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Review

microRNAs in chronic kidney disease

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ABSTRACT

Chronic kidney disease (CKD) results in high morbidity and mortality worldwide causing a huge socioeconomic burden. MicroRNA (miRNA) exert critical regulatory functions by targeting downstream genes and have been associated with many pathophysiologic processes including CKD. In fact, many studies have shown that the expression of various miRNAs was significantly changed in CKD. Current investigations have focused on revealing the relationship between miRNAs and CKD states including diabetic nephropathy, lupus nephritis, focal segmental glomerulosclerosis and IgA nephropathy. In this review, we summarize the latest advances elucidating miRNA involvement in the progression of CKD and demonstrate that miRNAs have the potential to be effective biomarkers and therapeutic targets for subsequent treatment.

1. Introduction

Chronic kidney disease (CKD) is an important cause of morbidity and mortality worldwide with a cumulative mortality rate of 20.6% over the past 10 years [1]. Renal fibrosis, the endpoint of CKD, is characterized as an abnormal tissue regeneration process that causes cellular stress and tissue damage [2–4]. Renal fibrosis is associated with the dysregulation of several chemokines and growth factors, including transforming growth factor-β1, (TGF-β1) renin-angiotensin system, lipid metabolism factor, and uremic toxins [5–12].

Recent studies have shown that the expressions of miRNAs are altered in CKD, and miRNAs play important roles in CKD (Table 1). miRNAs, a type of non-coding RNAs, is transcribed from DNA sequences into primary miRNAs, processed into precursor miRNAs and then to mature miRNAs, which generally target the 3′ untranslated region of the target mRNAs to promote the degradation or translational inhibition of mRNAs [13] (Fig. 1). The mature miRNAs, which play an important part in different biological and pathological processes, are small non-coding single-stranded RNAs that consist of approximately 18–25 nucleotides [14]. miRNAs exert the major cellular regulatory processes, such as migration, proliferation, differentiation, and apoptosis [15,16]. Many studies have demonstrated that miRNAs are closely associated with the occurrence and development of CKD [17,18]. Herein, we reviewed the recent advances of miRNAs in the clinical progression of CKD, and highlighted that miRNAs could be used as the biomarkers and therapeutic targets for CKD.

2. Regulation of miRNAs in DN

Diabetic nephropathy (DN) is characterized by glomerular basement membrane thickening, podocyte foot processes destabilization, mesangial cells (MC) proliferation, and extracellular matrix (ECM) accumulation [19,20]. Podocyte apoptosis, MC hypertrophy, oxidative damage, and inflammation play major roles in the pathological progress of DN, and the altered expression of miRNAs is observed in all these processes, which indicate the critical role of miRNAs [21–23].

2.1. Regulation of miRNAs on fibrosis

Both miR-23b and miR-30e were downregulated in the renal tissues of db/db mice, whereas miR-135a was upregulated [24–26]. miR-23b was identified as a suppressor of epithelial-to-mesenchymal transition (EMT) in DN and miR-23b overexpression attenuated EMT by targeting the high-mobility group A2 through PI3K-AKT signaling pathway in high glucose (HG)-induced human proximal tubule epithelial (HK-2) cells. In addition, the increase in miR-23b improved renal morphology, fibrotic responses, and renal functions in db/db mice [24]. The downregulation of miR-30e in DN resulted in increased GLIPR-2 expression and accelerated EMT and inhibited renal tubule epithelial cell proliferation, while miR-30e overexpression downregulated the expression of vimentin, alpha-smooth muscle actin (α-SMA), collagen I and fibronectin, and upregulated E-cadherin expression. These results indicated the renoprotective effect of miR-30e in DN [25]. miR-135a was progressively increased in the serum and kidney of DN patients, the

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Table 1
Expression changes of different miRNAs in CKD.

Status	MicroRNAs	Changes	Organs or cells	Targets	Ref.
DN	miR-23b	Down	Renal tissue of db/db mice HG-induced HK2 cells	HMGA2	[24]
	miR-30e	Down	Renal tissue of db/db mice HG-induced RTECs	GLIPR-2	[25]
	miR-135a	Down	Kidneys of type 2 diabetic rats	Egrl	[26]
	miR-181a-5p	Down	Renal tissues of type 2 diabetic rats HG-induced HK2 cells	Egrl	[27]
	miR-27a	Up	Glomeruli of DN rat HG-induced GMCs	PPAR	[28]
	miR-23a	Up	Renal tissues of diabetic patients HG-induced HK2 cells	SnoN	[29]
	miR-34a-5p	Up	Renal tissues of HFD/STZ-induced DN mice	SIRTI	[30]
	miR-217	Up	HG-induced podocytes	PTEN	[31]
	miR-29c	Up	Kidney glomeruli of db/db mice HG-induced podocytes	Spry1	[32]
	miR-20b	Up	HG-induced podocytes	SIRT7	[33]
	miR-218	Up	HG-induced podocytes	HO-1	[34]
	miR-34c	Down	HG-induced podocytes	Notch1 and Jagged1	[35]
	miR-134-5p	Up	Renal tissue of db/db mice HG-induced podocytes	Bcl-2	[36]
	miR-27a	Up	Glomeruli of DN rat HG-induced GMCs	PPAR	[37]
	miR-30s	Down	Glomeruli of DN rat HG-induced podocytes	Mtdh	[38]
	miR-214	Up	Renal cortex of diabetic db/db mice HG-induced MCs	PTEN	[23]
	miR-196a	Down	Kidney cortex of mice	p27/kip1	[39]
	miR-451	Down	Kidney tissue of db/db DN mice HG-induced MCs	Ywhaz	[40]
	miR-155	Up	HG-induced HK-2 cells	Sirtl	[41]
	miR-146a	Down	Kidney tissue of DN mice HG-induced HK-2 cells	Nox4	[42]
	miR-25	Down	Serum and kidney tissues of DN patients	PTEN	[43]
	miR-451	Down	PBMCs of DN patients HG-induced MCs	LMP7	[44]
	miR-21	Up	Kidney tissue and serum in DN mice	Smad7	[45]
LN	miR-9	Up	Renal tissue of LN patients	STK3	[50]
	hsa-miR-371-5p	Down	Kidney tissue of patients with LN	HIF-1 alpha	[51]
	miR-130b	Up	Blood samples of lupus nephritis patients	PTEN	[52]
	miR-10a	Down	Renal tissue of class III and IV LN patients HMCs treated with LN antibodies	IL8	[48]
	miR-148a-3p	Up	Glomeruli and serum of LN mice	PTEN	[53]
	miR-663a/miR-423-5p	Up	Renal tissues of LN patients and mice	TNIP2	[54]
	miR-146a	Down	PBMCs of LN patients	TRAF6	[55]
	miR-410	Down	Renal tissue of MRL/lpr mice	IL-6	[56]
	let-7	Up	Renal tissue of LN patients	TNFAIP3	[57]
FSGS	miR-135a	Up	Glomeruli of FSGS patients ADR-treated MPC5	TRPC1	[62]
	miR-135a and miR-135b	Up	Glomeruli of FSGS patients ADR-treated podocytes	GSK3 beta	[63]
	miR-193a	Up	Glomeruli of FSGS patients	PODXL and NPHS1	[58]
	miR-206	Up	Glomeruli of FSGS mice	WT1	[64]
	miR-30s	Down	Podocytes of FSGS patients	TRPC6, PPP3CA, PPP3CB, PPP3R1and NFATC3	[65]
IgAN	miR-374b	Up	B cells of IgAN patients	PTEN and Cosmc	[68]
	let-7b	Up	PBMCs and B-lymphocytes of IgAN patients	GALNT2	[66]
	miR-148b	Up	PBMCs of IgAN patients	C1GALT1	[69]
	miR-200bc/429 cluster	Down	Renal tissues of IgAN IgAN podocytes and HK2 cells	TWEAK	[70]
	miR-29b-3p	Down	Renal tissues of IgAN patients	CDK6	[71]
	miR-320	Up	Renal tissues and urinary of IgAN patients	PTEN	[72]
	miR-21	Up	Glomerular and tubular-interstitial tissues of IgAN patients IgAN podocytes and HK2 cells	PTEN	[73]
UUO	miR-382	Up	Kidneys of UUO mice	HSPD1	[74]
UUO	miR-302d	Up	Kidneys of UUO mice	T beta RII	[75]
Ang II-induced fibrosis	miR-29b	Down	Ang II-induced NRK-52E cells	PIK3R2	[77]
UUO	miR-21	Up	Kidneys of UUO mice	Smad7	[76]
TGFβ-induced fibrosis	miR-200a	Down	TGFβ-induce HK-2 cells	CTNNB1	[78]
UUO	miR-34a	Up	Kidneys of UUO mice TGF-β1-treated fibroblasts	Bcl-2	[79]
Ang II-induced fibrosis	miR-221	Down	Kidneys of Ang II-induced mice Ang II-induced NRK-49F cells	Ets-1	[80]
5/6 nephrectomy	miR-29c	Down	Kidneys of 5/6 nephrectomy rat	COL2A1 and TPM1	[81]

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Table 1 (*continued*)

Status	MicroRNAs	Changes	Organs or cells	Targets	Ref.
RPGN	miR-92a	Up	Podocytes of RPGN patients and mice	p57(Kip2)	[82]

DN: diabetic nephropathy. LN: lupus nephritis. FSGS: focal segmental glomerulosclerosis. IgAN: IgA nephropathy. UUO: unilateral ureteral obstruction. RPGN: rapidly progressive glomerulonephritis.

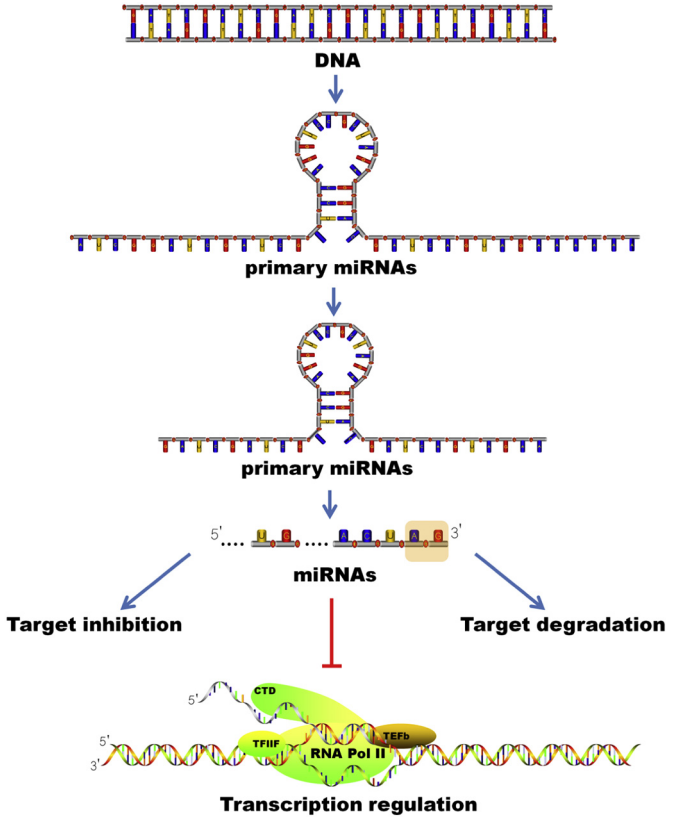

Fig. 1.. The mechanisms of the regulation of miRNAs on targets genes. miRNAs transcribe from DNA sequences into primary miRNAs and then processes into precursor miRNAs and then mature miRNAs that generally target 3' untranslated region of target mRNAs to promote degradation or translational inhibition of mRNAs.

renal tissue of db/db mice, and HG-induced human mesangial cells (HMCs) and HK-2 cells. miR-135a promoted the synthesis of ECM, including fibronectin and collagen I by downregulating the level of transient receptor potential channel (TRPC) 1 [26]. The expression of miR-181a-5p was reduced in the kidney of DN rats, while miR-27a was increased in streptozotocin (STZ)-induced DN rats. The upregulation of miR-181a-5p alleviated fibrosis by decreasing the expression of transcriptional regulator (EGRL) to reduce the levels of pro-fibrotic genes fibronectin and collagen I in HK-2 cells. The proliferation of MCs and the expression of profibrotic genes, ECM accumulation, and proteinuria were inhibited; however, the expression of PPARγ was promoted in STZ-induced DN rats when miR-27a was knocked down or antagonized [27,28]. The expression of miR-23a and miR-34a-5p were upregulated in the renal tissues of patients with type 2 diabetes and DN mice, respectively, that led to the downregulation of SnoN expression, more severe fibrosis, and activation of EMT in HG-induced HK-2 cells. The overexpression of miR-34a-5p promoted fibrosis by inhibiting the silent information regulator 1 (SIRT1) expression, which plays the central role in tubulointerstitial fibrosis in DN [29,30]. These findings suggested that miRNAs affected the progression of renal fibrosis in DN by targeting their respective targets to regulate the expression of fibrosis-related genes. In addition, the abnormal expression levels of miRNAs were associated with kidney dysfunction.

2.2. Regulation of miRNAs on podocytes apoptosis

Apoptosis of podocytes is a prominent feature of DN. The alteration of miRNA expression levels plays an important role in regulating the apoptosis of podocytes in DN. For example, the expressions of miR-217, miR-29c, miR-20b, and miR-218 were significantly upregulated, whereas the expression of miR-34c was downregulated in HG-induced podocytes [31–35]. Knockdown of miR-217 attenuated the podocyte injury and restored insulin resistance and defective autophagy in HG-cultured podocytes in vitro. Inhibition of phosphatase and tensin homolog (PTEN), the target of miR-217 associated with cell viability and apoptosis, improved podocyte injury and insulin resistance and also suppressed autophagy restoration [31]. The overexpression of miR-29c promoted podocyte apoptosis, ECM accumulation, and the activation of Rho kinase that mediated various pathways involved in DN and reduced the level of its target Spry1 protein. Knockdown of miR-29c reduced albuminuria and mesangial matrix accumulation in db/db mice [32]. The dysregulation of miR-20b enhanced podocytes apoptosis, but this process could be prevented by its target gene silent information regulator 1 (SIRT7) [33]. The upregulation of miR-218 promoted podocyte apoptosis and p38 MAPK activation by downregulating HO-1 expression in HG-treated podocytes [34]. The overexpression of miR-34c inhibited podocyte apoptosis induced by HG and downregulated its targets Notch1, Jagged1, pro-apoptotic protein Bax, caspase-3 and phosphorylated p53 whereas upregulated the level of anti-apoptotic gene Bcl-2 expression [35]. In addition, the upregulating miR-134-5p expression was identified in the kidney tissues of db/db mice and podocytes treated by HG; miR-134-5p led to the apoptosis of podocyte and the downregulation of nephrin (a pivotal protein for renal filtration barrier). Bcl-2 was identified as the target of miR-134-5p [36]. The increased miR-27a expression was observed in patients with DN and HG-treated podocytes while the expression of miR-30s was downregulated in the glomeruli of DN rat and HG-treated podocytes [37,38]. Overexpression of miR-27a promoted podocyte apoptosis and EMT and aggravated podocyte injury by upregulating Snail1 and α-SMA expression and downregulating podocin and synaptopodin expression. miR-27a induced impaired renal function and podocyte injury via the activation of PPARγ/β-catenin signaling in DN rats [37]. Moreover, miR-30s upregulation induced mouse podocytes (MPC5) apoptosis by upregulating the expression of metadherin (Mtdh) (a potent modulator of podocyte apoptosis) to activate p38 MAPK pathway [38]. These studies indicated that several miRNAs were involved in podocyte apoptosis, suggesting that miRNAs may serve as a novel therapeutic target to improve podocyte apoptosis in DN.

2.3. Regulation of miRNAs on MC hypertrophy and autophagy

Glomerular MC hypertrophy is one of the most important pathological features of DN. Relevant studies have shown that the expression levels of some miRNAs can regulate MC hypertrophy. For example, it was demonstrated that miR-214 expression was increased whereas miR-451 expression was decreased in the kidneys of db/db mice. The expression of miR-155 was upregulated in the patients with DN, whereas the expression of miR-196a was downregulated in the kidneys of DN mice [23,39–41]. Moreover, the overexpression of miR-155 reduced the expression of autophagy-associated proteins LC3-II and ATG5. In

addition, the overexpression of miR-196a significantly inhibited the expression of p27/kip1 and restored the hypertrophic morphology of MC. Oppositely, inhibition of miR-214 expression markedly upregulated PTEN expression that can inhibit MC hypertrophy, reduced the expression of SM22, α-SMA, and collagen IV, and attenuated albuminuria and mesangial expansion [23]. In addition, the knockdown of p27/kip1 attenuated MC hypertrophy induced by miR-196a inhibition [39]. The overexpression of miR-451 repressed MC hypertrophy and the expression of p-p38 MAPK and p-MKK3 by inhibiting YWHAZ [40]. In conclusion, the expression of miRNAs can regulate MC hypertrophy and autophagy in DN.

2.4. Regulation of miRNAs on oxidative stress and inflammation

Oxidative stress and inflammation also contribute to DN [21]. Numerous studies have shown that miRNAs can regulate the generation of reactive oxygen species (ROS) and expression of inflammation-related genes. For example, the level of miR-146a, miR-25, and miR-451 were declined in the serum and kidney tissues of patients with DN and kidney tissues of DN mice [42–44]. The overexpression of miR-146a downregulated NOX4 and reduced ROS generation to alleviate oxidative stress and inflammation [42]. The overexpression of miR-25 reduced ROS production and inhibited the apoptosis of renal tubular epithelial cells induced by HG by activating PTEN/AKT pathway [43]. The downregulation of miR-451 prevented the activation of LMP7/NF-κB pathway. The overexpression of miR-451 resulted in the reduction of urinary microalbumin excretion, blood glucose, and glomerular injury in the kidneys of db/db DN mice and also inhibited proinflammatory molecules transcription including tumor necrosis factor-α (TNF-α), interleukin-18 (IL-18), myeloid differentiation factor88 (MYD88), and intercellular adhesion molecule-1 (ICAM-1) in MC [44].

The expression of miR-21 was significantly increased and followed by the downregulation of Smad7 in the kidney tissues and serum in DN mice. Serum miR-21 was associated with renal function, which was characterized by an increase in albumin-creatinine ratio (ACR) and decrease in creatinine clearance. Moreover, the expression of miR-21 was positively correlated with the expression of collagen IV [45].

3. Regulation of miRNA in lupus nephritis (LN)

Lupus nephritis (LN) is the most common complication of systemic lupus erythematosus, and nearly 30% of these will develop to end-stage renal disease (ESRD) and the hallmarks of LN performed as the injury of podocyte injury and HMC proliferation [46–48]. Therefore, inflammation mediated by autoimmune in glomerulus and interstitium is the primary cause of LN [49].

3.1. Regulation of miRNAs on MC proliferation or apoptosis in LN

The expression of miR-9 was upregulated, whereas the expression of hsa-miR-371-5p was downregulated in the kidney tissues of patients with LN [50,51]. The overexpression of miR-9 inhibited the expression of serine/threonine kinase 3 (STK3), whereas miR-9 deficiency resulted in STK3 upregulation, enhanced viability and decreased apoptosis of MC, and the activation of MAPK pathway. This study first demonstrated that the expression of miR-9 improved LN by regulating STK3 and MAPK pathways [50]. The overexpression of hsa-miR-371-5p repressed the proliferation of HMC and induced the apoptosis of HMC by enhancing HIF-1α expression [51]. In addition, the levels of miR-130b and miR-148a-3p were elevated in the blood samples of patients with LN and glomeruli and serum of LN mice, respectively, whereas miR-10a was decreased [48,52,53]. The downregulation of miR-130b reduced the expression of PTEN and promoted the apoptosis of MC [52]. The upregulation of miR-148a-3p promoted the proliferation of MC and the expression of proliferating cell nuclear antigen (PCNA), whereas it reduced the phosphatase and tensin homology on PTEN level. The inhibition of miR-148a-3p or the overexpression of PTEN inhibited the proliferation of MC [53]. Collectively, the expression of miRNAs can regulate MC hypertrophy and apoptosis in LN.

3.2. Regulation of miRNAs on inflammatory cytokines in LN

Both miR-663a/miR-423-5p and Let-7 were increased in the kidney tissues of patients with LN, whereas miR-146a and miR-410 were decreased in the peripheral blood monouclear cells (PBMCs) of patients with LN and kidney tissues of MRL/lpr mice [54–57]. The expression of TNFAIP3 interacting protein 2 (TNIP2) was downregulated by miR-663a or miR-423-5p mimic transfection, whereas TNIP2 expression was upregulated by miR-663a or miR-423-5p inhibition in HEK293T cells, indicating a negative correlation between miR-663a/miR-423-5p and TNIP2 [54]. In addition, the expression of miR-146a showed a reversible relationship with inflammatory cytokines interleukin-1β (IL-1β), interleukin-6 (IL-6), interleukin-8 (IL-8), and TNF-α, whereas TNF receptor-associated factor 6 showed a positive correlation [55]. Moreover, the expression of miR-410 was declined in the kidney tissues of MRL/lpr mice. The overexpression of miR-410 significantly reduced IL-6 and fibrotic factors (TGF-β1, collagen I, collagen III) to inhibit fibrosis in SV40MES13 cells [56]. The increase of let-7 inhibited the expression of tumor necrosis factor and α-induced protein 3, whereas it enhanced the activity of NF-κB in HEK293T cells [57].

4. Regulation of miRNAs in focal segmental glomerulosclerosis (FSGS)

FSGS is a frequent glomerular disease, which is a critical cause of ESRD and characterized by the flattening of podocyte foot processes, tubular atrophy, glomerular sclerosis, and interstitial fibrosis [58–60]. The expressions of miR-17, miR-451, miR-106a, and miR-19b were differently decreased in the plasma of patients with FSGS. The overexpression of miR-106a reduced PTEN, Bcl-2-like protein 11, and C-X-C motif chemokine ligand 14 expression and inhibited podocyte apoptosis [61]. However, the expression of miR-135a, miR-135b, miR-193a, and miR-206 were elevated in the glomeruli of patients with FSGS, whereas the expression of miR-30s was reduced in the podocytes of patients with FSGS [58,62–65]. The upregulation of miR-135a inhibited TRPC1 expression in the glomeruli of patients with FSGS and adriamycin-treated MPC5. The ectopic expression of miR-135a aggravated podocyte injury and accelerated podocyte apoptosis and disordered podocyte cytoskeleton [62]. In addition, the overexpression of miR-135a and miR-135b caused the activation of Wnt/β-catenin signaling pathway and induced the nuclear translocation of β-catenin in MPC5. The ectopic expression of miR-135a and miR-135b resulted in the disarray of the podocyte cytoskeleton and podocyte injury [63]. The upregulation of miR-193a expression repressed the expression of Wilms tumor 1 (WT1) and thereby downregulated podocalyxin and nephrin expression and several other genes vital for the podocytes architecture [58]. The upregulation of miR-206 expression led to podocyte injury. The overexpression of miR-206 repressed synaptopodin expression by downregulating WT1 expression [64]. Another study demonstrated that the deficiency of miR-30s enhanced the levels of pivotal components of calcium/calcineurin signaling which may lead to podocyte injury, including transient receptor potential channel 6 (TRPC6), protein phosphatase 3 catalytic subunit alpha (PPP3CA), protein phosphatase 3 catalytic subunit (PPP3C) α, protein phosphatase 3 catalytic subunit (PPP3C) β, protein phosphatase 3, regulatory subunit B, alpha (PPP3R1), and nuclear factors of activated T-cells c3 (NFATC3) at mRNA levels [65].

5. Regulation of miRNA in IgAN

Immunoglobulin A nephropathy (IgAN) is a common form of primary glomerulonephritis characterized by aberrant *O*-glycosylation in

the hinge region of IgA1 and mesangial deposition of pathogenic IgA or injury to MCs [66]. IgAN has various potential biomarkers including Baff, ST6GALNAC2, C1GALT1, and Cosmc in PBMCs and also IgA1 and galactose-deficient IgA1 in plasma [67]. Several recent studies have reported that miRNAs are associated with the pathology of IgAN.

Upregulation of miR-374b was found in the peripheral blood mononuclear cells cultures (PBMCs) of patients with IgAN as well as let-7b or miR-148b were differently expressed in PBMCs of patients with IgAN [66,68,69]. Upregulation of miR-374b promoted the proliferation of B cells and aberrant glycosylation of IgA1 by upregulating PTEN and Cosmc expression [68]. The overexpression of let-7b reduced the expression of GALNT2, which catalyzed the formation of *O*-glycan [66]. The overexpression of miR-148b inhibited the expression of C1GALT1, whereas it increased the level of Gal-deficient IgA1 to promote aberrant *O*-glycosylation of IgA1 [69]. These results demonstrated that abnormal expression of miRNAs led to the abnormal *O*-glycosylation process of IgA1, which induced IgAN. Targeting miRNAs may be a novel strategy for the treatment of IgAN. Several studies showed that the levels of miR-200bc/429 cluster and miR-29b-3p were declined in the kidney tissues of patients with IgAN [70,71]. The overexpression of miR-200bc/429 cluster inhibited the release of inflammatory cytokines monocyte chemoattractant protein-1 (MCP-1), IL-6 and regulated on activation, normal T cell expressed and secreted (RANTES), and the activation of the NF-κB pathway mediated by TWEAK in podocytes and HK-2 cells, suggesting that miR-200bc/429 cluster can regulate IgAN inflammation [70]. The downregulation of miR-29b-3p can inhibit inflammation by activating the NF-κB pathway via upregulating CDK6 in the kidney tissues of patients with IgAN [71]. These studies indicated that miRNAs played an important role in IgAN by regulating the release of inflammatory cytokines.

In addition, the expression of miR-320 was markedly increased in kidney tissues and urine of patients with IgAN [72]. The expression of miR-21 was markedly increased in glomerular and interstitium of patients with IgAN and in podocytes and HK-2 cells. The inhibition of miR-21 prevented fibrosis and AKT activation by promoting the expression of PTEN in podocytes and HK-2 cells from IgAN [73].

6. Regulation of miRNA in other types of CKD

Except for the four common CKD mentioned in the previous sections, the regulation of miRNAs also plays an important role in other types of CKD such as AngII-induced EMT, unilateral ureteral obstruction (UUO)-induced fibrosis, and crescentic rapidly progressive glomerulonephritis (RPGN). The expressions of miR-382 and miR-302d were elevated in the kidneys of UUO mice [74,75]. The overexpression of miR-382 led to the downregulation of heat shock protein family D (Hsp60) member 1 (HSPD1) expression and consequently enhanced renal tubulointerstitial fibrosis [74]. The upregulation of miR-302d reduced the expression of TGF-β type II receptor, the target of miR-302d, EMT, and the mesangial production of fibronectin in renal epithelial cell HKC8 [75]. The level of miR-21 was progressively upregulated in the kidney tissues of UUO mice and in activated rat kidney fibroblasts treated by TGF-β1. The overexpression of miR-21 promoted fibrosis and fibroblasts activation by regulating TGF-β1/Smad signaling pathway [76]. In addition, the decreased miR-29b was found in NRK-52E cells treated by AngII, and its downregulation promoted EMT by activating PI3K/AKT signaling pathway [77]. The expression of miR-200a was decreased in TGF-β1-treated HK-2 cells, and its downregulation upregulated the expression of β-catenin and EMT process [78].

The expression of miR-34a, which promoted tubular cell apoptosis by downregulating anti-apoptotic protein Bcl-2, was significantly upregulated in tubulointerstitium and the microvesicles of kidney tissues in UUO mice and TGF-β1-treated fibroblasts [79]. However, the expression of miR-221 was downregulated in the fibrotic kidney tissues of mice and NRK-49F cells treated with AngII. The expression of miR-221 inhibited the expression of transcription factor ETS proto-oncogene 1 (Ets-1) that promoted the activation of fibroblasts [80]. The expression of miR-29c was decreased in the kidneys of 5/6 nephrectomized rats, which promoted interstitial fibrosis by upregulating collagen I and tropomyosin 1α expression [81]. The expression of miR-92a was significantly increased level in the podocytes of patients with RPGN and mice. Knockdown of miR-92a upregulated the expression of p57/Kip2 and attenuated glomerular injury and albuminuria [82].

7. Conclusion

The regulation of miRNAs plays an important role in the pathogenesis of CKD, and its alterations affect the development of CKD. The expression of miRNAs is associated with multiple cellular processes and various types of CKD, and it has the potential to be the biomarkers and therapeutic targets for CKD treatment. Further *in vitro* and *in vivo* studies are required to elucidate the underlying mechanisms of miRNAs in CKD. Although many miRNAs have yet to be studied, we anticipate that these have the potential to be used clinically in the future.

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