Review Article

MicroRNA-26a: An Emerging Regulator of Renal Biology and Disease

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Keywords

miR-26a · Kidney disease · Mesangial cell · Regulatory T cell · Podocyte

Abstract

MicroRNAs (miRNAs) are short, single-stranded, noncoding RNAs that modulate many key biological processes by simultaneously suppressing multiple target genes. Among them, miR-26a, a conserved miRNA among vertebrates, is highly expressed in various tissues. Accumulating evidence demonstrates that miR-26a plays pivotal roles in cellular differentiation, cell growth, apoptosis, and metastasis, thereby participating in the initiation and development of various human diseases, such as metabolic disease and cancer. More recently, miR-26a was found as a versatile regulator of renal biology and disease. miR-26a is intensively involved in the maintenance of podocyte homeostasis and the actin cytoskeleton. It is also able to modulate the homeostasis and function of mesangial cells. In addition, miR-26a affects the expansion of regulatory T cells in the context of ischemia-reperfusion injury and autoimmune diabetes and thus protects the renal system from immune attack. These available data strongly suggest that renal miR-26a possesses critical pathological functions and represents a potential target for renal disease therapies. This review summarizes current knowledge of miR-26a in renal biology and disease, laying the foundation for exploring its previously unknown functions and mechanisms in the renal system.

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Introduction

Kidney is a bean-shaped organ which is extremely critical for maintaining osmotic and acid–base balance of blood. It is also responsible for removal of toxic substance and release of certain important hormones. Diabetes, hypertension, improper diet and use of analgesics, expose of detrimental chemicals or genetic mutations raise the potential for kidney damage or diseases, namely nephropathy [1]. Nephropathy is very common. About 12.5% Americans suffer from chronic nephropathy. Acute kidney disease could directly cause renal failure and death [2]. On cellular scale, podocytes, mesangial cells (MCs), and T cells are often involved as dominant etiologic factors [3].

Many genes have been found contributing to the susceptibility of kidney diseases. Emerging research demonstrate miRNAs also intricately linked to renal biology [4]. miRNAs are a group of naturally transcribed, small noncoding RNAs (ncRNAs). They and those long ncRNAs consist of about 98% RNA transcripts transcribed from human genome but without protein products, and form an indispensable regulatory signaling network [5]. Accumulating findings have shown a tight connection between kidney diseases initiation and development and certain miRNAs [3, 4].

Herein, we summarized the recent progress of a representative important miRNA-miRNA-26a which we have studied, especially its functions link to podocytes, MCs, and T cells in nephrology. We updated the overview of miRNA-26a on renal biology, and provided the insights into the potential of miRNA-26a as a novel potential diagnostic marker and therapeutic target in clinic.

miRNA Biogenesis and Function

miRNAs are endogenous small noncoding RNAs (20–25 nucleotides in length, single stranded). They expressed in plants and animals and were evolutionarily conserved [6, 7]. The initial form of miRNAs is known as primary miRNAs (pri-miRNA). These molecules range in length from 300 to 1,000 nucleotides when transcribed from genomic DNA by RNA polymerase II. Pri-miRNAs are subsequently processed by Drosha complex and generate miRNA precursors (pre-miRNAs), which have a hairpin structure and a length of approximate 90 nucleotides. Pre-miRNAs are then translocated from the nucleus to the cytoplasm via the exportin transfer system [8]. In the cytoplasm, pre-miRNAs are cleaved into transient double-stranded miRNA molecules (about 20–24 nucleotides in length) through the activity of Dicer. The double-stranded miRNAs are then uncoiled to mature single-stranded miRNAs complementary to the passenger mRNA [9]. The mature single-stranded miRNA interacts with Argonaute (AGO) to form the RNA-induced silencing complex (RISC), which directs the post-transcriptional repression of target mRNAs through complementary sites [10–13]. Some miRNAs are involved in direct mRNA cleavage at the sites having extensive complementarity in the open reading frames (ORF) of the target mRNAs, while another type translationally represses gene expression by combining with the 3'-untranslated region (UTR) of protein-coding genes. There is also the third type of miRNAs which may function as a combination of both the above two mechanisms. Single miRNA can potentially silence the expression of large numbers (even hundreds) of target genes, consisting a complex regulatory network which modulates multiple target genes expression [14, 15].

miRNAs play essential roles in different cellular and organismal processes, including cell proliferation, differentiation, development, apoptosis, autophagy and necroptosis [16–18]. Previous studies have indicated that more than 1000 miRNAs are involved in regulating at least 50–60% of protein-coding genes in human [19–21]. Moreover, miRNAs have been

shown to be involved in the development of many human diseases [22–25]. For example, miRNAs play essential roles in cancer progress [26, 27], cardiovascular diseases, kidney diseases and improper immune responses in macrophages [28–32]. Several miRNAs (e.g., miR-21, miR-29a, miR-30s, miR-146a, miR-192, miR-193, and miR-200) are exploited as important biomarkers of renal diseases [33–39]. Specifically, miR-30s is shown to be tightly associated with podocyte injury and glucocorticoids, whereas miR-193a induces focal segmental glomerulosclerosis through down-regulating WT1 [35, 38].

miR-26 is highly conserved between humans and mice and is localized at three sites in the genome (chromosome 3 [miR-26a₁], chromosome 12 [miR-26a₂], and chromosome 2 [miR-26b]). There are two different nucleotides between the mature sequences of miR-26a and miR-26b, whereas miR-26a-1 and miR-26a-2 have fully identical sequences arising from the 5' arm of the respective precursors [40]. Plenty of publications reported that miR-26a plays an important role in various diseases [41–43], and most of them focused on cancer or cancer-related diseases, including colorectal, breast, ovarian, and gastric cancers [42, 44–47]. For example, miR-26a promotes cell proliferation and apoptosis by targeting phosphatase and tensin homolog (*PTEN*), Cyclin D1, and Bcl-2 in cancer cells [48–50]. miR-26 family members and their target genes cooperate to block the G₁/S-phase transition by synergistically activating the pRb protein in physiological and pathological conditions [51]. Additionally, miR-26a functions in cardiovascular diseases by controlling multiple signaling pathways related to angiogenesis, endothelial cell growth, and left ventricle function after myocardial infarction. Analysis of miR-26 family members in different types of cardiac cells [52–54], including endothelial cells, vascular smooth muscle cells, cardiomyocytes, and cardiac fibroblasts, has shown that miR-26 may have important functions in various cardiovascular repair mechanisms [55, 56]. Intriguingly, miR-26a has also been found to negatively regulate glycogen synthase kinase (GSK) 3 β expression, thereby altering Wnt signaling by modulating the levels of β -catenin and its downstream target C/EBP α during osteogenesis differentiation [57, 58]. Besides, miR-26a also targets Tob1, a negative regulator of bone morphogenic protein (BMP)/Smad signaling, resulting in rescue of bone regeneration deficiency [59]. Our recent studies showed that miR-26a targets ten eleven translocation (TET) enzymes (*TET1/TET2/TET3*) and thymine DNA glycosylase (*TDG*) to regulate pancreatic cell differentiation [60]. miR-26a also targeted several critical genes for glucose metabolism, lipid metabolism, and insulin signaling, indicating miR-26a could be further exploited as a potential therapeutic target for type 2 diabetes [61]. Furthermore, increasing evidences show that miR-26a plays a pivotal role in liver physiology and enhances autophagy function to protect against ethanol-induced acute liver injury [62].

Recent studies have indicated that miR-26a has functions in kidney diseases, particularly podocyte injury [63]. Furthermore, miR-26a regulates the expression of genes involved in podocyte differentiation and cytoskeleton formation, and the level of miR-26a in injured podocytes is lower than that in normal podocytes [64]. In this review, we discuss the roles of miR-26a in kidney diseases.

miR-26a in Podocyte Diseases

Podocytes are a type of terminally differentiated epithelial cells specifically found in glomeruli. They are attached to the outside of the glomerular basement membrane (GBM) [65]. Podocytes are critical in maintaining structure and function of the glomerular filtration barrier in the GBM, and contributing to keep the stability of the glomerular capillary [66]. Podocyte injury and loss are major underlying pathological mechanisms in kidney diseases [67]. Multiple signaling pathways are implicated in the process of podocyte injury, although the complexity of podocyte injury in kidney diseases has not been fully elucidated [68–70].

miRNAs have been shown to play essential roles in cytoskeletal dynamics and other biological processes in podocytes, including proliferation, differentiation, and function [71, 72]. In mutant podocytes with specific deletion of Dicer, cytoskeletal dynamics are largely altered, thereby inducing proteinuria and glomerulosclerosis [63]. Multiple other abnormalities have also been observed in podocytes from glomerular-damaged mice, including immune-complex deposition with podocyte foot-process effacement and double-contoured GBMs. These phenotypes are accompanied by significant increases of glomerular area size, glomerular cell number, and sclerosis score compared with those in normal podocytes [63].

Next-generation RNA sequencing analysis identified 10 miRNAs expressed at high levels in normal glomeruli from healthy C57BL/6 mice; among them, miR-26a was the most abundantly expressed miRNA, with particularly high levels in the cytoplasm of podocyte [64]. In patients and mice with glomerulonephritis (GN), glomerular miR-26a expresses significantly less when compared with healthy individuals. Moreover, miR-26a expression level is higher in the glomerulus than in the tubulointerstitium. The level of glomerular miR-26a is positively correlated with *Podxl*, *Synpo*, *Cd2ap*, *Myh9*, *Acta2*, and *Vim*, but negatively correlated with uACR. All of these targets are directly related to cytoskeleton organization or actin protein synthesis, which are extremely important for podocyte function, thus they are also correlated with glomerular dysfunction. Moreover, miR-26a decreases in lipopolysaccharide (LPS)- or puromycin aminonucleoside (PAN)-treated podocytes compared to normal podocytes. Since the complex architecture and function of podocytes relies on elaborate organization of actin filaments and stable control of protein synthesis, miR-26a may play an important role in maintaining podocyte homeostasis and the actin cytoskeleton.

Structural and functional changes of podocytes are often due to metabolic and hemodynamic dysregulation in patients with diabetes [73]. Indeed, podocyte injury and loss have been reported in the context of diabetic nephropathy and may result in glomerular injury. Intriguingly, recent studies have shown that connective tissue growth factor (*CTGF*), a direct target of miR-26, is strongly induced by transforming growth factor (TGF)- β in a SMAD-dependent manner and is involved in podocyte injury. Moreover, the abundance of miR-26a in human and mouse with diabetes is much lower than in normal, healthy individuals. miR-26a is highly expressed in glomeruli, not only within podocytes but also in tubules, and ducts of the kidney. Altered *miR-26a* expression may result in dysfunction of the TGF- β signaling pathway during the progression of diabetic nephropathy.

miR-26a in Mesangial Pathology in Glomerular Disease

MCs, along with endothelial cells and glomerular visceral cells, comprise the glomerular cell population, which functions to maintain the structural and functional integrity of the glomerular microvascular bed [74]. MCs contribute to mesangial matrix homeostasis, regulate the filtration surface area, phagocytose apoptotic cells, and facilitate formation of the glomerular capillaries [75, 76]. In reaction to immunologic or hemodynamic injury, MCs undergo apoptosis or hypertrophy owing to excessive production of growth factors, cytokines, chemokines, and matrix proteins [77–80]. These factors are able to exert autocrine or paracrine effects on MCs or other glomerular cells. Besides, MCs may also respond to podocyte and endothelial cell injury or structural/genetic abnormalities in the GBM [81]. Additionally, MCs play an important role in metabolic- and immune-mediated glomerular diseases, such as diabetic nephropathy and IgA nephropathy [82, 83].

Several key miRNAs (e.g., miR-26a, miR-27a, miR-30b, miR-100, miR-199a, and miR-217) were reported to sit at the center to mediate the functions of MCs [82–87]. A recent report

added support by showing that miR-26a was significantly increased in MCs upon high levels of glucose. Moreover, high glucose level also enhanced miR-26a expression in proximal tubular epithelial cells and podocytes. In contrast to the pathological effects caused by miR-26a deficient in podocytes and T cells, here accumulating miR-26a suppressed the expression of the critical tumor-suppressor protein PTEN, resulting in activation of Akt signaling pathway. Activated Akt signal increased phosphorylation of tuberlin and PRAS40, which are endogenous suppressors of mammalian target of rapamycin complex 1 (mTORC1). As one of the consequences, elevated activity of mTORC1 induced MC hypertrophy and matrix proteins [82].

Manipulation of miR-26a expression in human MCs showed that miR-26a participated in cell cycle regulation via controlling the expression of several key genes, including *CCNE2* and *E2F8*. Both of them were involved in the G₁/S transition, and *CCNE2* was also predicted to be a direct target of miR-26a [88, 89]. A previous research reported a small chemical trastuzumab could induce miR-26a expression and suppress the expression of human epidermal growth factor receptor 2 (HER-2) and cell cycle-related genes in breast cancer cells and MCs [83]. In kidneys and urine of patients with lupus nephritis (LN), HER-2 expression is dramatically augmented, while miR-26a expression is decreased. Moreover, HER-2 abundance is also increased in the glomeruli of NZM2410 mice. As a model, interferon (IFN) α and IFN regulatory factor 1 (IRF-1)-induced HER-2 expression decreases miR-26a, and derepresses cell cycle genes transcription in human MCs. Furthermore, the expression levels of two LN biomarkers, monocyte chemotactic protein (MCP)-1 and vascular cell adhesion protein 1 (VCAM-1), are significantly repressed in MCs with miR-26a overexpression. Therefore, HER-2 and miR-26a could be exploited as potential biomarkers of LN.

miR-26a in T Cells Mediated Kidney Disease

Immune cells, including natural killer (NK) cells, T cells, B cells, macrophages, and neutrophils, are well known as participators in early renal injury [90–93]. Renal vascular disease (RVD) is one of the major causes of kidney injury, and may eventually lead to end-stage renal disease and severe cardiovascular events [94]. Furthermore, renal ischemia-reperfusion injury (IRI) is a primary cause of acute kidney injury (AKI), which largely increases the risk of acute rejection, and delays graft function in kidney transplantation. Upon ischemia, various endogenous ligands are released, activating innate immune cells to trigger innate immune response. These events could be characterized by tubular cell apoptosis and interstitial fibrosis. Previous report demonstrated that the expression level of miR-26a was much lower in human and swine with RVD comparing healthy individuals. Compromised *miR-26a* expression in kidney tubular cells elevates the possibility of cell apoptosis. This process was reversed by co-culture with ad-MSCs in vitro, which could restore miR-26a expression levels. To sum up, decrease of miR-26a may be associated with stenotic kidney damage in RVD, and miR-26a could be considered as a potential therapeutic target for regeneration upon kidney injury.

Previous reports showed that IRI increased infiltration of both neutrophils and macrophages into renal tissues to cause tubular injury [95]. Interestingly, the expression level of miR-26a is also lower in IRI tissues than that in normal tissues. Decreased miR-26a reduces the proportion of regulatory T cells (Tregs) in the population of CD4⁺ T cells, and blocks Foxp3 expression in IRI tissues, whereas miR-26a overexpression promotes Tregs/CD4⁺ T cells ratio expansion. Furthermore, miR-26a is capable to increase TGF- β 1 expression through repressing interleukin (IL)-6. Thus, miR-26a also plays a regulatory role in renal immune responses against IRI by promoting Treg population expansion.

Fig. 1. The molecular and cellular mechanisms of miR-26a in kidney cells.

Another study revealed that miR-26a prevented autoimmune diabetes in prediabetic NOD mice, and alleviated hyperglycemia symptom in newly diagnosed patients [96]. However, these effects are largely dependent on the suppression of autoreactive T cells and the increased expansion of Tregs via miR-26a in vivo and in vitro. Collectively, these findings indicate that miR-26a also plays a crucial role in preventing autoimmune diabetes.

miR-26a Is a Diagnostic Biomarker and Therapeutic Target in Kidney Disease

Cytoskeletal genes encode actin and intermediate filament proteins. Stable expression of cytoskeletal genes is extremely important in maintaining cellular shape and cellular function. During podocyte differentiation, miR-26a is essential for keeping cytoskeletal genes expression. Reduction of miR-26a could cause podocyte injury, due to imbalanced expression of these genes both on mRNA and protein level.

TGF- β /SMAD signal stimulates the production of extracellular matrix (ECM), and promotes pathogenesis of diabetic nephropathy. *CTGF*, a downstream regulator of TGF- β , could suppress TGF- β /SMAD signaling. Inhibition of *CTGF* might be used as a promising therapeutic strategy in diabetic nephropathy management. miR-26a suppresses *CTGF* gene expression at post-transcriptional level, thus attenuating TGF- β signaling and ECM accumulation in cultured human podocytes under diabetic conditions. Thus, modulation of miR-26a expression may be developed as a therapy for diabetic nephropathy.

miR-26a expression is elevated in glomerular MCs in response to high glucose. Moreover, miR-26a suppresses tumor-suppressor protein PTEN expression and promotes Akt signal

Table 1. Summary of main signal pathways involved in renal pathology and associated factors which are also regulated by miRNA-26a

Signal pathways targeted by miR-26a	Gene name (targets)
Wnt	GSK3B (3), WNT5A (2), CREBBP (2), PPP2R5A (1), FRAT2 (1), NLK (2), P LCB1 (1), PPP3CB (1), VANGL2 (1), LEF1 (1)
TGFβ	SMAD1 (2), SMAD4 (3), INHBB (1), ACVR1C (2)
p53	PTEN (3), CREBBP (2), CDK6 (2), BID (1), PMAIP1 (1)
mTOR	PTEN (3), ULK1 (2), PRKAA2 (1), RPS6KA6 (1), ULK2 (2)
MAPK	FGF9 (1), MAP3K2 (2), DUSP5 (1), PAK2 (1), CACNB4 (1), MRAS (1), TAOK1 (1), NLK (2), PPP3CB (1), RPS6KA6 (3), FGF21 (1), PPM1B (1), CACN B2 (1), MEF2C (1), MKNK2 (1)
Notch	JAG1 (2)

Predicted targets of miR-26a identified using TargetScan and miRBase online database were listed in Table 1. Bold font represents the targets which have been confirmed. The number represents the number of miRNA-26a binding sites. Activation of WNT, TGFβ, p53, mTOR, MAPK, and Notch signaling pathway is related to kidney fibrosis.

transduction, mediating high glucose-induced MC hypertrophy and matrix protein expression. These signaling events occur through PRAS40 and tuberlin inactivation. Here, PRAS40 and tuberlin act as negative regulators of mTORC1. Thus, high glucose-induced miR-26a expression acts as a potent mediator of the PTEN/Akt/mTORC1 signaling pathways, driving MC hypertrophy and matrix protein expression. With a potential pathological role in MC hypertrophy, miR-26a may be an effective therapy target for prevention of diabetic complications in kidney.

Furthermore, MCs activation restores miR-26a expression to antagonize cell apoptosis, suggesting that miR-26a could also be a therapeutic target for alleviating adverse effects in kidney damage. miR-26a also acts as a regulator in innate immunity upon the renal inflammatory in IRI.

Overexpression of miR-26a attenuates renal IRI and promotes Treg expansion by inhibiting IL-6. Increased miR-26a prolongs the normoglycemic time and promotes Treg expansion in NOD mice, and hyperglycemia phenotype is reversed in newly hyperglycemic NOD mice. Although further investigation is required to clarify the precise and detailed molecular and cellular mechanisms involved in immunoregulation, there are studies sufficiently support the therapeutic potential of miR-26a for autoimmune diabetes suppression. Further analytic studies on miR-26a expression and biologic function in human are necessary.

Conclusion

miR-26a is capable to regulate multiple critical genes in different pathways (Table 1), affecting various diverse renal pathophysiology (Fig. 1). Attributing to its tissue-specificity and powerful regulatory ability, manipulating miR-26a expression could be a potential novel therapeutic approach for the treatment of several renal diseases. For identifying more downstream targets of miR-26a, systematic in vivo or in vitro analyses are required. Such studies may further support to exploit potential of miR-26a or its targets as promising therapeutic candidates.

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Disclosure Statement

The authors state no conflicts of interest.

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