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Long noncoding RNAs in renal diseases

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Abstract

Long noncoding RNAs (lncRNAs) play critical roles in eukaryotic gene regulation and diseases, rather than being merely transcriptional "noise". Over the past decade, the study of lncRNAs has emerged as a burgeoning field of research and expanded our knowledge of their functions and underlining mechanisms in both normal and malignant cells. However, lncRNAs are still one of the least understood groups of transcripts. Here, we review the classifications and functions of lncRNAs and their roles in renal diseases. This review will provide insights into the roles of lncRNAs in pathogenesis, diagnosis and therapeutics of renal diseases and indications of lncRNAs as potential targets for the treatment of kidney diseases.

Keywords: lncRNAs, Renal diseases

Introduction

Eukaryotic genomes transcribe a broad spectrum of RNA molecules, with extensive diversity in their abundance, size and protein-coding capacities. Remarkably, only less than 2% of the human genome is transcribed into protein-coding RNA [1]. The rest of human genome is also mostly transcribed, but into a huge array of RNAs without the capability of coding proteins, hence the name "noncoding RNAs". They were initially considered as transcriptional noises or the dark matter of biology [2]. Till many years after, an increasing number of noncoding RNAs, especially miRNAs (microRNAs), piRNAs (Piwi-associated RNAs) and lncRNAs, were found to have crucial functions in gene regulation and are heavily involved in multiple physiological and pathological processes [1].

Unlike well-studied microRNAs, little is known about functions and underlining mechanisms of lncRNAs. In this important emerging field, researches over the past decade have shown that lncRNAs interfere with tissue homeostasis and play a role in renal pathological processes. However, to date, the study of lncRNAs in renal diseases is still in its infancy. In this review, we summarize available studies indicating that lncRNAs are heavily involved in kidney development and disease, and propose lncRNAs as novel biomarkers for clinical diagnosis and potential therapeutic targets in renal diseases.

Identification of lncRNAs

LncRNAs, defined as noncoding RNA molecules longer than 200 nucleotides, were described with an emphasis initially in 2002 by Okazaki et al. in a large-scale sequencing study of full-length cDNA libraries in mice [3]. However, it is very difficult to distinguish lncRNAs from protein-coding transcripts. Although protein-coding transcripts are commonly characterized by the presence of an open reading frame (ORF) with more than 100 amino acids, some lncRNAs may also be predicted to contain such a long ORF [4]. Besides, some transcripts can be transformed between coding and non-coding isoforms. For example, SRA (steroid receptor RNA activator), a well-characterized lncRNA, can also encode a protein that functions antagonistically to its alternative roles as lncRNA [5]. On the other hand, p53 mRNA, the messenger RNA (mRNA) coding for a tumor suppressor, can also bind the Mdm2 (Mouse double minute 2 homolog) protein and function as a regulator directly at the RNA level [6]. To date, systematic methods for lncRNA identification have not been fully established, while a few commonly recognized criteria exists, such as sequence structure, size, presence of ORFs and codon substitution frequency.

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Classifications of lncRNAs

As a broad concept, lncRNAs encompass a few types of RNA transcripts. According to their location in the genome, lncRNAs can be classified into seven broad categories as following: (a) sense lncRNAs, (b) antisense lncRNAs, (c) bidirectional lncRNAs, (d) intronic lncRNAs, (e) intergenic lncRNAs and (f) enhancer lncRNAs (illustrated in Fig. 1). When it comes to concrete functions, lncRNAs can be divided into four groups, namely, (a) signal lncRNAs, (b) decoy lncRNAs, (c) guide lncRNAs and (d) scaffold lncRNAs (described in Fig. 2). LncRNAs can be found within the nuclear or cytoplasmic fractions. Cytoplasmic lncRNAs can work as microRNA sponges or miRNA precursors to either reduce or increase the expression and function of microRNAs [4]. They can also recognize target mRNAs to interact with the cellular translational machinery [4]. Nuclear lncRNAs exert its effects on chromatin architecture either in a *cis*-acting way (lncRNAs regulate the expression of neighboring genes) or in a *trans*-acting way (lncRNAs regulate the expression of distant genes). Besides, for some nuclear lncRNAs, it is not clear whether they function in *cis* or *trans* [7].

Functions of lncRNAs

LncRNAs can regulate gene expression to affect many important physiological processes in multiple roles, to name only a few, as chromatin modifiers, X chromosome inactivator, enhancers, transcriptional regulators and post-transcriptional regulators.

Chromatin modifiers

LncRNAs have been demonstrated to participate in chromatin modification in a critical way, which subsequently affects multiple important biological processes including neurogenesis and stem cell pluripotency [8]. LncRNAs regulate the state of chromatin by recruiting chromatin remodeling proteins to specific genomic loci. For instance, Hox genes are a class of homeotic genes related to the temporal and spatial developmental axes where hundreds of lncRNAs have been shown to be critical [9]. One of these lncRNAs, HOTAIR (Hox

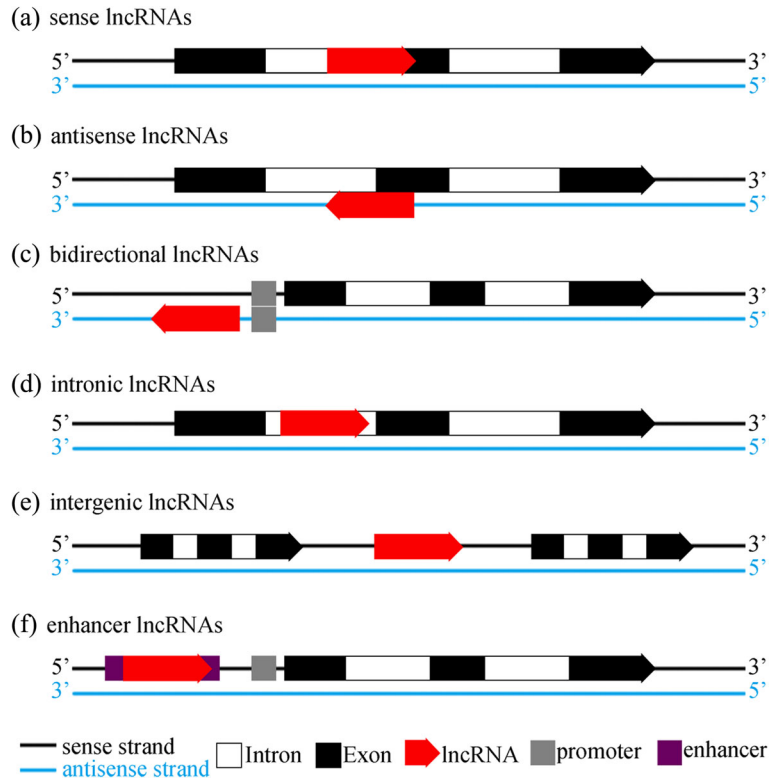

Fig. 1 Illustration of the classifications of lncRNAs. **a** Sense lncRNAs are transcribed from the same strand of protein-coding genes, overlapping exons from the protein-coding genes. **b** Antisense lncRNAs are transcribed from the opposite strand of protein-coding genes, overlapping exons of protein-coding genes on the antisense strand. **c** Bidirectional lncRNAs are located on the opposite stand of protein-coding genes and transcribed from close proximity (less than 1000 base pairs) of their neighboring genes. **d** Intronic lncRNAs are derived entirely from introns of protein-coding genes. **e** Intergenic lncRNAs lie within intergenic regions. **f** Enhancer lncRNAs originate from the enhancer regions of protein-coding genes

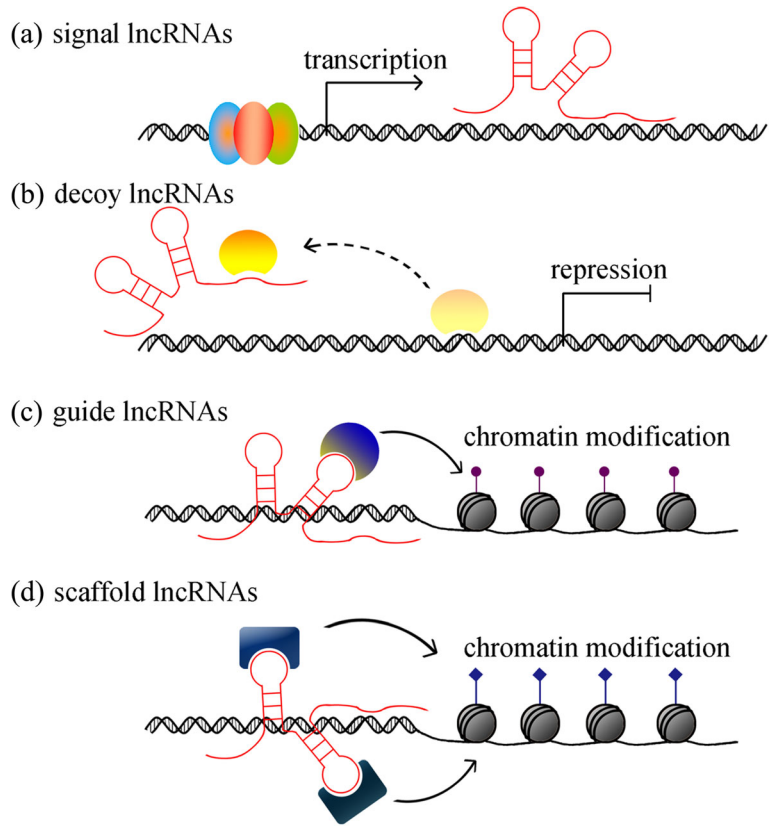

Fig. 2 Schematic diagram of the modes of action of lncRNAs. **a** Signal lncRNAs are transcribed with spatiotemporal precision and expressed in response to developmental cues, concerting the combinatorial actions of transcription factors (shown as colored ovals) to regulate gene expressions. **b** Decoy lncRNAs act as competing endogenous RNA molecules that titrate away transcription factors or other proteins from the chromatin to exert functions like repressing the transcription of target mRNAs. **c** Guide lncRNAs recruit ribonucleoprotein complexes to target genes for chromatin modification. **d** Scaffold lncRNAs bring multiple enzymes together to form a chromatin-modifying complex that either suppresses or initiates transcription

transcript antisense RNA) originates from HoxC locus and silences HoxD genes spanning over 40 kb by recruiting PRC2 (Polycomb repressive complex-2) in a *trans*-acting way, finally leading to a repressive chromatin state [9]. To be noted, PRC2 is a histone methyltransferase required for epigenetic silencing and thereby an important chromatin modifying factor. Besides HOTAIR, thousands of RNAs can bind PRC2 in vivo, although this raises questions about binding specificity and function in different chromatin contexts [10]. Nevertheless, it has been a prototype for lncRNAs interacting with PRC2 to alter the chromatin state [11]. Other well-studied lncRNAs known to bind PRC2 include Xist (X-inactive specific transcript) [12], Kcnq1ot1 (KCNQ1 overlapping transcript 1) [13], Braveheart [14], ANRASSF1 [15], etc. For example, Kcnq1ot1 is a lncRNA acting as an important mediator for imprinting. The promoter of Kcnq1ot1 maps to the ICRs (imprinting control regions) of Kcnq1 gene, which encodes a protein for a voltage-gated potassium channel responsible for the repolarization of the cardiac action potential. Kcnq1ot1 interacts with Dnmt1 (DNA (cytosine-5)--methyltransferase 1) to establish the placental-specific imprinting of genes within the Kcnq1 domain [16]. Besides, Kcnq1ot1 induces the methylation of histone H3 on lysine 9 and lysine 27 by recruiting the histone methyltransferases G9a and PRC2 [13]. Xist is required for the X-inactivation process during early development in female mammals, as only one X chromosome will remain active. The other X chromosomes expressing Xist will be coated with it and packaged into a transcriptionally-inactive heterochromatic structure [12]. In this process, Xist will recruit a series of proteins including PRC2, SPEN, SAF-A (Scaffold Attachment Factor-A) and LBR to initiate the X chromosome inactivation in *cis* [17], while leaving the other X chromosome lacking Xist active [12]. Another lncRNAs, Firre is also involved in the X-inactivation process by anchoring the inactive X

chromosome to the position adjacent to the nucleolus [17]. To sum up, nuclear lncRNAs exerts its effect on chromatin state mostly through interaction with chromatin modifying proteins.

Enhancers

A subset of lncRNAs are transcribed from active enhancers and promote the expression of corresponding protein-coding genes in return, hence the name enhancer lncRNAs. In 2010, Kim et al. coined the concept of enhancer RNAs based on the phenomena that RNA polymerase II located to approximately 3000 activated enhancers and that RNAs could be produced from the extragenic enhancer regions of protein-coding genes [18]. Almost at the same time, Shiekhattar lab reported lncRNAs with enhancer-like functions. They characterized several *cis*-acting lncRNAs using GENCODE annotation of the human genome and discovered an RNA-dependent potentiation of gene expression mediated by the ncRNA-a1–7 in particular [19]. Besides, the Evf2 noncoding RNA, which originates from the Dlx-5/6 ultraconserved region, can interact with Dlx-2 to induce transcriptional enhancement of Dlx-2 in a target and homeodomain-specific way [20]. The HSR1 (heat shock RNA-1), which is constitutively expressed in human and rodent cells, works along with eEF1A and actively mediates the activation process of the HSF1 (heat-shock transcription factor 1) [21]. Steroid receptor RNA activator (SRA) also acts as a noncoding transcript to coactivate steroid receptor [5]. Rosenfeld et al. also reported that PRNCR1 and PCGEM1 bind to the AR (androgen receptor) and potently enhance the AR-mediated gene activation programs in prostate cancer cells [22]. However, so far, the functional mechanism of enhancer lncRNAs have not yet been firmly established. More efforts need to be made into revealing the secrets of enhancer lncRNAs in various biological processes.

Transcriptional regulators

Transcriptional regulations of eukaryotic genes are achieved through many ways, including traditional direct interactions of proteins with DNA regulatory elements and, more recently identified, specific interactions between RNAs, DNAs and/or proteins. Thus, lncRNAs are now known as an important facet of such transcriptional regulations. For *cis*-acting lncRNA, its genomic origin is critical for its function, as it will alter the expression of protein-coding genes nearby. It may function through the transcription activity itself rather than the product: if the promoter of another gene lies in close proximity, it may cause the collision between transcriptional machineries on both genes, which is also dubbed "transcriptional interference". For example, active transcription of lncRNA SRG1 will repress the transcription of its downstream SER3 gene in yeast, because the 3′ end of SRG1 overlap with the SER3 promoter. If SRG1 transcription is prematurely terminated, the repression of SER3 will be alleviated [2]. Also, in yeast, transcription of some lncRNAs facilitates the accessibility of protein-coding genes to RNA polymerases through altering chromatin structure, such as promoting transcription initiation at the FBP1 (Fructose-1,6-bisphosphatase 1) gene [23]. On the other hand, lncRNAs may also act in *trans*, affecting transcription via its binding to transcription factors. For instance, the lncRNA 7SK binds to the elongation factor P-TEFb and downregulates its kinase activity in order to inhibit transcription elongation by Pol II [24].

Post-transcriptional regulators

LncRNAs exert post-transcriptional regulation mainly in two ways, splicing regulation and translational control. Firstly, lncRNAs can either bind to splicing factors in a competition manner or bind to mRNA itself through base-pairing to block mRNA splicing. MALAT-1 (Metastasis-associated in lung adenocarcinoma transcript-1) is an abundant ~ 7 kb lncRNA that interacts with the serine/arginine-rich (SR) splicing factors. It was suggested to regulate phosphorylation of SR proteins to modulate their distribution in nuclear speckles, thereby affecting alternative splicing of pre-mRNAs [25]. MIAT (Myocardial infarction associated transcript) is another lncRNA containing a highly-conserved tandem repeats of UACUAAC, which has been characterized as a conserved intron branch point that can bind SF1 (splicing factor 1) with a higher affinity than the divergent branch point sequence, thus repressing splicing and the formation of spliceosomal complex on other transcripts [26]. LUST (LUCA-15-specific transcript) is an antisense transcript of RBM5 (RNA binding motif protein 5) and a sense-strand regulatory sequence of RBM5 in disguise, which is considered to modulate the expression of RBM5 splicing variants [27]. Secondly, lncRNAs can bind ribosome or translation factors to control protein translation. For example, snaR (small NF90-associated RNAs) and Gadd7 (growth arrested DNA-damage inducible gene 7) are two examples of translational control by lncRNAs through binding to ribosomes [28]. On the other hand, BC1 (Brain cytoplasmic RNA 1) and BC200 (200 nt brain cytoplasmic RNA), represent examples of translational repression by lncRNAs through binding to translation factors such as eI4FA (eukaryotic translation initiation factor 4A), PABP (poly (A)-binding protein) and other factors [29]. Thirdly, some lncRNAs can be related to both splicing and translation. One example is Zeb2NAT (Zeb2 natural antisense transcript), a ~ 1.2 kb lncRNA overlapping the 5′ splicing site of an intron, whose retention is required for the translation of Zeb2

(zinc finger E-box binding homeobox 2). Zeb2NAT can repress the intron splicing and thereby promote Zeb2 translation [30]. Finally, lncRNAs can also function as microRNA sponges or microRNA precursors to participate in the post-transcriptional modulation. MicroRNAs are a class of small single-stranded RNAs without protein-coding capacity. MicroRNAs can repress mRNA translation or facilitate mRNA degradation via binding to the 3′-UTR (3′ untranslated region) of their target mRNAs. In that case, a few lncRNAs can alter mRNA levels through influencing corresponding microRNA levels. H19, a well-studied lncRNA, functions as a molecular sponge to sequester let-7, while at the same time serves as a precursor of miR-675-3p [31, 32]. LncRNAs with similar functions have been reported and summarized in reference [33].

Research methods for lncRNAs

Generally, similar experimental procedures have been used for quantification and identification of lncRNA as coding transcripts although with some modification in downstream processing. LncRNA are often quantified together with mRNA using sequencing or microarray techniques, RNA-seq and -chip respectively, in the same biological samples. RNA-seq has the advantage to identify novel RNA transcripts and developed rapidly in the last decades. In addition to the common application of next-generation sequencing (NGS), recent advances in RNA-seq include single cell sequencing [34], single molecule sequencing [35], and in situ sequencing of fixed tissue [36]. On the other hand, transcriptome microarray is still in use and provides benefits as equally well-developed data analyses with a lower stochastic variability. Particularly in clinical studies, microarrays even outperform RNA-seq for standard analysis of gene expressions when it comes to reproducibility and cost [37].

In terms of functional analysis for lncRNAs, small interfering RNAs or antisense oligonucleotides for knocking down targeted lncRNA, and overexpression constructs to increase certain lncRNA expression levels are traditional methods to reveal their roles in vivo. In recent years, the revolutionizing CRISPR (clustered regularly interspaced short palindromic repeats) systems have been incorporated to maneuver the transcript level by either CRISPR activation or CRISPR inhibin (CRISPRa/i) [38, 39] or for genome editing of lncRNA locus of interest. For nuclear lncRNAs, to study the associations between lncRNAs and chromatin, ChIRP (Chromatin Isolation by RNA Purification) [40], CHART (capture hybridization analysis of RNA targets) [41], RAP (RNA antisense purification) [42] and GRID-seq (capture in situ global RNA interactions with DNA by deep sequencing) [43] are among the most advanced technologies to identify the binding sites of lncRNAs genome-wide. ChIRP, CHART and RAP can study only one known lncRNA, while GRID-seq provides global detection and analysis of RNA-chromatin interactions with high specificity and sensitivity [43]. To explore the interactions between lncRNAs and proteins, RIP (RNA immunoprecipitation) [44] and CLIP (UV crosslinking and immunoprecipitation) [45], iCLIP (individual-nucleotide resolution CLIP) [46] can be utilized to capture the lncRNA-binding proteins. Similar strategies can be applied to cytoplasmic lncRNAs, which usually function as miRNA sponges or precursors. In addition, with accumulating studies of lncRNA, a number of databases have emerged over the past few years with a particular interest in curating lncRNAs, to name only a few, NONCODE [47], ChipBase [48], lncRNAdb [49], LNCipedia [50] and LncRNADisease [51].

LncRNAs in renal diseases

There is an increasing number of evidences showing the important roles of lncRNAs in diverse human diseases. However, studies on lncRNAs in renal diseases are still in its infancy and mainly restricted to renal cancer. There are very few reports on lncRNAs' function in other types of renal diseases, such as acute kidney injury, renal fibrosis, polycystic kidney disease, diabetic kidney disease, lupus nephritis and renal transplantation. Here, we discuss major researches published so far on lncRNAs in renal diseases.

Renal cancer

As lncRNAs play important roles in regulating major pathways in cell growth, proliferation, differentiation, apoptosis and survival, dysregulation of lncRNAs can promote tumorigenesis and progression of kidney cancer, especially in renal cell carcinoma (RCC). For example, the oncogenic lncRNA HOTAIR promotes RCC tumorigenesis through AXL signaling by acting as a ceRNA (competing endogenous RNA) to sequester miR-217, a tumor suppressor, to facilitate HIF-1 (hypoxia-inducible factor 1) expression and to upregulate AXL level. The lncRNA-MRCCAT1 (metastatic renal cell carcinoma-associated transcript 1) is highly expressed in clear cell renal cell carcinoma (ccRCC) and promotes metastatic properties of ccRCC [52]. Besides, the upregulations of lncRNA-UCA1 (urothelial carcinoma associated 1) [53], lncRNA-ATB [54], lncRNA-H19 [55] and lncRNA-FTX [56] are also involved in RCC tumorigenesis and proposed to be important biomarkers for RCC. On the other hand, lncRNAs can also play anti-tumor roles. For example, lncRNA-SARCC (Suppressing Androgen Receptor in Renal Cell Carcinoma) is differentially modulated in a VHL (von Hippel-Lindau)-dependent way under hypoxia, suppressing the proliferation of

VHL-mutant RCC cell yet promoting the growth of VHL-normal RCC cell [57]. Decreases of lncRNAs such as NBAT-1 (neuroblastoma associated transcript-1) [58] and CASC2 [59] (cancer susceptibility candidate 2) are associated with poor prognosis in patients with RCC. To date, novel lncRNAs continue to be identified, such as lnc-BMP2–2, lnc-CPN2–1, lnc-ACACA-1, lnc-FOXG1–2 and lnc-TTC34–3, which were predicted by computational analyses to participate in RNA-protein interaction networks including spliceosome and other complexes in RCC [60]. Remarkably, it is reported that intronic antisense lncRNAs are commonly expressed in RCC tumors, the majority of which is evolutionarily conserved and possibly modulated by epigenetic modifications [61]. Besides, a recent study shows that lncRNA can also be packaged into exosomes and function critically to promote the progress of renal carcinoma. Le et al. identified lncARSR (lncRNA activated in RCC with sunitinib resistance), which acts as competing endogenous RNA for miR-34 and miR-449 to promote c-MET and AXL expression. In addition, lncARSR can be packaged into exosomes and transmitted to sensitive cells to disseminate sunitinib resistance [62]. Although studies are accumulating over the past decade, our knowledge of the underlying mechanisms of lncRNAs' role in renal malignancies is still rudimental, which needs more efforts to be made.

Acute kidney injury

Studies on lncRNAs in acute kidney injury (AKI) can be counted on fingers. One case is the hypoxia-responsive lncRNA GAS5, which is upregulated in renal ischemia/reperfusion (I/R) injury along with the increased expressions of p53 and TSP-1 (thrombospondin 1), promoting cell apoptosis in kidney [63]. Another case is the lncRNA MALAT-1, which is highly expressed in ischemic kidneys and plasma samples of patients with AKI, indicating a potential role of MALAT-1 in the induction of AKI [64]. However, MALAT-1 was later reported to be dispensable for renal I/R injury [65]. LncRNA-PRINS (psoriasis susceptibility-related RNA gene induced by stress) is induced by HIF-1α under hypoxia and shows specific interaction with RANTES (regulated on activation, normal T-cell expressed and secreted protein), which recruits circulating leukocytes and aggravates kidney injury [66]. In addition, Lorenzen et al. identified a novel intronic antisense lncRNA as an independent predictor of mortality in critically Ill patients with AKI, dubbed TapSAKI (transcript predicting survival in AKI), which is enriched in tubular epithelial cells and increased in plasma samples of AKI patients [67]. However, it still remains elusive whether these circulating lncRNAs are incorporated into exosomes and secreted into the circulating system.

Renal fibrosis / chronic kidney disease

The lncRNA np_5318 is a novel intronic lncRNA, which is located between the first and second exons of Erbb4 in mouse genome and thereby named as Erbb4-IR. Feng et al. reported that TGF-beta 1 can highly increase Erbb4-IR expression via a Smad3-dependent manner in the fibrotic kidney of mouse, suggesting that Erbb4-IR is a specific therapeutic target for chronic kidney disease [68]. Wang et al. reported the lncRNA ZEB1-AS1 (zinc finger E-box binding homeobox1-antisense RNA 1) exerted an anti-fibrotic role in diabetic nephropathy [69]. Xie et al. reported lncRNA H19 overexpression promoted renal fibrosis [70]. Chen et al. characterized downregulation of an intergenic lncRNA LINC00963, which suppresses RIF (renal interstitial fibrosis) and OS (oxidative stress) of CRF (chronic renal failure) through activation of the FoxO (forkhead box O) signaling pathway [71]. Zhou et al. demonstrated that lncRNA HOTAIR participated in renal interstitial fibrosis through upregulating miR-124 to block Notch1 pathway [72].

Diabetic nephropathy

Hundreds of lncRNAs are deregulated in diabetic nephropathy (DN) [73], which might participate in pathogenesis of DN, according to a recent study using microarray analysis on lncRNAs in DN. However, only a handful of these deregulated lncRNAs have been demonstrated to affect proliferation and fibrosis in DN, including CYP4B1-PS1–001 [74], ENSMUST00000147869 [75], NR_033515 [76], Dlx6os1 [77] and LINC00968 [78]. Yet, several lncRNAs can be potential therapeutic targets for DN, such as MALAT1. Reducing MALAT1 levels can improve renal functions after duodenal-jejunal bypass in diabetic rats [79]. Increasing expression of lncRNA TUG1 (taurine upregulated gene 1) can attenuate podocyte apoptosis, alleviate extracellular matrix accumulation and protect diabetic rats from DN [80, 81]. Besides, TUG1 was also reported to regulate mitochondrial bioenergetics in DN [82].

Polycystic kidney disease / lupus nephritis / glomerulonephritis

There are few reports on lncRNAs in polycystic kidney disease, lupus nephritis or glomerulonephritis. One microarray study characterized thousands of lncRNAs in patients with IgA-negative MsPGN (mesangial proliferative glomerulonephritis) [83]. LncRNA Hoxb3os, which regulates mTOR signaling, was found to be deregulated in polycystic kidney disease [84]. The lncRNA NEAT1 (Nuclear Enriched Abundant Transcript 1) was

characterized as a novel inflammatory mediator in human lupus. Yet it is still unclear whether renal functions in patients with lupus would be affected by NEAT1 [85].

Kidney transplantation

Even less studies have been carried out when it comes to lncRNAs in kidney transplantation. Chen et al. compared differential expressions of lncRNAs by microarray between control samples and samples from patients with acute rejection (AR) after renal transplantation, implying that lncRNAs might take part in the pathogenesis of AR [86]. Lorenzen et al. detected lncRNAs in urine of patients with AR and identified urinary lncRNA RP11-354P17.15–001 as a novel noninvasive biomarker for renal AR [87]. Ge et al. identified two lncRNAs (AF264622 and AB209021) from peripheral blood, which can predict renal AR following transplantation [88]. Shang et al. screened lncRNA expression patterns in recipients with urothelial cancer after kidney transplantation and suggested that lncRNAs have critical roles in UC carcinogenesis [89]. However, potential regulatory mechanisms of lncRNAs in renal transplantation are seldomly explored. Only two studies on lncRNA-ATB [90] and LncRNA-PRINS [91] did some initial research on the underlying mechanisms involved in the rejection of renal allografts.

Future perspectives for the clinical use of lncRNAs in renal diseases

As a newly developed research field, lncRNAs rapidly become a "hotspot" and provide new insights for potential clinical uses. On one hand, numerous lncRNAs have been discovered exhibiting specific expression patterns in various diseases, not only in tissues but also in body fluids including blood and urine. Thereby, lncRNAs could be developed for novel biomarkers to predict and supervise the progression of diseases. However, the quantity and stability of lncRNAs in the circulating and urinary systems make it hardly practical to use lncRNAs as non-invasive biomarkers with current detection limits. On the other hand, many lncRNAs have been demonstrated to directly regulate effector genes critical for the occurrence and development of diseases. From this standpoint, lncRNAs are also attractive therapeutic targets. For example, utilizing antisense oligonucleotides (ASOs) to knockdown MALAT1 can result in slower tumor growth and a reduction in metastasis in mammary tumors, indicating MALAT1 ASOs might provide a potential treatment for breast cancer [92]. In renal diseases, the potential clinical application of lncRNA studies are similar to other human diseases, focusing on biomarkers and therapeutic targets, and may provide new insights into diagnosis and therapy of renal diseases. Nevertheless, up to now, no clinical trials of lncRNAs have been documented.

Conclusion

We summarized lncRNAs and their research status in renal diseases in this review. Although lncRNAs studies have increased a lot over the past decade, they are still at the starting stage regarding to kidney diseases for the time being. More efforts need to be made to explore the potential mechanisms and significant roles of lncRNAs during the pathogenesis, diagnosis and treatment of renal diseases, which will expand our understanding of renal disease pathophysiology and drive new strategies for the diagnosis and treatment for renal diseases.

Abbreviations

3′-UTR: 3′ untranslated region; AKI: Acute kidney injury; AR: Acute rejection; AR: Androgen receptor; BC1: Brain cytoplasmic RNA 1; BC200: 200 nt brain cytoplasmic RNA; CASC2: Cancer susceptibility candidate 2; ccRCC: Clear cell renal cell carcinoma; ceRNA: Competing endogenous RNA; DN: Diabetic nephropathy; Dnmt1: DNA (cytosine-5)-methyltransferase 1; eI4FA: Eukaryotic translation initiation factor 4A; FBP1: Fructose-1,6-bisphosphatase 1; FoxO: Forkhead box O; Gadd7: Growth arrested DNA-damage inducible gene 7; HIF-1: Hypoxia-inducible factor 1; HOTAIR: Hox transcript antisense RNA; HSF1: Heat-shock transcription factor 1; HSR1: Heat shock RNA-1; I/R: Ischemia/reperfusion; ICRs: Imprinting control regions; Kcnq1ot1: KCNQ1 overlapping transcript 1; LncRNA: Long noncoding RNA; LUST: LUCA-15-specific transcript; MALAT-1: Metastasis-associated in lung adenocarcinoma transcript-1; Mdm2: Mouse double minute 2 homolog; MIAT: Myocardial infarction associated transcript; miRNAs: microRNAs; MRCCAT1: Metastatic renal cell carcinoma-associated transcript 1; mRNA: Messenger RNA; MsPGN: Mesangial proliferative glomerulonephritis; NBAT-1: Neuroblastoma associated transcript-1; NEAT1: Nuclear Enriched Abundant Transcript 1; ORF: Open reading frame; OS: Oxidative stress; PABP: Poly (A)-binding protein; piRNAs: piwi-associated RNAs; PRC2: Polycomb repressive complex-2; PRINS: Psoriasis susceptibility-related RNA gene induced by stress; RANTES: Regulated on activation, normal T-cell expressed and secreted; RBM5: RNA binding motif protein 5; RCC: Renal cell carcinoma; RIF: Renal interstitial fibrosis; SAF-A: Scaffold Attachment Factor-A; SARCC: Suppressing Androgen Receptor in Renal Cell Carcinoma; SF1: Splicing factor 1; snaR: Small NF90-associated RNAs; SRA: Steroid receptor RNA activator; TapSAKI: Transcript predicting survival in AKI; TSP-1: Thrombospondin 1; TUG1: Taurine upregulated gene 1; UCA1: Urothelial carcinoma associated 1; VHL: Von Hippel-Lindau; Xist: X-inactive specific transcript; ZEB1-AS1: Zinc finger E-box binding homeobox1-antisense RNA 1; Zeb2: Zinc finger E-box binding homeobox 2; Zeb2NAT: Zeb2 natural antisense transcript

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