REVIEW

Long Non-coding RNAs in the Cytoplasm

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Abstract An enormous amount of long non-coding RNAs (lncRNAs) transcribed from eukaryotic genome are important regulators in different aspects of cellular events. Cytoplasm is the residence and the site of action for many lncRNAs. The cytoplasmic lncRNAs play indispensable roles with multiple molecular mechanisms in animal and human cells. In this review, we mainly talk about functions and the underlying mechanisms of lncRNAs in the cytoplasm. We highlight relatively well-studied examples of cytoplasmic lncRNAs for their roles in modulating mRNA stability, regulating mRNA translation, serving as competing endogenous RNAs, functioning as precursors of microRNAs, and mediating protein modifications. We also elaborate the perspectives of cytoplasmic lncRNA studies.

Introduction

Mammalian genome is pervasively transcribed into many different complex families of RNA. However, less than 2% of mammalian genome is transcribed into mRNA to encode proteins, whereas a major portion of the genome is transcribed into interweaved and overlapping transcripts that include thousands of non-coding RNA (ncRNA) transcripts [1,2]. ncRNAs more than 200 nucleotides in length are called long ncRNAs (lncRNAs), which are often transcribed by RNA polymerase II [3,4]. These lncRNAs are usually devoid of open reading frames (ORFs), with or without the 3’ polyadenylation [5–8]. Interestingly, expression of lncRNA is more tissue-specific than that of mRNA [9].

In the last several years, a large number of nuclear lncRNAs have been discovered. These lncRNAs play diverse roles in the nucleus through various mechanisms [10]. For example, nuclear lncRNAs control the epigenetic state of particular genes [11], participate in transcriptional regulation [12], get involved in alternative splicing and constitute subnuclear compartments [13,14].

Although for most if not all of the lncRNAs, nucleus is the place of biogenesis and processing, cytoplasm is the final residence and site of action for some lncRNAs. Biogenesis of lncRNAs is quite complicated and share many features of protein-coding RNAs. Within the nucleus, they occupy the chromatin fraction. 17% of lncRNAs vs. 15% of mRNAs are enriched in the nucleus, whereas 4% vs. 26%, respectively, are enriched in the cytoplasm [6]. Many lncRNA-mediated mechanisms of gene regulation have been identified in the
cytoplasm [8,15,16]. In the last decade or so, thousands of cytoplasmic lncRNAs have been discovered, indicating their importance for multiple cellular activities. In this review we highlight the functions and underlying mechanisms of some important cytoplasmic lncRNAs that are responsible for post-transcriptional regulations such as on mRNA stability and translational control.

Modulation of mRNA stability

In the cytoplasm, several lncRNAs target mRNA transcripts and modulate mRNA stability. Some lncRNAs such as half-STAU1-binding site RNAs (1/2-sbsRNAs) and growth arrested DNA-damage inducible gene 7 (BACE1-AS) increase the stability of mRNA, while others such as antisense transcript for β-secretase 1 (BACE1-AS) and the terminal differentiation-induced ncRNA (TINCR) increase mRNA stability.

1/2-sbsRNAs

mRNAs can be degraded via stau1 (STAU1)-mediated mRNA decay (SMD), when their 3' untranslated region (3' UTR) binds to STAU1 [17]. STAU1 is a double-stranded RNA (dsRNA)-binding protein, which binds within 3' UTR of translationally-active mRNA [14,18]. STAU1 binds to a complex structure of 19-bp stem with 100 nt apex within the 5' UTR of an SMD target and another Alu element in a cytoplasmic, polyadenylated lncRNA [18]. These lncRNAs transactivate the binding of STAU1 to mRNA as only STAU1 could be immunoprecipitated with lncRNAs called 1/2-sbsRNAs, thus unveiling a pivotal strategy of recruiting proteins to mRNAs and mediating the mRNA decay (Figure 1A). However, not all mRNAs containing Alu element in their 3' UTR are targeted for SMD, despite the presence of complementary 1/2-sbsRNAs that target other mRNA for SMD [17]. One of the 378 identified 1/2-sbsRNAs in humans, 1/2-sbsRNA1 contains a single Alu element that base pairs with the Alu element in the 3' UTR of an SMD target and another Alu element in a cytoplasmic, polyadenylated lncRNA [18]. These lncRNAs transactivate the binding of STAU1 to mRNA as only STAU1 could be immunoprecipitated with lncRNAs called 1/2-sbsRNAs, thus unveiling a pivotal strategy of recruiting proteins to mRNAs and mediating the mRNA decay (Figure 1A). However, not all mRNAs containing Alu element in their 3' UTR are targeted for SMD, despite the presence of complementary 1/2-sbsRNAs that target other mRNA for SMD [17]. One of the 378 identified 1/2-sbsRNAs in humans, 1/2-sbsRNA1 contains a single Alu element that base pairs with the Alu element in the 3' UTR of an SMD target and another Alu element in a cytoplasmic, polyadenylated lncRNA [18]. These lncRNAs transactivate the binding of STAU1 to mRNA as only STAU1 could be immunoprecipitated with lncRNAs called 1/2-sbsRNAs, thus unveiling a pivotal strategy of recruiting proteins to mRNAs and mediating the mRNA decay (Figure 1A).

BACE1-AS

Expression of the conserved non-coding BACE1-AS increases BACE1 mRNA stability when HEK-SW cells are exposed to cellular stressors like amyloid-β1–42 (Aβ1–42) [33]. BACE1-AS renders BACE1 mRNA stability by masking the binding site of miR-485-5p (Figure 1A). BACE1-AS and miR-485-5p compete for binding in the sixth exon of BACE1 mRNA. The sense-antisense RNA duplex between BACE1 and BACE1-AS in the cytoplasm potentially perturb the interaction between miR-485-5p and BACE1 mRNA, which to some extent, explains the mRNA stabilization by BACE1-AS transcript [34].

TINCR

The TINCR gene resides on chromosome 19 in humans and encodes a predominantly cytoplasmic 3.7-kb lncRNA. TINCR regulates human epidermal differentiation by post transcriptional mechanism [35]. Previously found as an uncharacterized lncRNA, TINCR is now believed to be the most highly-induced lncRNA during epidermal differentiation [35,36]. TINCR binds to mRNA through a 25-nt 'TINCR box' motif, which is robustly enriched in the interacted mRNAs. TINCR RNA has a strong affinity for STA1 protein [17,35,37,38]. TINCR-STAU1 complex mediates the stabilization of differentiation-related mRNAs, such as KRT80 encoding
keratin 80 in an ultraviolet protection factor 1/2 (UPF1/2)-
independent manner, however the exact mechanism remains
obscure [39].

Modulation of translation

Gene expression control at translational level plays a crucial
role in multiple biological systems and provides valuable
means for the spatiotemporal management of complex protein
dynamics in eukaryotic cells [40–42]. Some lncRNAs also get
involved in such regulation at the translational level, which
can either repress (as exemplified for lincRNA-p21 below) or
promote (as exemplified for AS Uchl1 below) translation.

lincRNA-p21

The human lincRNA-p21 is also known as tumor protein p53
pathway corepressor 1 (Trp53cor1). lincRNA-p21 is ~3.0 kb
in length, and the encoding gene is located ~15 kb upstream
of p21/cdkn1a gene [23]. It is more abundant in cytoplasm
compared to nucleus, known to co-distribute with ribosomes
[43]. As a post-transcriptional modulator, lincRNA-p21 can
negatively regulate the translation of CTNNB1 (β-catenin)
and JUNB transcripts by imperfectly base pairing at different
sites in the coding and untranslated regions (both 5' and 3'
UTRs) of CTNNB1 (15 sites) and JUNB mRNAs (8 sites).
When the level of Hu antigen R (HuR), a ubiquitous RNA
binding protein, reduces, lincRNA-p21 becomes stable and
interacts with its target transcripts including CTNNB1 and
JUNB mRNAs. The resulting lincRNA-p21–mRNA complex
can enhance the interaction between mRNAs and the transla-
tional repressors RCK as well as Fragile X mental retardation
protein (FMRP). Consequently, translation of the target tran-
scripts is repressed through reduced polysome sizes and ribo-
some drop-off (Figure 1B) [43,44].

AS Uchl1

A recent study reported the discovery of a spliced nuclear-enriched antisense transcript (AS Uchl1) complementary to
the mRNA that encodes mouse ubiquitin carboxy terminal
hydrolase L1 (Uchl1) [45]. Uchl1 is an enzyme specifically
expressed in dopaminergic neurons [24,46,47]. The activity of
the AS Uchl1 depends on the presence of a 73-nt overlapping
sequence complementary with 5’ end of Uchl1 mRNA and
an embedded inverted SINEB2 repetitive element (Figure 1B) [45]. Under normal physiological conditions, AS Uchl1 is enriched in the nucleus, and upon rapamycin treatment, inhibition of mTORC1 triggers the transport of AS Uchl1 to the cytoplasm, which then targets the overlapping Uchl1 mRNA to active polysomes for cap-independent translation. Exact molecular mechanism as to how AS Uchl1 promotes the translation of Uchl1 mRNA under stress conditions is still elusive.

Competing endogenous RNAs

Coding and non-coding RNAs can regulate each other through their ability to compete for miRNA binding. lncRNAs harboring multiple binding sites of identical miRNA are called competing endogenous RNAs (ceRNAs) [48]. ceRNA can sequester miRNAs and therefore protect their target mRNAs from repression [49–53]. This activity was first discovered in Arabidopsis thaliana and later in mammals [53,54]. Multiple ceRNAs have been identified, and we present some as examples below.

**HULC**

Hepatocellular carcinoma (HCC) is one of the most fatal cancers [55]. Recent studies have indicated that a large number of lncRNAs are functionally deregulated in HCC [56–59]. Among these, highly up-regulated in liver cancer (HULC) is a novel mRNA-like ncRNA. It is present in the cytoplasm, spliced, polyadenylated, and resembles the mammalian LTR transposon 1A [60]. As reflected by its name, HULC is highly upregulated in HCC, and it is also detected in gastric cancer and colorectal carcinomas that metastasize to the liver [60–62]. The HULC gene resides on chromosome 6p24.3 in humans and is conserved in primates. It is about 1.6 kb in length and contains two exons. Expression of HULC gene in Hep3B cells can be up-regulated by the transcription factor cAMP responsive element binding protein (CREB). HULC acts as endogenous sponge of miR-372 [63]. HULC binding to miR-372 reduces mRNA-mediated translational repression of protein kinase cAMP-activated catalytic subunit beta (PRKACB), one of the target genes of miR-372 [63]. PRKACB can induce phosphorylation of CREB, which in turn stimulates HULC expression, thus forming a feedforward loop [63].

**linc-MD1**

linc-MD1 is a muscle-specific lncRNA, which is indispensable for the timing of muscle differentiation and plays an important role in myogenesis [64]. linc-MD1 acts as a natural decoy for two muscle-specific miRNAs, miR-133 and miR-135 (Figure 1C) [64]. Expression of mastermind-like-1 (MAML1) is controlled by miR-133, and myocyte-specific enhancer factor 2C (MEF2C) is the target of miR-135 [64]. MAML1 and MEF2C are important myogenic factors required for activation of muscle-specific genes. MEF2C binds to the promoter region of cardiac muscle genes and positively regulates the differentiation of muscle cells [65,66], while MAML1 acts as a transcription coactivator in some signal transduction pathways (such as Notch signaling) related to muscle differentiation [67]. With the depletion of linc-MD1, expression of both MAML1 and MEF2C is repressed, whereas over expression of linc-MD1 resulted in high levels of MAML1 and MEF2C. These observations argue for a direct competition between linc-MD1 and mRNAs for miRNA binding [64].

**linc-RoR**

The lncRNA regulator of reprogramming (linc-RoR) functions as microRNA (miRNA) sponge against miR-145. Interaction between linc-RoR and miR-145 prevents mRNA of some important transcription factors (TFs) like Oct4, sox2, and Nanog in human embryonic stem cells (hESCs) from miRNA-mediated regulation [68,69]. The expression of linc-RoR is positively correlated with the undifferentiated state of hESCs [69].

**CDR1as and circSry**

Recently, additional examples of ceRNA were found in circu lar RNAs (circRNAs), which represent a newly identified large class of lncRNAs [70–72]. circRNAs can be formed by back-splicing of the 5’ end of an upstream exon with the 3’ end of the same exon or a downstream exon. Although some cir cRNAs such as ElciRNAs are predominantly localized in the nucleus, circRNAs are generally cytoplasmic. circRNAs appear to be non-coding and lack the association with poly somes [71,73]. Two cytoplasmic circRNAs have been reported to act as miRNA sponge. The first one is the cerebellar degeneration-related protein 1 antisense transcript (CDR1as, also called ciRS-7), which is a sponge for miR-7 (Figure 1C). CDR1as contains 74 miR-7 seed matches, out of which 63 are conserved in mammals [72]. The other one is a testis-specific circRNA encoded by the gene sex-determining region Y (circSry), which contains 16 putative binding sites for miR-138 [71,72,74]. These two circRNAs may be special cases, and it may not be a general phenomenon for circRNAs to function as miRNA sponges [75].

**Precursor of miRNAs**

A genome-wide survey predicted that nearly 100 lncRNAs encode miRNAs [76]. These lncRNAs may not be predominantly cytoplasmic, but they may be processed in the nucleus and cytoplasm to give rise to functional miRNAs.

**H19**

H19 is one of the best known imprinting genes expressed from the maternal allele and required for proper muscle differentiation and muscle regeneration [77–79]. The H19 gene is present on chromosomes 11 and 7 in humans and mice, respectively [80,81]. There is no conserved ORF sequence in H19 RNA between mice and human. Although the H19 gene is imprinted paternally, the H19 RNA itself does not take part in imprinting mechanism [82]. Studies based on structure prediction suggest that H19 is a ncRNA, 2.3-kb long, capped, spliced, and polyadenylated [82,83]. It is reported that H19 lncRNA acts as a molecular sponge for let-7 family of miRNAs in a HEK293 cell line [84]. Depleting H19 causes accelerated muscle differentiation, which can be recapitulated by let-7
overexpression [84]. In the cytoplasm of undifferentiated multipotent mesenchymal C2C12 cells, H19 interacts with the K homology-type splicing regulatory protein (KSRP).

Such binding favors KSRP-mediated destabilization of myogenin transcripts [85]. Besides the aforementioned roles of H19, exon 1 of H19 also gives rise to miR-675-3p and miR-675-5p (Figure 1D). miR-675-3p targets the gene encoding the anti-differentiation TFs smad1 and smad5, which are crucial components of the bone morphogenetic protein (BMP) pathway [86], whereas miR-675-5p targets the gene encoding DNA replication initiation factor Cdc6 [86].

In this regard, H19 has a pro-differentiation function in primary myoblasts and regenerating skeletal muscles due to the resulting miR-675-3p and miR-675-5p [86,87]. H19 is also found to regulate placenta growth. Insulin like growth factor 2 (Igf2), which is also targeted by miR-675-3p, is an important regulator of growth and is upregulated in H19-deficient placenta [88]. H19 is also found to modulate gastric cancer cell proliferation through miR-675, by targeting the gene encoding the tumor suppressor runt domain transcription factor1 (RUNX1). Thus H19/miR-675 regulates the expression of RUNX1 to modulate gastric cancer [89].

**line-MD1 (again)**

We discussed line-MD1 as a ceRNA before. However, line-MD1 primary transcript also harbors the pri-miR-133b sequence. If cleaved by Drosha in the nucleus, line-MD1 can give rise to a miRNA precursor. Recently, HuR protein is described as another component of line-MD1 regulatory circuitry [90]. HuR is known to contribute to muscle differentiation [91]. HuR interacts with many coding and non-coding RNAs, indicating its pleiotropic RNA binding activity [92,93]. HuR binds to and favors line-MD1 accumulation at the expense of miR-133 biogenesis. HuR also recruits miR-133 onto line-MD1 in the cytoplasm, thereby reinforcing this regulatory circuitry. There is an inverse correlation between levels of HuR and miR-133b. HuR binds the base of the pri-miR-133b stem loop, and physically interferes with microprocessor activity [90]. Further investigations have to be carried out to answer how the processing and function of line-MD1 are regulated either as the pri-miR-133b in the nucleus or as sponge for miR-133b when exported to the cytoplasm as an unprocessed transcript.

**Regulation of protein modification**

In the recent years, several lncRNAs are identified to modulate modifications of cytoplasmic proteins such as ubiquitination/deubiquitination or phosphorylation/dephosphorylation.

**lnc-DC**

Expression of lnc-DC is almost exclusive to human conventional dendritic cells (DCs) [94]. lnc-DC could help activate STAT3 by binding to it in the cytoplasm, thus promoting the phosphorylation and preventing dephosphorylation of STAT3. Knockdown of lnc-DC inhibited the differentiation to the DC lineage as well as the functions of DCs [94].

**NKILA**

NF-κB interacting lncRNA (NKILA) binds directly to IκB and blocks IKK-induced IκB phosphorylation, thus inhibiting NF-κB activation (Figure 1E) [95]. The expression of NKILA is also upregulated by NF-κB. NKILA interacts with the NF-κB/IκB complex, and seems to keep the NF-κB pathway from over-activation and to suppress cancer metastasis [95].

**Another role of lincRNA-p21**

lincRNA-p21 was reported to regulate the ubiquitination of HIF-1α, a transcription factor crucial to hypoxia-induced effects such as Warburg effect [96]. lincRNA-p21 is induced by HIF-1α under hypoxia condition, and binds to both HIF-1α and von Hippel–Lindau tumor suppressor (VHL) protein. Such binding blocks the interaction between VHL and HIF-1α, thus inhibiting VHL-mediated ubiquitination of HIF-1α. This positive feedback loop between HIF-1α and lincRNA-p21 promotes glycolysis under hypoxia [96].

**Perspectives**

lncRNAs are recognized as major regulators in life events such as gene expression, cell differentiation, and tumorigenesis. In this article, we summarized the roles of some lncRNAs in the cytoplasm. lncRNAs can function in the posttranscriptional gene expression such as mRNA stability and translation. Through RNA–protein or RNA–RNA interaction, cytoplasmic lncRNAs could also serve as ceRNAs, miRNA precursors, or modulators of protein phosphorylation. Recent findings have shown that certain transcripts previously-annotated as lncRNAs in fact can be translated to produce small bioactive peptides [97–100]. For instance, the conserved micropeptide myoregulin (MLN) was found to be encoded by a skeletal muscle-specific RNA, a previously putative lncRNA [100]. MLN shows structural and functional similarity with SERCA inhibitors, phospholamban and sarcolipin. Interacting directly with SERCA, MLN disrupts the Ca^{2+} uptake into the sarcoplasmic reticulum [100]. Similarly, the endogenous 34-amino acid micropeptide dwarf open reading frame (DWORF) is encoded by another putative muscle-specific lncRNA. DWORF enhances muscle performance by physically interacting with SERCA inhibitors such as phospholamban, sarcolipin, and MLN [100]. These examples demonstrated that some (although maybe limited in numbers) transcripts that are previously annotated as lncRNAs are actually coding, and thus should be considered as mRNAs. Given the vast amount of lncRNAs identified, and many of them are associated with noncoding functions, it is no doubt that more functions and functional working mechanisms are yet to be explored for the large number of cytoplasmic lncRNAs. Regulation of lncRNA localization is important to coordinate their functions in the nucleus or in the cytoplasm. There should exist machinery either directly or indirectly to transport specific lncRNAs into the cytoplasm, and maybe further to special subcellular locations or complexes. The final localization, concentration, and functions of a specific lncRNA have to be fine tuned by the RNA biogenesis, transportation,
degradation, and maybe even modifications. Substantial efforts are required to investigate these aspects.

A single lncRNA can have multiple roles. For example, both H19 and linc-MD1 can function as ceRNAs as well as precursors for miRNAs. How these different roles of the same lncRNA are coordinated remains to be addressed. On the other hand, there are undoubtedly more roles and functional mechanisms remain unknown for cytoplasmic lncRNAs. With the extensive investigations of the eukaryotic transcriptome by means of RNA sequencing, most of the lncRNAs including cytoplasmic ones may have already been described. Further studies on these lncRNAs may help to classify them into sub-classes based on their biogenesis and functions.

Competing interests

The authors declare no competing interests.

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