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Review

The ways of action of long non-coding RNAs in cytoplasm and nucleus

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ABSTRACT

Over the past fifteen years, small regulatory RNAs, such as siRNA and miRNA, have been extensively investigated and the underlying molecular mechanisms have been well documented, suggesting that ncRNAs play a major function in many cellular processes. An expanding body of evidence reveals that long non-coding RNAs (lncRNAs), once described as dark matter, are involved in diverse cellular progresses, including regulation of gene expression, dosage compensation, genomic imprinting, nuclear organization and nuclear–cytoplasm trafficking via a number of complex mechanisms. The emerging links between lncRNAs and diseases as well as their tissue-specific expression patterns also indicate that lncRNAs comprise a core transcriptional regulatory circuitry. The function of lncRNAs is based on their sequence and structure; and they can combine with DNA, RNA, and proteins both in the nucleus and the cytoplasm. However, detailed insights into their biological and mechanistic functions are only beginning to emerge. In this review, we will mainly talk about diverse ways of action of lncRNAs in different sub-cellular locations and provide clues for following studies.

1. Introduction

As early as 1990, scientists found a non-coding RNA when they aimed to find new protein-coding genes involved in a particular biological function by screening the cDNA library of a fetal liver, which is different from classic non-coding RNAs such as ribosomal RNAs (rRNAs) and transfer RNAs (tRNAs) (Brannan et al., 1990; Brown et al., 1991). At that time, the main object studied was associated with genes encoding proteins and much less was known about non-coding RNAs. The number of human protein-coding genes is less than 2% of the whole genome sequence even though it has recently settled at approximately 20,000 (Ponting and Belgard, 2010; Stein, 2004). But it is now clear that up to 90% of eukaryotic genomes are transcribed, generating an extraordinary range of RNAs with no coding capacity (Costa, 2010; ENCODE Project Consortium et al., 2007). Based on transcript size, these non-coding RNAs can be grouped into two major classes: small non-coding RNAs (<200 bp) and long non-coding RNAs (lncRNAs; ≥200 nt). To date, the most extensively studied small RNAs are microRNAs (miRNAs). In this review, we will mainly talk about diverse ways of action of lncRNAs in the cytoplasm and the nucleus.

LncRNAs share many features of mRNAs as they are frequently transcribed by RNA polymerase II and are generally spliced, 5′ capped, and polyadenylated. They are also marked by trimethylation of lysine4 of histone H3 (H3K4me3) at their promoter and trimethylation of lysine36 of histone H3 (H3K36me3) along the length of the transcribed region (Guttman et al., 2009; Khalil et al., 2009; Mikkelsen et al., 2007). However, not all of lncRNAs are like these. Some of them do not have polyadenosine tail (poly(A) tail) such as MALAT1 (Wilusz et al., 2012), asOct4-pseudogene 5 (Hawkins and Morris, 2010), and BC200 RNA (Chen et al., 1997; Iacoangeli et al., 2004). Compared with protein-coding genes, lncRNAs have limited coding potential as indicated by the lack of significant open reading frames (ORFs), typical initiation codon, 3-untranslated regions (UTRs) and termination codon (Ramskold et al., 2009). What is more, the expression of lncRNAs is much lower and more tissue-specificity (Mercer et al., 2008). However, in the nucleus and the cytoplasm, lncRNAs are involved in various physiological and pathological processes at epigenetic, transcriptional or post-transcriptional level to regulate the expression of related genes. So investigation of the sub-cellular distribution of lncRNAs has the potential to greatly expand our knowledge of not only the function of lncRNAs but also the guidance for newly discovered lncRNAs.

Abbreviations: siRNA, small interfering RNA; miRNAs, microRNAs; lncRNAs, long non-coding RNAs; rRNAs, ribosomal RNAs; tRNAs, transfer RNAs; H3K4me3, trimethylation of lysine4 of histone H3; H3K36me3, trimethylation of lysine36 of histone H3; ORFs, open reading frames; UTRs, untranslated regions; T-UCRs, transcribed-ultraconserved regions; SMD, Staufen1 (STAU1)-mediated mRNA decay; 1/2-sbsRNAs, 1/2-Staufen1-binding site lncRNAs; Cdk6, cyclin-dependent kinase 6; TDP-43, TAR DNA-binding protein; SINEB2, B2 short interspersed elements; hnRNP, heterogeneous nuclear ribonucleoprotein; RNP, ribonucleoprotein; RPA, RNase protection assay; ceRNAs, competing endogenous RNAs; CBX7, chromobox 7; PRC, Polycomb Repressive Complex; GR, glucocorticoid receptor; GRE, glucocorticoid response element; SRA, Steroid receptor RNA; Pc2, Polycomb2; ICGs, interchromatin granules; PcGs, Polycomb bodies; NoDS, nucleolar detention sequence; Slc22a3, Solute carrier family 22 member 3; DNMT1, DNA methyltransferase 1; Dlx, distal-less homeobox; TLR, Toll-like receptor; PSPs, paraspeckles; NEAT1, nuclear-enriched autosomal transcript 1.

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2. Classification of lncRNAs

With the development of high-throughput sequencing technology and computational methods for assembling the transcriptome, more and more lncRNAs are being constantly discovered (Cheng et al., 2005; Prensner et al., 2011). Recent observations of novel long ncRNA species have led to a complex set of terms and terminologies used to describe a given lncRNA. These include antisense lncRNAs, sense lncRNAs, intergenic lncRNAs, transcribed-ultraconserved regions (T-UCRs) and enhancer-lncRNAs (Djebali et al., 2012; He et al., 2008; Louro et al., 2009; St Laurent et al., 2012; Wang et al., 2011a). Depending on their relationships with the nearest protein-coding genes, lncRNAs can be classified in five different ways (Fig. 1): (1) sense, or (2) antisense, lncRNAs that are located on the same strand or the opposite strand of the nearest protein-coding genes; (3) bidirectional, lncRNAs that locate on the opposite strand from a protein coding gene whose transcription is initiated less than 1000 base pairs away; (4) intronic, lncRNAs that locate inside the introns of a protein-coding gene; and (5) intergenic, lncRNAs that locate in the interval regions between two protein-coding genes (Ponting et al., 2009).

3. Function of lncRNAs

LncRNAs initially were considered as byproduct of transcription of RNA polymerase II. They had been described as “dark matter” and did not have a biological function. However, whole genome transcriptomic analyses have identified large numbers of dynamically expressed long non-coding RNAs, many of which are involved in a variety of biological functions. Increasing numbers of lncRNAs have been shown to have functional roles in body development and tumorigenesis by regulating related gene expression. During body development, large intergenic non-coding RNA-RoR regulates reprogramming of human induced pluripotent stem cells (Loewer et al., 2010). LncRNA_ES1/2/3 promotes pluripotency and neuronal differentiation by association with chromatin modifiers and transcription factors (Ng et al., 2012). Linc-MD1 takes part in the timing of muscle differentiation and acts as a natural decoy for microRNA-133/135, thus controlling the factors involved in the myogenic program (Cesana et al., 2011). In neoplastic disease, lncRNAs may function as tumor suppressors (Huang et al., 2013; Liu et al., 2013; Yang et al., 2013) and oncogenes (Matouk et al., 2007; Yang et al., 2011a) in cancer just like protein-coding genes and microRNAs. In addition, lncRNAs can also regulate synapse formation by modulating the expression of genes related to synapse formation and/or maintenance (Bernard et al., 2010), involving in inflammation signaling (Rapicavoli et al., 2013), and can even be used as prognostic indicators (Xie et al., 2013; Zhang et al., 2013b).

It is common for protein-coding mRNAs to traffic or localize in certain cellular sub-compartments and the same to lncRNAs. Generally, lncRNAs can function in the nucleus, or in the cytoplasm, or in both, some of which even constitute a new sub-cellular compartment (Sone et al., 2007). LncRNAs can participate in the regulation of gene expression via various ways in the cytoplasm and the nucleus (Table 1). Here, we will talk about the ways of action of lncRNAs from two aspects.

4. The ways of action of lncRNAs in the cytoplasm

In the cytoplasm, lncRNAs regulate gene expression mainly at post-transcriptional level. On the one hand, lncRNAs can facilitate mRNA decay, stabilize mRNAs, and promote or inhibit the translation of target mRNAs through extended base-pairing. On the other hand, lncRNAs can also function as the precursor of microRNAs or compete for microRNA-mediated inhibition, leading to increasing expression of the mRNA (Fig. 2).

4.1. Decrease the stability of mRNAs

LncRNAs can facilitate the degradation of mRNA in two ways: (1) The degradation of Staufen1 (STAU1)-mediated mRNA decay (SMD) needs STAU1 binding with the 3′-untranslated regions (3′UTRs) of SMD target mRNAs. A recent study demonstrates that an Alu element of the cytoplasmic 1/2-sbsRNAs (1/2-Staufen 1-binding site lncRNAs) promotes mRNA decay by partially base-pairing with another Alu element within the 3′UTR of an SMD target mRNA. An individual lncRNA can downregulate a subset of SMD targets and distinct lncRNAs can

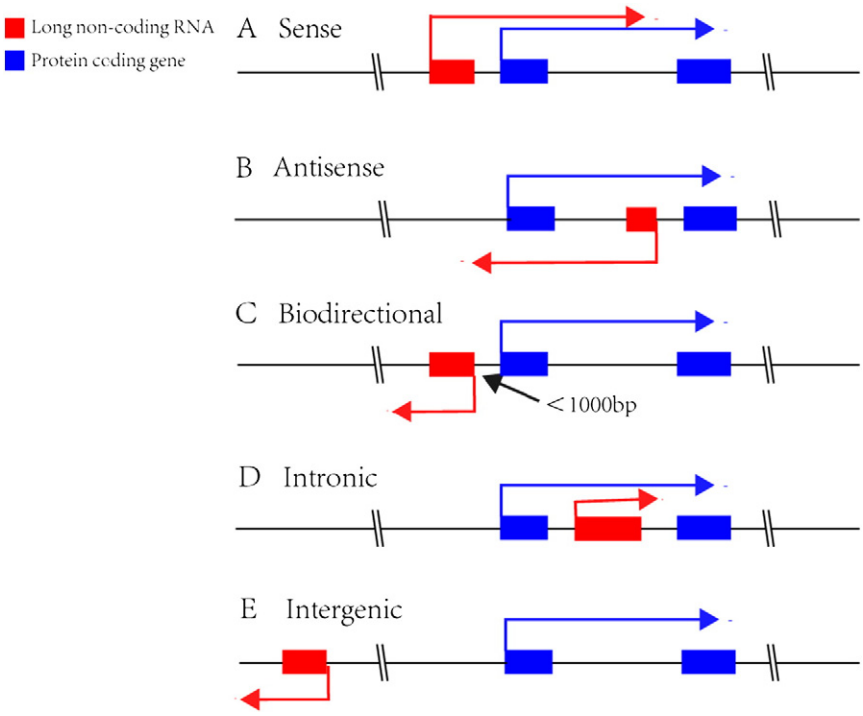

Fig. 1. Overview of five broad categories of lncRNAs. (A) Sense. (B) Antisense. (C) Bidirectional. (D) Intronic. (E) Intergenic.