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Review

Long non-coding RNAs: An essential emerging field in kidney pathogenesis

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ABSTRACT

Human Genome Project has made it clear that a majority of the genome is transcribed into the non-coding RNAs including microRNAs as well as long non-coding RNAs (lncRNAs) which both can affect different features of cells. LncRNAs are long heterogenous RNAs that regulate gene expression and a variety of signaling pathways involved in cellular homeostasis and development. Studies over the past decade have shown that lncRNAs have a major role in the kidney pathogenesis. The effective roles of lncRNAs have been recognized in renal ischemia, injury, inflammation, fibrosis, glomerular diseases, renal transplantation, and renal cell carcinoma. The present review outlines the role and function of lncRNAs in kidney pathogenesis as novel essential regulators. Molecular mechanism insights into the functions of lncRNAs in kidney pathophysiological processes may contribute to effective future therapeutics.

1. Introduction

Large-scale transcriptome analyses using high-technology efforts such as tilling arrays, RNA-sequencing, standard cDNA cloning, and cap-analysis of gene expression (CAGE) indicated that the majority of the genome is transcribed (~80%) at some point during growth into the coding and non-coding RNAs (ncRNAs) [1,2]. ncRNAs are classified into small (< 200 nucleotides) and long (> 200 nucleotides) transcripts based on their size. Small ncRNAs including microRNAs (miRNAs), small interfering RNAs (siRNA), and small nucleolar RNAs (snoRNAs) are involved in the regulation of various biological processes [3]. Both of these ncRNA groups can affect the different features of cells, including cell proliferation, differentiation, stress response, senescence, immune activation, and cell death, as well as pathophysiological conditions [4,5].

In the recent years, the roles of microRNAs in kidney physiology and diseases including kidney fibrosis [6], diabetic nephropathy [7], renal transplantation [8–10], acute rejection [11], nephrotic syndrome [12], polycystic kidney [13], acute kidney injury (AKI) [14,15], and chronic kidney disease (CKD) progression [16,17] have been extensively studied. Similar to microRNAs, lncRNAs can inhibit gene expressions at both the transcriptional and posttranscriptional levels. Additionally, lncRNAs can act as sponges of microRNAs and as scaffolds to recruit chromatin modification complexes [18]. Furthermore, lncRNAs participate in different signaling pathways involved in cell development and homeostasis [19,20]. However, little is known about their function in kidney physiology and diseases and their role remains a matter of intense research.

The following sections review the roles of lncRNAs in kidney pathogenesis. Absolutely, this point of view holds great promise to expand our understanding of the underlying mechanisms of lncRNAs in the progression of kidney diseases that may contribute to effective future therapeutics.

2. Characteristics of lncRNAs

The number of identified lncRNAs in the genome of normal tissues, different cell lines, and tumor samples is in a steep increase. Based on GENCODE (version 27, http://www.gencodegenes.org), 15,778 lncRNA (27908 transcripts), and 19,836 protein-coding genes have been recognized in the human genome, so far. LncRNAs are heterogeneous RNAs due to different biogenesis and processing pathways; however, they show some similarities to protein-coding mRNAs [21]. LncRNAs are transcribed by RNA polymerase II in similar histone modification profiles (H3K4me3 and H3K36me3) and can similarly be subjected to post-transcriptional modifications such as 5′-capping, polyadenylation, and splicing [22–24]. There are also some differences between lncRNAs and mRNAs. LncRNAs predominantly are two-exon transcripts with slightly longer exon and intron compared with mRNAs and have no well-established protein-coding potential [22,25]. The exons of

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lncRNAs are more conserved than the ancestral repeat (AR) sequences, and their promoters are more conserved than the promoter of protein-coding genes [22]. The evolutionary origin of lncRNAs is relatively unclear; in a study Kapusta et al. identified that the transposable elements are ubiquitously found in lncRNA reservoir in zebrafish (66%), mouse (68%), and human (75%) which is much higher than the occurrence of these elements in protein-coding genes (4%) [26]. There is some evidences showing that transposable elements can help the diversification of the pre-existing lncRNAs and also some instances support the idea that lncRNAs emerge from sequences containing transposable elements (*e.g.* evolving as a part of transposons) [26]. LncRNAs are tissue-specific and the analysis of lncRNAs expression in some human organs and brain showed their lower level of expression in comparison to the protein-coding genes. They are mostly found in nucleus particularly in the chromatin fraction rather than in cytosol [22]. LncRNAs based on genomic location are categorized into intergenic and intragenic lncRNAs. Intergenic lncRNAs (lincRNA) do not overlap with protein-coding genes and constitute the largest group of lncRNAs (64%). Intragenic lncRNAs overlap with protein-coding genes and are further divided into four sub-classes with respect to their position to the closest protein-coding gene. These include overlapping, intronic, antisense, and bidirectional lncRNAs [27,28]. Overlapping lncRNAs harbor a protein-coding gene within their intronic region in the sense direction. Intronic lncRNA is localized within the intron of a coding gene. Antisense RNAs, share within a number of coding genes in opposite direction and are more stable than intronic lncRNAs and mRNAs [21]. Bidirectional lncRNAs originate partially from 5´ region of a coding gene in the opposite direction.

3. Molecular mechanisms of lncRNAs

Initial investigations showed low sequence conservation among lncRNAs from different species, hence, the possibility of functional roles of lncRNAs was debated and implied the idea of lncRNAs as transcriptional noise [29]. In the last decade, various studies showed that they can interact with DNA, RNA, and proteins and also participate in many biological processes [30]. Even though the number of lncRNAs is steadily increasing, little is known about the potential roles of annotated lncRNAs. Moreover, it should be noted that not all of lncRNAs are active in biological processes, some are possibly byproducts of regulatory elements such as enhancers [31]. Here, we briefly discuss the molecular mechanisms of lncRNAs in regulating gene expression in three steps namely chromatin modification, transcriptional, and post-transcriptional steps (Fig. 1).

3.1. Chromatin modification

The transcription process can be regulated by the manipulation of chromatin structure and recruiting modifying complexes to the chromatin. Khalil et al. studied different human cell types and showed that a significant number (at least ≈38%) of various lncRNAs are connected with chromatin-modifying complexes such as PRC2 (H3K27 methylase), SMCX (a histone H3K4me3 demethylase), and CoREST (repressor of neuronal genes) [32]. LncRNAs can act as scaffolds and simultaneously recruit multiple modifying complexes and bring them to the close proximity of chromatin [33]. Hox transcript antisense RNA (HOTAIR), a lncRNA transcribed from the HOX-C locus, is able to simultaneously bind to PRC2 and LSD1 (H3K4 demethylase) complexes *via* its two different domains. Tethering different complexes to distinct domains of lncRNAs effectively coordinates their activity [33]. Deletion of separate domains of lncRNAs does not abolish the activity conducted by the other domains [34].

X chromosome inactivation and genomic imprinting are two processes in order to equalize the gene dosage in diploid cells. X chromosome inactivation happens in female cells and inactivates one of the two X chromosomes. Inactivation happens as a result of some synergistic events in which a number of identified lncRNAs such as Xist, Tsix, Xite, RepA, and Jpx are involved [35]. Xist is expressed from the inactive X chromosome and has a pivotal function in X chromosome inactivation through transcriptional silencing by recruiting of histone deacetylase 3 [36], inducing repressive chromatin modifications by recruiting of PRC2 [37], and also spreading across the chromosome in regions in the proximity of Xist locus [34]. Moreover, Xist is able to remodel the three-dimensional structure of chromatin which is required to repress transcription [38]. Many other proteins have been also discovered which bind to Xist; however, the function of most of these remains undiscovered [39].

In genomic imprinting, the expression of a number of genes (*e.g.* H19, Igf2, and Dlk-1) is epigenetically suppressed in a sex-dependent manner. The precise mechanism of many of these allele-specific modifications is not completely understood. Transcriptional interference is a mechanism that Airn (antisense to Igf2r RNA non-coding) lncRNA uses to silence the Igf2r (insulin-like growth factor II) gene on a paternal chromosome. The overlap between Airn coding region and Igf2r promoter inhibits the recruitment of RNA polymerase II to the coding gene. Therefore, in this case, the lncRNA product is not necessary for gene silencing [31].

3.2. Transcriptional regulation

LncRNAs can interfere with the transcription process by direct interaction with RNA polymerase II [40], pre-initiation complex [41], and transcription factors and regulators [42]. Enhancer RNAs (elncRNAs) are transcription regulators transcribed from enhancer elements in the genome and are mostly spliced and polyadenylated [30]. ElncRNAs regulate either nearby or distal protein-coding genes or even those located on other chromosomes. ElncRNAs bind a specific mediator complex and by creating a loop, bridge the enhancer to the promoter and increase the transcription [43,44]. A human colorectal cancer-specific enhancer lncRNA, CCAT1-L, was found to interact with CTCF protein, a mediator protein in chromatin looping, and creates a loop between MYC oncogene and its enhancer. This looping process leads to positive regulation of MYC transcription and plays a role in tumorigenesis [43]. Based on the Fig. 1, lncRNAs can also indirectly affect transcription by controlling the transportation of transcription regulators from cytosol to the nucleus [45].

3.3. Post-transcriptional regulation

Gene expression can also be modulated by lncRNAs post-transcriptionally. LncRNAs target mRNA processing in various steps such as alternative splicing [46] along with mRNA stabilization and degradation [47]. RNA-RNA pairing between non-coding antisense transcripts of β-secretase-1, a key enzyme in Alzheimer, with enzyme coding mRNA stabilizes the mRNA which subsequently elevates the concentration of brain β-secretase-1 and consequent amyloid-beta peptide [47]. Moreover, lncRNAs are able to interfere with the translation of target mRNAs [48]. Another regulatory mechanism through which lncRNAs control gene expression is controlling miRNA biogenesis, distribution, and degradation. miRNAs originated from exonic or intronic regions of some coding and non-coding genes or are transcribed from miRNA genes regulated by RNA polymerase II [30]. Moreover, there are examples of lncRNAs which harbor miRNA genes in their exonic or intronic regions. For example, some studies have shown the importance of miR675 originated from lncRNA H19 exon1 in regulating the expression of the target genes involved in biological processes such as cell proliferation (CDK6 in glioma) [49], apoptosis (VADC1 in diabetic cardiomyopathy) [50], and metastasis (c-Cbl in breast cancer) [51].

There is increasing evidence indicating that lncRNAs can negatively regulate miRNAs [52,53]. The overexpression of lncRNA CCAT2 in colorectal cancer promotes the tumor growth. Recently it has been shown that lncRNA CCAT2 in colon cancer stem cells decreases the