Published in final edited form as:
Curr Opin Nephrol Hypertens. 2012 July ; 21(4): 410–416. doi:10.1097/MNH.0b013e328354e559.

MicroRNAs and fibrosis

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Abstract

Purpose of review—MicroRNAs (miRNAs) are short noncoding RNAs that inhibit gene expression in plants and animals. miRNAs have emerged as key players in virtually all aspects of mammalian biology. Aberrant miRNA expression is observed in numerous human diseases such as diabetes, hypercholesterolemia, cancer, and tissue fibrosis. Therefore, approaches to correct miRNA expression represent the novel therapeutic strategies for these diseases.

Recent findings—miRNAs are essential for kidney development and homeostasis. Aberrant miRNA expression is observed in the mouse models of kidney fibrosis. Three TGF-β-regulated miRNA families, miR-21, miR-200, and miR-29 have been shown to modulate renal fibrosis. miR-21, through a feed-forward loop, amplifies TGF-β signaling and promotes fibrosis. Conversely, miR-200 and miR-29 reduce fibrosis by inhibiting epithelial-tomesenchymal transition and preventing the deposition of extracellular matrix, respectively. Inhibition of miR-21 expression or augmenting miR-29 expression prevents kidney fibrosis in mice.

Summary—Aberrant miRNA expression perturbs signaling pathways that lead to progression of kidney fibrosis. Thus, miRNAs represent novel biomarkers and therapeutic targets in the treatment of kidney fibrosis.

Keywords

kidney fibrosis; microRNA; miR-200; miR-21; miR-29

INTRODUCTION

MicroRNAs (miRNAs) are short – approximately 22 nucleotide – single-stranded RNAs that constitute the endogenous RNA-interference pathway in plants and animals. miRNAs were initially discovered in the nematode *Caenorhabditis elegans* by Drs. Victor Ambros, Gary Ruvkin, and their colleagues. *Lin-4*, the first discovered miRNA, was shown to be essential for *C. elegans* larval development [1]. For 7 years after this discovery, it was believed that miRNAs were peculiar to nematodes because *lin-4* is not conserved in other organisms. However, this perception quickly changed after the discovery of another miRNA, *let-7*, which is also required for *C. elegans* larval development [2]. Unlike *lin-4, let-7* is conserved – in size, nucleotide sequence, and expression profile – among all animals with bilateral symmetry [3]. These observations led to the examination of roles of miRNAs in other taxa. Little over a decade later, we now know that over 1000 conserved miRNAs are encoded by the human genome, and miRNAs are implicated in diverse biological processes ranging

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Conflicts of interest There are no conflicts of interest.

from implantation of the embryo, stem cell biology, and development of vital organs to metabolism and innate immunity [4–8]. Furthermore, aberrant miRNA expression is observed in numerous human diseases, and correction of miRNA expression is emerging as a novel therapeutic strategy [9–12].

miRNAs: GENOMIC ORGANIZATION, BIOGENESIS, AND FUNCTION

miRNAs are found in intergenic and intragenic locations in the genome. The intergenic miRNAs have their own regulatory elements and therefore function as independent transcriptional units. In contrast, the intragenic miRNAs are located in the introns (or rarely exons) of known genes, and a majority of them are co-transcribed and co-expressed with the host gene. Some intragenic miRNAs have their own regulatory elements and are transcribed independent of their host genes. Nearly half of all human miRNAs are encoded as polycistronic transcripts that generate multiple miRNAs.

miRNA biogenesis begins in the nucleus, where RNA polymerase II-dependent transcription produces a capped and polyadenylated transcript known as primary miRNA (pri-miRNA). Pri-miRNAs are processed by the RNase III endonuclease, Drosha, and its cofactor, DGCR8, into smaller 70-nt stem-looped structures known as precursor miRNAs (pre-miRNAs). Pre-miRNAs are transported to the cytosol from the nucleus by Exportin 5 where further processing by a second RNase III, Dicer, leads to the generation of 19–25 nt miRNA–miRNA* duplexes [13,14]. The miRNA strand is preferentially retained and becomes the mature miRNA, whereas the miRNA* strand is degraded. Occasionally, the miRNA* strand is also retained and functions as a mature miRNA. Subsequently, the mature miRNA is loaded on to the miRNA-induced silencing complex (miRISC), where binding to target mRNAs, either with perfect complementarity – an extremely rare occurrence in animals – or with imperfect complementarity, results in posttranscriptional gene silencing (Fig. 1).

PREDICTING mRNA TARGETS OF miRNAs

Nucleotides 2–8 at the 5′ end of a mature miRNA are referred to as the `seed-sequence'. Watson–Crick basepairing between miRNA seed-sequence and the 3′-UTRs of target mRNAs is essential for miRNA-mediated gene silencing [15–17]. The position and accessibility of the miRNA-binding site, secondary structure of the target mRNA, and the presence of other miRNA-binding sites or RNA-binding proteins in close proximity influences miRNA–mRNA interactions [16]. miRNA-binding sites that are evolutionarily conserved are considered more functionally relevant than the non-conserved binding sites. By incorporating these observations, bioinformatics-based algorithms predict that each miRNA has hundreds of conserved mRNA targets [18]. Despite these advances, miRNA target prediction remains a significant challenge. There are considerable differences in the mRNA targets predicted by various algorithms. It has been suggested that even nonconserved miRNA-binding sites are biologically relevant. This raises the possibility that each miRNA family can target thousands of mRNAs [19,20]. In addition to 3′-UTRs, there are examples of some miRNAs that bind to 5′-UTRs or coding regions of mRNAs and induce gene repression [20,21]. If this is true for all miRNAs, it would increase the number of total mRNA targets for each miRNA by several fold.

POTENTIAL OF miRNAs AS THERAPEUTIC AGENTS

The basic understanding of miRNA biology has led to the development of novel approaches to manipulate miRNA expression and function [12,22,23■■]. The approaches use synthetic oligonucleotides that either inhibit or enhance the expression of a specific miRNA (Fig. 1). The inhibitors, called antimiRs, have a sequence that is complementary to a mature miRNA

of interest. Thus, the antimiRs bind and sequester specific miRNAs and relieve the repression of the target mRNAs. Conversely, miRNA-mimics are duplex oligonucleotides with a sequence identical to a mature miRNA of interest. Once inside the cell, the miRNA-mimics associate with the miRISC complex and posttranscriptionally inhibit the target mRNAs. AntimiRs possess the characteristics of an ideal therapeutic agent (Fig. 2) [23■■]. Moreover, they represent novel tools to study the biological roles of specific miRNAs *in vitro* and *in vivo*.

ROLE OF miRNAs IN KIDNEY DEVELOPMENT AND HOMEOSTASIS

Embryonic kidney development involves a series of reciprocal interactions between the ureteric bud and metanephric mesenchyme. The ureteric bud induces the metanephric mesenchyme to give rise to the renal vesicle. Conversely, the metanephric mesenchyme induces branching of the ureteric bud. Renal vesicles differentiate into glomeruli and tubules, whereas the ureteric bud forms the collecting system. Recent studies have shown that miRNAs are essential in these processes. Ureteric bud-specific inactivation of the miRNA-processing enzyme Dicer results in premature termination of branching morphogenesis of ureteric buds, thus arresting kidney development [24■]. Ablation of *Dicer* from nephron progenitors in metanephric mesenchyme leads to the depletion of these cells and prematurely terminates renal vesicle formation [24■,25■]. Whether miRNAs are required for renal tubule development subsequent to renal vesicle formation is not well understood.

miRNAs also play critical roles in maintaining kidney homeostasis. Podocyte-specific inactivation of *Dicer* produces proteinuria, glomerulosclerosis, and kidney failure, indicating that miRNAs are essential for podocyte homeostasis [26–28]. The role of miRNAs in renal tubule homeostasis is not well understood. Inactivation of *Dicer* in postnatal proximal tubules does not affect their histology or function [29], but whether miRNAs are required for the maintenance of other segments of the renal tubule is not known. Although these studies demonstrate the importance of miRNAs in kidney development and podocyte homeostasis, the specific miRNAs that mediate the actions of Dicer are currently not known. An important caveat to these studies is that some of the effects observed due to deletion of *Dicer* may occur because of miRNA-independent functions of Dicer [30■■].

miRNAs AND KIDNEY FIBROSIS

Chronic kidney disease (CKD), a condition that affects over 20 million Americans, is characterized by a progressive loss of glomerular filtration rate. The histopathological feature of CKD is tubulointerstitial fibrosis, in which tubular epithelial cell loss is accompanied by the deposition of extracellular matrix (ECM) and accumulation of fibroblasts and inflammatory cells in the interstitium. The transforming growth factor (TGF)-β/Smad pathway is a key promoter of tubulointerstitial fibrosis [31]. In this pathway, binding of activated TGF-β to its receptor leads to the recruitment and phosphorylation of receptor-activated Smads (R-Smads). The R-Smads then bind to Smad4 and form a heterodimeric complex. This complex enters the nucleus where it binds to the promoters of genes containing Smad-binding element (SBE) and regulates transcription. Through the induction of target genes, TGF-β signaling promotes fibroblast survival and proliferation, induces epithelial-tomesenchymal transition (EMT), and leads to the deposition and remodeling of ECM. The repertoire of TGF-β-targeted genes includes miRNAs. Three miRNA families, miR-21, miR-200, and miR-29, are regulated by TGF-β and have been shown to modulate renal fibrosis by promoting fibroblast proliferation, inhibiting EMT, and preventing deposition and remodeling of ECM (Fig. 3).

miR-21

In humans, miR-21 maps to chromosome 17q23.2, where it overlaps with the protein-coding gene *TMEM49*. Despite its intragenic location, miR-21 has its own promoter and is transcribed independent of *TMEM49*. miR-21 is widely expressed, but miR-21 knockout mice demonstrate normal histology and are viable and fertile, indicating that miR-21 is dispensable for normal development [32]. miR-21 is among the most highly upregulated miRNAs during tissue injury such as myocardial infarction (MI) and acute kidney injury [32,33]. These findings suggest that the normal function of miR-21 is to limit injury and aid in the tissue repair. Consistent with this notion, miR-21 is upregulated by ischemic preconditioning of the heart [34]. Ischemic preconditioning refers to a phenomenon in which short episodes of sublethal ischemia protect tissue from a subsequent larger ischemic event. Inhibition of miR-21 during ischemic preconditioning attenuates cardiac protection from subsequent injury [34].

Paradoxically, persistent overexpression of miR-21 perturbs tissue repair and contributes to tissue fibrosis. miR-21 is upregulated in cardiac fibroblasts in failing mouse and human hearts, and antimiR-mediated inhibition of miR-21 attenuates fibrosis and improves cardiac function in mouse models of heart failure [11]. The antifibrotic effects of miR-21 inhibitors are also observed in lung and kidney. miR-21 is upregulated in the lungs of patients with idiopathic pulmonary fibrosis (IPF), and inhibition of miR-21 attenuates fibrosis in mouse models of lung fibrosis [35■]. miR-21 expression increases in the kidneys of mice subjected to unilateral ureteral obstruction (UUO) or ischemic reperfusion injury (IRI), the two well established animal models of kidney fibrosis, and inhibition of miR-21 attenuates kidney fibrosis in these mice [33,36■,37■]. Thus, inhibition of miR-21 is a novel therapeutic strategy for progressive tissue fibrosis.

In contrast to these studies, it was shown that miR-21-null mice are not protected from cardiac fibrosis in response to a variety of cardiac stresses [32]. The divergent results suggest confounding factors such as off-target effects when using antimiRs to inhibit miR-21 expression. The differences highlight the need to use both genetic and pharmaceutical approaches to understand the functions of miRNAs.

The TGF-β/Smad pathway is one mechanism by which miR-21 expression is increased in fibrotic tissues (Fig. 3). TGF-β signaling promotes miR-21 synthesis not only by increasing transcription, but also by enhancing posttranscriptional processing of pri-miR-21. Davis *et al*. [38] showed that in vascular smooth muscle cells, R-Smads physically interact with subunits of the Drosha microprocessor complex and promote the processing of pri-miR-21 into mature miR-21. A recent study found that in renal epithelial cells, R-Smads bind to the SBE located in the miR-21 promoter and induce pri-miR-21 transcription [36■]. miR-21 in turn promotes the TGF-β signaling by repressing Smad7, an inhibitor of the TGF-β/Smad pathway. Thus, miR-21 functions in a feed-forward loop that leads to TGF-β signal amplification. miR-21 also promotes fibrosis through other mechanisms such as activation of ERK/MAP kinase signaling, and inhibiting apoptosis and promoting proliferation of fibroblasts [11].

miR-200

The miR-200 family consists of five members: miR-200a, miR-200b, miR-200c, miR-429, and miR-141. In humans, a polycistronic transcript from chromosome 1 gives rise to miR-200a, miR-200b, and miR-429, whereas miR-200c and miR-141 are derived from a bicistronic transcript from chromosome 12 (Table 1). On the basis of their seed-sequence, the family members can be classified into two functional groups. Group 1 comprises miR-200b, miR-200c, and miR-429, and group 2 comprises miR-200a and miR-141.

Because of the differences in seed sequence, the two groups have different mRNA targets. miR-200 is enriched in kidney and lung, where it functions to maintain epithelial differentiation.

miR-200 has recently been implicated in tissue fibrosis. The expression of miR-200 is decreased in a mouse model of lung fibrosis, and delivery of miR-200c reduces fibrosis [39■]. A recent study found that the expression of miR-200a and miR-141c is reduced in the kidneys of mice subjected to UUO [40■]. In contrast, another study found that expression of miR-200s is increased in mice subjected to UUO [41■]. Despite the already elevated level of miR-200s, delivery of miR-200b-precursor to further increase miR-200 expression ameliorated fibrosis in these mice [41■].

The mechanism for the antifibrotic effects of miR-200 may involve prevention of EMT (Fig. 3) [42]. During EMT, polarized epithelial cells lose cell–cell and cell–basement membrane interactions, and acquire mesenchymal properties such as increased migratory capacity. It is believed that proximal tubule epithelial cells undergo EMT in response to UUO and contribute to renal fibrosis [43]. TGF-β signaling, through activation of mesenchymal transcription factors such as *Zeb1* and *Zeb2*, is a potent inducer of EMT. Conversely, in in-vitro assays, miR-200s prevent TGF-β-mediated EMT through repression of *Zeb1* and *Zeb2* [44]. miR-200s are also predicted to repress TGF-β2 itself, which may inhibit EMT and prevent fibrosis. However, the notion that EMT contributes to renal fibrosis has been recently challenged. Therefore, careful in-vivo studies will be needed to clarify the role of miR-200 and EMT in the kidney.

miR-29

The miR-29 family consists of three members that are encoded from two distinct genomic loci. In humans, a bicistronic transcript from chromosome 7q32.3 gives rise to miR-29b-1 and miR-29a, whereas miR-29b-2 and miR-29c are derived from a bicistronic transcript from chromosome 1q32.2 (Table 1). All members have an identical seed sequence which allows the targeting of the same genes. The miR-29s are widely expressed with the most prominent expression in the kidney, lung and heart [45]. We have found that the expression of miR-29 is dramatically upregulated (~300-fold) in kidneys of adult mice compared to newborn mice. A similar pattern of expression is also observed in other organs. Consistent with the temporal regulation of expression, miR-29 has been shown to function as a tumor suppressor and promote cellular senescence and differentiation [46].

The most well documented function of miR-29 is its role in the prevention of tissue fibrosis. miR-29 is downregulated in the fibrotic border zone of myocardial infarction, in lungs of IPF patients, and in skin fibroblasts of systemic sclerosis patients [45,47,48]. Expression of miR-29 is also decreased in mouse models of renal fibrosis [49■,50■], and delivery of miR-29 attenuates renal fibrosis in these mice [49■]. Several studies have implicated TGF-β signaling in the downregulation of miR-29. Treatment of myocardial fibroblasts, skin fibroblasts, proximal tubule cells, podocytes, and other cells with TGF-β causes the downregulation of miR-29 [45,50■]. The mechanism may involve Smad3-mediated repression of the miR-29b-2–29c cluster through a regulatory element located approximately 22 kb upstream from the cluster [49■].

The antifibrotic effects of miR-29 occur, in part, through inhibition of TGF-β-mediated deposition and remodeling of ECM (Fig. 3). At least 20 different ECM-related genes – some of which are induced by TGF-β signaling – are predicted to be miR-29 targets. Several of these genes have been validated as genuine miR-29 targets [45]. Because miR-29 is predicted to inhibit TGF-β2, it may also exert antifibrotic effects through inhibition of TGF-β signaling.

CONCLUSION

miRNAs are essential for kidney development and homeostasis. Expression of several miRNAs is perturbed in renal fibrosis, and studies in the mouse models of heart, lung, and kidney fibrosis has provided novel insights into the mechanism by which aberrant miRNA expression contributes to tissue fibrosis. Three TGF-β-regulated miRNA families, miR-21, miR-200, and miR-29, have been shown to modulate tissue fibrosis *via* different mechanisms (Fig. 3). Despite these advances, the normal functions of these miRNAs and a comprehensive list of their biologically relevant mRNA targets are not known. Therefore, a lot of work remains to be done.

Acknowledgments

The authors thank Drs Sachin Hajarnis and Peter Igarashi for helpful comments during the preparation of this manuscript. Work from the authors' laboratory is supported by grants from the National Institutes of Health/ National Institute of Diabetes and Digestive and Kidney Diseases (KO8 DK084311-01 to VP and 5RC1DK086887-02 to Peter Igarashi) and the UT Southwestern O'Brien Kidney Research Core Center (NIH P30DK079328). L.N. is supported by an NIH training grant (T32DK007257).

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KEY POINTS

- miRNAs are essential for kidney development and homeostasis.
- miR-21 is upregulated in the mouse models of renal fibrosis, and inhibition of miR-21 attenuates fibrosis. miR-21 causes fibrosis by promoting fibroblast survival.
- miR-200 is downregulated in the mouse models of renal fibrosis. miR-200 attenuates fibrosis by preventing EMT.
- miR-29 is downregulated in the mouse models of renal fibrosis, and delivery of miR-29 attenuates the fibrosis. miR-29 attenuates fibrosis by preventing ECM deposition and remodeling.
- AntimiRs and miRNA-mimics represent novel therapeutic agents for tissue fibrosis.

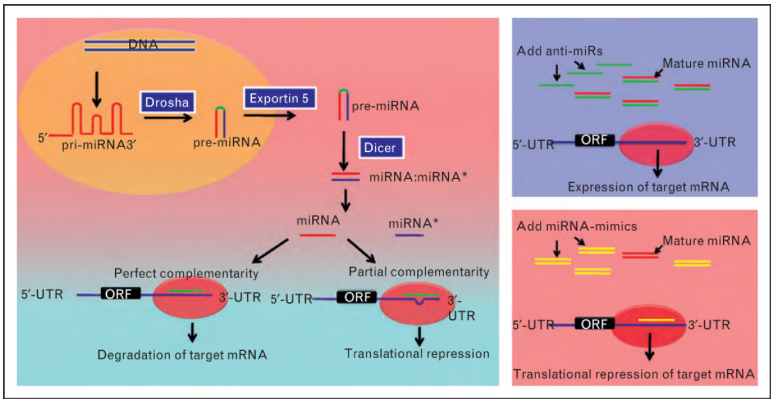

FIGURE 1.

The biogenesis and function of miRNAs, and mechanism of modulation of miRNA expression and function by antimiRs and miRNA-mimics.

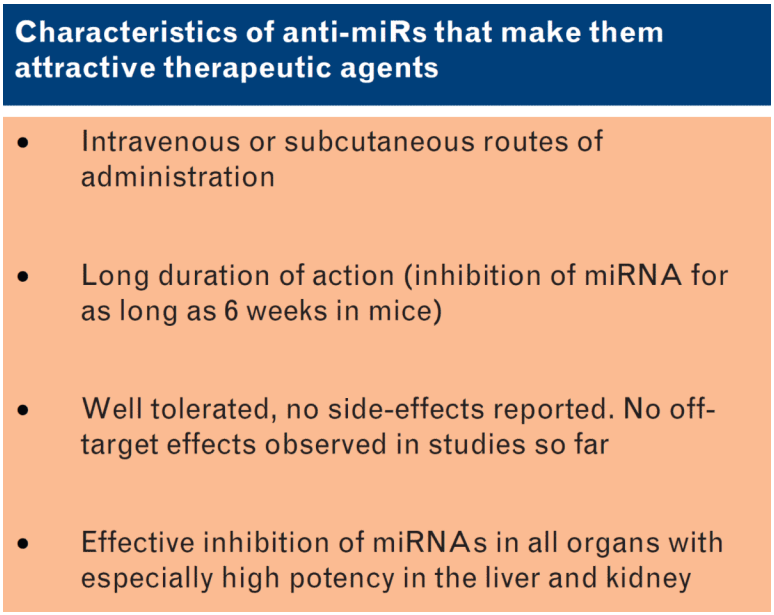

FIGURE 2.
Characteristics that make antimiRs attractive therapeutic targets.

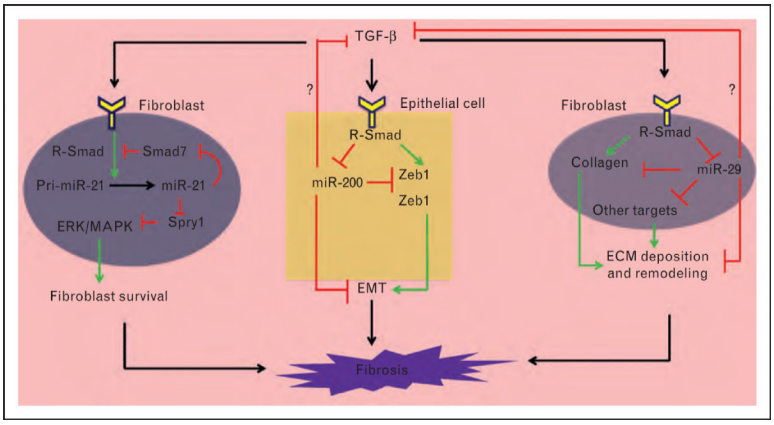

FIGURE 3.

Mechanisms by which miR-21, miR-200, and miR-29 modulate tissue fibrosis. miR-21, through a feed-forward loop, amplifies TGF-β signaling and promotes fibrosis. Conversely, miR-200 and miR-29 attenuate fibrosis by inhibiting epithelial-to-mesenchymal transition and preventing the deposition of extracellular matrix (ECM), respectively.

Table 1

Genomic organization, mRNA targets, and mechanism of fibrosis of miR-200, miR-29, and miR-21

miRNA	Members	Genomic location (humans)	Notable targets	Potential mechanism of fibrosis
miR-200	miR-200a	Chr 1p36.33 (miR-200b~429)	Zeb1, Zeb2	Prevention of epithelial-to-mesenchymal transition
	miR-200b	Chr 12p13.31 (miR-200c~141)		
	miR-200c			
	miR-429			
	miR-141			
miR-29	miR-29a	Chr7q32.3 (miR-29a~29b-1)	Collagens 1a1, 3a1, 4a1, 5a1,5a2, 5a3, 7a1, 8a1	Inhibits extracellular matrix deposition and remodeling
	miR-29b	Chr 1q32.2 (miR-29c~29b-2)		
	miR-29c		Fibrillin	
miR-21	miR-21	Chr 17q23.2	Smad7, Spry1, Pten	Promotes fibroblast survival