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Review

Long non-coding RNAs as novel diagnostic and therapeutic targets in kidney disease

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Abstract

Long non-coding RNAs (lncRNAs) have critical roles in the development of many diseases including kidney disease. An increasing number of studies have shown that lncRNAs are involved in kidney development and that their dysregulation can result in distinct disease processes, including acute kidney injury (AKI), chronic kidney disease (CKD), and renal cell carcinoma (RCC). Understanding the roles of lncRNAs in kidney disease may provide new diagnostic and therapeutic opportunities in the clinic. This review provides an overview of lncRNA characteristics, biological function and discusses specific studies that provide insight into the function and potential application of lncRNAs in kidney disease treatment.

Keywords: Long non-coding RNAs; Kidney disease; Renal inflammation; Renal fibrosis; Diabetic nephritis; Renal cell carcinoma

With the increasing number of annotations revealed by high throughput sequencing in the genome, it has been possible for researchers to understand its make up better. These annotations have shown that less than 2% of the human genome is protein-coding, and the major portion of the genome is "non-coding" region. Since the number of protein-coding genes is limited, non-coding RNAs (ncRNAs) have become the target of a lot of research in human disease. These ncRNAs can be classified, by their matured length, into several categories long ncRNAs (lncRNAs), which are ≥200 nucleotides in length, and short ncRNAs, which are <200 nucleotides long. Short ncRNAs include moieties like microRNAs (miRNAs) which function by base-pairing with complementary sequences within mRNA molecules to silence gene expression, and have been extensively evaluated over the past two decades.[1]

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LncRNAs have distinct functional roles in most organisms, they can regulate gene expression and function diversely, including acting as scaffolds, decoys, guides, enhancers and can act through genomic targeting, regulation *in cis* or *trans*.[2] These lncRNAs are further classified as natural antisense transcripts, overlapping lncRNAs, long intergenic ncRNAs (lincRNA) and intronic ncRNAs based on their relationship with protein-coding genes.[3] Unlike miRNAs, which are well-conserved at a sequence level in humans and mice, lncRNAs do not have the same degree of conservation. However, lncRNAs frequently exhibit evolutionarily conserved function, secondary structure, and regions of microhomology, despite their low overall sequence similarity.[4]

Following the technological improvements and cost reductions of high through-put RNA-sequencing, the number of annotated and functionally analyzed lncRNAs has rapidly expanded, and there are continuously increasing numbers of characterized lncRNAs available from various databases, including NONCODE (http://www.noncode.org/). Initial studies in the cancer field have shown that lncRNAs play prominent roles in various cancers and an increasing number of studies have shown that lncRNAs play important roles in a number of other human diseases in addition to cancer.

Kidneys play several important roles in normal physiology, including maintenance of the stable composition of the blood, secretion of important hormones, and they contribute to mineral and blood pressure homeostasis amongst others. Loss or impaired kidney function is a common outcome of several metabolic disorders, including hypertension and diabetes. Recent evidence suggests that gene regulatory mechanisms involving both coding and non-coding RNA are critical to renal function as well as disease progression. Given that the literature around miRNAs in kidney disease is well summarized, and the role of some classes of ncRNAs (including small interfering RNAs (siRNAs), small nucleolar RNAs (snoRNAs) and piwi interacting RNAs (piRNAs)) in remain largely undescribed, this review has been restricted to lncRNAs and their role in kidney disease.

Seminal studies have shown that lncRNAs are involved in kidney development and their dysregulation can result in distinct pathogenic processes, including acute kidney injury (AKI), chronic kidney disease (CKD), and renal cell carcinoma (RCC). Considering the wide range of described lncRNA functions, evaluation of the roles of lncRNAs in kidney disease could provide new diagnostic and therapeutic opportunities. This review provides an overview of lncRNA biology and discusses specific studies that have provided key insights into the function and potential application of lncRNAs in kidney disease.

LncRNAs in acute kidney injury

AKI usually occurs after acute ischemia, toxicity, sepsis or hypoxia and results in severe damage of the kidney and increases the risk of mortality. Metastasis associated lung adenocarcinoma transcript 1 (MALAT1) was found to be upregulated in kidney biopsies and plasma samples from patients with AKI. Increased MALAT1 expression was also reported in murine hypoxic kidney tissue and cultured hypoxic endothelial and proximal tubular epithelial cells.[5] In cultured human proximal tubular epithelial cells, a number of differentially regulated lncRNAs were identified during the hypoxic and inflammatory responses using RNA-sequencing (RNA-seq). However, only 14 (2% of the total lncRNAs and 7.2% of all differentially expressed lncRNAs) overlapped between these two conditions. MIR210HG, linc-ATP13A4-8, and linc-KIAA1737-2 were the most highly upregulated lncRNAs and were also detected in human proximal tubules isolated from kidney transplant biopsies.[6] Liu et al[7] found that lncRNA taurine upregulated 1 (TUG1) was expressed at low levels in the serum of patients with sepsis-associated AKI when compared to the healthy control. In rat mesangial cells, TUG1 overexpression relieved LPS-induced injury and suppressed the activation of NF-κB signaling, which was markedly reversed following miR-142-3p upregulation. These findings reveal that downregulation of lncRNA TUG1 may promote the development and progression of sepsis-associated AKI via regulation of the miR-142-3p/Sirtuin 1 (SIRT1) axis and modulating NF-κB activation.

LncRNAs in renal inflammation and fibrosis

Renal inflammation and fibrosis are common manifestations lead to end-stage renal disease. Mouse models of unilateral ureteral obstruction (UUO) and anti-glomerular basement membrane glomerulonephritis (anti-GBM GN) are commonly used to study renal inflammation and fibrosis. In our previous study, RNA-seq was used to identify a number of differentially expressed lncRNAs in UUO and anti-GBM GN animal models.[8] Novel Smad3-depedent lncRNAs including np_5318, np_17856 and Arid2-IR (np_28496) were identified in both models in a

Smad3-dependent manner.[8] Our group found that knockdown of Arid2-IR blunted NF-κB-driven renal inflammation without affecting transforming growth factor-β (TGF-β1)/Smad3-mediated renal fibrosis in the obstructed kidney *in vivo*. Down-regulation of Arid2-IR in UUO kidneys by short hairpin RNA (shRNA) significantly reduced the infiltration of macrophages and T cells, cytokine production and activation of NF-κB signaling.[9] Feng et al[10] found that Erbb4-IR was highly upregulated in the fibrotic kidneys of mice in unilateral ureteral obstructive nephropathy. Silencing of Erbb4-IR blocked TGF-β1-induced collagen I and alpha-smooth muscle actin (α-SMA) expression *in vitro* and effectively attenuated renal fibrosis in the UUO kidney by targeting the Smad7 3′ UTR, which is an inhibitor of TGF-β/Smad3 signaling. Wang et al[11] found lnc-TSI, a Smad3-interacting lncRNA regulated by Smad3, specifically inhibited TGF-β-induced Smad3 phosphorylation and downstream profibrotic gene expression. Delivery of human lnc-TSI into the UUO mouse model inhibited phosphorylation of Smad3 in the kidney and attenuated renal fibrosis. Lnc-TSI renal expression negatively correlated with the renal fibrosis index ($r = -0.56$, $P < 0.001$) after adjusting for cofounders in a cohort of 58 patients with biopsy-confirmed IgA nephropathy (IgAN). In repeated biopsy kidney tissues from 32 IgAN patients, researchers showed that low expression of renal lnc-TSI at initial biopsy resulted in significantly greater increases in their renal fibrosis index and stronger declines in renal function at repeat biopsy at a mean of 48 months of follow-up, when compared to those with baseline lnc-TSI expression greater than or equal to the median.[11] These results provide initial support for their application as novel therapeutic targets for renal inflammation and fibrosis.

LncRNAs in diabetic kidney disease

Diabetic kidney disease (DKD) is a major renal complication in diabetes that results in renal dysfunction, and accounts for approximately 50% of end-stage renal disease (ESRD) in the developed world.[12] LncRNAs have garnered increased attention for their putative roles in the pathogenesis of DKD. Using a genome-wide single nucleotide polymorphism association study, variants in lncRNA plasmacytoma variant translocation 1 (PVT1) have been shown to have strong associations with the development of ESRD in type 1 and type 2 diabetes. High glucose induces PVT1, Fibronectin 1, *COL4A1*, TGF-β1, and plasminogen activator inhibitor 1 (PAI-1) expression. In addition, PVT1 knockdown significantly reduces the expression levels of the major ECM proteins. This indicates that PVT1 may mediate the development and progression of diabetic nephropathy through ECM accumulation.[13,14] Yang et al[15] found that Arid2-IR expression increased in high-fat diet and streptozotocin (STZ)-induced type 2 diabetic mice and in mouse mesangial cells cultured with high glucose, mimicking diabetes. Knockdown of Arid2-IR in mouse mesangial cells reduced high glucose induced expression of *COL1A1* and *α-SMA*. Their data suggests that increased Arid2-IR likely contributes to ECM production in DKD. *CYP4B1-PS1-001*, a novel lncRNA identified by Wang's group, significantly decreases in the early stages of pathogenesis in diabetic db/db mice, and its overexpression can inhibit proliferation and fibrosis of mesangial cells. In addition, they found that lncRNA *CYP4B1-PS1-001* regulates proliferation and fibrosis in diabetic nephropathy depending on its interaction with nucleolin. Degradation of *CYP4B1-PS1-001*-associated nucleolin was mediated by the ubiquitin proteasome-dependent pathway.[16,17] LncRNA MALAT1 is overexpressed in multiple tumors, including liver cancer, lung cancer, bladder cancer and colorectal cancer. It was also found to be upregulated in a mouse model of DKD, and MALAT1 siRNA partially restored podocyte function and prohibited β-catenin nuclear accumulation in mouse models of DKD.[18] Yi et al[19] showed that lncRNA Gm4419 could activate the NF-κB pathway by directly interacting with NF-κB-p50 during the progression of diabetic nephropathy (DN). They found that Gm4419 may participate in the inflammation, fibrosis, and proliferation of mesangial cells under high-glucose conditions via the NF-κB/NLRP3 inflammasome signaling pathway.

Some reports also suggest that co-regulation of lncRNAs and miRNAs could mediate some of the renal injuries associated with DKD. Sun et al[20] found that lncRNA Erbb4-IR was highly expressed in db/db mice and specifically induced advanced glycosylation end products (AGEs) via a Smad3-dependent mechanism. Knockdown of Erbb4-IR protects against the development of Type 2 diabetes, by protecting against elevated microalbuminuria, serum creatinine, and progressive renal fibrosis in db/db mice. It also blocked AGE-induced collagen I and IV expression in mouse mesangial cells and mouse tubular epithelial cells (mTECs). Mechanistically, Erbb4-IR was able to bind the 3′ untranslated region of miR-29b genomic sequence to suppress miR-29b expression at a transcriptional level. LncRNA 1700020I14Rik alleviates

cell proliferation and fibrosis in DKD through miR-34a-5p/Sirt1/HIF-1α signaling.[21] LncRNA MALAT1 was found to regulate renal tubular epithelial cell pyroptosis by modulating the miR-23c target gene (ELAVL1) in DN.[22] In a murine model of DN, RNA-seq analysis of kidney glomeruli was used to identify Tug1 as a differentially expressed lncRNA in the diabetic milieu. Duan et al[23] found that LncRNA TUG1 alleviates extracellular matrix accumulation via mediation of microRNA-377 (miR-377) targeting of *PPARγ* in DN. LncRNA TUG1 acts as an endogenous sponge for miR-377 and downregulates miR-377 expression levels, thereby relieving the inhibition of its target gene *PPARγ* and thus reduces the accumulation of ECM proteins in mesangial cells. They also showed that TUG1 bound with the TUG1-binding element (TBE) to enhancing *Ppargc1a* promoter activity. These results provide novel insight into the pathogenesis of DN, and could provide future therapeutic or diagnostic targets.

LncRNAs in polycystic kidney disease

Autosomal dominant polycystic kidney disease (ADPKD) is a debilitating disease characterized by the accumulation of numerous fluid-filled cysts in the kidney. ADPKD is primarily caused by mutations in two genes, *PKD1* and *PKD2*. Aboudehen et al[24] used deep RNA-seq to identify dysregulated lncRNAs in kidney-specific *PKD1* and *PKD2* mutant mouse models of ADPKD. An evolutionarily conserved lncRNA named Hoxb3os was shown to be down-regulated in cystic kidneys of *PKD1* and *PKD2* mutant mice. Consistent with these results, the human orthologous HOXB3-AS1 lncRNA was down-regulated in cystic kidneys from ADPKD patients. Deletion of Hoxb3os by a Clustered Regularly Interspaced Short Palindromic Repeats/CRISPR associated protein (CRISPR/Cas9) system in mIMCD3 cells resulted in increased phosphorylation of mTOR and its downstream targets, including p70 S6 kinase, ribosomal protein S6, and the translation repressor 4E-BP1. These findings confirmed that Hoxb3os is a novel lncRNA that acts as a negative regulator for ADPKD through the regulation of mTOR signaling and mitochondrial respiration.

LncRNAs in renal cell carcinoma

Renal cell carcinoma is one of the leading causes of cancer-related deaths, making up about 3% of all adult malignancies and ranking in the top ten cancers worldwide. However, the potential roles of lncRNAs in metastatic RCC are still unclear. Recently, a series of studies exploring lncRNAs have identified these novel RNA moieties as gene regulators and prognostic markers in several cancers, including RCC.

Xiao et al[25] identified a kidney specific lncRNA FILNC1 (FoxO-induced long non-coding RNA 1) which is downregulated in renal cancer cells. FILNC1 deficiency leads to enhanced glucose uptake and lactate production through upregulation of c-Myc and promotes renal tumor development. FILNC1 is downregulated in renal cell carcinoma and its low expression correlates with poor clinical outcome in renal cell carcinoma patients. Li et al[26] identified a novel lncRNA named metastatic renal cell carcinoma-associated transcript 1 (MRCCAT1) using microarray analysis. MRCCAT1 is highly expressed in metastatic clear cell RCC (ccRCC) tissues and its expression is associated with metastatic properties of ccRCC. Multivariate Cox regression analysis revealed that MRCCAT1 is an independent prognostic factor for ccRCC patients. MRCCAT1 promotes ccRCC cell proliferation, migration, and invasion through the repression of NPR3 and subsequent activation of the p38-MAPK signaling pathway. Quinn et al[4] identified a lncRNA, named lncARSR (lncRNA activated in RCC with sunitinib resistance), which correlates with clinically poor sunitinib response. lncARSR promoted sunitinib resistance via competitive binding of miR-34/miR-449 to facilitate *AXL* and *c-MET* expression in RCC cells. Treatment of sunitinib-resistant RCC with locked nucleic acids targeting lncARSR or an *AXL/c-MET* inhibitor restored sunitinib response. Therefore, lncARSR may serve as a predictor and potential therapeutic target for sunitinib resistant RCC. LncRNA MALAT1 is deregulated in many cancers. Hirata et al[27] found that MALAT1 expression was higher in human RCC tissues, where it was associated with reduced patient survival. They further explored the effect of RNA silencing of MALAT1 and reported decreased RCC cell proliferation and invasion as well as increased apoptosis. Mechanistic investigations showed that MALAT1 was transcriptionally activated by c-Fos and that it interacted with EZH2 and miR-205. This finding indicated overexpression of MALAT1 confers an oncogenic function in RCC that may offer a novel theranostic marker in this disease.

LncRNAs as biomarkers and therapeutic targets

LncRNAs are expressed in a cell type-, tissue-, developmental stage or disease state-specific pattern,

making them good candidates for disease specific biomarkers. In cancer, lncRNAs are usually differentially expressed in various body fluids depending on cancer type. Some circulating lncRNAs have already been shown to be promising and sensitive biomarkers. Dysregulated expression of lncRNAs is strongly linked to the development of various tumors and can be relatively effectively detected in patient's body fluids in a variety of cancers.[28]

Seminal studies have highlighted potential importance of ncRNAs as new therapeutic targets, diagnostic or prognostic biomarkers in several diseases including application in the prevention and treatment of kidney diseases. A large clinical trial is using siRNA (QPI-1002) that targets p53 mRNA, localized to the kidney, and is designed to transiently limit p53-induced apoptosis and thereby mitigate programmed cell death and kidney injury after transplantation.[29] Unlike kidney biopsies, urine is easily accessible and thus identification of biomarkers in this bodily fluid would greatly facilitate the use of biomarkers in kidney disease. Khurana et al[30] performed an RNA-sequencing study on urinary exosomes isolated from healthy controls and CKD patients at different stages of CKD (I, II, III, or IV). Their results showed that miRNA-181a appeared as the most robust and stable potential biomarker for CKD, as it is significantly decreased, about 200-fold, in exosomes from patients when compared to healthy controls. In addition to the miRNAs, eight antisense RNAs (EAF1-AS1, PCBP1-AS1, RP11-315I20.1, RP11-378E13.4, RP11-68I3.2, RP11-700F16.3, RP11-98D18.1, and RP11−1382.1) were found to be differentially expressed in CKD patient exosomes when compared to healthy controls. This study identified that differentially expressed urinary exosome ncRNAs may be suitable biomarkers in CKD.[30]

Conclusions and perspectives

The application of next generation sequencing has revealed an extensive landscape of noncoding RNAs. It is becoming evident that lncRNAs are critical regulators and participate in variety diseases using several distinct mechanisms involving all the components of the cellular machinery. Overexpression or deficiency of lncRNA genes has been implicated in kidney diseases including AKI, CKD, DKD, evidence suggests that lncRNAs can not only function as biomarkers, but also as pathogenic mediators of kidney diseases. Thus, the identification and characterization of lncRNAs associated with kidney disease may represent a promising research strategy in the resolution of renal disorder pathogenesis and could result in the development of precision therapies for kidney disease.

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Conflict of interest

None.

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