Chapter 13

MicroRNAs and Polycystic Kidney Disease

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Abstract

MicroRNAs (miRNAs) are a class of small non protein-coding RNAs that function as inhibitors of post-transcriptional gene expression in plants and animals. Over a thousand different miRNAs are known to be encoded by the human genome, the majority of which are conserved in other species. miRNAs are essential for virtually all aspects of mammalian biology, including development of key organs such the brain, the heart, and the kidney. More importantly, miRNAs are implicated in the pathogenesis of numerous common human diseases, and pharmaceutical manipulation of miRNA function has emerged as an exciting new therapeutic approach for cancer and kidney diseases. Several lines of evidence have connected miRNAs to the pathogenesis of polycystic kidney disease (PKD). miRNAs

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are aberrantly expressed in cystic kidneys and this aberrant expression is thought to regulate key aspects of cyst pathogenesis such as cyst epithelial cell proliferation and apoptosis as well as dosage of the various cystic kidney disease genes. In this chapter, we briefly discuss the basic biology of miRNAs and their role in kidney development, and highlight the role of three miRNA families – miR-17 and related miRNAs, miR-200 family and miR-21- in the pathogenesis of PKD.

Key words: MicroRNAs; miR-17~92; miR-21; miR-200; Polycystic kidney disease

Introduction

MicroRNAs (miRNAs) are a class of small (approximately 22-nucleotide long) non protein-coding RNAs that function as inhibitors of post-transcriptional gene expression in plants and animals (1, 2). Drs. Victor Ambros, Gary Ruvkin and their colleagues first discovered miRNAs in the nematode *Caenorhabditis elegans* in the early 1990's (3, 4). For nearly a decade after this discovery, it was thought that miRNAs represented a phenomenon that was unique and limited to lower organisms. However, this assumption changed in the year 2000, when the first mammalian miRNA, called let-7, was described (5, 6). The discovery of let-7 sparked great interest in identifying new miRNAs, understanding miRNA biology in mammalian development, and studying the role of miRNAs in pathogenesis of common human diseases. Nearly fifteen years later, we now know that thousands of evolutionarily-conserved miRNAs are encoded by the human genome and that miRNAs are implicated in virtually all aspects of mammalian biology – ranging from embryogenesis and aging to metabolism and immunity. More importantly, miRNAs have emerged as key players in the pathogenesis of numerous human diseases (7, 8) such as cancer (9-14), diabetes (15), obesity (16, 17), infectious diseases (18) and even genetic disorders such as polycystic kidney disease (PKD) (19-24). A novel class of drugs, called antimirs and miRNA-mimics, that can manipulate miRNA function are currently in various stages of pre-clinical and clinical testing, raising hope that someday a miRNA-based therapeutic approach can be used to treat common human diseases (11, 25, 26).

MiRNAs: biogenesis, function and role in kidney development

Based on their genomic location, miRNAs can be classified into two groups: intragenic miRNAs or intergenic miRNAs. Intragenic miRNAs are located within introns or rarely exons of known protein-coding genes, and are generally co-transcribed with their host gene. In contrast, the intergenic miRNAs are located outside of any known protein-coding

genes and function as independent transcriptional units. Biogenesis of miRNAs involves RNA-polymerase II-dependent transcription of a relatively large capped and polyadenylated transcript known as primary miRNA (pri-miRNA). Pri-miRNA is processed by the RNase III endonuclease, Drosha, and its cofactor, Dgcr8 into smaller stem-looped structures known as precursor miRNAs (pre-miRNA). Pre-miRNAs are transported out of the nucleus by Exportin 5 into the cytosol, where further processing by a second RNase III enzyme, Dicer, leads to the generation of 19-25 nucleotide mature miRNA. The nucleotide sequence 2 through 8 at the 5'-end of the mature miRNA is referred to as the 'seed-sequence'. The mature miRNA associates with the miRNA-induced silencing complex (miRISC), where Watson-Crick base-pairing between the seed-sequence of a mature miRNA and complementary sequences primarily located within 3'-UTRs of mRNAs results in post-transcriptional gene silencing (Figure 1). In this manner, miRNAs function as sequence-specific inhibitors of mRNA translation(27). miRNA-mediated regulation of mRNA expression is likely to be extremely complex. Bioinformatic algorithms predict that each miRNA could potentially inhibit thousands of mRNAs(28-35). Each mRNA, in turn, may possess binding sites for numerous unique miRNAs. Additional factors that further complicate the regulation of mRNA expression by miRNAs include the secondary structure of the mRNA and binding of proteins to mRNAs in close proximity to miRNA-binding sites. Recent studies have shown that some miRNAs can be produced independent of the canonical Drosha-Dicer pathway and that miRNAs can inhibit mRNA translation by binding to coding regions and 5'-UTRs of mRNAs. Thus, a lot remains to be learned about the basic miRNA biology.

miRNAs are implicated in development of various organs, including the kidney (36, 37). Kidney development involves interactions between two embryonic structures, the metanephric mesenchyme (MM) and the ureteric bud (UB). The MM is a precursor tissue composed of renal progenitor cells that gives rise to glomeruli and nephrons. The UB is a 'T'-shaped epithelial structure that eventually gives rise to the collecting ducts. Signals from the UB induce the progenitor cells of the MM to undergo differentiation. Conversely, the MM sends signals to the UB, which causes UB to undergo branching. This process of reciprocal signaling between the MM and UB is repeated innumerable times to eventually give rise to nearly one million nephrons and collecting ducts. Mutations of cystic kidney disease genes, particularly those implicated in childhood forms of PKD are known to disrupt normal kidney development. Therefore, pathogenesis of some forms of PKD can be traced back to abnormal kidney development. miRNAs have been shown to regulate virtually all processes in kidney development (36-39). Inhibiting miRNA function in the UB or MM prevents UB branching and MM differentiation, respectively, ultimately resulting in renal agenesis or dysplastic kidneys. Inhibiting miRNA function at later stages of kidney development, specifically in the

elongating renal tubules without affecting UB branching and MM differentiation, results in the formation of numerous tubular and glomerular cysts, a phenotype that is reminiscent of PKD (40). Intriguingly, the proposed mechanism by which miRNAs may regulate normal renal tubule elongation is by modulating the expression of various cystic kidney disease genes, in particular the autosomal dominant polycystic kidney disease (ADPKD) gene *PKD1*(40). Thus, these observations provide the earliest and a direct link between miRNAs, kidney development and cyst pathogenesis.

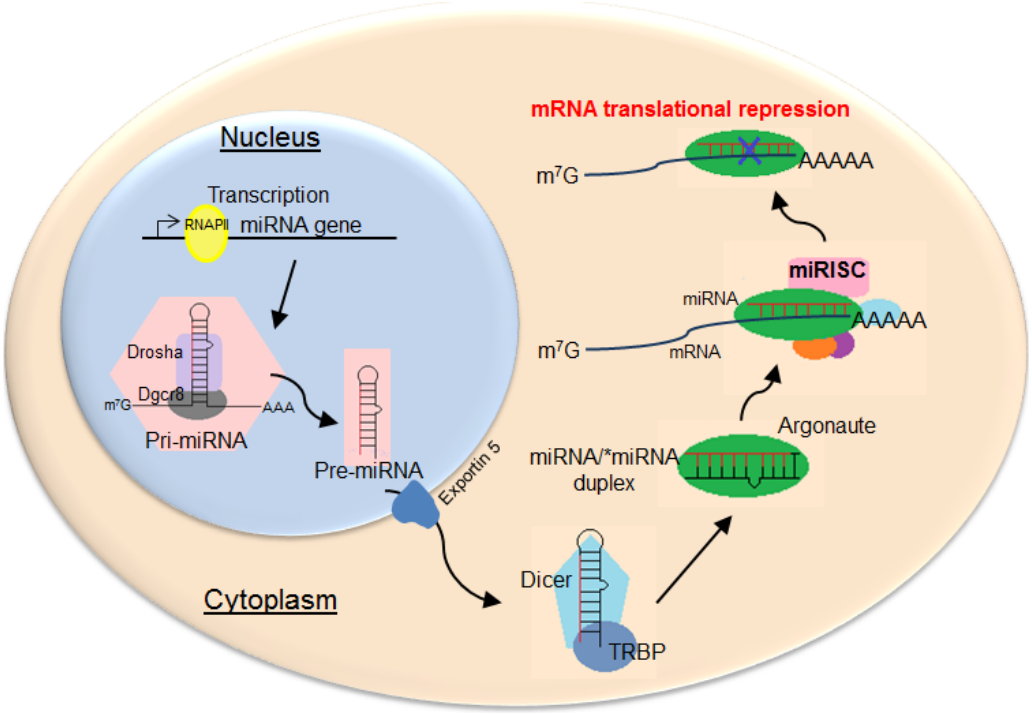

Figure 1. A schematic of miRNA biogenesis and function in animals. miRNA biogenesis begins in the nucleus, where RNA-polymerase II-dependent (RNAPII) transcription of a relatively large capped and polyadenylated transcript known as primary miRNA (pri-miRNA). Pri-miRNA is processed by the RNase III endonuclease, Drosha, and its cofactor, Dgcr8 into smaller stem-looped structures known as precursor miRNAs (pre-miRNA). Pre-miRNAs are transported out of the nucleus by Exportin 5 into the cytosol, where further processing by a second RNase III enzyme, Dicer, leads to the generation of mature miRNA. The mature miRNA associates with the miRNA-induced silencing complex (miRISC), where Watson-Crick base-pairing between the seed-sequence of a mature miRNA and complementary sequences primarily located within 3′-UTRs of mRNAs results in post-transcriptional gene silencing.

MiRNAs that regulate PKD pathogenesis

Emerging evidence from studies performed on rodent models and bio-specimens obtained from human ADPKD patients suggests that aberrant expression of many miRNAs may underlie disease progression in PKD. In this section, we will primarily discuss the role of three families of miRNAs in the pathogenesis of PKD; miR-17 and related clusters, miR-200 and miR-21.

miR-17 and related miRNAs

The miR-17 family of miRNAs consists of fifteen miRNAs that are located as three distinct clusters on different chromosomes. In humans, the first cluster - miR-17~92, is located within the third intron of the non-protein coding gene, *MIR17HG (C13orf25)* on chromosome 13 (13q31.1-q33-1). The cluster consists of miR-17, miR-18a, miR-19a, miR-20a, miR-19b-1, and miR-92-1. The second cluster – miR-106b~25, is located in the 13th intron of *MCM7* on chromosome 7 (7q22.1) and consists of miR-106b, miR-93, and miR-25. The third cluster – miR-106a/363 is located on chromosome X (Xq26.2) and consists of miR-106a, miR-18b, miR-20b, miR-19b-2, miR-92a-2 and miR-363. Based on their seed sequences, the fifteen miRNAs can be grouped into four families - the miR-17, the miR-18, the miR-19, and the miR-92 family. The four families target different mRNAs; however they are predicted to repress multiple mRNA targets within the same pathways, thus regulating entire signaling nodes.

The miR-17~92 cluster is expressed at high levels in embryonic cells and is essential for normal development of various organs (41, 42). Microdeletions of the miR-17~92 cluster cause Feingold syndrome, a human developmental disorder that is characterized by defects in the skeletal and gastrointestinal system (43). Some patients with Feingold syndrome also have mental retardation and kidney and heart developmental abnormalities. Consistent with these findings, deletion of miR-17~92 in mice produces skeletal, heart, brain and kidney developmental defects (44, 45). Several lines of evidence have proved that the miR-17~92 cluster is a bonafide oncogenic miRNA cluster (10, 46). First, the miR-17 family and related miRNAs are upregulated in various human cancers (47), which include those of the kidney, colon, breast, prostate, stomach, and the pancreas. The oncogenic transcription factor, c-Myc binds to the promoter region of miR-17~92 and activates its transcription (48, 49). Second, forced expression of these miRNAs aggravates, whereas inhibiting miR-17~92 slows, cancer growth in mice (50-53). Lastly, the miR-17~92 cluster promotes proliferation of cells through direct and indirect inhibition of numerous tumor suppressor genes and promotes proliferation of cells.

While the miR-17~92 cluster and related miRNAs have been studied extensively in cancer, their role in kidney diseases is not completely understood. Studies by our group have conclusively proved that the miR-17~92 cluster is pathogenic in PKD (23). The expression of the miR-17~92 cluster is increased in orthologous as well as non-orthologous mouse models of PKD. Kidney-specific over-expression of the miR-17~92 cluster leads to cyst formation. Conversely, deletion of the cluster in a mouse model of PKD ameliorates the cystic phenotype, improves renal function and prolongs survival. One of the mechanisms through which the miR-17~92 cluster aggravates to cyst growth is by promoting proliferation of the cyst epithelial cells. Overexpression of the miR-17~92 cluster in the kidney leads to increased proliferation of cells lining the cysts, while deletion of the cluster in a model of PKD, decreased proliferation. A novel mechanism for cyst growth in PKD has been uncovered, which involves post-transcriptional regulation of cystic kidney disease genes by members of the miR-17~92 cluster. The ADPKD genes, *Pkd1* and *Pkd2* harbor conserved binding sites within their 3′-UTRs for members of the miR-17 family, while the hepatocyte nuclear factor 1-beta gene (*HNF-1β)* has conserved binding sites for the miR-25 family within its 3′-UTR. HNF-1β is an epithelial-specific transcription that regulates the expression of multiple cystic kidney disease genes (54, 55). In humans, mutations of *HNF-1β* produces cystic kidney disease and early-onset diabetes mellitus, a syndrome called renal cysts and diabetes (RCAD) (56). Several lines of evidence indicate that miR-17 represses these cystic genes *in vitro* and *in vivo*. In mouse kidneys, over-expression of the miR-17~92 cluster leads to decreases in the expression of *Pkd1*, *Pkd2*, *Pkhd1* and *Hnf-1β*, while kidney-specific deletion of the miR-17~92 cluster in a PKD mouse model leads to upregulation of the same set of cystic genes. In cultured renal epithelial cells, reporter assays indicate that miR-17 represses *Pkd1* and *Pkd2*, while miR-25 represses *Hnf-1β* by directly binding to their 3′-UTRs. In addition, mutation of the miR-17 and miR-25 binding sites within the 3′-UTRs of *Pkd1*, *Pkd2* and *Hnf-1β*, respectively, abrogated the miRNA mediated repression. The autosomal recessive polycystic kidney disease (ARPKD) gene, *Pkhd1* does not harbor binding sites for miR-17; however, its expression is directly regulated by *Hnf-1β*, which explains the change in its levels in miR-17 overexpressing cells and miR-17~92 knockout kidneys (57). In addition, bioinformatic analysis indicates that a number of genes that are mutated in humans with cystic diseases and developmental disorders are targets of the miR-17/18/19 and 25 families. Thus, miR-17 may promote cyst growth in PKD by directly and indirectly modulating the gene dosage of a large network of cystic kidney disease genes. Reduced gene dosage of ADPKD genes has been proposed as a new mechanism for cyst pathogenesis (58-60). The hypothesis states that kidney cysts form in ADPKD patients because the dosage of ADPKD genes falls below a critical threshold. Mutations that moderately reduce ADPKD gene dosage cause a milder form of the disease, whereas more deleterious mutations that severely reduce ADPKD gene dosage cause an aggressive form of disease. In this scenario, miR-17 may act as a modifier of disease

progression in ADPKD. Increased levels of miR-17 can further reduce ADPKD gene dosage and aggravate disease progression. Importantly, inhibiting miR-17 may increase the ADPKD gene dosage and retard disease progression.

miR-200 miRNA family

The miR-200 family comprises five members – miR-200a, miR-200b, miR-200c, miR-141, and miR-429. These miRNAs are located as two clusters on separate chromosomes. In humans, the miR-200b~miR-429 cluster is located on chromosome 1(1p36.33), while the miR-200c and miR-141 cluster is located on chromosome 12 (12p13.31). Based on their seed sequences the five miRNAs are divided into two subgroups – group I comprises miR-200a and miR-141 while group II comprises miR-200b, miR-200c and miR-429; however, these two groups regulate many of the same mRNA targets. Several lines of emerging evidence suggest that the miR-200 miRNA family plays an important role in renal tubule development and cyst pathogenesis. First, the expression of miR-200 family members is highly enriched in the normal kidney tubules whereas its expression is reduced in injured kidney tubules. Second, kidney tubule-specific knockout of the miRNA biogenesis enzyme, *Dicer*, leads to significant down regulation in the expression of all five members of the miR-200 family and formation of kidney tubule-derived cysts (40). Furthermore, miR-200 knockdown in cultured renal epithelial cells inhibits tubulogenesis and produces cyst-like structures, thus implicating miR-200 in the maintenance of normal renal tubule structure and preventing cyst formation. Third, miR-200 is known to regulate the expression of the ADPKD gene, *PKD1*. Bioinformatic analysis of *PKD1* 3'-UTR has identified two evolutionary-conserved binding sites for the miR-200 members. The miR-200 family members directly bind to *PKD1* 3'-UTR and inhibit its translation. Thus, miR-200 may regulate cyst pathogenesis through modulation of *PKD1* gene dosage. Fourth, the transcription of miR-200 is regulated by another cystic kidney disease gene, *Hnf-1β* (61). In mice, kidney tubule-specific deletion of *Hnf-1β* results in decreased expression of miR-200 miRNA family members and causes renal cysts. HNF-1β is known to promote the expression of key cystic kidney disease genes including the ADPKD gene *PKD2* and the ARPKD gene *PKHD1*. Interestingly, HNF-1β binds to a promoter region upstream of the miR-200 gene and directly controls the transcription of the miR-200b~429 cluster via a long non-coding RNA. Thus, along with *PKD2* and *PKHD1*, miR-200 belongs to a network of cystic kidney disease genes regulated by HNF-1β.

The cellular mechanism by which miR-200 regulates cyst pathogenesis may involve epithelial-to-mesenchymal transformation (EMT), a process in which epithelial cells lose polarity (e.g. apical-basal polarity) and acquire mesenchymal properties such as increased migratory capacity. miR-200 is known to maintain epithelial integrity and inhibit EMT, at

least in part, through direct inhibition of mesenchymal transcription factors *ZEB1*, *ZEB2* and transforming growth factor-β (*TGF-β2)*, a potent inducer of EMT (62-68). However, renal tubule epithelia in kidneys of *Dicer* and *Hnf-1β* mutant mice do not appear to undergo EMT (40). These cells might be undergoing 'partial EMT' wherein they simultaneously express both epithelial and mesenchymal markers. This has been observed in the kidney-specific HNF-1β knockout mice, as the expression of miR-200 targets - Zeb2 and TGFβ2 are increased several fold, while the expression of epithelial polarity protein, E-cadherin, is unchanged (61). While the role of partial EMT in aggravating cyst growth currently remains uncharacterized, partial EMT of renal tubule epithelia has been recently shown to promote renal tubule injury and kidney fibrosis (69). In summary, miR-200 members help maintain renal tubule homeostasis by preventing cells from undergoing partial EMT and regulating the dose of genes involved in cystic kidney disease.

miR-21

In humans, miR-21 is located on chromosome 17q23.2, where it overlaps with a protein-coding gene called Vacuole membrane protein 1 or *Vmp1*. Despite its intergenic location, the transcription of miR-21 is regulated independently of its host gene *Vmp1* through its own unique promoter. Even though miR-21 is expressed at high levels in multiple normal tissues, such as the heart, the liver and the kidney, miR-21 knockout mice display no overt phenotype, are fertile and live a normal life span (70). Thus, miR-21 is dispensable for normal development. Instead, the physiologic function of miR-21 may be in aiding organ regeneration after injury by promoting proliferation and/or inhibiting apoptosis of cells (71). This function of miR-21 is often 'hijacked' in the context of cancer to fuel the growth of malignant cells. miR-21 is dubbed oncomir because it is frequently amplified in multiple forms of cancers, where it is thought to promote proliferation and inhibit apoptosis of malignant cells by directly repressing a network of tumor suppressor genes (12, 72-74). Another disease in which miR-21 has been extensively studied is tissue fibrosis. While miR-21 may be necessary for recovery after acute injury, persistent elevation of miR-21 is thought to promote fibrosis (75, 76), particularly in the kidney. Several lines of converging evidence have shown that inhibiting miR-21 retards the progression of kidney fibrosis in murine models (77-79). These observations have provided the basis for initiating clinical trials to assess the safety and therapeutic efficacy of antimir-21 drugs in patients with Alport syndrome, a genetic condition that cause progressive kidney fibrosis.

Given that cancer and PKD share several common characteristics, it is not surprising that miR-21 has also been implicated in the pathogenesis of PKD. Our initial observations indicate that miR-21 is markedly up-regulated in multiple rodent models of PKD. miR-21 expression is also increased in cyst epithelial cells from human ADPKD samples. An

intriguing aspect of miR-21 transcriptional regulation is that its expression is activated by cAMP-CREB signaling. Thus, aberrant cAMP signaling may mediate its cyst promoting effects, at least in part, through up-regulation of miR-21. miR-21 expression is also activated by other cyst promoting pathways such as Janus Kinase (JAK)/STAT and mitogen activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) pathways indicating that multiple pathogenic signaling pathways converge and cooperatively activate miR-21expression. Importantly, inhibiting miR-21 expression slows cyst growth in a mouse model of ADPKD. Like cancer, miR-21 aggravates cyst growth by inhibiting apoptosis and promoting the survival of cyst epithelia. A potential molecular mechanism by which miR-21 aggravates cyst growth may be through direct inhibition of the pro-apoptotic, tumor suppressor *Pdcd4*. Interestingly, *Pdcd4* knockout mice spontaneously develop kidney cysts indicating that *Pdcd4* inhibition is sufficient to produce cysts. In summary, increased levels of miR-21 may promote disease progression in ADPKD by promoting the survival of cyst epithelial cells.

Other miRNAs

Several other microRNAs have been implicated in the pathogenesis of PKD. Microarray-based screening approaches have been used to identify miRNAs that are aberrantly expressed in mouse and rat models of PKD as well as human ADPKD samples (80, 81). These studies have shown that miR-214, miR-185, miR-146b, miR-503, miR-34a and miR-10 are upregulated whereas miR-204 and miR-488 are downregulated in cystic kidneys compared to normal kidneys. An aberrant miRNA expression profile has also been observed in epithelial cells derived from bile duct cysts from animal models of ARPKD (82, 83). Though insightful, further studies will be required to determine if the differentially expressed miRNAs directly promote PKD pathogenesis.

The potential for a miRNA-based therapeutic approach in PKD

The basic understanding of miRNA biology and the fact that miRNAs appear to play direct pathogenic roles in various diseases has led to the development of novel miRNA-based therapeutic approaches. These approaches involve the use of synthetic oligonucleotides called antimirs and miRNA-mimics (25, 26, 84, 85). Antimirs harbor sequences that are complementary, whereas miRNA-mimics harbor sequences that are identical to the sequences of a mature miRNA of interest. Once inside the cell, the antimirs bind to the targeted miRNAs and inhibit their function. In contrast, the miRNA-mimics associate with the miRISC complex and 'mimic' the function of the targeted miRNAs. While both antimirs and miRNA-mimics are being developed as novel drugs, antimirs have shown more early

promise. Antimirs possess several characteristics that make them an ideal therapeutic agent for a chronic disease such as PKD. Antimirs inhibit miRNA function most efficiently in the kidney and the liver, the two organs most affected by ADPKD and ARPKD. Antimirs can be self-administered (similar to insulin) and appear to be safe with no adverse effects reported in human clinical trial (18). Interestingly, antimirs have a long duration of action (as long as 4 weeks) (26) and may need to be taken only once every few weeks. These attributes are particularly well-suited for treatment of a chronic disease like ADPKD, which will require life-long therapy. As highlighted in above sections, miR-17 and miR-21 directly promote cyst growth in PKD. Therefore, it is tempting to speculate that antimir-mediated inhibition of miR-17 and/or miR-21 can be used as a therapeutic approach to slow cyst growth. Another possibility is that antimirs may be used along with other drugs, such as tolvaptan(86), to synergistically slow disease progression in ADPKD.

Despite this early excitement, significant challenges remain with regards to using antimirs to treat ADPKD. While antimirs are easily delivered to normal kidneys, delivery to cystic kidneys may not be that straightforward because the cystic kidney is severely anatomically distorted. Moreover, the majority of cysts in PKD arise in the distal segments of nephron and collecting ducts, while the antimirs primarily appear to be taken up by proximal tubules. Finally, while antimirs are well-tolerated in short term clinical trials, whether they can be safely tolerated for long periods of time is not known. Recently, early-stage clinical trials have been launched to test the therapeutic potential of antimir-21 in a genetic disorder called Alport syndrome that causes kidney fibrosis and like ADPKD will also require life-long therapy. These studies will provide important insights into whether antimirs can be safely used for long-term therapy.

Conclusion

miRNAs have emerged as important new regulators of normal kidney development as well as being involved in the pathogenesis of many kidney diseases, including PKD. At least three different miRNAs families – miR-17 and related miRNAs, miR-200 family and miR-21- have been implicated in the pathogenesis of PKD (Figure 2). These miRNAs are thought to promote cyst pathogenesis through regulation of key aspects of cyst pathogenesis such as proliferation and apoptosis of cyst epithelia, and direct regulation of PKD gene dosage. New approaches involving antimirs that pharmaceutically inhibit miRNA function holds promise as a novel therapeutic strategy for PKD.

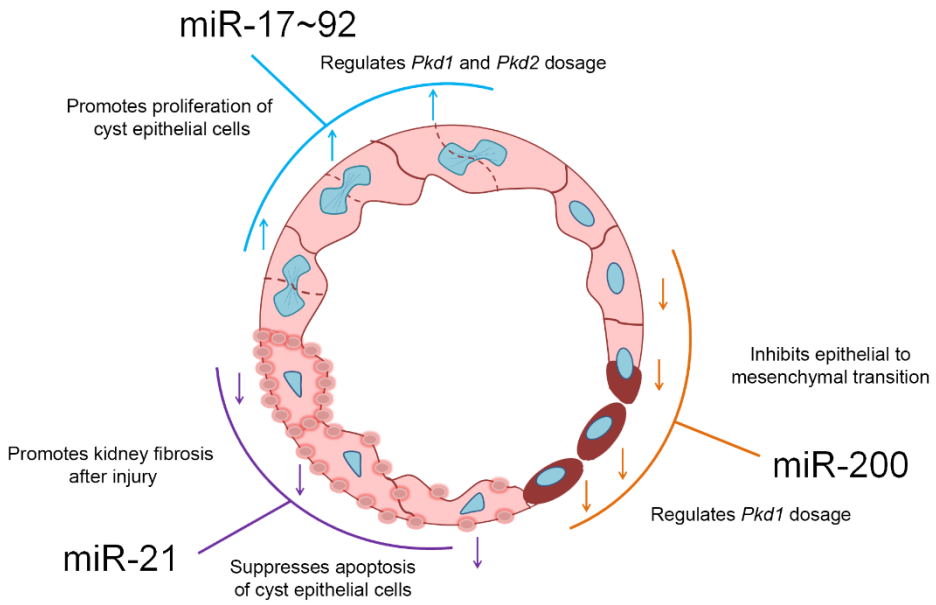

Figure 2. A model for potential mechanisms by which miRNAs regulate cyst growth. miR-17 promotes proliferation of cyst epithelia and reduces ADPKD gene dosage. miR-21 inhibits apoptosis and thus, promotes survival of cyst epithelial cells. miR-200 reduces Pkd1 gene dosage and inhibits epithelial to mesenchymal transition (EMT). Loss of miR-200 may result in partial-EMT and increased Pkd1 dosage, which collectively may aggravate cyst growth.

Conflict of interest

The authors declare that they have no conflict of interest with respect to research, authorship and/or publication of this book chapter.

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