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REVIEW

Role of noncoding RNAs in diseases

Beena M Kadakkuzha

The Scripps Research Institute, 130 Scripps Way, Jupiter, FL 33458, USA

Correspondence: Beena M Kadakkuzha
E-mail: Kadakkuzha.beena@gmail.com
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Most of the fundamental biological processes involve specific interaction between RNA molecules, both protein-coding and noncoding RNAs, and proteins. The RNA-protein interactions results in the formation of ribonucleoprotein complexes (RNPs) and altercations in the levels and structure of either can affect the associated cellular function. Recent studies suggest that non-protein coding share of the genome is aggressively involved in multiple functions, such as gene expression, chromatin modification, cell proliferation and in a wide range of diseases. Further studies on the mechanisms by which ncRNAs operate would yield a wealth of information regarding their functional roles and the growing understanding of RNA biology to develop new RNA-based tools for developing therapeutics.

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Introduction

Ribonucleic acids (RNA) were earlier considered as a lowly messenger molecule that carries genetic information coded in the deoxy-ribonucleic acid (DNA) to the proteins. However, myriad of discoveries since the late 1970s demonstrated the versatility of RNA molecules. In addition to carrying genetic information, RNA can fold up into complex structures that catalyze different chemical reaction. These classes of catalytic RNAs are known as ribozymes, and the finding earned Thomas Cech and Sidney Altman the Nobel Prize in Chemistry in 1989. Furthermore, there are RNAs such as ribozymes and riboswitches, which bind metal ions and metabolites, and the binding causes structural changes in the RNA secondary and tertiary structure, leading to its own gene expression variation [1,2]. All these discoveries demonstrated the emerging role of RNAs as the regulators of basic cellular functions [3]. Once it was discovered that RNA could both carry information as well as catalyze chemical reactions, RNA occupied center stage leading to the "RNA world" hypothesis. Using advanced methods, it has been discovered that intrinsically, RNA structure is highly flexible and limited to transitions between the few conformations that favor stable base-pairing and stacking interactions [1, 4, 5].

The transcriptome

For long time it was thought that the transcriptome is mainly composed of mRNAs and few regulatory RNAs such as tRNAs, rRNAs etc. Nevertheless, recent progresses in high-throughput RNA sequencing techniques have revealed the complexity of genomes in higher organisms. Approximately 22,000 protein-coding genes have been identified in the human genome [6]. However, this constitutes only 2% of the genome and more than 70% of the human genome is transcribed into non-protein coding transcripts, which was previously considered as genomic junk or noise [7]. Noncoding RNAs (ncRNAs) regulate a myriad of biological functions such as transcription, chromatin remodeling, RNA splicing, and translation [8]. Unlike ribozymes and riboswitches, where the RNA structure itself regulates the biological function, most ncRNAs function as RNA-protein complexes. Nevertheless, it is no more

considered as transcriptional noise but as key regulatory layer of molecular function. The noncoding portion of the transcriptome is further divided into these following categories: miRNAs, piRNAs, snoRNAs, lncRNAs and lincRNAs.

microRNAs in diseases

The most extensively studied group of ncRNAs are microRNAs (miRNAs), which are small ~22 nucleotides (nt) duplex RNAs generated from miRNA precursor transcripts by processing steps tightly regulated by members of the RNAse III family, Drosha and Dicer [9,10]. miRNAs facilitate gene silencing by regulating the translation of mRNA into proteins [11]. During miRNA mediated translation inhibition, one of the two strands of the miRNA is incorporated into the active sites of the argonaute proteins. This single strand acts as a guide molecule for Watson–Crick base pairing with complementary sequences in target mRNAs [12]. miRNAs inhibit target mRNA translation by leading the RNA-induced silencing complex (RISC) to the 3'untranslated regions (UTRs) of target transcripts [12]. Many miRNAs are known to regulate the translation of multiple transcripts simultaneously and the inhibition of mRNA translation by miRNAs occurs in two ways; regulating inhibition of translation initiation and transcript degradation [12, 13]. miRNAs are believed to modulate translation of more than half of mRNAs which makes them regulators of key processes, including development, differentiation, metabolism, aging and degeneration [12,13]. There are roughly 2200 miRNA genes have been reported to exist in the mammalian genome, and from that list over 1000 belong to the human genome [14]. A comprehensive review that explains the role of miRNAs as important new regulatory molecules in different human diseases is discussed elsewhere [15].

piRNAs: new layer of cellular regulation

A new class of noncoding small RNAs recently getting attention is the Piwi-interacting RNAs (piRNAs), predominantly present in the germline, which interact with Piwi proteins [16]. PiRNAs are typically 24-32 nucleotide (nt) long and found in *Drosophila*, zebrafish and mammals [17]. PiRNAs are formed from long single-stranded RNA precursors that are mostly coded by repetitive intergenic sequences in the genome and are formed via a Dicer-independent mechanism [17]. PiRNAs seem to play vital roles during germline development through a series of RNA-mediated mechanisms; mainly epigenetic silencing of transposons through DNA methylation [17].

Recently, it was reported that piRNA-pathway disorders increase the number of repeats of retrotransposon, leading to DNA damage [18]. Since DNA damage is a hallmark of tumor genesis in germline and somatic cells, piRNAs may be dis-regulated and play key roles in tumorigenesis. Recent evidence suggests that piRNAs have been identified in human cancer cells, where they regulate processes like *de novo* DNA methylation, leading to tumorigenesis [19]. Recently, a piRNA named piR-651/823 recognized by gastroenterologists is involved in gastric carcinogenesis [20]. piR-651/823 also represented as an efficient diagnostic biomarker of gastric cancer that can be detected in the blood and gastric juice [20].

SnoRNAS

Small nucleolar RNAs (SnoRNAs) are a large family of moderately well characterized noncoding RNAs (ncRNAs). SnoRNAs are involved in the processing of other RNAs, such as tRNA, rRNA and small nuclear RNA (snRNAs) [21,22]. Within the cell, snoRNAs interact with specific proteins to form small nucleolarribonucleoprote in particles (snoRNPs). Most of the snoRNAs carry two short sequence elements, called boxes C and D which are essential for binding of a common snoRNP protein component, fibrillarin [23]. Recently, it has been reported that snoRNAs and fibrillarin are overexpressed in both murine and human breast cancer and prostate cancers [24]. The snoRNAs and fibrillarin overexpression is in fact driving tumorigenicity *in vitro* and *in vivo*. Using microarrays and quantitative PCR (qPCR), Valleron et al., investigated snoRNA regulation in cancer cells [25]. The study found specific patterns of snoRNA accumulation in acute myeloblastic and acute lymphoblastic leukemias [25]. Furthermore, a recent study showed overexpression of six snoRNAs in tumor tissues of non-small-cell lung cancer (NSCLC), the leading cause of cancer death [26]. Together, these studies indicate that snoRNAs have critical role in cancer initiation. Additionally, human snoRNA, HBII-52 is associated with two neurological disorders: Prader-Willi Syndrome and Angelman syndrome [27].

Long noncoding RNAs: novel regulators of physiology and disease

Long noncoding RNAs (lncRNAs) are a heterogeneous group of noncoding transcripts typically 200 to thousands of nucleotides in length. This group of ncRNA constitutes the largest portion of the mammalian noncoding transcriptome [28]. The number of lncRNAs reported in human as well as lower organisms is ever expanding and many of these lncRNAs are estimated to carry out key functions in fundamental cellular processes, thus adding another level of complexity to our understanding of genomic regulation [28]. The expression pattern and distribution of lncRNAs found to

be tissue and cell-type specific, indicating unique functions of lncRNAs [29, 30]. Earlier studies had proposed a number of different mechanisms by which lncRNAs regulate chromatin and transcriptional machinery [31]. A well-known function of lncRNAs is to mediate epigenetic modifications of DNA by recruiting chromatin remodeling complexes to specific loci [32]. A classic example is the human *HOX* loci, where temporal and spatial expression of hundreds of lncRNAs is highly structured. These lncRNAs regulate chromatin accessibility through key processes that involves histone modification enzymes and RNA polymerase [33]. Another example is the *X* chromosome inactivation where X-inactive specific transcript (*XIST*) lncRNA recruits the polycomb complex to silence the *X* chromosome from which it is transcribed [34]. A lncRNA transcribed from the opposite strand to *XIST* is called *TSIX*, which play a key role in *X*-chromosome inactivation by regulating expression levels of *XIST* [32]. A recent study showed that an endogenously expressed antisense RNA transcribed from opposite strand of *APOA1* gene cluster in humans regulates the his tone methylation and *APOA1* expression in HepG2 cells. Together, these examples suggest the vital functional role played by lncRNAs [35].

From emerging studies, it is very evident that lncRNAs participate in a wide range of biological processes [30]. Past decade in RNA research clearly implies the role of lncRNA in nearly every fundamental cellular process from chromatin organization, mRNA splicing, RNA degradation, and translation. The exact mechanisms by which lncRNAs regulate these key functions are still elusive. Multiple lines of evidence connect dysfunctions of lncRNAs to diverse human diseases [36]. These dysfunctions involve variations in the primary and secondary structures that affect the binding or association of lncRNA with its target protein, DNA, and/or RNA. Additionally, altercations in the expression levels of lncRNAs as well as their associated RNA-binding proteins can lead to many diseases [36].

There are many lncRNAs involved in cell cycle regulation and directly linked to various types of cancers. Two well-known examples are *ANRIL* and *HOTAIR*, both affect the chromatin structure by acting as scaffold molecules via interaction with chromatin modification complexes [37,38]. Overexpression of ANRIL and HOTAIR causes variations to the chromatin structure leading to cancer development and progression. *ANRIL* is a lncRNA antisense to *INK4b/ARF/INK4a* locus encodes three tumor suppressor genes. A recent study demonstrated the interaction between *ANRIL* and the Pc/Chromobox 7 (CBX7) protein, a key member of the polycomb repressive complex 1 (PRC1) [39]. The study also showed that there is a correlation between reduced *INK4a* levels and increased levels of both *CBX7* and *ANRIL* in prostate cancer tissues [39]. *HOTAIR* is another lncRNA that is involved in chromatin remodeling and there is increasing evidence that *HOTAIR* play vital role in cancer progression as increased expression of *HOTAIR* was reported in breast cancer. [38, 40] *HOTAIR* interacts with the polycomb repressive complex 2 (PRC2) and aberrations in *HOTAIR* expression level cause increased PRC2 repressive activity, leading to breast cancer progression [38].

MALAT-1 (metastasis-associated in lung adenocarcinoma transcript) is another lncRNA that regulates alternative splicing as well as transcriptional regulation. *MALAT-1* regulates the cellular distribution of pre-mRNA splicing factors to nuclear speckles, via modulating phosphorylation of specific proteins [41]. *MALAT-1* is highly abundant in central nervous system where it regulates neuronal synapse formation, density and maturation [42], thus affecting synaptogenesis. So far multiple studies showed that *MALAT1* is involved in lung and colorectal cancer metastasis [43, 44].

Beta-site amyloid precursor protein (APP)-cleaving enzyme 1 (BACE1) is an aspartyl protease that cleaves APP at the β-site in the formation of amyloid β-peptide (Aβ). Buildup of the Aβ neuropeptide has been associated with many neurological disorders, underscoring the significance of *BACE1* regulation [45]. The antisense lncRNA of *BACE1* (*BACE1-AS*) is transcribed from the opposite strand of *BACE1*. Emerging studies suggested elevated levels of Aβ, *BACE1* proteins, and *BACE1-AS* had been identified in patients with Alzheimer's disease (AD). *BACE1-AS* is an example where altered expression levels of lncRNA play a critical role in the pathogenesis of AD [45].

Conclusion

Increasing number of studies has shown that ncRNAs have important roles in cellular physiology and are associated with a wide range of diseases. NcRNAs are now becoming potential targets for disease diagnosis and prognosis. While there are thousands of ncRNA identified in the past, only a few are reported to be involved in the development and progression of diseases. One caveat is the lack of knowledge about the molecular mechanisms by which these ncRNAs operate. Currently, bioinformatics methods are used to predict potential associations of ncRNAs with protein coding genes and their role in different diseases. More and more studies that dissect the molecular mechanisms of ncRNAs will hopefully shine more light onto the ncRNA mediated cellular processes in the near future.

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