Review

Tiny Non-coding RNAs in Body Fluids, Possible Biomarkers for Autosomal Dominant Polycystic Kidney Disease

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The functional and structural disease with autosomal dominant inheritance (ADPKD) shows a poly cystic nature is described by the presence of epithelial cysts in the human renal parenchyma. There are no standard and reliable biomarkers for the detection of ADPKD in early stages which delays the therapeutic approaches. Ideal biomarkers of ADPKD, should have high sensitivity, specificity, and excellent association with disease pathogenesis and development. Both in vitro cellular and in vivo studies on animal models proved the significant roles of miRNAs in the course of ADPKD. In addition, different studies have explored miRNAs up or down regulation both in renal tissue and extracellular fluids in ADPKD which represent novel indicators applicable for diagnosis or targeted therapy. Since urine is a non-invasive, easily accessible sample for ADPKD, it could be the best sample for diagnosis. Additionally, due to early action of miRNAs for regulation the gene expression or because of their unique chemical properties, detectable urine miRNAs can be employed as appropriate biomarkers for timely diagnosis or intensive care of the progression of renal destruction or response to treatment. In this review, the specific microRNAs involved in the pathogenesis of PKD will be discussed with a particular focus on extracellular miRNAs with possibility for application as biomarkers.

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INTRODUCTION

Polycystic kidney disease (PKD) remains the frequent heritable cause of renal malfunction in all age groups. Autosomal dominant polycystic kidney disease (ADPKD) as a type of PKD is the prominent reason for end-stage kidney parenchyma failure in five to ten percent of all patients on chronic dialysis. The incidence of ADPKD is expected to be between 1:400 and 1:1000.[1-3] The disease is regarded as growth and spreading out of multiple renal cysts, increasing kidney size that accompanying with hypertension, abdominal pain, cyst hemorrhage, gross hematuria and nephrolithiasis. With increasing age, alteration of normal kidney construction and ESRD happens in a large percentage of patients typically after the fourth decade of life. The accuracy of ultrasonography is suboptimal for diagnosis and exclusion in patients with the age < 30 years who are at risk for ADPKD. On the other hand, the detection of < 5 renal cysts by magnetic resonance imaging (MRI) is enough for disease exclusion. In addition, recent studies demonstrated that the existence of ten cysts detected by MRI in total offers a strong separation of the affected from unaffected cases.[4,5]

The destructive course of ADPKD describes the reason for the increasing concentration of clinicians on directing effective protection for the

illness on the basis of early diagnosis, evaluation of clinical course and its prognosis. However, the lack of biochemical markers intended for early detection which are sensitive and simply popular in clinical practice is a major difficulty. By definition, biomarkers are measureable features of biological processes.[6] In other words, biological molecule/s in blood, urine or other bio-fluids, as an indication of a healthy or unusual progress of illness. In recent years, many research projects have been directed towards determination of proper biomarker on the basis of cellular and molecular disease course.

On molecular view of point, ADPKD originates from some mutations in two related genes: Polycystin 1 (PKD1) or Polycystin 2 (PKD2).[7] Many efforts have been made for elucidating the cellular plus molecular basis that is responsible for renal cystogenesis and progress in heritable ADPKD. Recently reported evidence support the role of epithelial cell proliferation, extracellular matrix remodeling, and trans-epithelial fluid secretion regarding development of ADPKD (1). Other studies have initiated to demonstrate intracellular mechanisms involved in abnormal cell proliferation along with fluid accumulations.[8] In this regard, a well investigation of the fundamental mechanisms for the genesis and development of kidney tissue malfunctions in ADPKD is immediately needed to direct a well illness management, identification of biomarkers and detection of therapeutic targets.

There are different types of RNAs which work in various duties in body. An important group of RNAs are microRNAs. They are transcribed from some regions of nuclear DNA by RNA polymerase. From structural point of view, they are small RNAs around 22-29 nucleotide at mature form which are processed form of larger pri-miRNAs or pre-miRNAs. The microRNAs are known post transcriptional regulators of gene expression.[9] They have a region named seed sequence, often 7-9 nucleotide, with the potential to recognize the attachment of complementary site at the 3′ untranslated region of mRNA (UTR). After joining certain microRNA to target mRNA, this mRNA will send to degradation or block from entering to ribosome.[10] Therefore, miRNAs can regulate the expression of genes at transcription level.[11]

Undoubtedly, miRNAs contribute to the network of initial kidney development. However, the role of these tiny RNAs for the period of later phases of renal tubule maturation needs to be fully understood.[12]

Current studies directed on overall microRNA profiling revealed that their expression pattern is meaningfully different in ADPKD models as compared with normal kidney cells. Suggesting that miRNAs are actively involved in ADPKD disease genesis, progression, and prognosis.[13]

The urine as the kidney bio-fluid is a byproduct of the body metabolism contains water, toxins, salts and other side metabolites that finish up in the blood. The urinary tract in particular kidney filters and other parts of the tract eliminate those waste metabolites from blood.[14]

Investigating urinary molecular content alterations, either concentrations of particular microRNAs or proteins in urine specimens could be a straight and logical method to evaluate the perturbation of molecular systems in kidney.[15] Besides, the investigations of microRNAs in other body fluids in particular, blood might provide biomolecules as a result of the functions or dysfunctions of kidney tissue during the progression of ADPKD. Regarding ADPKD, preferably, biomarkers must exhibit immediate changes in the amount of cyst development, like blood pressure, glycated hemoglobin measurements, and cholesterol for predicting the long term outcomes of administered prescriptions. Hence, biomarkers may perhaps be employed to help early discovery, evaluate progression risk, screen ADPKD progression, recognize active factors in pathogenesis, and inform regarding the successfulness of used interventions.[16] At present, there are no standard biomarkers for ADPKD detection or follow up of the therapeutic approaches.[17] In nephrology, renal function is an indicator of the kidney performance. In this way, glomerular filtration rate (GFR) refers to the stream rate of waste fluid filtered via kidneys. A reverse association of GFR with entire kidney volume and has the potential to be used as a biological marker but considerable inter subject variation limits its application as a biomarker.[18] Notably, the circulating microRNAs are also focused for detection in plasma or serum during the progression of different diseases, and are hopeful biomarkers. On the other hand, the biological responsibilities of extra-cellular microRNAs remain

to be understood. There are theories supporting the idea that extracellular miRNA may carry cell to cell signals.[19]

The present review will focus on microRNAs involved in ADPKD, in particular, the extracellular miRNAs with diagnostic value.

EXTRA CELLULAR MIRNAS, SOURCE AND BIOGENESIS

The microRNAs are newly discovered group of non-protein coding tiny RNAs, with a length of 20-22 nucleotides in mature form.[10] The known role for miRNAs is post-transcriptional control of gene expression via complementary matching with 3′ untranslated region (UTR) of mRNAs. They usually are transcribed in the form of primary miRNAs (pri-miRNAs), then the Drosha ribonucleases process them to 70 nt pre-miRNAs.[11] The pre-miRNA connects to the exportin 5 protein which is a Ran-guanosine-59-triphosphate–dependent transporter. The exportin 5, controls the carrying of pre-miRNA into the cytoplasm. The second ribonuclease in the miRNA processing steps is Dicer which produces a small RNA duplex (double stranded). The duplex contains miRNA:miRNA*, the guide strand of the microRNA and its corresponding complementary thread. The complementary strand is degraded and guide strand is assembled with a complex containing target mRNA to form RNA induced silencing complex (RISC) (Figure 1). The miRNAs are mostly assumed to act as intracellular modulators of gene regulation. The tissue specific distribution of some miRNAs implies that they actively contribute in main functions of several tissue/organs[9,20] for instance; the miR-122 is liver-specific[9] and miR-124 is abundant in neurological tissues.[21] Conversely, recent studies have reported that miRNAs circulate in blood, urine, bronchial

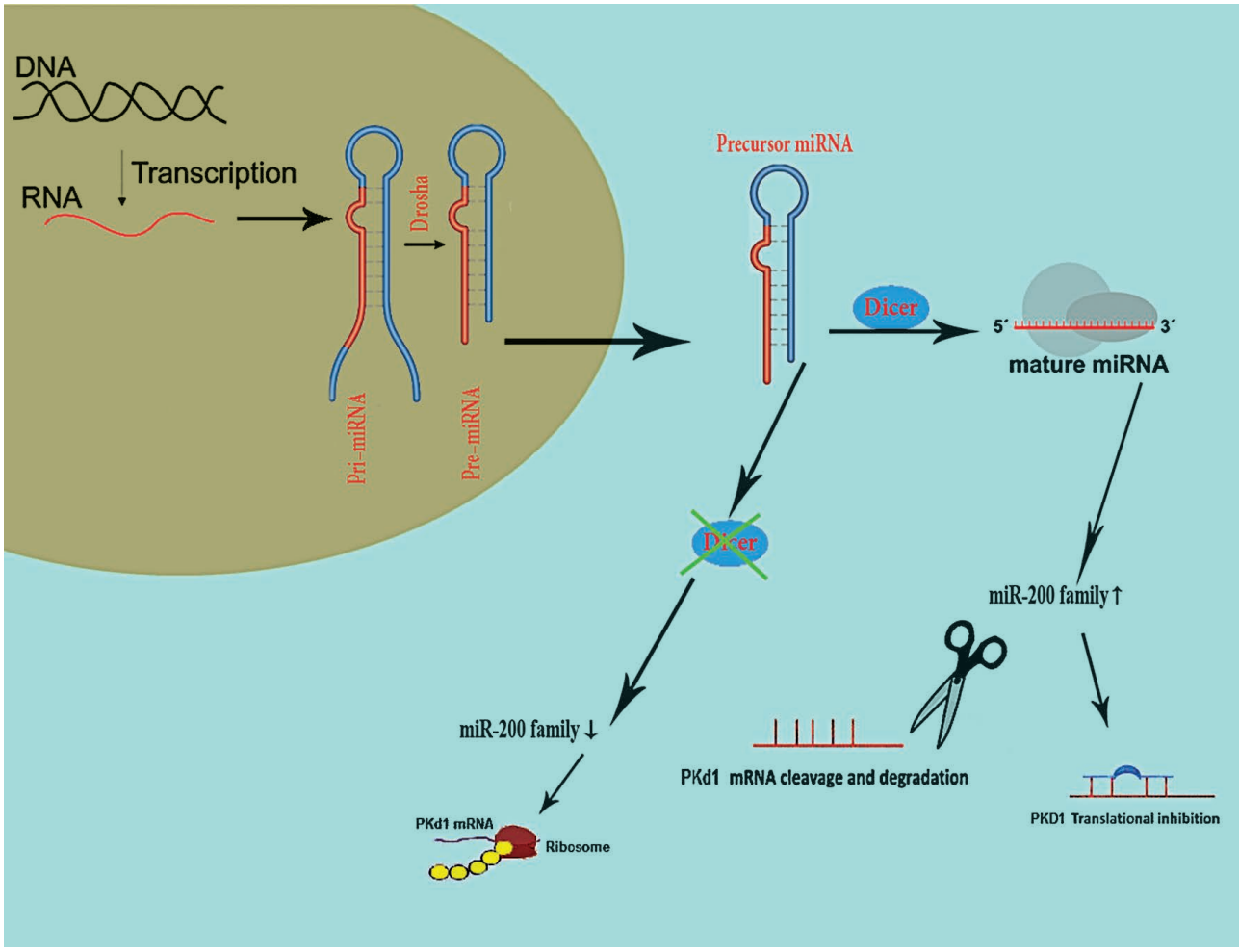

Figure 1. The role of miR-200 family down regulation by Dicer inactivation on PKD development. The dicer inactivation caused down regulation of kidney tissue specific miRNAs and thus activation of PKD1.

lavage, cerebrospinal fluid, breast milk, tear, amniotic fluid, semen, plasma, and colostrum.[15] The extracellular microRNAs are surprisingly stable in body fluids, hence, may be suitable as biomarkers with diagnostic or prognostic value. Remarkably, circulating microRNAs may transfer genetic orders from donor to recipient, thus changing biological courses by means of transcriptional regulations.[22] The circulating microRNAs in blood and urine could be managed to have an application in kidney disease diagnosis or prognosis. The extracellular miRNAs could act as biomarkers for disease and during apoptosis or injuries. In addition, extracellular miRNAs are secreted by cells as genetic information transmitters during the cellular crosstalk. The nucleases are known for digestion of the phosphodiester bonds in DNA, RNA, and DNA-RNA hybrids.[23] Body fluids are full of nucleases, which is the natural protective defense of body against foreign genetic materials such as viral genomes. Being in circulation necessitates for circulating miRNAs to be protected against nucleases mediated degradation.

In this way, the recent literature represented that extracellular microRNAs existing in saliva, plasma, serum, and urine are associated with a number of pathological conditions and diseases[15] and number of protective mechanisms for circulating miRNA transport have been described which are discussed below.

The informative vesicles or microvesicles are secreted in the form of exosomes from the cell surface into surrounding fluids and play a strategic role in cross talking between cells.[24] Microvesicles are not permeable to nucleases, thus lipid or membrane incorporation of microRNAs in the form of exosomes or microvesicles with different sizes can be an excellent strategy for stabilizing extracellular miRNAs.[25] Bigger microvesicles range in dimensions from 100 nm to 1μm are secreted from the cells, in specific physiologic or stressful conditions and smaller exosomes (30 to 100 nm) are budded from the multivesicular groups.[26] The RISC complex should be assembled with microvesicles as a perquisite for the loading of miRNAs into exosomes. Also, neutral sphingomyelinase 2 has been shown to regulate the exosome release.[27] The other mechanism for miRNA stabilization in body fluids is transporting in RNA binding proteins. The popular miRNA binding protein in plasma is Argonaute 2. The Argonaute 2 is a fragment of RISC protein complex. Although, Argonaute 2 protects majorities of microRNAs in plasma from nuclease degradation, minor fraction of them are transferred by microvesicles.[17] Wang et al. reported that Nucleophosmin 1 could bind to miRNA and contribute to transportation of miRNAs.[28] Another mechanism of miRNA protection is the apoptotic bodies which are released via cell programmed death, for instance the endothelial apoptotic bodies carry miR-126.[29]

Moreover, the HDL has been shown to transmit circulating miRNAs. The native HDL was combined with miRNAs then the cultured hepatocytes were treated with and interestingly, the HDL mediated delivery of miR-223 by means of scavenger receptor (class B, type I) caused up-regulation of the miRNA level and down regulation of its target mRNAs.[30]

Further mechanisms underlying the noteworthy constancy of miRNAs in the nuclease abundant milieu of natural fluids might exist and need to be discovered.

POLYCYSTIC KIDNEY DISEASE (PKD)

Polycystic kidney disease (PKD) is a prevalent genetic disorder affecting the function of kidneys both in the young and elderly.[31] In general, PKD is inherited and less commonly, it is observed in patients who have other serious kidney disorders. Three types of PKD have been described including autosomal dominant (ADPKD), recessive (ARPKD), and acquired cystic kidney disease (ACKD).[32] ADPKD also is named adult PKD which accounts for a majority of cases (90%). A person with an ADPKD suffering parent, has a fifty percent chance for disease development. The ADPKD symptoms typically develop in the ages of 30-40 and in rare cases during childhood.[33-35] The disruption of PKD1 and PKD2 genes causes ADPKD, which affects almost 1 in every 1,000 adults worldwide. The two genes encode two membrane proteins, including PKD1 and PKD2, which play an important role as the calcium signal transmission channel, that protects epithelial cell proliferation and differentiation in renal tissue.[36] The disease frequency and type is different, the first type occurs because of a mutation occurrence in PKD1 gene (85 to 90 % patients), and the second is due to a mutation in PKD2 gene (10 to 15 % of the patients).[37] ADPKD comprises of cystic lesions in organs such as the liver, spleen, seminal vesicles, pancreas, and vascular disorders, such as

intracranial aneurysms, abdominal and inguinal hernias, expansion of the aortic root, mitral valve prolapse and separation of the thoracic aorta, also early-onset hypertension.[38] ADPKD progression rate and incidence are unpredictable. Examination of possible therapeutics is hindered by absence of biomarkers with satisfying effects. The glomerular filtration rate become very limited as a late event in the course of ADPKD which happens after permanent damage to about 60% percent of normal renal parenchyma.[39] The criteria for diagnosis of ADPKD included a positive family history and kidneys ultrasonography.[40]

However, ARPKD has a recessive inheritance manner and an affected person shows two gene mutations in the PKHD1 gene, thus one mutated allele is present from each parent.[41]

The ACKD is a disease of later periods in life, is acquired not inherited, and often occurs in persons who suffering from other kidney problems/failure.[42] PKD is described by increasing the number of cysts in the kidney tubules, and often occurs in the last stage of renal disease. ADPKD is reported as the most common renal illness as well as the 4th leading cause of end-stage renal disorders. The renal cysts observed in ADPKD contribute to morbidity which can be harmful for patients. The gross hematuria and pain are described in around 60% of patients. ADPKD eventually results in the destruction of renal parenchyma in over 50 percent of cases.[43-46]

ROLE of microRNAs in PKD PATHOGENESIS

In the healthy kidney development, miRNAs regulate a number of essential biological courses including, the renal cell development, renal senescence, water homeostasis, sodium/potassium regulation, regulation of tonicity, and renin production.[47] As well, several evidences demonstrated the starring role of miRNAs in the pathogenesis of ADPKD renal cysts: First, the inhibition of miRNA biogenesis in mature renal tubes caused multiple cysts of the tubular and glomerular type.[12] Second, the aberrant expression of miRNAs resulted in an increase in the growth of cysts in PKD mice model,[48] and finally, miRNAs control the expression of many genes involved in the PKD disease.[12,48-50]

In recent studies, the role of miRNAs in kidney growth, physiology and pathophysiology has been examined. Therefore, recognizing the functions of miRNAs in the kidneys may result in a new approach to treatment of kidney disorders.[51]

miRNAs are important players in the pathogenesis of different renal disease, such as renal carcinoma, acute renal damage, diabetic nephropathy, transplant refusal, and also, PKD.[52] As a result, miRNAs can be used as biological markers for identifying various renal diseases.[53-54] Similarly, the levels of renal biopsy from human microRNAs has been stated as altered amounts in different kidney disorders.[14] The distribution of miRNAs is different among tissue/organs and each tissue has its own signature. In this way, a number of miRNAs showed tissue specific expression, specifically transcribed in certain tissues, they are actively involved in corresponding tissue's function and identity.[55] In the cystic kidneys, the expression of miRNAs is aberrant which is assumed to regulate crucial aspects of cyst pathogenesis for instance the out of control proliferation of cyst epithelial cell and apoptosis along with levels of the various PKD related genes. In kidney tissue miR-200 family is enriched and highly expressed miRNAs.[12]

In patients, suffering from IgA nephropathy (IgAN), urinary levels of miR-429, miR-200a, and -200b are very low, and the level of reduction is in correlation with the severity plus rate of progression.[56]

Inside the kidneys, the rate of miR-155 and miR-146a were considerably increased in IgAN and the amount of overexpression is linked to histological and clinical severity of its course. Thus miR-146a plus miR-155 may take a part in the pathophysiology of IgAN.[57]

Former studies have been described that miRNAs reveal the phases of the certain disease, including the formation of cancerous tumors. Diseases that are associated with cysts, such as PKD, and other diseases related with the formation of cysts in organs such as ovary, liver, and pancreas, have routine activities of cystogenesis in the particular tissue.[58]

The diseases associated with the formation of cysts, that can be one of their uses as a biomarker for diagnosis of these diseases, which causes creating a new approach to diagnosis of renal disease.[59] A change in the expression levels of miRNAs remains a strong method in gene therapy for their effect on post-transcriptional processes by which several genes are controlled in one treatment.[60] It

was discovered that an increase in the number of cysts and progress in ADPKD is associated with expression levels of PKD1.[61]

Patel et al. reported that inactivation of the miRNA processing, Dicer protein, during maturation of renal tubules yields both tubular and glomerular different cysts in mouse. Besides, Dicer ablation is concomitant with down-regulation of miR-200 and up-regulation of the expression of PKD specific gene (PKD1) (Figure 1). As well, in vitro prevention of miR-200 functioning in renal epithelial cells (REC) blocked the tubulogenesis process and resulted in up-regulation of Pkd1. The bioinformatic studies revealed that miR-200b/c/429 controls the Pkd1 gene expression via post transcriptional repression over two binding sites which are conserved, located in the 3′-UTR of PKD1 (Table 1). On the other hand, up-regulation of PKD1 in RECs is necessary to develop cyst-like assemblies. Hence, miRNAs are vital for the development of renal tubules, and PKD1 mRNA is a target RNA for miR-200 suggesting that miRNAs may modify PKD1 mRNA levels and take a part in the commencement of cystogenesis process.[12] Studies have documented that several microRNAs target PKD genes highlighting that microRNAs contribute to kidney cystogenesis.[50] The PKD2 gene is a known target of miR-17, thus up-regulation of miR-17 can stimulate irregular cell proliferation.[62] It was demonstrated that the 3-UTR (untranslated region) of PKD1 was less conserved than that of PKD2, miR-17 connects to the 3-UTR of PKD2, and suppresses the appearance of PKD2 at post transcriptional level (Table 1). Also, it was shown that upregulation of miR-17 can increase cellular proliferation through suppression of PKD2 in Human Embryonic Kidney cells 293 (HEK 293T).[62] In addition, study on mice models of PKD revealed that the miR-17~92 cluster become up regulated and overexpression of miR-17~92 resulted in cysts formation in normal mouse.[48]

Also, they found that miR- 17~92 cluster is actively involved in pathogenicity of PKD in mice, because of its ability to adjust the values of the PKD genes in cells.[48]

Additionally, the pathophysiological features of the disease developed in transgenic mouse expressing microRNAs which target PKD1.[49] It was shown that the RNA-binding protein bicaudal C (Bicc1), was effective in regulating PKD disease by suppression of the miR-17 family.[49] Signaling pathways affecting pkd rats include Transforming growth factor beta (TGF-b), Mammalian target of rapamycin (mTOR), Mitogen-activated protein

Table 1. Seed Cite Matching of PKD1 and PKD2 Genes with microRNAs (Target Scan Database)

MicroRNA/Target	Predicted Pairing of Seed Region	Cite Type
Position 49-56 of PKD1 3'UTR	5' ...GGAGUGGACACCGCUCAGUAUUA...	8mer
	|||||||	
hsa-miR-200b-3p	3' AGUAGUAAUGGUCCGUCAUAAU	
Position 49-56 of PKD1 3' UTR	5' ...GGAGUGGACACCGCUCAGUAUUA...	8mer
	|||||||	
hsa-miR-200c-3p	3' AGGUAGUAAUGGGCCGUCAUAAU	
Position 223-229 of PKD1 3' UTR	5' ...UUGGGAAGGACACAGCAGUAUUG...	7mer-m8
	|||||||	
hsa-miR-200b-3p	3' AGUAGUAAUGGUCCGUCAUAAU	
Position 223-229 of PKD1 3' UTR	5' ...UUGGGAAGGACACAGCAGUAUUG...	7mer-m8
	|||||||	
hsa-miR-200c-3p	3' AGGUAGUAAUGGGCCGUCAUAAU	
Position 132-139 of PKD2 3' UTR	5' ...GAUUGCUAAUCUUCUGCACUUUA...	8mer
	|||||||	
hsa-miR-17-5p	3' GAUGGACGUGACAUUCGUGAAAC	
Position 1043-1049 of PKD2 3' UTR	5' ...ACGCCUGUAAUCCCAGCACUUUG...	7mer-m8
	|||||||	
hsa-miR-17-5p	3' GAUGGACGUGACAUUCGUGAAAC	
Position 132-139 of PKD2 3' UTR	5' ...GAUUGCUAAUCUUCUGCACUUUA...	8mer
	|||||||	
hsa-miR-20a-5p	3' GAUGGACGUGAUAUUCGUGAAAU	
Position 132-139 of PKD2 3' UTR	5' ...GAUUGCUAAUCUUCUGCACUUUA...	8mer
	|||||||	
hsa-miR-20b-5p	3' GAUGGACGUGAUACUCGUGAAAC	

kinase (MAPK), Wnt and Janus kinase/signal transducer and activator of transcription (JAK/STAT). In addition, 30 miRNAs were expressed in a different way, including miR-217 miR-128, miR-21, miR-147 and miR-31 and a significant number of mRNA: miRNA pairs were recognized that should be validated.[63] Lee et al. revealed that microRNA15a levels were down regulated in patients carrying liver dysfunction, congenital hepatic fibrosis, ARPKD, ADPKD.[64] These results in augmented abundancy of the cell-cycle controller, Cdc25A (as straight target of miR15a) and supported cell proliferation and created cysts at in vitro conditions.[65] Pandy and colleagues reported that the microRNAs including miR-31, miR-21, miR-147, miR-217, and miR-128 are actively contributing to gene regulation. Also, Pandey et al, checked these micro-RNAs changes in animal models of PKD.[66] However, other researchers has been proven that there are 30 miRs with different expressions in PKD rats, that micro-RNA 217 and microRNA 31 were reported for the first time in the kidney.[67]

Due to disturbances in many cell activities including cellular cycle control, cellular proliferation, cyclic adenosine monophosphate (cAMP) and calcium signaling pathway, Epidermal growth factor (EGF)-stimulated MAPK signaling pathway and watery discharge participate to the production of hepatic cysts, the possible role of microRNAs in control of these activities is considerable. It is interesting to know that, nearly half of all miRNAs identified in PKD of the SPRD-cy rats 51 are equal to microRNAs discovered in cystic cholangiocytes from the PKD rat origin. Thus studies confirmed that cellular pathways regulated by miRNAs are similar in the polycystic liver pathogenesis and renal disorders.[68]

Using the Target Scan Database, we can state that the PKD1 gene takes two possible binding sites for miR-429 and miR-200b /c, as well as miR-20, miR-17-5p, miR-519, miR-93, and miR-106 (summarized in Table 1) (reference: http://www.targetscan.org).[69-70] The PKD2 gene, which is one of the factors controlling cell growth in PKD, has two binding sites for miR-17, and these miRNAs can be linked to either of these sites in PKD2 3′UTR under in vitro systems. Research teams suggested that the PKD phenotype in mouse is due to impairment in the family planning of miR-17. Internal inflammation and fibrosis are the clinical symptoms of PKD that appear in all types of the disease. TGF-β facilitates TGF-β-induced Collagen genes in mice mesangial cells (MCs) increase expression of miR-192 by decreasing Zinc finger E-box-binding homeobox 2 (ZEB2).[71,72] TGF-β can also reduce the expression of microRNAs from miR-192 and miR-200 family, which consequently induces epithelial-to-mesenchymal transition (EMT (Figure 2)). The members of miR-200 family control various cancers and kidney-derived epithelial cell

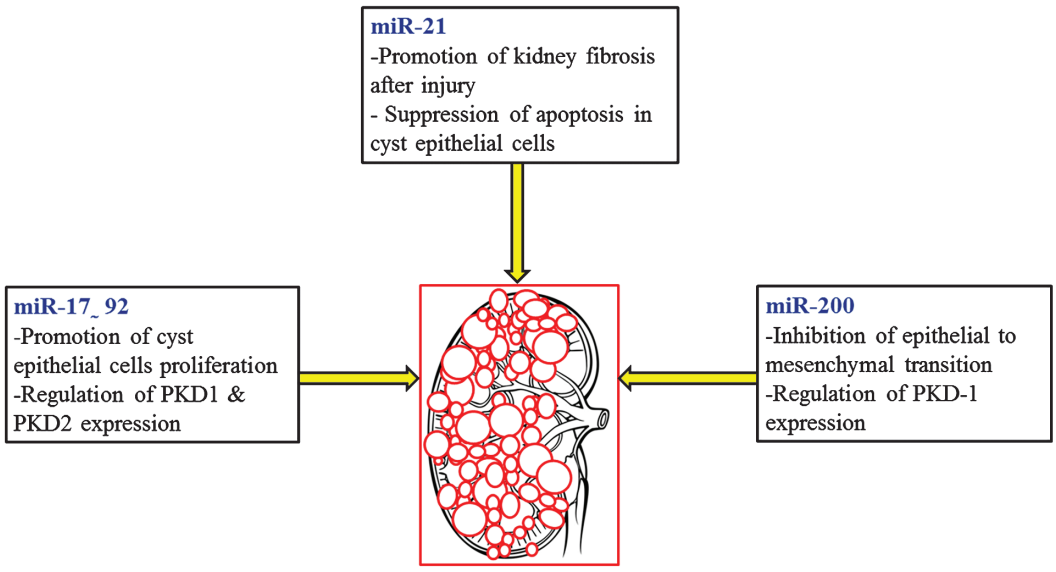

Figure 2. The potential mechanisms for the roles of three main miRNAs for development of poly cystic kidney disease and cyst growth. This figure shows that microRNAs are actively involved in cystogenesis process.

lines through the overexpression ZEB1 and ZEB2, which both Suppress E- cadherin.[73-5]

The miR-200 family prevents the Ummah, which reduces renal fibrosis, therefore they have potential for being a target in the treatment of fibrosis-related kidney disease.[31]

Three families of miRNAs including miR-200, miR-21, and miR-29 are controlled by TGF-B in fibrosis caused by kidneys. By increasing TGF-B signaling, miR-21 cause's fibrosis while miR-200 and miR-29 by inhibiting (EMT) reduce fibrosis and inhibiting the installation of extracellular matrix (ECM). Prevention of miR-21 expression or augmented expression of miR-29 inhibits the development of renal fibrosis in mice.[76] The vessels and ECM yields a number of soluble bio-factors which influence the biology of neighboring cells in diverse dynamic ways.[38]

It has been shown that a large number of miRNAs directly affect the cell cycle control genes that ultimately lead to PKD. These miRNAs can be derived from miRs-10a, -30a-5p, -96, -126-5p, -182, -200a, -204, -429 and -488.[70]

Probably PKD1 has two locations for miRNA attachment: connects to the first region of miR-200b/c and miR-429, while connecting to the second region of miR17-5p, miR-20, miR-93, miR-106 and miR-519.[77] The 3' UTR mRNA of PKD2 gene shows three probabilities for connecting to miRNA: region one with the binding properties similar to PKD1 region two; region two with the ability to bind miR-539 and region three with binding potential to miR-194. Hurtean et al. demonstrated in vivo conditions, there is an interaction amongst microRNA-200c and its predictable targets, but devours no effect on PKD1 gene expression.[78-9] Sun et al. showed an in vitro condition to explore the interaction between microR-17 and PKD2, as its probable targets,[79] demonstrating that miR-17 can interact with PKD2 3 'UTR. In addition, upregulation of miR-17 has shown to reduce PKD2 protein level in HEK293T however, mRNA levels were not affected.[77]

It has been shown that in mice Bicc1 -/- knockout expression of the enzyme synthase adenylate cyclase-6 (AC6) and cAMP pathway was increased in PKD mouse.

Three K homology domains and a SAM motif are present in Bicc1 protein which is present and expressed abundantly in proximal tubules. The domains can attach to AC6 mRNA, then the miR-125a joins, while the domain permits degradation via Argonaute and TNRC6A/GW182. Moreover, Bicc1 prompts silence/degradation of the protein kinase inhibitorα via miR-27a. Consequently, Bicc1 is required on these mRNAs as targets for directing silencing process through certain miRNAs. The suppression of AC6 via Bicc1 can elucidate the reason for the observation that cysts in ADPKD patients favorably originate from distal tubules.[80]

Bartram and colleagues were established a model based on deletion of Dicer as the miRNA processing enzyme for emerging mice renal tubules plus parts in the ureteric bud. Dicer knockout showed a considerable decrease of tubular branching in mouse kidneys elucidating renal hypoplasia. Additionally, they proved that the Pkd1 gene interacts with miR-20, which can contribute to the construction of cysts in the model.[81] MiR-17 and miR-200, as well as related miRNAs, can control cystic development through inhibition of genes involved in the growth of renal cysts. By modifying the function of miRNA, the expression of the genes in the CKD can be improved, and this action will be effective in treating PKD.[82]

Overexpression of microRNA-199a-5p tested in ADPKD tissues stimulated cellular proliferation through repressing Cyclin-Dependent Kinase Inhibitor p57 (CDKN1C/p57), it has been suggested that miR-199a-5p is a suitable treatment option for ADPKD.[83] A study reported that miR-365–1 can regulate the expression of PKD and hepatic disease 1 (PKHD1).[47] The miRNA potential is promising for use as a biomarker for diagnosis of cystic diseases. Since there is a good vision about how miRNAs can form cysts, this insight can lead to new treatments for patients with cystic disease.[50] There is a difference between mRNAs and deregulated miRNAs in rats with PKD. The findings showed that a number of microRNAs may be related in controlling pathways in ADPKD and miRNAs and probable targets were identified in ADPKD. They can also be considered as an effective option for anti-fibrotic treatment.[66]

In addition to the proliferative basis for cyst formation in APKD, other corresponding mechanism for stabilization of cysts in APKD could be prevention of apoptosis in renal cells during cystogenesi. In this way, miRNAs are linked to different types of cell death and regulate apoptosis

related genes at various cell types.[84]

Decreasing the expression of the microRNA195 prevents MCs from apoptosis, proposing that the anti-apoptosis mechanisms in a microRNA-controlled fashion might actively involve in the beginning of diabetic nephropathy.[85] Investigations have been shown that miR-21 prevents apoptosis start in cyst epithelial cells, to be expected via direct suppression of correspond target gene in programmed cell death. Thus, miR-21, in collaboration with cAMP, promotes the progression of the PKD disease, thus, increases the incidence and stability of cysts. It has been suggested that if miR-21 can be prevented it can be considered as a potential therapeutic line to slow down progression of cyst in PKD.[86] The BCL-2 is an anti-apoptotic gene, mice which are knock out for it present PKD, gray hair, growth retardation, lymphopenia and early death. The known regulator of BCL2 is microRNA-181. The miR-181a-mediated down-regulation of BCL2 mRNA expression might be an adapting factor that intensifies the phenotype and manifestations of PKD1.[87] Taken together, the role of three microRNA families including miR-200, miR-17, and miR-21should be highlighted in pathogenesis of PKD.

CIRCULATING miRNAs in PKD AS BIOMARKERS

Certainly, all biomolecules of disease molecular information, originating from nuclear or mitochondrial DNA, coding or non-coding RNAs, oligo peptides or proteins, lipids, and other metabolites present in body fluids free or bounded in membrane vesicles, could be useful for disease management.[88] Along with diagnosis biomarkers, the predictive biomarkers can be employed for assessing the responses to administered treatments that are valuable in medicine.[89] A perfect biomarker must be accessible by non-invasive procedures, low cost, specific to disease, and consistent early signal of disease prior to emergence of clinical symptoms.[90]

While most existing biomarkers are known proteins, protein based biomarkers are challenging due to the difficulties in detection of proteins in blood samples, post translational modifications and low quantities of proteins in body fluids, plus technical problems for providing high affinity detection methods. As a result, those complexities persuade scientists to seek for other alternative biomolecules with the accurate diagnostic value, sensitivity and specificity. In addition to cellular and tissue microRNAs, the researchers have found evidence for the presence of some miRNAs in body bio-fluids[91] including blood, serum, plasma, cerebrospineal fluid, peritoneal fluid, saliva, and urine. The current gold standard method for diagnosis of the intrinsic renal disease is the biopsy. However, biopsy from renal tissue is invasive and can cause major complications in 3% of cases. During progression of renal disease, urine may convey soluble wastes following renal filtration.

The urine is easily accessible and can be collected with less invasive methods than others or biopsies.[92]

Currently in clinical practice, documentation of PKD is focused on increasing in the serum creatinine, however, the levels of serum creatinine increase at very late stages in the course of the ADPKD, just after the irreversible serious damage of parenchyma[93] and thus are unreliable in the acute conditions.

Among different macromolecules, detecting exact miRNA species, is normally easier. The complimentary miRNA oligonucleotides could be synthesized which provide adequate detection specificity and PCR can be employed to increase the limit of detection. Use of microRNAs as biomarkers is preferred because of their lower complexity, absence of post processing modifications, tissue-restricted expression, simple amplification methods, and conservative nature of them between model organisms and human.[15] The studies focused on urine contents showed evidence of the presence of miRNAs, as potential biomarkers and their persistence in body fluids has made them ideal for use in diagnosis.[94]

Reducing renal functions and the possibility for progression into failure, which ultimately leads to dialysis, is associated with expression of urinary miR-21 and miR-216a. Thus these miRNAs have a potential to be utilized as biological markers of Chronic kidney disease (CKD).[95]

At present, there is no sensitive method to evaluate ADPKD progression or its diagnosis in the primary stages and this hinders the control of illness.

Differential expression investigations of miRNAs and their possible targets recognized by deep sequencing are proper candidates for additional

exploration and illustrating the mechanisms of renal allograft fibrosis.[39] Reducing miR-192 in the kidney may lead to renal dysfunction, such as development of PKD.[71]

Currently, there is no specific known biomarker for ADPKD. But a reverse association of GFR with whole kidney volume has been reported, considerable inter-subject variation restricts its role to be used as a PKD biomarker.[46] Ideal biomarkers for ADPKD progression must reveal short-term alterations in rate of cyst growth. As a result, biomarkers should support early detection, measure progression risk, screen disease progression, and notify on the success of therapeutic regimens.[16] In a study using NMR spectroscopy of urine small molecules showed difference between APKD patients having progressive disease from those with end-stage, patients carrying chronic kidney disorders and healthy relatives(39, 96). Also very limited number of studies, up to our knowledge have focused on urinary miRNAs as biomarkers of ADPKD (summarized in Table 2). The main study is directed by Ben DOV and colleagues which showed both up-regulation and down regulation of some miRNAs in urinary specimens.[39] Also, there is an emergency need for investigations of urine miRNAs for finding new biomarkers and insights for ADPKD.

There is a broad range of inconsistency in different studies which necessitates the development of a standard protocol for biomarkers in body fluids expression profile studies.[97] In some kidney diseases, including diabetic nephropathy, PKD and lupus nephritis, specific miRNAs cause clinical manifestations of the disease in several ways, including the stimulation of fibrotic pathways for anatomical fluctuations that cause proteinuria. Expressing the variety of kidney miRNAs in both areas of normal growth and disease processes, miRNAs have become a valuable tool for detecting and discovering appropriate treatment opportunities for pathologic courses that disturb the kidneys.[98]

MicroRNAs exist in body fluids including blood and urine. Circulating microRNAs which are resistant to the nucleases distinguished in body bio-fluids such as serum and urine are new biomarkers of renal diseases, such as Acute Kidney Injury and PKD.[99]

The importance of the function of modified miRNA expression has been studied during the progress of renal pathologies and the appearance of evolving miRNA-based therapies and diagnostic policies for early diagnosis and management of renal diseases.[100] Additionally, the transformative capacity of microRNAs in treatment and translational medicine focusing on drug-mediated renal impairment.[101] It has been proven that miRNAs existing in the urine are associated with renal disorders and also associated with pathophysiological processes. Obviously, more

Table 2. Studies on Urinary miRNAs as ADPKD Biomarkers

NO	Study Title	Method of Detection	Specimens	Excluded Samples	Studied miRNAs	Ref
1	"Urine MicroRNA as Potential Biomarkers of Autosomal Dominant Polycystic Kidney Disease Progression: Description of miRNA Profiles at Baseline"	Sequencing and annotation of small-RNA cDNA libraries	Urine specimens from 20 patients with ADPKD	Patients with active immune disorders affecting the kidneys were excluded	miR-1 , miR-133 (both down regulated) -miR-223, miR-199a, and miR-199b (all upregulated)	[102]
2	"Pilot Study of RNA as a Biomarker for Autosomal Dominant Polycystic Kidney Disease"	A technique for isolation of miRNAs from urine samples , biochemical and computational analysis of small RNAs from these samples	20 Urine specimens patients with ADPKD compared with 20 patients having other causes of chronic kidney disease	Symptoms or presence of bacterial infection determined by urine culture-Use of systemic steroids within a week prior to screening- other medical or psychological condition that make the candidate not qualified	A profile of isolated urine miRNAs	[103]
3	"Stability of miRNA in human urine supports its biomarker potential"	Isolation of miRNA from urine and Quantitative real-time PCR techniques	urine samples were obtained from eight healthy individuals (four males and four females)	No exclusion	miR-16, miR-21	[104]

studies are needed to apply them to the diagnosis and treatment of multiple cystic diseases, especially kidney disease with multiple cysts, and further investigation is needed.[14]

CONCLUSION AND FUTURE PERSPECTIVE

At present, the evidences support the theory of extracellular microRNAs recovered from various biological fluids including urine, blood products (serum & plasma) or other as a possible regulator of disease course and ideal biomarkers for ADPKD. However, several limitations restrict their immediate use including lack of confirmed microRNAs as biomarkers and inconsistent results obtained in studies of circulating or extracellular miRNAs owing to experimental and technical setup. It is necessary to consider several important points before scheming the extracellular miRNAs studies. Firstly, low level of miRNAs in bio-fluids is a major limitation hence, essential to take the precise platform which it permits investigating low volume of input miRNAs. Now, the priority in studies are focused on refining the procedures to retrieve the maximum volume of total RNA from the body fluid specimens with the purpose of profiling extra cellular miRNAs. Another issue is the type of circulating microRNAs investigated for instance microvesicles or exosomes bounded, protein-associated, or HDL linked miRNAs. As previously mentioned, all types of release and carriage of miRNAs are not biologically viable; so, it is recommended to concentrate on single form of them, for example exosomal or protein bounded miRNAs, in comparison with total miRNAs existing in a biological fluid. Definitely, as a developing field extracellular miRNAs study as possible biomarkers still necessitate a significant technical advancement. As a result, with the intention of obtaining consistent results from those studies, development of a standardized practice is necessary. Undoubtedly, scientists will be capable to overcome the restrictions in extracellular microRNAs investigations which will significantly increase our knowledge regarding disease biology, early detection, and make it possible to develop novel therapeutic approaches..

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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