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A mini review of noncoding RNAs in the pathogenesis of polycystic kidney disease

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Abstract

Polycystic kidney disease (PKD) is a genetic disorder characterized by the growth of numerous cysts in the kidneys, leading to kidney enlargement and progressive renal failure. Recent advances have indicated a pivotal role of noncoding RNAs (ncRNAs), including microRNAs (miRNAs), long noncoding RNAs (lncRNAs), circular RNAs (circRNAs) and PIWI-interacting RNAs (piRNAs), in the pathogenesis of PKD, potentially through regulating gene expression and cellular processes related to cyst formation, inflammation, and fibrosis. This review summarizes current knowledge of noncoding RNAs, explores their potential as biomarkers and therapeutic targets, and proposes potential directions for future research to further elucidate their roles in disease progression.

Keywords: Noncoding RNA, polycystic kidney disease, therapeutic target, miRNA, lncRNA, gene expression, signaling pathway



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INTRODUCTION

Polycystic kidney disease (PKD) is a debilitating genetic disorder characterized by the growth of numerous fluid-filled cysts in the kidneys, leading to kidney enlargement and progressive renal failure, although other organs, such as the liver, may also be affected^[1,2]. There are two main forms of monogenic cystic kidney diseases, including autosomal dominant polycystic kidney disease (ADPKD) and autosomal recessive polycystic kidney disease (ARPKD). ADPKD is the most prevalent form of PKD, primarily caused by mutations in *PKD1* and *PKD2* genes, with *PKD1* mutations accounting for approximately 78%-85% of cases^[2-4]. Notably, there are also patients suffering from ADPKD but without a genetic family history^[5]. The phenotypic variability suggests other potential genetic and epigenetic factors beyond the mutations, necessitating a further understanding of the molecular mechanisms driving cyst formation and progression to develop therapeutic targets^[6]. Over the years, accumulating studies have highlighted the critical involvement of noncoding RNAs, particularly microRNAs (miRNAs), in the pathogenesis of PKD, potentially by regulating gene expression and cellular processes related to cyst formation, inflammation, and fibrosis^[3,7-9]. This review aims to synthesize current knowledge regarding the significance of noncoding RNAs in PKD pathogenesis, evaluate their potential as biomarkers and therapeutic targets, and identify key research directions in the field.

PATHOPHYSIOLOGY OF PKD

Genetic basis

Mutations in *PKD1* or *PKD2*, which are localized on Chromosome 16p13.3 and chromosome 4q13, respectively, have been identified as the leading causes of ADPKD, occurring in 1 in every 400 to 1 in every 1000 live births at a conservative estimate^[10,11]. The two genes encode two large membrane proteins, polycystin 1 (PC1) and polycystin 2 (PC2). PC1 is a multifunctional transmembrane glycoprotein that mediates cell-cell and cell-matrix interactions, and PC2, a member of the transient receptor potential (TRP) channel superfamily, facilitates cation conduction and mechanosensory signal transduction, particularly in the primary cilia and the endoplasmic reticulum (ER)^[1,2,12-20]. PC1 and PC2 form a heterodimeric complex via the interaction of the coiled-coil motifs in the carboxy-terminal tails, which likely functions at primary cilia^[2], whereas the detailed roles of PC1 and the PC1-PC2 complex in the development of PKD are still enigmatic. In all ADPKD patients, approximately 85% of ADPKD cases are attributed to mutations in the *PKD1* gene, with mutations in *PKD2* accounting for the remaining^[2-4]. The severity of the disease often correlates with the type and location of mutations within these genes, with *PKD1* mutations typically leading to a more aggressive phenotype compared to *PKD2* mutations^[21]. This genetic variation markedly influences disease progression, referring to a “dosage-dependent effect” of PKD proteins, where reduced PKD protein levels impact critical cellular signaling pathways including calcium, cyclic AMP (cAMP), and Mammalian target of rapamycin (mTOR) signaling pathways, consequently promoting cyst growth and kidney fibrosis^[2].

ARPKD is relatively rarer but much more severe in the clinical course, which typically manifests perinatally or in childhood, and patients often die perinatally or in infancy, with clinical manifestations including enlarged cystic and fibrotic kidneys, hepatobiliary duct malformation, portal hypertension, pulmonary hypoplasia, and hepatic fibrosis^[1,2,22]. ARPKD is primarily caused by mutations in two genes^[23]. The majority of ARPKD cases result from mutations in polycystic kidney and hepatic disease 1 (*PKHD1*), located on chromosome 6p12. This gene encodes a ciliary protein fibrocystin (PFC) (also known as polyductin). Less frequently, mutations in DAZ-interacting zinc finger protein 1 (*DZIP1L*), which encodes another ciliary protein, have also been associated with moderate ARPKD^[23]. PFC may act as a ciliary receptor protein, but its detailed functions are not fully elucidated due to the presence of various splicing variants. *DZIP1L* protein localizes to the ciliary transition zone and may play a critical role in transporting gene products into

the ciliary axoneme^[24]. Interestingly, there is a potential crosstalk between these two ARPKD genes and the *PKD1/2*. Interactions between FPC and PC2 have been shown to occur in the cilia, where these two proteins can form a complex and drive PC2 channel activity [24de14,21]. Loss of DZIP1L has been reported to prohibit the localization of PC1 and PC2 to the ciliary axoneme, which may result in the accumulation of the PC1 and PC2 in the ciliary basal body/transition zone [24de 17]. These interactions suggest shared pathogenic pathways between ARPKD and ADPKD, and there might be additional genetic and epigenetic factors beyond the primary mutations^[6].

Several other minor PKD genes have also been identified in recent years, such as *GANAB*, *IFT140*, *DNAJB11*, *PRKCSH*, and *SEC63*^[25-27]. One of the representative genes is *GANAB*, which encodes glucosidase II α (GII α) and has been implicated in mild ADPKD and severe polycystic liver disease (ADPLD), with mutations disrupting PC1 maturation and ciliary localization^[28,29]. This *GANAB*'s liver-dominant disease indicates the importance of genotype-phenotype correlations. The *IFT140* gene, encoding a core component of the intraflagellar transport complex A (IFT-A), plays a crucial role in retrograde ciliary trafficking and ciliary membrane protein entry^[30]. *IFT140*'s proximity to *PKD1* on chromosome 16p13.3 can further complicate diagnostics, as *PKD1* variants may modify the *IFT140* phenotype^[30]. *DNAJB11* is associated with atypical ADPKD, often presenting with mild kidney disease but familial end-stage renal disease (ESRD), and functions in ER protein folding, affecting PC1/PC2 processing^[31]. *PRKCSH* and *SEC63*, primarily linked to ADPLD, may also present with renal cysts, and *PRKCSH* encodes GII β (a *GANAB* partner), while *SEC63* aids ER protein translocation, both influencing PC1 maturation^[32].

Emerging evidence suggests polygenic effects modify ADPKD progression, though large-scale genome-wide association studies (GWAS) remain limited. Current studies implicate genes like *GANAB* in phenotypic variability^[4], while mechanistic studies link *PKD1* dysfunction to vascular manifestations including hypertension^[33]. Additional modifier genes continue to be identified through comprehensive sequencing approaches^[34]. These indicate the genetic heterogeneity of PKD, necessitating comprehensive genomic testing such as whole-genome sequencing (WGS) for accurate diagnosis, particularly in atypical cases.

Molecular pathways involved in PKD

Accumulating evidence has shown a critical role of dysregulated molecular pathways, including cAMP, Wnt, mTOR, vascular endothelial growth factor (VEGF), Myelocytomatosis viral oncogene homolog (c-MYC), and Hippo in both ADPKD and ARPKD^[2,35,36], aside from the significance of genetic mutations. Studies have demonstrated that deficiency of either PC1 or PC2 results in decreased intracellular calcium levels. This calcium depletion triggers a signaling cascade characterized by: (1) enhanced activity of adenylyl cyclase isoforms 5 and 6 (AC5/6), coupled with (2) diminished phosphodiesterase 1 (PDE1) activity. These dual regulatory effects collectively lead to the pathological accumulation of cAMP. The elevated cAMP levels subsequently activate protein kinase A (PKA) in renal epithelial cells, which in turn phosphorylates the cAMP response element-binding protein (CREB), thereby potentiating its transcriptional regulatory activity^[6,37]. Other novel mechanisms for dysregulation of cAMP signaling in cystic kidney diseases have been revealed in recent years. cAMP has been shown to exert negative feedback by downregulating both *PKD2* expression and phosphodiesterase 4C (*PDE4C*) activity. These findings suggest that targeted inhibition of AC5 or pharmacological activation of *PDE4C* may represent promising therapeutic strategies to normalize aberrant cAMP levels in polycystic kidney disease^[36].

Wnt signaling has also been identified to be critical in PKD^[38,39]. Wnts are secreted glycoproteins, playing pivotal roles in many biological processes such as embryonic development, cell fate determination, and tissue homeostasis^[40]. Several studies have suggested that canonical Wnt signaling plays an important role in

cystic kidney disease via its downstream target β -catenin. Genetic ablation of kinesin II subunit (Kif3a) in mice led to the upregulation of β -catenin in cyst epithelium and produced cystic kidneys^[41]. The extracellular domain of PC1 has been illustrated to bind to Wnt ligands and trigger Ca^{2+} influx through heterodimer complex formation with PC2^[42], and the cytosolic domain of PC1 downregulated canonical Wnt signaling by binding to β -catenin^[43]. All these findings highlighted a complex interplay between genetic factors and molecular signaling pathways in the pathophysiology of PKD.

The mTOR signaling pathway is another key player in the development of PKD. Dysregulation of mTOR signaling was related to enhanced cellular growth and inhibition of cell apoptosis, thereby resulting in cyst development^[44]. Activation of the phosphatidylinositol-3-kinase (PI3K)/RAC- α serine/threonine-protein kinase (AKT)/mTOR signaling cascade has been specifically implicated in enhancing renal cyst growth and expansion^[45]. Notably, research has revealed that PC1 exerts inhibitory effects on mTOR signaling through two distinct mechanisms: (1) direct interaction with tuberous sclerosis complex 2 (TSC2) that modulates its subcellular localization, thereby preventing AKT-mediated phosphorylation and subsequent tuberin inactivation^[46,47]; and (2) facilitation of TSC2-TSC1 complex formation via its C-terminal domain, which further suppresses mTOR pathway activation^[46]. Some studies showed rapamycin, an mTOR inhibitor, might have promising therapeutic effects in reducing kidney volume in ADPKD patients^[48]. Blocking of mTOR using NVP-BEZ235, a dual PI3K/mTOR inhibitor, resulted in alleviated renal function and morphology in ADPKD animal models^[49]. Recently, it was found that mTOR, together with ERK and Rb, could be regulated under p68 signaling activation in cyst lining epithelial cells and contributed to cyst growth in ADPKD, suggesting additional therapeutic nodes^[50,51].

The VEGF pathway has been implicated in promoting cyst angiogenesis in recent years. In polycystic liver disease, cystic cells secrete VEGF, which in turn stimulates cyst growth and vascular remodeling through a PKA/RAS/ERK/HIF1 α -dependent mechanism^[52]. Elevation of serum VEGF alpha (VEGF-A) along with urinary angiotensinogen (AGT) were significantly upregulated in ADPKD patients as compared with healthy controls^[53]. Of note, Coban *et al.* demonstrated in a comparative study that there was no association of VEGF with total kidney volume (TKV) or renal failure in ADPKD patients^[54]. This contradiction warrants further investigations on the more detailed function of VEGF signaling in PKD disease.

Recent studies highlighted a significant role of c-MYC in PKD progression. c-MYC appears to function as a critical downstream target of the Wnt- β -catenin signaling pathway upon the activation of transcriptional coactivator with PDZ-binding motif (TAZ), a Hippo signaling effector involved in cystogenesis in polycystic kidney disease^[55]. Later, it was found that genetic switches near *MYC*, *JUN*, and *FOS* genes in PKD models. Removing these switches reduced expression of these genes, slowed cell growth, and inhibited cyst formation. Additionally, blocking energy metabolism or activating PPAR α lowered H3K27ac levels at *MYC* enhancers^[56]. In addition, altered Hippo signaling dysregulation has also been illustrated in PKD progression by regulating organ size and cell proliferation through two key transcriptional co-regulators, Yes-associated protein 1 (YAP) and TAZ. Nuclear localization of YAP/TAZ is frequently detected in cystic renal tissue, whereas epithelial YAP activation was shown in ARPKD patients^[57]. Although these multiple dysregulated pathways have been implicated in PKD pathogenesis, their precise molecular mechanisms, temporal interactions, and cell-type specific contributions remain incompletely understood, particularly regarding: (1) how PC1/PC2 dysfunction precisely coordinates these pathways; (2) the hierarchical relationships between calcium signaling, metabolic reprogramming, and transcriptional networks; and (3) stage-dependent pathway dominance during cyst initiation versus expansion, necessitating further mechanistic studies to elucidate these complex interactions for targeted therapeutic development.

ROLE OF NONCODING RNAS IN PKD

MicroRNAs

MicroRNAs (miRNAs) are small noncoding RNAs of approximately 22 nucleotides, and have been demonstrated to play a pivotal role in the pathogenesis of PKD by regulating various cellular processes, including proliferation, apoptosis, and inflammatory responses. Dysregulation of miRNAs has been implicated in the development and progression of cystic kidneys^[58,59]. Among these miRNAs, the miR-17 family, particularly miR-17, has been identified to be critically involved in PKD development^[59,60]. Reportedly, miR-17 was upregulated in both murine and human kidney cysts^[61], which was associated with cyst growth by prohibiting mitochondrial function and enhancing cell proliferation^[61]. The miR-17 family has also been implicated in metabolic reprogramming within cystic cells, where it repressed oxidative phosphorylation and promoted cellular proliferation through the inhibition of pathways such as peroxisome proliferator-activated receptor alpha (PPAR α)^[58]. Genetic deletion of miR-17 improved mitochondrial function and reduced cyst growth in ADPKD models, and improved renal function^[61-63], as well as decreasing mTOR activation and inflammatory responses associated with PKD progression^[63,64]. Genetic deletion of miR-17~92 slowed cyst proliferation and improved renal function, further confirming the therapeutic potential of targeting miR-17^[63].

Upregulation of many other miRNAs, such as miR-21, an oncogenic miRNA, was also observed in cystic kidneys and disease progression potentially by inhibiting cell apoptosis via repressing its target gene *PDCD4*^[65], which was concomitantly linked to the cAMP signaling pathway, a key pathway frequently activated in PKD, ultimately driving the expression of miR-21 within the cysts^[65]. Upregulated miR-199a-5p levels have been shown in diseased kidneys of PKD/Mhm rats and renal tissues of ADPKD patients^[66,67]. Very recently, Lai *et al.* showed that miR-17-5p, miR-21-5p, and miR-199-5p correlated positively with the eGFR slope instead of the eGFR in ADPKD patients. Both total fibrotic volume and height-adjusted total fibrotic volume were positively and significantly correlated to miR 21-5p and miR 199-5p, but not to TKV (cm³) and height-adjusted total kidney volume (htTKV)^[68]. Moreover, miR-182 has also been shown to be positively correlated with fibrosis in cyst-lined epithelial cells, mediated through the TGF- β 1/Smad3 signaling pathway^[69].

Specifically, studies illustrated that miR-15a was downregulated in cystic livers associated with both ARPKD and ADPKD^[70], which led to increased expression of CDC25A, thus promoting cellular proliferation and cystogenesis. Downregulation of miR-192 and miR-194 contributed to the later stages of cystogenesis by promoting epithelial-mesenchymal transition (EMT) - a process closely linked to cyst enlargement^[71]. In contrast, restoring miR-192 and miR-194 levels has been shown to reduce cyst size in experimental models^[71]. The miR-200 family is another extensively studied miRNA family in the context of ADPKD. miR-200 maintains epithelial integrity and prevents EMT^[72], which was associated with a decrease in miR-200 levels and downregulation of hepatocyte nuclear factor-1 β (HNF-1 β), a transcription factor that regulates gene expression in the kidney, liver, pancreas, and other epithelial organs^[73-75]. miR-200 expression was significantly reduced after tubule-specific deletion of *HNF1B*, and knockdown of miR-200 in cultured renal epithelial cells inhibited tubulogenesis and produced cyst-like structures, which might be achieved by modulation of PKD1 expression by binding to the 3'UTR of the *PKD1* transcript^[73]. Of note, in this study, the miR-200 cluster was encoded by a long noncoding transcript that was regulated by HNF-1 β ^[73]. In another conditional Dicer knockout model, which lacked functional miRNA biogenesis, downregulation of miR-200 resulted in PC1 overexpression and precipitated cyst formation^[72]. These findings suggested a critical and complicated role of miR-200 in PKD progression. Decreased expression of miR-20b-5p and miR-106a-5p was observed in a mouse model where *PKD2* was specifically knocked out, and they were shown to be correlated with disease progress by regulating KLF12, a transcription factor implicated in tumorigenesis^[76]. These findings highlighted the multifaceted roles of miRNAs in regulating fibrosis, cell

cycle, and apoptosis in the context of PKD, emphasizing their potential as therapeutic targets.

Long noncoding RNAs

In recent years, lncRNAs have emerged as crucial regulators in PKD. Dysregulated lncRNAs, including H19, PVT1, DNM3OS, and the like, have been identified in *PKD1* mutant kidneys^[77,78]. Notably, H19 has been shown to suppress *PKD1* expression, thus promoting atherosclerotic changes associated with CKD progression^[79]. Among these lncRNAs, PVT1 displayed the highest upregulation in both cystic metanephric organ culture (MOC) and cystic kidneys. It plays a role in modulating c-MYC protein levels, thereby influencing cyst progression^[77]. PVT1 is located on mouse chromosome 15 and spans a large genomic region of 225 kb. This locus is syntenically conserved between mice and humans^[77]. Conversely, the downregulation of PVT1 has been shown to suppress cyst growth and reduce c-MYC protein levels^[77].

Another prominent example is HOXB3OS, which has been shown to be downregulated in cystic kidneys from both *PKD1* and *PKD2* mutant mice, as well as in humans with ADPKD^[78,80]. Deletion of HOXB3OS resulted in the activation of mTOR/AKT signaling pathways, leading to increased kidney cell proliferation and exacerbated cyst growth^[78]. Re-expression of HOXB3OS in mutant cells restored p-mTOR as well as p-RS6 and p-S6K to normal levels and partially rescued the metabolic abnormality^[78]. Notably, the mTOR pathway has also been demonstrated to be under the regulation of some other lncRNAs, such as NEAT and MALAT1. Overexpression of NEAT1 in liver cells increased the levels of p-mTOR and p-S6K, and inhibition of NEAT1 significantly downregulated mTOR signaling^[81]. MALAT1 could aggravate tubular damage by activating Nox4/AMPK/mTOR signaling in diabetic nephropathy^[82]. These findings implicated that these lncRNAs might be indirectly involved in the pathogenesis of PKD.

Interestingly, some studies revealed that miR-214 and its host lncRNA DNM3OS were upregulated in both ADPKD mouse models and human cystic kidneys, primarily originating from interstitial cells in the cyst microenvironment; and inhibition of miR-214 unexpectedly exacerbated cyst growth in *PKD*-mutant mice^[83]. This study further identified a protective feedback mechanism where inflammatory TLR4/IFN- γ /STAT1 pathways activated miR-214 expression, which in turn suppressed TLR4 to limit macrophage accumulation, inflammation, and cyst progression^[83]. These findings indicated miR-214 and DNM3OS upregulation and their cooperation might be a compensatory anti-inflammatory response in ADPKD pathogenesis.

Despite these findings, it remains unclear whether other lncRNAs are involved in the pathogenesis of PKD and what roles they may play or how they interact with miRNAs. Given that lncRNAs often regulate various cellular processes and dysfunctions by sponging multiple miRNAs, their potential interplay with miRNAs may further complicate the regulatory dynamics in ADPKD. Therefore, a more integrated analysis of these noncoding RNAs is needed.

Other noncoding RNAs

CircRNAs, with their covalently closed loop structure, and PIWI-interacting RNAs (piRNAs) are emerging research subjects in various diseases^[84,85]. CircRNAs often act as competing endogenous RNA (ceRNA) to regulate gene expression by acting as miRNA sponges. For instance, circ_0040994 depletion alleviates lipopolysaccharide (LPS)-induced HK2 cell injury through the miR-17-5p/TRPM7 axis^[86]. CircRNAs have also been illustrated in regulating multiple signaling pathways. Circ_0002970 promotes fibroblast-like synoviocyte invasion and the inflammatory response through Hippo/YAP signaling to induce CTGF/CCN1 expression in rheumatoid arthritis^[87]. However, whole transcriptome-wide screenings of circRNA-mediated ceRNA networks associated with PKD are still lacking. PiRNAs, which play essential roles in gene regulation by silencing transposable elements and protecting oncogenes and tumor suppressors, are even

less studied in kidney disease^[88]. Very recently, several piRNAs have been identified to be significantly involved in the pathogenesis of diabetic kidney disease^[89,90] and renal cell carcinoma^[91]. Their roles in PKD pathogenesis are still in need of further investigation.

NONCODING RNAS AS BIOMARKERS AND THERAPEUTIC TARGETS

Urinary microRNAs as biomarkers

Recent studies have demonstrated the potential of urinary microRNAs as non-invasive biomarkers for ADPKD. Kocyigit *et al.* identified 18 microRNAs that exhibited significant differences in abundance between ADPKD patients and healthy controls, with specific microRNAs like miR-3907 significantly correlated with renal function decline^[92], suggesting its potential as a biomarker. Additionally, increased levels of miR-3907 were associated with greater than 10% loss of glomerular filtration rate (GFR) over a 12-month period, indicating a predictive capacity of this miRNA^[92]. Later, they observed that telomere length and TERRA expression levels were altered in ADPKD patients, suggesting potential epigenetic biomarkers that could reflect disease progression and severity^[93]. Furthermore, a comprehensive profiling of urinary exosome microRNAs in ADPKD patients was conducted, which revealed that miR-192-5p and miR-30 family members were significantly downregulated in these patients and correlated with disease severity^[94]. These findings suggest that specific urinary microRNAs could not only serve as biomarkers for disease severity but also improve diagnostic performance in distinguishing between early- and late-stage ADPKD.

Beyond the diagnostic value, urinary microRNAs may also hold prognostic significance. Recent studies have demonstrated the potential of urinary microRNAs to inform tailored treatment strategies, thereby improving patient outcomes^[95]. For example, miR-1225, located within the *PKD1* gene locus, has been shown to be modifiable to enhance its expression, presenting a novel approach to therapeutic intervention in ADPKD^[96]. Notably, microRNAs such as miR-16 and miR-25 have been identified as potential biomarkers for assessing the risk of intracranial aneurysms, further expanding the prognostic applications of microRNA research in ADPKD^[97]. In addition, miR-3907 has been identified as a potential predictive biomarker for renal function decline in ADPKD patients^[92]. Further studies involving larger cohorts of PKD patients are needed to identify additional urinary microRNA biomarkers and to elucidate the underlying mechanisms of cystogenesis and disease progression in PKD.

LncRNAs have also garnered attention as potential biomarkers for kidney diseases. Urinary levels of lncRNAs such as MEG3, ARNIL, MALAT1, and TUG1 have been found to correlate with disease progression in lupus nephritis^[98] and diabetic nephropathy^[99]. More recently, a large multicenter case-control study identified three circRNA panels (circ_0075792, circ_0005397, and circ_0000976) that might function as significant biomarkers for detecting HBV-related hepatocellular carcinoma^[100]. Although data on urinary lncRNAs, circRNAs, and piRNAs in the pathogenesis of PKD remain limited, these molecules show promising potential as non-invasive tools for aiding in PKD diagnosis and prognosis. Further studies are needed to validate their roles and clinical applications.

Therapeutic implications of targeting noncoding RNAs

The therapeutic potential of targeting noncoding RNAs, particularly microRNAs, has gained significant attention in ADPKD. Over the years, studies have emphasized the development of anti-miRNA approaches and small molecule inhibitors to mitigate the dysregulated expression of specific microRNAs that contribute to disease progression. Hajarnis *et al.* demonstrated that targeting the miR-17 family could effectively slow down cyst growth in mouse models of ADPKD, with anti-miR-17 oligonucleotides showing protective effects in both short-term and long-term studies^[61]. Similarly, Patel *et al.* reported that inhibiting miR-17~92

cluster upregulated PKD-related gene expression, including *PKD1*, *PKD2*, and *HNF-1 β* , suggesting its therapeutic potential^[101]. Furthermore, RGLS4326 (farabursen), an anti-miR-17 oligonucleotide, was shown to preferentially accumulate in renal tissues and effectively inhibit miR-17, leading to reduced cyst proliferation and improved renal function in preclinical models^[63,102]. Notably, this oligonucleotide recently yielded positive results in a phase 1b multiple ascending dose (MAD) trial^[103]. More recently, Chakraborty and Yu observed that restoring PKD gene expression combined with antagomir therapy against miR-17 reduced cyst formation and preserved kidney function, further underlining the significance of this microRNA in ADPKD therapy^[1]. Aside from this, studies have demonstrated that Anti-sense oligonucleotides (ASOs) targeting miR-21 can also mitigate disease progression in animal models, suggesting another promising therapeutic avenue^[96].

Recent studies have shown that the cystic fibrosis transmembrane conductance regulator gene (CFTR) may be regulated post-transcriptionally by a series of microRNAs. This was demonstrated through the use of agomiRNAs mimicking miR-145-5p, miR-101-3p, and miR-335-5p^[104]. In particular, the authors reported that treatment with agomiR-145-5p resulted in the strongest inhibition of CFTR mRNA accumulation and CFTR protein production *in vitro*^[104]. CFTR functions as a chloride channel that promotes intracystic fluid secretion and, thus, cyst progression in ADPKD^[105,106]. Moreover, studies have illustrated that the CFTR corrector VX-809 (or called Lumacaftor) can restore proper CFTR localization and holds therapeutic potential for ARPKD^[106]. Collectively, these findings suggest that miRNAs involved in CFTR regulation may represent promising therapeutic targets for PKD.

The development of targeted delivery systems for anti-miRNA therapeutics represents a significant advance in ADPKD treatment^[5], enabling precise, renal tubular cell-specific delivery of microRNA plasmids, enhancing the efficacy of cyst-reducing therapies and supporting personalized management of ADPKD. Current research is exploring innovative approaches, such as dietary plant-derived miRNAs that may regulate PKD1 expression^[107]. Additionally, CRISPR/Cas9 gene-editing tools have been employed to investigate the functional roles of identified ncRNAs both *in vitro* and *in vivo*. By knocking out or modulating the expression of specific ncRNAs, researchers can assess their contributions to cystogenesis and renal function, thereby paving the way for targeted gene therapies^[1]. Examples include the use of highly translatable mRNAs^[108,109] and various other vectors^[110-112]. Nevertheless, additional studies are required to develop novel therapeutic strategies that go beyond conventional pharmacological interventions.

Targeting lncRNAs has also been implicated in recent years. For instance, Eckberg *et al.* demonstrated successful knockdown of *PVT1*, a lncRNA implicated in cystogenesis, using shRNA in metanephric organ cultures^[77]. This knockdown significantly reduced cyst growth, suggesting that therapeutic strategies aimed at inhibiting dysregulated lncRNAs could mitigate the pathological effects of cyst formation^[96]. Despite the promise of ncRNA-targeted therapies, challenges remain, including optimizing kidney-specific delivery, minimizing off-target effects, and ensuring long-term safety. Future research should focus on refining delivery systems and exploring the therapeutic potential of other ncRNAs, such as circRNAs and piRNAs, whose roles in disease pathogenesis and therapeutic potential remain largely uncharacterized, to advance precision medicine for PKD.

CHALLENGES AND FUTURE DIRECTIONS

The evolving understanding of ncRNAs in PKD pathogenesis presents both exciting opportunities and considerable challenges. Current research has identified key roles for ncRNAs (e.g., the miR-17 family) in regulating cystogenesis in PKD through multiple pathways. However, several challenges persist: (1) incomplete characterization of ncRNA interaction networks and their synergistic effects during disease

progression, (2) limited knowledge of other ncRNAs, such as circRNAs, which have potential as stable miRNA sponges despite their emerging importance^[113], and (3) technical hurdles in differentiating pathogenic ncRNA alterations from secondary, non-causal alterations.

Methodological innovations offer promising solutions. Single-cell RNA sequencing and CRISPR screening platforms now enable cell type-specific mapping of ncRNA dysregulation, while emerging multi-omics approaches can uncover novel ncRNA-mRNA-protein networks beyond genetic mutations^[114]. Nevertheless, the field lacks: (1) animal models that accurately replicate human ncRNA biology, (2) standardized protocols for longitudinal ncRNA profiling across different disease stages, and (3) integrated databases correlating ncRNA signatures with clinical outcomes.

Future research should prioritize three key areas: (1) mechanistic studies aimed at identifying master regulator ncRNAs driving PKD pathogenesis, (2) development of minimally invasive ncRNA biomarkers, such as urinary biomarkers, and (3) acceleration of clinical translation for delivery platforms emerging from ongoing gene therapy trials. By integrating fundamental ncRNA biology with advanced therapeutic technologies, this multidisciplinary approach holds significant promise for the development of precision ncRNA-targeted interventions for PKD patients.

CONCLUSIONS

This review highlights the critical roles of ncRNAs in PKD pathogenesis, emphasizing three fundamental insights with important translational implications. First, dysregulated ncRNAs (particularly the miR-17 family, PVT1, and H19) act as master regulators of cystogenesis by directly modulating PKD-related genes (PKD1/2) and key signaling pathways, including mTOR, cAMP, and Wnt/ β -catenin. Second, urinary ncRNA signatures, such as miR-3907, demonstrate clinical utility as stage-specific biomarkers that may outperform conventional measures like TKV for early disease detection and monitoring progression. Third, therapeutic targeting of pathogenic ncRNAs has achieved proof-of-concept success in preclinical models, exemplified by the phase 1b trial of RGLS4326 and CRISPR-based ncRNA modulation strategies. To translate these findings into clinical practice, focused efforts are needed in three priority areas: (1) conducting detailed mechanistic studies to further elucidate master regulator ncRNAs in PKD pathogenesis, (2) developing minimally invasive ncRNA biomarkers, such as urinary biomarkers, and (3) expediting the clinical translation of delivery platforms from ongoing gene therapy trials. These coordinated efforts will be essential to transform ncRNA research into tangible improvements in the diagnosis, prognosis, and treatment of PKD.

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Authors' contributions

Designed the review framework and prepared the initial draft: Hu M, Li Z

Supervised subsequent revisions with substantive contributions from all other authors: Hu M

All authors approved the final version of the manuscript.

Availability of data and materials

This review article synthesizes findings from previously published studies. All data and materials referenced in this manuscript are available in the cited publications. No new datasets were generated or analyzed specifically for this review.

Conflicts of interest

Hu M is a Junior Editorial Board member of *Journal of Translational Genetics and Genomics*. Hu M was not involved in any steps of editorial processing, notably including reviewer selection, manuscript handling, or decision making. The other authors declared that there are no conflicts of interest.

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