Non-Coding RNAs in Kidney Diseases

Subjects: Urology & Nephrology
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Acute kidney injury (AKI) is characterized by an acute loss of renal function that reduces urinary excretion of toxic substances. The accumulation of these waste products in blood can be lethal depending on the duration and severity of AKI, triggering the use of dialysis to ensure patient survival. The pathophysiology of AKI is complex, including a number of processes that promote direct tubular cell death, obstruction and activation of renal vessels and tubular lumen, exacerbated inflammatory response and oxidative stress.

Keywords: non-coding RNA ; microRNA ; long non-coding RNA ; chronic kidney disease ; acute kidney disease ; IgA nephropathy ; gene regulation

1. Introduction

From that time onwards, many RNA species have been described. ncRNAs are numerous and highly adapted in their roles in modern organisms, as RNA molecules are well designed to specifically recognize other RNAs and DNA by complementary base pairing. They function as post-transcriptional regulatory molecules, interacting with specific mRNAs and determining protein expression. In the non-coding transcriptome, secondary and tertiary structures are crucial for their interaction with proteins or other nucleic acids.

In the last two decades, the small microRNAs (miRNAs) have arisen as important regulators of most pathophysiological mechanisms [1][2][3]. miRNAs are around 20–25 nucleotides long, single stranded RNAs. During miRNA biogenesis the double stranded miRNA-3p/miRNA-5p duplex is unwound to single strands by the RNA-induced silencing complex (RISC) that presents the mature miRNA to its target mRNAs, triggering gene silencing in a post-transcriptional manner. The analysis of miRNAs in biofluids, including serum and plasma, has been proposed as a minimally invasive diagnostic approach to detect changes of the physiological status of patients.

Alongside the short miRNAs, a long list of bigger transcripts called long non-coding RNAs Physiologically, lncRNAs have been shown to modulate gene regulation at all levels (including but not limited to promoter activity, epigenetics, translation and transcription efficiency, intracellular trafficking) As in the case with other tissues, the kidney expresses tens of thousands of lncRNAs sequences that are often conserved with coding genes. lncRNAs are divided into four categories: long intervening/intergenic non-coding RNAs, intronic lncRNAs, sense lncRNAs (including pseudogenes) and antisense lncRNAs [4].

As lncRNAs are implicated in all levels of the gene regulation process, we can find them deregulated in a variety of pathophysiological processes, particularly in diseases involving genomic imprinting and cancer [5].

Over recent years, lncRNAs have been increasingly recognized as being implicated in the pathophysiology of various kidney diseases. The aim of the present review is to examine the current literature regarding this field, the molecular mechanisms involved, and the value of lncRNAs as emerging prognostic biomarkers in renal diseases. Finally, we will also outline new therapeutic approaches targeting lncRNA to decrease renal damage.

2. Role of lncRNAs in Renal Diseases

Acute kidney injury (AKI) is characterized by an acute loss of renal function that reduces urinary excretion of toxic substances. The pathophysiology of AKI is complex, including a number of processes that promote direct tubular cell death, obstruction and activation of renal vessels and tubular lumen, exacerbated inflammatory response and oxidative stress. LncRNAs regulate numerous genes and mechanisms involved in the pathophysiology of AKI, serving both as biomarkers and therapeutical targets against renal damage. In the next section of the review, we will update recent findings about the role of lncRNAs in different AKI subtypes, including sepsis, ischemia reperfusion, drug-induced and obstructive subtypes (Table 1).

In recent years, several studies have demonstrated the key role of lncRNAs in septic-induced AKI (SI-AKI). In this study, the lncRNA TCONS_00021712 was the most upregulated and TCONS_00016406 In line with these data, reduced renal lncRNA 6406 expression was observed in an experimental model of SI-AKI induced by administration of lipopolysaccharide (LPS) [6]. LncRNA 6406 decreased LPS-mediated inflammation, oxidative stress and cell death via regulation of miR-687/PTEN axis [6].

The expression of MALAT1 was increased in experimental LPS-induced AKI and LPS-treated renal cells, increasing renal injury and NF-κB activation throughout downregulation of miR-146a [7]. Another lncRNA upregulated in septic patients with AKI Furthermore, NEAT1 downregulation promoted M2-macrophage polarization via miR-125a-5p/TRAF6/TAK1 axis and ameliorated LPS-harmful effects in RAW264.7 cells [8]. NEAT1 silencing reduced kidney injury, ameliorated renal function, inflammation (TNF-α, IL-1β, IL-6), lipid peroxidation and cell death via miR-27a-3p/TAB3 axis in a cecal ligation puncture

Overexpression of TUG1 was protective in HK-2 cells treated with LPS by inhibiting miR-223 expression and modulating NF-kB In this study, overexpression of HOXA-AS2 played a protective role in this syndrome via miR-106b-5p and inhibiting the Wnt/β-catenin and NF-κB pathways. The lncRNA, CASC2 plasma levels were reduced and negatively correlated with AKI severity in septic patients [9]. In vitro experiments in HK-2 cells reported the protective role of CASC2 against LPS-mediated apoptosis, oxidative stress and inflammation by suppressing the miR-155 and NF-κB

TapSAKI induced cell death and inflammatory response via miR-22/PTEN/TLR4/NF-κB In another study, overexpression of lncRNA PVT1 in HK-2 treated with LPS and PVT1 downregulation increased the cell growth and reduced inflammation by inhibiting JNK/NF-κB and TNFα signaling pathways [10]. HOTAIR inhibited miR-22 and promoted cell death and HMGB1 expression, whereas its suppression ameliorated renal function. In contrast with this data, a later study in SI-AKI induced by cecal ligation puncture demonstrated that HOTAIR overexpression reduced renal damage, inflammation and cell death in the kidney by downregulating the miR-34a/Bcl-2 signaling pathway [11].

DANCR promoted cell viability and inhibited cell death by sequestering miR-214 and regulating Krüppel-like factor 6 expression. LncRNA CRNDE was also downregulated in an experimental model of urine-derived SI-AKI and in HK-2 and HEK293 cells treated with LPS [12]. CRNDE deficiency decreased renal function and increased cell death by inhibiting miR-181a-5p/PPARα pathway, while CRNDE overexpression proved beneficial against LPS-mediated effects. Similarly, another study demonstrated that CRNDE overexpression activated TLR4/NF-κB pathway

The lncRNA (sepsis-induced kidney injury associated transcript 1) plays a key role in SI-AKI by increasing cell death in HK-2 cells treated with LPS via miR-96/FOXA1 axis [13]. MIAT was upregulated in kidneys from LPS-injected rats and in NRK-52E cells treated with LPS, while miR-29a was decreased, suggesting an interaction between MIAT and miR-29a [14]. Moreover, in the lncRNA Whey acidic protein/Four-Disulfide Core domain 21 (Wfdc21), renal expression was increased in a cecal ligation and puncture SI-AKI model in mice and in LPS-stimulated RAW264.7 cells [15].

In HK-2 cells treated with LPS, LINC00261 overexpression inhibited cell death and inflammation via the miR-654-5p/SOCS3/NF-κB pathway. A recent study described the lncRNA DLX6 antisense RNA 1 (DLX6-AS1) to be increased in serum of septic AKI patients and in HK-2 cells treated with LPS [16]. As in the case of SNHG5, the lncRNA small nucleolus RNA host gene 14 (SNHG14) was increased in LPS-treated HK-2 cells due to the activation of the TLR4/NF-κB pathway. This study demonstrated that SNHG14 plays a key role in cellular injury due to LPS by increasing oxidative stress, inflammation and cell death through activation of IRAK4/NF-κB and IL-6R/STAT3 signaling via miR-93 [17].

One of the most common processes inducing AKI is ischemia reperfusion (I/R). I/R injury is caused by the blockade of blood flow, leading to hypoxia and accumulation of metabolic products in the kidney, followed by a period of reperfusion that enhances renal injury by activating an inflammatory response [18][5][19].

In this study, the lncRNA NONHSAT183385.1 was increased in human tubular epithelial cells after hypoxia and reoxygenation, suggesting a key role in this pathological setting. Microarray data were further confirmed by gene expression analysis, showing upregulation of several lncRNAs ENSMUST00000139773, and AK078749. Gene ontology analysis showed that these lncRNAs participated in multiple biological processes in I/R, including glycine, serine, threonine metabolism and inflammatory pathways.

The lncRNA X-inactive specific transcript (Xist) has been shown to increase in I/R damaged kidneys and in renal cells after hypoxia/reoxygenation treatment, inducing apoptosis and inflammation through the modulation of miR-124-3p and its target gene Overexpression of the lncRNA H19 in an experimental I/R model, improved renal function and angiogenesis, and diminished inflammation and apoptosis throughout regulation of miR-30a-5p [20]. However, gene deletion of MALAT1 in mice did not improve renal function, tubular injury, inflammation or fibrosis [21]. In another study, downregulation of MALAT1 in cultured hypoxic cells significantly increased expression of HIF-1α, IL-6, TNF-α and NF-κB

In cultured tubular cells, upregulation of the lncRNA EGOT diminished hypoxia/reoxygenation mediated autophagy via interaction with the RNA-binding protein Hu antigen R (HuR) and further regulation of the ATG7/16L1 expressions [22]. LINC00520 was upregulated in I/R injured rats and in hypoxic tubular epithelial cells, being associated with a reduction of miR-27b and increased levels of the Oncostatin M receptor (OSMR) [23]. The gene blockade of LINC00520 reduced renal damage through the attenuation of OSMR levels and PI3K/AKT signaling pathway [23]. The LncRNA MEG3 was also found to be elevated in human tubuloepithelial cells, aggravating hypoxia/reoxygenation induced apoptosis throughout regulation of the miR-129-5p/HMGB1 axis [24].

Effects of LncRNAs in experimental AKI.

One of the most remarkable nephrotoxic agents is cisplatin, which induces inflammation, cell death and tubular cell injury [25][26]. Zhou et al. explored the role of lncRNA XLOC-032768 in cisplatin-induced AKI in vivo and in vitro. Their results show that overexpression of this lncRNA decreased apoptosis and TNF-mediated inflammation in mice and cells exposed to cisplatin [27]. LRNA9884 was also increased in the nucleus of renal epithelial tubular cells in a cisplatin-induced AKI model [28].

Obstructive nephropathy is a recurrent cause of AKI [29]. If not treated in time, AKI associated to obstructive nephropathy can eventually lead to chronic kidney disease (CKD). The best experimental approach to study the AKI–CKD transition is the murine model of unilateral ureteral obstruction (UUO) [30]. The UUO model is characterized by a reduced GFR and blood flow, oxidative stress, renal cell death and tubulointerstitial fibrosis.

Sun et al. examined the differential expression of lncRNAs in kidneys from UUO mice. and TCONS_01496394, which are involved in the modulation of the profibrotic TGF-β/Smad pathway. Additional urine analysis reported upregulation of 625 lncRNAs and downregulation of 177 lncRNAs, some of which (NONRATT044682, 361619 and 689064) could be possible biomarkers of renal fibrosis. Moreover, lcRNA 74.1 overexpression reduced fibrosis by activating autophagy and the Nrf2-keap1 pathway in cultured HK-2 cells and the UUO model [31][32].

TGF-β upregulated lncRNAs MIAT and H19 in renal cells, suggesting an important role of these lncRNA in renal interstitial fibrosis [33][34][35]. Supporting this hypothesis, deletion of H19 reduced production of α-SMA and collagen IV in UUO mice and HK-2 cells [35].

lncRNA HOTAIR expression was upregulated in UUO, inhibiting miR-124 expression in UUO mice [36]. Since miR-124 blocked the Notch1 signaling pathway and prevented fibrosis and epithelial to mesenchymal transition, HOTAIR suppression promoted the development of fibrosis and chronic renal failure [37]. Finally, deficiency of the lncRNAGas5 aggravated renal fibrosis in the UUO mice [38].

They observed that the link between these two miRNAs serum levels, the mortality, the CV diseases and the renal events appears to depend on the eGFR in CKD. Furthermore, this study investigated whether urinary extracellular RNAs (exRNAs) are derived from kidney related cells. For this matter, they employed a cell culture system reflecting CKD by exposing renal proximal tubular epithelial cells (RPTECs) to oncostatin M (OSM) Finally, this study identified a significant number of potential diagnostic biomarkers that might be employed in CKD in future research.

Another study published in 2019 found that lncRNAs NOP14-AS1 and HCP5 were potential prognostic biomarkers in CKD [39]. They first compared the expression profiles of several lncRNAs in healthy individuals and CKD patients with normal controls. They screened 821 significantly differentially expressed mRNAs and lncRNAs using Limma (www.bioconductor.org/packages/release/bioc/html/limma.html (accessed on 22 January 2021) between CKD and control samples. In summary, this study suggested that several lncRNAs (i.e., NOP14-AS1 and HCP5) were potential prognostic biomarkers for CKD progression.

Furthermore, Chun-Fu Lai et al. reported that elevated plasma level of lncRNA DKFZP434I0714 was a reliable biomarker in uremic patients to predict adverse CV outcomes [40]. The authors validated that elevated plasma level of lncRNA DKFZP434I0714 predicts adverse CV outcomes and death in patients with end stage renal disease (ESRD). Further analyses revealed that lncRNA DKFZP434I0714 was increased in human aortic endothelial cells (HAEC) stressed with hypoxia and is involved in endothelial dysfunction and inflammation. VCAM-1 (vascular cells adhesion molecule 1), increased the expression of eNOS (endothelial nitric oxide synthase) and reduced hypoxia-mediated endothelial cell apoptosis and monocyte adhesion.

Taken together, these data collectively suggest a potential role of lncRNA DKFZP434I0714 as a new class of prognostic biomarker of adverse CV outcomes in ESRD patients, showing its involvement in the pathogenesis of endothelial dysfunction, vascular inflammation and atherosclerosis. Indeed, the present study revealed that lncRNA DKFZP434I0714 is involved in the pathogenesis of endothelial dysfunction, vascular inflammation and atherosclerosis.

Santer et al. studied whether the presence of CKD modified the association of plasma LIPCAR (long intergenic non-coding RNA predicting cardiac remodeling) with left ventricular (LV) remodeling and CV outcomes in patients with heart failure (HF) [41]. In this study, plasma LIPCAR levels were independently associated with higher risk of hospitalization in elderly HF patients without CKD. Plasma LIPCAR could be a predictor of HF outcomes in elderly patients without CKD. Table 2 summarizes some of the ncRN prognostic biomarkers for CKD.

Arbiol-Roca et al. were the first to study the association of antisense RNA in the INK4 locus (ANRIL) polymorphisms with Major Adverse CV Events (MACE) in CKD patients in Hemodialysis (HD) [42]. HD is a therapeutic procedure to remove fluid and waste products from the patient's blood used in the management of acute and chronic renal disease. Using a multivariate model, ANRIL polymorphism rs10757278 was the only one that showed a statistically significant relationship with MACE and diabetes mellitus. Those findings of ANRIL polymorphisms may contribute in the future to the management of MACE in the HD population.

A recent study in human aortic smooth muscle cells (HA-VSMCs) by Bao et al. found that osteogenic differentiation induced by high phosphorus may be regulated by eight lncRNAs (NONHSAT058810.2, NONHSAT197162.1, NONHSAT 033640.2, NONHSAT036152.2, NONHSAT179247.1, NONHSAT162315.1, NONHSAT061050.2 and NONHSAT006046.2) [43]. All these lncRNAs may regulate the expression of transcription factors (TFs), such as STAT1, KAT2A, GATA2, TAF7 and REST. Altogether, this working list of lncRNAs may be associated with osteogenic differentiation induced by high phosphorus.

They used the UUO mouse model of kidney fibrosis in which they performed translating ribosome affinity purification (TRAP). The study identified a total of 439 lncRNAs expressed in PT, of which, 143 underwent differential regulation during fibrosis. RNA in situ hybridization (ISH) of Snhg18 (high expression) and Gm20513 (low expression), two representative lncRNAs, confirmed the fibrotic-induced expression patterns. Finally, they implemented a data-driven approach to identify key transcription factors that lead to disease progression in kidney fibrosis.

LncRNAs have also been associated with renal fibrosis via TGF-β, a master regulator of fibrosis that promotes renal fibrosis, via lncRNAs implicated in TGF-β1 isoform [44]. Although TGF-β1 has a dominant role to promote renal fibrosis, its effector Smad proteins (Smad2, Smad3 and Smad4) exert distinct and even opposing functions in the regulation of fibrosis. They found that Ptprd-IR knockdown attenuated NF-κB activation and its inflammatory targets in cultured tubular epithelial cells and UUO mice. These findings open novel therapies against inflammation and fibrosis in CKD by targeting lncRNAs, although data are currently limited.

In the publication of Long et al., LncRNA taurine-upregulated 1 (Tug1) has been reported to play a role in diabetic nephropathy (DN) [45][46]. They found that glomerular Tug1 levels were decreased in diabetic mice as well as in renal biopsies from diabetic patients. The authors demonstrated that Tug1 regulates mitochondrial function in podocytes via PGC-1α (Peroxisome proliferator activated receptor-γ Coactivator-1 α). Moreover, transgenic mice that overexpressed Tug1 specifically in podocytes were protected from diabetes-induced CKD, suggesting that this lncRNA may be a possible therapeutic target to treat kidney disease and/or diabetes.

RNA deep-sequencing techniques in glomeruli from streptozotocin-induced diabetes identified a cluster of nearly 40 miRNAs regulated by the lncRNA lnc-Megacluster (lnc-MGC) [47]. This lncRNA was under the control of CHOP (endoplasmic reticulum stress-related transcription factor). Inhibition of lnc-MGC decreased the expression of key cluster kidney miRNAs, triggering early diabetic nephropathy (DN).

Xist has already shown to be active in several roles, including X-chromosome silencing and tumoral progression. Xist was overexpressed in experimental DN and renal biopsies from DN patients. Moreover, Xist downregulation triggered miR-93-5p overexpression, which in turn diminished Cyclin Dependent Kinase Inhibitor 1A (CDKN1A) expression, alleviating renal interstitial fibrosis in DN. The authors showed that either silencing of SORBS2 or knockdown of KCNQ1OT1 diminished NF-κB-mediated proliferation, fibrosis and apoptosis in renal cells exposed to high glucose concentrations.

Yang et al. studied the lncRNA profiles of patients with diabetes mellitus and DN [48]. In this article, 245 lncRNAs were upregulated and 680 downregulated in the serum of diabetic patients as compared with healthy individuals, while 45 and 813 lncRNAs were up- and downregulated, respectively, in the serum of DN patients compared with diabetic patients [48] ARAP1-AS2 and ARAP1 may serve as new biomarkers for diabetes and DN. ARAP1-AS2, in the pathogenesis of diabetes in cytoskeleton rearrangement under high glucose conditions and epithelial–mesenchymal transition indicating an important role in diabetic renal fibrosis [49].

Increased expression of the pro-apoptotic lncRNA-p21 was found in monocytes and urinary cells from patients with lupus nephritis (LN), correlating with the activity of disease (33,396,699). The lncRNAs RP11-2B6.2 and CircHLA-C were increased in renal biopsies from patients with LN [50][51]. LncRNA found in dendritic cells (lnc-DC) was also found to be elevated in patients with LN, mainly in those with active LN [52]. As well, circRNA_002453 plasma level was found to be elevated in patients with LN, being positively correlated with proteinuria and kidney disease activity [53].

Patients with focal segmental glomerulosclerosis (FSGS) showed higher expression of LncRNA LOC105375913 Further experiments in tubular cells and experimental mice demonstrated that LOC105375913 inhibited miR-27b, thus promoting overexpression of Snail and tubulointerstitial fibrosis. In other study, it was demonstrated that LncRNA LOC105374325 caused podocyte injury in individuals with FSGS [54]. The authors showed that LOC105374325 reduced miR-34c and miR-196a/b levels, resulting in an increased expression of the pro-apoptotic proteins Bax and Bak.

More recently, a microarray analysis in monocytes from IgA nephropathy patients and healthy individuals identified more than 250 differentially expressed lncRNAs and Similar results were found in other studies applying a system biology approach, where 217 lncRNA differentially expressed in PBMCs were suggested as potential factors involved in IgA nephropathy pathophysiology [55]. In this article, HOTAIR was the topmost lncRNA in regulating differentially expressed genes/miRNAs in IgA nephropathy. A recent study determined serum levels of exosomal lncRNA in patients with IgAN and found that the lncRNA-G21551 was down-regulated and may be a potential surrogate biomarker of the disease [56].

The role of lncRNA has also been explored in membranous nephropathy (MN), where increased levels of the lncRNA Xist were found in urinary samples of MN patients and kidneys from mice with MN [57]. In cultured podocytes, down-regulation of lncRNA Xist inhibited angiotensin II-mediated apoptosis by suppressing the miR-217-TLR4 pathway [58].

Xist expression has been shown to be decreased in renal cell carcinoma [59]. The lncRNA ANRIL is overexpressed in several cancers, including malignant breast cells, and In general, ANRIL overexpression in tumour cells favours proliferation and cell survival, while its inhibition decreases tumour mass and increases apoptosis. In renal cell carcinoma, MALAT1 is highly expressed and interacts with miR-203 and BIRC5 to increase cell proliferation [60].

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