem cells have also been explored, and several groups have identified the rol of kidney stem cells in regeneration [15–17]. On the other hand, gene-tracking systems reveal that a majority of regenerative cells after AKI were tubular cells that had survived via de-differentiation and gained the stem cell phenotype [18,19]. Further exploration of regenerative mechanisms may lead to a novel therapy for AKI, and microRNAs (miRNAs) are among the important candidates for that.

miRNAs are non-coding and single-stranded RNAs of 19-23 nucleotides [20]. miRNAs silence their target genes in the post-transcriptional process through 3′-UTR binding, and are involved in a wide range of biological processes, including development, differentiation, cell proliferation, apoptosis, cancer metastasis, inflammation and fibrosis [20]. miRNAs were discovered in 1993 [21] and confirmed to exist in mammals in 2000 [22], and currently more than 2000 types of human miRNAs are registered in the database (miRBase), a data base of pre-miRNAs and miRNAs. It is reported that miRNAs work even if they are not necessarily complementary except for 2-8 on the 5′ side [23] [24], and it is estimated that more than 60% of human translated genes have at least one conserved miRNA-binding site [25], and that one miRNA has more than one hundred target mRNAs and controls various regulation [26]. Recently accumulated evidence reveals that miRNAs may be the potential biomarkers as well as therapeutic targets for AKI and AKI–CKD transition. In this review article, we summarize the current knowledge about miRNAs as promising biomarkers and potential therapeutic targets for AKI.

2. miRNA production and dynamics

In the maturation of miRNAs, most primary miRNA transcripts (pri-miRNAs) are transcribed by RNA polymerase II, followed by cleavage by microprocessor complex Drosha-DiGeorge syndrome critical region 8 (DGCr8) to precursor miRNAs (pre-miRNAs) [27]. After moving to the cytoplasm from the nucleus, the pre-miRNAs are cleaved by Dicer and form a miRNA duplex. The miRNA duplex interacts with Argonaute (AGO) proteins and forms a RNA-induced silencing complex (RISC), finally forming a mature single miRNA while the other strand is degraded. The mature miRNAs target mRNAs in the cytosol, leading to the inhibition of protein translation or mRNA degradation [28]. miRNAs can also be sorted into extracellular vesicles (EVs), such as exosomes, macrovesicles and apoptotic bodies, and these EVs may be secreted, circulating in the blood or urine, transferring into the recipient cells and acting in them [28]. miRNAs also secrete RNA-binding proteins, such as high-density lipoprotein (HDL) and AGO2. These miRNAs in the blood are called circulating miRNAs [28]. Especially in cancer research, these circulating miRNAs have been reported to be important biomarkers in liquid biopsy [29]. In kidney diseases, miRNAs in serum, plasma and urine as well as in kidney tissue have been explored as potential biomarkers, for example for nephrotic syndrome, IgA nephropathy, hypertensive nephropathy, diabetic nephropathy, CKD

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and AKI [30]. In addition, miRNAs are also explored as therapeutic targets for kidney diseases, including AKI.

3. miRNAs as biomarkers in AKI

3.1. Overview of biomarkes in AKI

Under AKI, the decrease in glomerular filtration rate leads to an increase in s-Cr after a delay of 24 to 48 hours [31], and a renal tubular disorder marker that precedes the s-Cr is thought to be useful for early diagnosis of AKI. Several tubular injury markers have been reported as AKI biomarkers, including KIM-1, L-FABP, IL-18, NAG and NGAL, which could indicate kidney damage prior to the increase in s-Cr [32,33]. In addition, cystatin C, clusterin and penkid have also been reported as the potential biomarkers [34,35]. Among these, NGAL was reported as one of the fastest markers for detecting tubular injury, particularly in the distal tubular segments [34]. In humans, elevated NGAL levels can be observed within 3 hrs after tubular injury and peak around 6-12 hrs. It is reported that IL-18 levels rise around 6 hrs after kidney damage and peak between 12-18 hrs [34]. It is also reported that urinary L-FABP may be elevated 2 hrs postoperatively in AKI patients, suggesting that 2 -hr postoperative urinary L-FABP may predict AKI [34]. It is also reported that G1 cell–cycle arrest markers, TIMP-2 and IGFBP7 expressions are increased during the early phase of cellular stress or injury. Indeed, the combination of TIMP2 and IGFBP7 ([TIMP-2] x [IGFBP7]) was reported as an accurate indicator for identifying the early phase of AKI [36]. In spite of these advances in early AKI diagnosis, they are not widely applied in clinical practice. Therefore, novel biomarkers would still be desirable for early AKI detection and predicting severity as well as for the differentiation of AKI etiologies, such as ischemic, drug-induced, contrast-induced and septic. From this point of view, miRNAs would be potent and novel biomarkers to solve these problems.

3.2. miRNAs as AKI biomarkers

A study that analyzed the profile of miRNA in normal human kidneys indicated 669 types of miRNAs, while 364 types of miRNAs were identified in normal mice [37]. Comparing the 20 most abundant types in humans and mice, 12 types of miRNAs, let-7c-5p, miR-10a-5p, miR-10b-5p, miR-143-3p, miR-181a-5p, miR-192-5p, miR-26a-5p, miR-27b-3p, miR-30a-5p, miR-30c-5p, miR-30d-5p and miR-92a-3p were held in common, while 8 types of miRNAs, let-7a-5p, let-7b-5p, miR-125a-5p, miR-125b-5p, miR-150-5p, miR-191-5p, miR-204-5p and miR-486-5p were specific to humans, and let-7f-5p, miR-101a-3p, miR-126a-5p, miR-16-5p, miR-21a-5p, miR-22-3p, miR-30e-5p and miR-378a-3p were specific to mice [37], suggesting some profile differences between the species. In addition, there was another study on the profile of the miRNA Tissue Atlas, where the human miRNA profile, including in kidneys, was analyzed [38]. Currently, there are several profile studies analyzing miRNAs as biomarkers for AKI, where blood or urine samples were applied (Table 1). One of the advantages of miRNA profile analysis is its stability against RNase and low pH as well as multiple freeze–thaw cycles [39]. It was reported that serum levels of a panel of 10 miRNAs (miR-101-3p, miR-127-3p, miR-210-3p, miR-126-3p, miR-26b-5p, miR-29a-3p, miR-146a-5p, miR-27a-3p, miR-93-3p and miR-10a-5p) may be useful as biomarkers of AKI in ICU, where the panel of miRNAs indicated a high diagnostic value [40]. Among these miRNAs, miR-210-3p, miR-126-3p, miR-29a-3p and miR-146a-5p were correlated with severity of AKI, diagnosed by AKIN criteria. Urinary miR-16 was 100-fold higher in AKI patients [41]. Similarly, urine miR-16-5p was increased in patients with AKI, suggesting a possible specific biomarker for AKI. On the other hand, plasma miR-16 was down-regulated in patients with AKI [42], indicating a possible difference between blood and urine. In the same study, up-regulation of plasma miR-210 and down-regulation of miR-320 were also reported. Among these, plasma miR-210 was also detected as an independent predictor of 28-day survival [42]. In the same line, serum levels of miR-29a and miR-10a-5p were increased in patients with sepsis-induced AKI, and these miRNAs were also detected as the predicting marker for 28-day survival [43]. In addition, urine miR-26b was also reported to be increased in patients with sepsis-induced AKI and was associated with mortality [44]. In the other study, urine miR-494 levels were 60-fold higher in

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patients with AKI [45]. In addition, serum miR-494 was up-regulated in child patients with AKI after cardiopulmonary bypass for congenital heart disease, where the combination of NGAL, Kim-1 and miR-494 showed the high area under the curve (AUC) to predict the death of children with postoperative AKI [46]. Increased plasma miR-494 as well as miR-210 was also reported to predict 28-day survival in patients with sepsis-induced AKI [47]. It was also reported that serum and urine miR-22-3p was down-regulated in sepsis-induced AKI patients, and it may serve as a biomarker to predict 28-day survival [48]. Urine levels of miR-21, miR-200c and miR-423 were reported to be increased in patients with AKI in ICU, and the combination of these miRNAs showed high AUC at 0.91 [49]. In addition, a change in miRNA is often specific to the individual etiologies for AKI. For example, plasma levels of miR-30a, miR-30c and miR-30e showed >two fold increase in patients with contrast-induced nephropathy (CIN) [50]. Another study also indicated the plasma levels of miR-30a and miR-30b as well as miR-188 in patients with CIN [51], suggesting a specific increase in the plasma miR-30 family in CIN. On the other hand, urine miR-30c-5p as well as miR-192-5p were increased in patients with AKI after cardiac surgery as early as 2 hrs post operation, suggesting a possible biomarker for predicting AKI after cardiac surgery [52]. Similarly, plasma miR-192 was also increased in patients with AKI at the time of ICU admission, remaining stable for 2 hrs and decreasing after 24 hrs, suggesting a time-dependent change in miR-192 [53]. Regarding early detection of AKI, increases in serum and urine levels of miR-452 in patients with sepsis-induced AKI were reported, where the sensitivity of urine miR-452 was higher than urine [TIMP-2] x [IGFBP7] [54]. As well as increased miRNAs, decreased expression was also reported. Serum miR-5100 was down-regulated in patients with AKI [55], and urine miR-155 was down-regulated in patients with AKI [56]. Regarding miR-21, there are several reports regarding biomarkers for AKI. For example, levels of serum, plasma and urine miR-21 were increased in patients with AKI after cardiac surgery [57,58]. In addition, urine and plasma miR-21 levels also predicted the need for post-operative renal replacement therapy, 30-day in-hospital mortality and prolonged stay in hospital or ICU [58]. Other than in AKI after cardiac surgery, serum miR-21 was also up-regulated in patients with sepsis-induced AKI [59]. On the other hand, decreased miR-21 levels in patients with AKI after cardiac surgery was also reported [60], where reduced post-operative serum and urine miR-21 levels could predict AKI development. In addition, it is also reported that baseline miR-21 before cardiac surgery could predict AKI development [61]. These results may reflect the complex regulation of miR-21 under AKI.

In summary, there are several promising miRNAs that could serve as possible biomarkers for early diagnosis, prediction of mortality and the specific pathology in AKI. Nevertheless, there are several problems relating to clinical use. For example, several types of samples, such as serum, plasma, urine and exosomal miRNAs, may be used for the analysis. Indeed, it is reported that serum and plasma may yield result differences. In addition, the collecting methods of miRNAs are different between reports, which may be one cause of the differences between the reports. Since miRNA volume is very limited, the methods of analysis and collection of EV may affect the results. Therefore, clinical procedures still need exploration.

Table 1. MiRNAs as potential biomarkers of AKI.

miRNA	Subtype	Species	Etiology	Expression	Sample	Ref.
miR-16	miR-16	Human/mice	-	Up	Urine	[41]
	miR-16	Human	-	Down	Plasma	[42]
	miR-16-5p	Human	-	Up	Urine	[62]
miR-30	miR-30a, c, e	Human/rats	Contrast	Up	Plasma	[50]
	miR-30a, e	Human/rats	Contrast	Up	Plasma	[51]
	miR-30c-5p	Human	Cardiac surgery	Up	Urine	[52]
miR-21	miR-21	Human	Cardiac surgery	Down	Serum/Urine	[60]
	miR-21	Human	Cardiac surgery	Up	Plasma/Urine	[58]
	miR-21	Human	Cardiac surgery	Up	Serum/Urine	[57]
	miR-21-3p	Human	Sepsis	UP	Serum	[59]
	miR-21	Human	-	Up	Urine	[49]

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	miR-21	Human	-	Up	Urine	[56]
miR-188	miR-188	Human	Contrast	Up	Plasma	[51]
miR-22	miR-22-3p	Human	Sepsis	Down	Serum/Urine	[48]
miR-29	miR-29a	Human	Sepsis	Up	Serum	[43]
miR-26	miR-26b	Human	Sepsis	Up	Urine	[44]
miR-155	miR-155	Human	-	Down	Urine	[56]
miR-10	miR-10a-5p	Human	Sepsis	Up	Serum	[43]
miR-192	miR-192-5p	Human	Cardiac surgery	Up	Urine	[52]
	miR-192	Human/rats	Cardiac surgery	Up	Plasma	[53]
miR-200	miR-200c	Human	-	Up	Urine	[49]
miR-210	miR-210	Human	-	Up	Plasma	[42]
	miR-210	Human	Sepsis	Up	Plasma	[47]
miR-423	miR-423	Human	-	Up	Urine	[49]
miR-452	miR-452	Human	Sepsis	Up	Serum/Urine	[54]
miR-494	miR-494	Human/mice	-	Up	Urine	[45]
	miR-494	Human	Cardiac surgery	Up	Serum	[46]
	miR-494	Human	Sepsis	Up	Plasma	[47]
miR-5100	miR-5100	Human	-	Down	Serum	[55]
miR-320	miR-320	Human	-	Down	Plasma	[42]

miRNA: microRNA.

4. miRNAs as therapeutic targets for AKI

4.1. Overview of treatment in AKI

Treating AKI is the ultimate challenge. According to the Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Acute Kidney Injury [63], there is no strong recommendation for its administration; thus, there is a demand for the development of new AKI therapeutic agents. As regeneration of kidneys can occur, there are several challenges involved. For example, stem cell therapy, including mesenchymal stem cells, kidney stem cells and induced pluripotent stem (iPS)-cell-derived nephron progenitor cells have been explored over several decades [14,64,65]. There are reports on direct replacement of transplanted stem cells [15,66], but currently, it appears likely that the dominant effect of transplanted stem cells is derived from the secreted factors from stem cells. For example, MSCs secrete a variety of factors, including soluble factors, cytokines, chemokines and growth factors [14]. In addition, MSCs secrete extracellular vesicles containing soluble proteins, mRNAs and miRNAs [13]. These factors transfer to the recipient cells, which mediate renoprotection (anti-apoptosis, anti-nectrosis, anti-inflammation, antinoxidative stress and aniti-fibrosis) and regeneration (cell prolifaretion, cell migraiton, tubular de-differentiation and angiogenesis) [67]. It is likely that extracellular vesicles are the predominant paracrine effects in AKI [67]. Which factors provide the dominant therapeutic effects? It was reported that EVs derived from MSCs with knockdown of Drosha, essential for miRNA production, failed to ameliorate I/R-induced AKI, while MSC-derived EVs without knockdown ameliorated AKI [68], suggesting that miRNAs in EVs might be the most important factors for renal protection and regeneration in AKI. Renoprotective miRNAs from MSCs were previously reported [67], where miR-21 and miR-30 mediated anti-apoptosis, miR-210 mediated angionegesis, miR-145 mediated autophagy, miR-15 and miR-16 ameliorated kidney fibrosis, miR-15, miR-16, miR-21 and let-7 ameliorated inflammation through the regulation of macrophage. In addition to MSCs, secreted factors from other stem cells, such as kidney stem cells and iPS-derived nephron progenitor cells, have also been reported to be renoprotective [14,64,65]. These trophic effects might be at least partly delivered via miRNAs. miRNAs from other cells, such as circulating inflammatory cells and tubular cells, might be involved in kidney damage and/or regeneration during AKI. Researchers still need to explore miRNA dynamics. Nevertheless, miRNAs might be novel therapeutic targets for AKI.

In addition, hypoxia–inducible factor (HIF)-prolyl hydroxylase (HIF-PHD) inhibitor has been

developed as a therapy for renal anemia [69]. Pharmacological activation of HIF regulates a variety of genes, including *Epo*, leading to hematopoiesis. Other than hematopoiesis, HIF-PHD inhibitor has also been shown to ameliorate AKI in rodent experimental models [70], including I/R-induced and drug-induced models with cisplatin, gentamicin and lipopolysaccharide (LPS). These protective mechanisms include anti-apoptosis via miR-21, anti-inflammation by macrophage reduction, reduced VCAM1, upregulation of angiogenesis via VEGF upregulation, and anti-oxidative stress via upregulation of Heme Oxygenase 1 (HO-1) [70]. As shown with increases in miR-21, these effects may be mediated at least partly via regulation of miRNAs. Indeed, it is reported that kidney ischemia activates HIF-1α, which in turn upregulates miR-21, leading to anti-apoptosis through the suppression of pro-apoptotic factor programmed cell death protein 4 (Pdcd4) and phosphatase and tensin homolog deleted from chromosome 10 (PTEN) [71]. HIF1 also increases miR-668 expression, which targets mitochondrial fission process protein 1 (MTP18), leading to the protection of kidney tubular cells via mitochondrial dynamics under ischemic AKI in humans and mice [72]. Activation of HIF also increases miR-489, leading to anti-apoptosis in kidney tubular cells during ischemic AKI though targeting repair sensor poly(ADP-ribose) polymerase 1 (PARP1) [73]. Taken together, these data suggest that the regulation of miRNA might be a novel and specific therapy against AKI.

4.2. Therapeutic targeting of miRNAs for AKI

Some of the most important evidence regarding miRNAs in AKI was reported in 2010, where knockouts of tubular miRNAs were analyzed in the rodent model [74]. The loxp-cre system was used to produce mice lacking Dicer, a key enzyme for miRNA production, in proximal tubular cells. The mice showed global downregulation of miRNAs in the kidney cortex and had normal kidney function and histology under normal conditions, while they were resistant to renal ischemia-reperfusion (I/R) injury, demonstrating the involvement of miRNAs under AKI. Since then, there has been accumulating evidence supporting miRNAs as potential therapeutic targets in AKI. Several miRNAs have been reported to have protective and/or pathogenic roles in AKI, regulating tubular apoptosis, tubulointerstitial fibrosis and inflammation in a variety of etiologies of AKI, including ischemia, drug and sepsis. Some miRNAs have common gene targets. For example, miR-30 and miR-26a target Snai1, regulating epithelial–mesenchymal transition (EMT), while miR-21, miR-17, miR-188 and miR-378 target PTEN, which is implicated in cell apoptosis, proliferation, inflammation and fibrosis [27]. The potential therapeutic targets of miRNAs for AKI are summarized in Table 2.

miR-21 is one of the most analyzed miRNAs, described as having double-edged-sword effects in kidneys [67] and both protective and pathogenic effects in kidney diseases. As a protective effect, miR-21 ameliorates I/R-induced AKI by inhibiting tubular cell apoptosis in I/R and LPS-induced AKI mice [71,75], targeting PTEN/Akt/mammalian target of rapamycin (mTOR) signaling and Cyclin-dependent kinase 6 (CDK6). miR-21 is also shown to inhibit maturation of dendritic cells through the PDCD4/ NFκ-B pathway [71] and CCR7 [76], thereby mediating anti-inflammatory effects in I/R-induced AKI mice. In addition, miR-21 is also shown to target mitogen-activated protein kinase kinase 3 (MKK3), inhibiting the downstream factors IL-6 and TNF-α levels, mediating anti-inflammatory effects [77]. On the other hand, as a pathogenic effect, miR-21 inhibits autophagy in I/R-AKI rats by targeting Rab11a [78]. In addition, long-term elevation of miR-21 might promote kidney fibrosis, including via PPARα [79]. Furthermore, miR-21 was shown to regulate energy metabolism via AKT/Cyclin-dependent kinase 2 (CDK2)-FOXO1 in a sepsis-induced rat AKI model, while it was unclear whether the regulation was protective or harmful for long-term prognosis [80]. Taken together, these data suggest that miR-21 may target several signaling pathways, involving cell apoptosis, inflammation and autophagy as well as energy metabolism under AKI. Similarly to miR-21, miR-30, miR-181, miR-22 and miR-590 are also reported to mediate anti-apoptosis and anti-inflammation effects in I/R-AKI rodent models. It was reported that MSC-derived extracellular vesicles ameliorated rat I/R-induced AKI by inhibiting cell apoptosis through miR-30, which targeted dynamin-related protein 1 (DRP1), thereby inhibiting mitochondrial fission [81]. In addition, injection of miR-30c-5p agomir, chemically modified double-stranded small RNA that mimics the miR-30c-5p, ameliorated rat I/R-induced AKI through transformation of M1 to M2 macrophages, mediating an

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anti-inflammatory effect via changes in inflammatory cytokines [82]. miR-181d-5p overexpression in the mouse model of I/R-induced AKI ameliorated kidney injury by reducing inflammatory mediators and apoptosis through targeting Krueppel-like factor 6 (KLF6) [83]. A renoprotective effect of miR-181 was also shown in a cisplatin-induced mouse AKI model by targeting PTEN [84] in LPS-induced AKI model through an anti-apoptosis effect by targeting GJB2 [85]. In addition, miR-181a-5p is reported to target NIMA-related kinase 7 (NEK7), thereby inhibiting pyroptosis in sepsis-induced AKI mice [86]. It was reported that in a sepsis-induced AKI mouse model, lncRNA TCONS_00016233, targeting miR-22, was upregulated in plasma, and TCONS_00016233 overexpression worsened sepsis-induced mouse AKI by downregulating miR-22, thus increasing the mir-22 target, with apoptosis-inducing factor mitochondrion-associated 1 (AIFM1) leading to apoptosis [87], indicating an anti-apoptosis effect of miR-22. In addition, miR-22 attenuated sepsis-induced rat AKI, targeting High Mobility Group Box 1 (HMGB1) and inhibiting the HMGB1/TLR4/NF-kB pathway [88]. Adenovirus expressing miR-590-3p via tail-vein injection in LPS-induced septic AKI mice ameliorated cell apoptosis and inflammation by targeting tumor necrosis factor receptor-associated factor 6 (TRAF6) [89]. miR-590-3p was also shown to oissibly increase autophagy and protect kidney injury by targeting TRAF6, which was evaluated in an in vitro I/R model using renal tubular epithelial cell line (HK-2 cells) [90].

There are several reports indicating an anti-apoptosis effect from miRNAs. miR-124 was shown to ameliorate I/R-induced mouse AKI, where miR-124 mimics reduced endoplasmic reticulum stress (ERS)-mediated apoptosis [91]. In addition to the anti-apoptosis mechanism, miR-124 also inhibited necroptosis by targeting PARP1 in an I/R-induced mouse AKI model [92]. miR-489 also targeted PARP1, mediating an anti-apoptosis effect, and miR-489 mimics protected against I/R mouse AKI [73]. miR-17-5p mimics suppressed death receptor 6 (DR6), mediating anti-apoptosis in an I/R-induced mouse AKI model [93]. Likewise, miR-424 mimics inhibited its target gene DR6, mediating anti-apoptosis in an I/R-induced mouse AKI model [94]. miR-5100 mimic injection into I/R-mice ameliorated kidney injury by inhibiting several apoptotic pathways [55]. miR-486-5p was shown to target PTEN, thereby mediating an anti-apoptosis effect in a mouse I/R-AKI model [95]. miR-191-5p mimic injection could inhibit cell apoptosis by targeting Oxidative stress responsive 1 (OXSR1) [96]. miR-290-5p activated by propofol ameliorated a sepsis-induced mouse AKI model by targeting C-C motif chemokine ligand 2 (CCL2), thereby mediating an anti-apoptosis effect [97]. In addition to the anti-apoptosis effect, an anti-inflammation effect by miRNAs has also been explored. miR-204/miR-211 mimics, targeting H6 Family Homeobox 1 (Hmx1), reduced kidney injury via immune suppression in candidemia-induced AKI mice [98]. miR-195-5p mimic injection ameliorated rat I/R-AKI by targeting vascular endothelial growth factor A (VEGFA) via anti-inflammatory and anti-oxidative stress [99]. miR-140-5p up-regulation by apigenin ameliorated I/R-induced AKI mice through targeting Chemokine (C-X-C Motif) Ligand 12 (CXCL2), thereby reducing inflammation [100]. In addition, miR-140-5p was shown to activate nuclear factor erythroid 2-related factor (Nrf2) pathway, thereby mediating anti-oxidative stress in cisplatin-induced AKI mice [101]. miR-27a targeting Toll-like receptor 4 (TLR4) inhibited inflammation in I/R-induced AKI [102]. In addition, overexpression of LINC00520, targeting miR-27b-3p, activated Oncostatin M Receptor (OSMR), leading to the PI3K/AKT pathway to aggravate kidney injury in I/R-induced AKI, while up-regulation of miR-27b-3p could accelerate recovery from AKI [103]. miR-146a-5p derived from human urine-derived stem cells protected against rat I/R-induced AKI by targeting interleukin 1 receptor associated kinase 1 (IRAK1), thereby inhibiting NF-κB signaling and infiltration of inflammatory cells [104]. Mice lacking miR-146 showed more extensive tubular injury, inflammatory infiltrates, and fibrosis than wild-type mice after I/R-induced AKI [105]. Furthermore, the renoprotective effect of miRNAs involves vascular, mitochondrial and podocyte protection. miR-210 was shown to activate VEGF signaling to regulate angiogenesis in I/R-induced AKI mice [106]. Overexpression of miR-126 in the hematopoietic compartment promoted vascular integrity and supported recovery of kidney injury after I/R-induced AKI mice [107]. miR-668 was shown to target mitochondrial protein 18 kDa (MTP18) to preserve mitochondrial dynamics and tubular cell survival

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in I/R-AKI mice [72]. miR-187 agomir injection in I/R protected against I/R-induced AKI and mediated podocyte protection, evaluated by nephrin expression by targeting acetylcholinesterase (AChE) [108].

There are several reports indicating MSC-related miRNAs as providing renoprotection via anti-apoptosis. MSC-derived exosome containing miR-199a-3p targeted semaphorin3A (SEMA3A), leading to the AKT and Extracellular signal-regulated kinase (ERK) pathway activation and ameliorated apoptosis [109]. Bone-marrow-derived MSCs ameliorate I/R-induced mouse AKI via miR-223, targeting NLR family pyrin domain containing 3 (NLRP3), thereby inhibiting apoptosis [110]. Human umbilical-cord-derived MSCs containing miR-125b-5p suppressed p53, leading to an anti-apoptosis effect [111]. Bone-marrow-derived MSCs reduced miR-107, increasing the expression of the miR-107 target, Ribosomal Protein S19 (RPS19), and protected from cisplatin-induced apoptosis [112]. In contrast, miR-107 was shown to induce TNF-α by targeting dual specificity phosphatase 7 (DUSP7), causing tubular injury [113]. Microvesicles from human Wharton's Jelly MSCs ameliorated I/R-induced rat AKI by suppressing C-X3-C Motif Chemokine 1 (CXCL1) and ameliorated inflammation and fibrosis partly via miR-16, miR-15a and miR-15b [114]. On the other hand, urine miR-16 transactivated by CCAAT enhancer binding protein beta (C/EBP-β) worsened I/R-induced AKI, causing apoptosis [41]. Bone-marrow-derived MSCs ameliorated cisplatin-induced AKI by inhibiting fibrosis through the regulation of miR-146a-5p and its target transcription Factor Dp-2 (Tfdp2) [115].

In addition to these renoprotective miRNAs, there are several pathogenic miRNAs under AKI, aggravating kidney injury by causing apoptosis, inflammation, mitochondrial damage and fibrosis. It is reported that the administration of antisense oligonucleotide inhibiting miR-182 ameliorated an I/R-induced AKI rat model [116]. In an other report, an miR-182 inhibitor ameliorated I/R-induced rat AKI and apoptosis by regulating the transcription factor 7-like-2 (TCF7L2)/ Wnt/β-catenin pathway [117]. miR-182 was also shown to target Forkhead box O3 (FoxO3), leading to cell apoptosis in an I/R-induced AKI rat model [118]. Similarly, there are several miRNAs reported to promote cell apoptosis under AKI, including miR-122, miR-301, miR-375, miR-188, miR-687, miR-24 and miR-218. miR-122 was suggested to target FoxO3, thereby causing cell apoptosis in cisplatin-induced AKI mice [119]. miR-301a-5p inhibition ameliorated vancomycin-induced AKI by reducing apoptosis [120]. miR-375 was reported to be induced in a cisplatin-induced mouse AKI model to repress hepatocyte nuclear factor 1 homeobox B (HNF-1β), leading to the promotion of tubular cell apoptosis [121]. miR-188 was shown to aggravate contrast-induced AKI by targeting Serine And Arginine Rich Splicing Factor 7 (SRSF7), leading to cell apoptosis [122]. miR-687 was shown to be interfered with by lncRNA TCONS_00016406, leading to an anti-apoptosis effect [123]. miR-24 silencing protected against I/R-induced mouse AKI by inhibiting cell apoptosis by targeting H2A histone family, member X, (H2A.X) and HO-1 [124]. It was also suggested that honokiol inhibited miR-218-5p, leading to an increase in its target HO-1, thereby mediating an anti-apoptosis effect in sepsis-induced mouse AKI [125]. Several miRNAs, namely, miR-494, miR106, miR-155 and miR-152, were shown to promote inflammation as well as apoptosis. It is reported that miR-494 down-regulation by lncRNA TUG1 reduced I/R-induced mouse AKI and cell apoptosis by regulating E-cadherin [126]. In addition, overexpression of miR-494 was shown to reduce activating transcription factor 3 (ATF3), leading to an increase in inflammatory mediators, such as IL-6 and monocyte chemotactic protein-1, exacerbating inflammation in I/R-induced mouse AKI [45]. Injection of miR-494 antagomir, chemically modified miR-494 antagonist, ameliorated LPS-induced mouse AKI via anti-apoptosis and anti-inflammation mechanisms by regulating the NF-κB signaling pathway [127]. It was reported that serum miR-106a was increased in sepsis-induced AKI mice, and miR-106a was suggested to target thrombospondin 2 (THBS2), leading to inflammation and apoptosis [128]. miR-155 inhibitor ameliorated LPS-induced mouse AKI through the reduction of inflammatory cells by regulating the target Suppressor Of Cytokine Signaling 1 (SOCS1) and Signal Transducer And Activator Of Transcription (STAT)1 mRNAs [129]. It was also reported that macrophage-derived exosomal miR-155 promoted tubular injury by targeting SOCS1 [130]. In addition, miR-155$^{-/-}$ mice were made resistant to cisplatin-induced AKI by reducing tubular cell apoptosis [130]. miR-155 was shown to be up-regulated in rat I/R-induced AKI and suggested to promote kidney injury and apoptosis by

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targeting Transcription factor 4 (TCF4)/Wnt/β-catenin signaling pathway [131]. miR-152-3p was suggested to promote cell apoptosis by silencing Sirtuin 7 (SIRT7) in I/R-induced rat AKI [132]. miR-152-3p was shown to promote sepsis-induced rat AKI by targeting ERBB receptor feedback inhibitor 1 (ERRFI1), leading to an increase in STAT3 expression, resulting in promoting cell apoptosis and inflammation [133]. miR-709 antagomir injection attenuated cisplatin-induced mouse AKI via a reduction in mitochondrial dysfunction by regulating miR-709 target gene mitochondrial transcriptional factor A (TFAM) [134].

Furthermore, similarly to miR-21, several miRNAs were shown to mediate both protective and pathogenic effects under AKI. miR-34 agomir injection ameliorated sepsis-induced mouse AKI via anti-inflammatory mechanism by targeting ubiquitin-like protein 4A (UBL4A) [135]. miR-34a induced via p53 was suggested to play a cytoprotective role in cell survival in cisplatin-induced mouse AKI [136]. In contrast to these renoprotective effects of miR-34, miR-34 was also shown to promote kidney injury under AKI. lncRNA HOX transcript antisense RNA (HOTAIR) overexpression ameliorated sepsis-induced rat AKI via an anti-apoptosis mechanism by targeting miR-34a and regulating its target B-cell lymphoma-2 (Bcl-2) [137]. It is also reported that increased miR-34a promoted acetylation of FOXO3 by repressing Sirtuin 1 (SIRT1), leadind to p53 activation and cell apoptosis in the cisplatin-induced mouse AKI model [119]. miR-34a was also suggested to suppress autophagy in kidney tubular cells by targeting autophagy related 4B cysteine peptidase (ATG4B) in I/R-induced mouse AKI [138]. miR-34a mimics prevented Nicotinamide phosphoribosyltransferase (NAMPT) expression, which suggest that they affected oxidized NAD (NAD^+) metabolism, leading to kidney dysfunction in I/R-induced AKI mice [139]. In contrast to the anti-apoptosis effect of miR-125b-5p from MSCs in I/R-induced AKI mice [111], miR-125 was also shown to disrupt mitochondrial dynamics by targeting modulate mitofusin1 (MFN1) in cisplatin-induced AKI mice, where anti-miR-125b treatment reduced cisplatin-induced mitochondrial fragmentation and kidney injury [140]. miR-150-5p agomar was shown to ameliorate sepsis-induced mouse AKI via an anti-apoptosis mechanism by targeting mitogen-activated protein kinase kinase kinase 3 (MEKK3)/JNK pathway [141]. On the other hand, it was also reported that deletion of miR-150 in mice protected against myocardial-infarction-induced AKI through anti-apoptosis and anti-fibrosis mechanism by targetinginsulin-like growth factor-1 receptor (IGF-1R) [142]. In addition, pretreatment with exosomes enriched in miR-150 worsened kidney fibrosis in I/R-induced AKI mice [143]. Similarly, kidney fibrosis was reduced by miR-150-5p-deficient tubular cell-derived exosome in I/R-induced AKI mice by regulating the miR-150 target gene, SOCS1 [144]. miR-214 is also shown to mediate both protective and pathogenic effects under AKI. Regarding renoprotective effects, miR-214 injection in I/R-induced mice ameliorated kidney injury by inhibiting apoptosis through targeting dickkopf WNT signaling pathway inhibitor 3 (Dkk3) [145]. Adenovirus-mediated miR-214 treatment inhibited excess autophagy through regulation of the PTEN/AKT/mTOR pathway, thereby limiting kidney injury in sepsis-induced AKI mice [146]. On the other hand, regarding pathogenic effects, it is reported that kidney proximal-tubular-cell-specific miR-214 knockout mice showed less kidney damage and less apoptosis after I/R-induced AKI by targeting mitofusin-2 (Mfn2) [147]. miR-214-5p antagomir ameliorated LPS-induced kidney inflammation and oxidative stress, while miR-214-5p agomir aggravated kidney injury, presumably by targeting glucagon-like peptide-1 receptor (GLP-1R) [148]. miR-214-30 antagomir protected against cisplatin-induced AKI in mice by inhibiting tubular cell ferroptosis by targeting Glutathione Peroxidase 4 (GPX4) [149]. Collectively, miRNAs have several gene targets, thus regulating a variety of mechanisms that may mediate protective and/or pathogenic effects under AKI, and it may depend on the etiologies of AKI and evaluating methods.

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Table 2. Potential therapeutic targets of miRNAs for AKI.

miRNA	Effect	Target	Model	Species	Function	Ref.
miR-21	Protective	PTEN/Akt/mTOR Pdcd4/NFκ-B	I/R	Mice	Anti-apoptosis Anti-inflammation	[71]
	Protective	MKK3	I/R	Mice	Anti-inflammation	[77]
	-	AKT/CDK2-FOXO1	Sepsis	Rats	Metabolism alteration	[80]
	Protective	CDK6	LPS	Mice	Anti-apoptosis	[75]
	Protective	CCR7	I/R	Mice	Anti-inflammation	[76]
	Pathogenic	Rab11a	I/R	Rats	Anti-autophagy	[78]
miR-30	Protective	DRP1	I/R	Rats	Anti-apoptosis	[81]
	Protective	M1-M2 macrophage transition	I/R	Rats	Anti-inflammation	[82]
miR-17	Protective	DR6	I/R	Mice	Anti-apoptosis	[93]
miR-5100	Protective	Apoptotic pathway	I/R	Mice	Anti-apoptosis	[55]
miR-187	Protective	AChE	I/R	-	Podocyte protection	[108]
miR-182	Pathogenic	-	I/R	Rats	-	[116]
	Pathogenic	TCF7L2/Wnt/β-catenin	I/R	Rats	Apoptosis	[117]
	Pathogenic	FoxO3	I/R	Rats	Apoptosis	[118]
miR-489	Protective	PARP1	I/R	Mice	Anti-apoptosis	[73]
miR-668	Protective	MTP18	I/R	Mice	Mitochondrial dynamics	[72]
miR-27	Protective	OSMR	I/R	Rats	PI3K/AKT signal	[103]
	Protective	TLR4	I/R	Rats	Anti-inflammation	[102]
miR-140	Protective	Nrf2	Cisplatin	Mice	Anti-oxidative stress	[101]
	Protective	CXCL12	I/R	Mice	Anti-inflammation	[100]
miR-125	Pathogenic	MFN1	Cisplatin	Mice	Mitochondrial damage	[140]
	Protective	P53	I/R	Mice	Anti-apoptosis	[111]
miR-122	Pathogenic	FoxO3	Cisplatin	Mice	Apoptosis	[119]
miR-150	Pathogenic	IGF-1R	Ischemic	Mice	Apoptosis Fibrosis	[142]
	Pathogenic	-	I/R	Mice	Fibrosis	[143]
	Pathogenic	SOCS1	I/R	Mice	Fibrosis	[144]
	Protective	MEKK3/JNK	LPS	Mice	Anti-apoptosis	[141]
miR-218	Pathogenic	HO-1	Sepsis	Mice	Apoptosis	[125]
miR-126	Protective	-	I/R	Mice	Vascular protection	[107]
miR-195	Protective	VEGFA	I/R	Rats	Anti-inflammation Anti-oxidative stress	[99]
miR-181	Protective	KLF6	I/R	Mice	Anti-apoptosis Anti-inflammation	[83]
	Protective	PTEN	Cisplatin	Mice	-	[84]
	Protective	GJB2	LPS	Mice	Anti-apoptosis	[85]
	Protective	NEK7	Sepsis	Mice	Anti-pyroptosis	[86]
miR-301	Pathogenic	-	Vancomycin	Mice	Apoptosis	[120]
miR-709	Pathogenic	TFAM	Cisplatin	Mice	Mitochondrial damage	[134]
mR-375	Pathogenic	HNF1b	Cisplatin	Mice	Apoptosis	[121]
miR-204	Protective	Hmx1	Candidemia	Mice	Anti-inflammation	[98]
miR-211	Protective	Hmx1	Candidemia	Mice	Anti-inflammation	[98]
miR-590	Protective	TRAF6	LPS	Mice	Anti-apoptosis Anti-inflammation	[89]
miR-152	Pathogenic	ERRFI1	Sepsis	Rats	Inflammation	[133]

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					Apoptosis	
	Pathogenic	SIRT7	I/R	Rats	Apoptosis	[132]
miR-155	Pathogenic	SOCS1/STAT1	LPS	Mice	Inflammation	[129]
	Pathogenic	TCF4/Wnt/β-catenin	I/R	Rats	Apoptosis	[131]
	Pathogenic	SOCS1	I/R	Mice	Tubular injury	[130]
	Pathogenic	-	Cisplatin	Mice	Apoptosis	[150]
miR-106	Pathogenic	THBS2	Sepsis	Mice	Inflammation Apoptosis	[128]
miR-22	Protective	AIFM1	Sepsis	Mice	Anti-apoptosis	[87]
	Protective	HMGB1	Sepsis	Rats	Anti-inflammation	[88]
miR-107	Protective	RPS19	I/R	Rats	Anti-apoptosis	[112]
	Pathogenic	DUSP7	Sepsis	Mice	Tubular injury	[113]
miR-290	Protective	CCL2	Sepsis	Mice	Anti-apoptosis	[97]
miR-34	Pathogenic	NAMPT	I/R	Mice	NAD depletion	[139]
	Pathogenic	Atg4B	I/R	Mice	Reduce autophagy	[138]
	Pathogenic	Bcl2	Sepsis	Rats	Apoptosis	[137]
	Pathogenic	SIRT1	Cisplatin	Mice	Apoptosis	[119]
	Protective	UBL4A	Sepsis	Mice	Anti-inflammation	[135]
	Protective	-	Cisplatin	Mice	Cytoprotective	[136]
miR-188	Pathogenic	SRSF7	Contrast	Rat	Apoptosis	[122]
miR-214	Pathogenic	Mfn2	I/R	Mice	Apoptosis	[147]
	Pathogenic	GLP-1R	LPS	Mice	Inflammation	[148]
	Pathogenic	GPX4	Cisplatin	Mice	Ferroptosis	[149]
	Protective	PTEN/AKT/mTOR	Sepsis	Mice	Autophagy regulation	[146]
	Protective	Dkk3	I/R	Mice	Anti-apoptosis	[145]
miR-124	Protective	PARP1	I/R	Mice	Anti-necroptosis	[92]
	Protective	-	I/R	Mice	Anti-apoptosis	[91]
miR-146	Protective	IRAK1	I/R	Rats	Anti-inflammation	[104]
	Protective	-	I/R	Mice	Anti-inflammation	[105]
	Protective	Tfdp2	Cisplatin	Mice	Anti-fibrosis	[115]
miR-687	Pathogenic	-	LPS	Mice	Apoptosis	[123]
miR-24	Pathogenic	H2A.X/HO-1	I/R	Mice	Apoptosis	[124]
miR-494	Pathogenic	ATF3	I/R	Mice	Inflammation	[45]
	Pathogenic	E-cadherin	I/R	Mice	Apoptosis	[126]
	Pathogenic	NF-κB signaling	LPS	Mice	Inflammation Apoptosis	[127]
miR-223	Protective	NLRP3	I/R	Mice	Anti-apoptosis	[110]
miR-15	Protective	CX3CL1	I/R	Rats	Anti-inflammation Anti-fibrosis	[114]
miR-16	Protective	CX3CL1	I/R	Rats	Anti-inflammation Anti-fibrosis	[114]
	Pathogenic	-	I/R	Mice	Anti-apoptosis	[41]
miR-199	Protective	Sema3A/AKT/ERK	I/R	Mice	Anti-apoptosis	[109]
miR-210	Protective	VEGF pathway	I/R	Mice	Angiogenesis	[106]
miR-486	Protective	PTEN	I/R	Mice	Anti-apoptosis	[95]
miR-424	Protective	DR6	I/R	Mice	Anti-apoptosis	[94]
miR-191	Protective	OXSR1	Sepsis	Rat	Anti-apoptosis	[96]

miRNA: microRNA; I/R: ischemia-reperfusion; LPS: lipopolysaccharide.

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4.3. Therapy targeting MiRNAs

Nucleic acid drugs can treat adults at the level of RNA. They are usually composed of oligonucleic acids linked by ten to several tens of bases, and act directly on the body without gene expression [151,152]. Nucleic acid drugs include antisense, siRNA, miRNA, decoy, aptamer and CpG oligodeoxynucleotides [153]. Among these, two approaches can be used for targeting miRNAs: antisense for inhibition-specific miRNA and miRNA-mimic injection. Clinical trials targeting miRNAs as nucleic acid medicine are currently still limited. Anti-miR was first conducted with miR-122 with locked nucleic acid in the form of Miravirsen for treating type C hepatitis [154]. Subsequently, antisense miR-155 (MRG-106) for T-cell lymphoma and mycosis fungoides was tested in a clinical trial [155]. A miR-10b antisense was in preclinical trials with dextran-coated iron oxide nanoparticles for multiple cancers [156–159]. miRNA mimic treatment was conducted with miR-34 in lipid nanoparticles in the form of MRX34 for targeting multiple cancers, including hepatic cancers [160–162]. Subsequently, a clinical trial (Phase 1) with miR-16 mimics (TargomiR) was conducted for mesothelioma and lung cancer using the bacterial minicell EnGeneIC delivery system [163].

Currently, treatment targeting miRNAs in kidney diseases in the clinical stage is limited. A phase 2 placebo-controlled randomized controlled trial for Alport syndrome (NCT02855268) using oligonucleotides of miR-21 is currently ongoing [164]. A phase 1 clinical trial in polycystic kidney disease patients using anti-miR-17 oligonucleotide, RGLS4326 is also being conducted (NCT04536688) [165]. Referring to the miRNA treatment for AKI, miR-5100 was recently detected as a potential AKI biomarker as well as a therapy target [55]. miR-5100 was downregulated in a rodent AKI model, and a miR-5100 mimic ameliorated I/R-induced AKI. In addition, in human serum samples, miR-5100 was downregulated, thus is possibly both a biomarker and a therapy target.

One of the most important challenges for miRNA targeting therapy is the use of drug delivery system (DDS) to transfer these anti-Mir or miR-mimics more efficiently. Antisense drugs composed of single-stranded oligonucleic acids must be translocated into cells because they function by complementary binding to intracellular RNA. However, the antisense is large in size and has a negative charge due to the phosphodiester bond, making it difficult for it to pass through biological membranes. Therefore, many antisense miRNA are attached with a phosphorothioate modification (Sylation). In addition, chemical modifications are also introduced into the sugar moiety of nucleic acids, thereby exerting efficacy without using carriers, such as liposomes. In contrast, miRNA mimics are normally composed of a double strand, and are thus larger than antisense miRNA, leading to further difficulty with cell membrane permeability. Therefore, miRNA mimic therapy in general requires DDS, such as lipid nanoparticles, polyplexes and polymeric micelles [166]. Exosome may be the natural DDS to transfer anti-MiR or Mir-mimics. There are two approaches indicated: post-loading and pre-loading, both of which still have difficulties in the efficient incorporation of target nucleic acids [167]. Receptors such as GalNACs can be used as asialoglycoporotein receptors [168]. In addition, miRNA mimics need to be recognized by RISC, and thus the degree of nucleic acid modification possibile is also limited. Treatment with nucleic acid drugs may also cause on-target toxicity (toxicity due to binding to target RNA) and off-target (toxicity due to binding to non-target RNA) [152]. It is notable that treatment targeting miRNAs might cause unexpected side effects [169], considering that one type of miRNA may regulate more than one hundred genes, including genes of interest.

5. Conclusions

In the present review article, we summarize the current knowledge about miRNAs as promising biomarkers and potential therapeutic targets for AKI. Recent accumulated evidence has revealed the vital role of miRNAs in both protective and pathogenic mechanisms under AKI, and possible strategies for their application as biomarkers for early diagnosis and prediction of mortality, as well as the identification of the specific pathology in AKI. The identification of etiology-specific miRNAs may uncover the disease mechanisms, leading to novel therapy for these diseases. Regarding the possible strategies for therapeutic options, there are two approaches: antisense for inhibition of pathogenic miRNA, and protective miRNA-mimic injection. Although investigation of miRNA-

targeted therapy for kidney diseases has just started and needs to confront several challenges before clinical use, including DDS and off-target effects involving non-target genes and organs, this research may open a new era in the management of AKI through the regulation of specific miRNAs in the future.

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