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Cytoplasmic functions of lncRNAs

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Abstract

Long noncoding RNAs (lncRNAs) are transcripts longer than 200 nucleotides found throughout the cell that lack protein-coding function. Their functions are closely linked to their interaction with RNA-binding proteins (RBPs) and nucleic acids. Nuclear lncRNAs have been studied extensively, revealing complexes with structural and regulatory roles that enable gene organization and control transcription. Cytoplasmic lncRNAs are less well understood, but accumulating evidence indicates that they also form complexes with diverse structural and regulatory functions. Here, we review our current knowledge of cytoplasmic lncRNAs and the different levels of gene regulation controlled by cytoplasmic lncRNA complexes, including mRNA turnover, translation, protein stability, sponging of cytosolic factors, and modulation of signaling pathways. We conclude by discussing areas of future study needed to investigate comprehensively the biology of lncRNAs, to further understand the impact of lncRNAs on physiology and design lncRNA-centered therapeutic strategies.

Keywords

noncoding RNA; post-transcriptional gene regulation; ribonucleoprotein complexes; lncRNA; circRNA; miRNA

Introduction

Long noncoding RNAs (lncRNAs)

The identification of complete transcriptomes in a wide range of species, including human, revealed that a vast portion of transcripts do not encode protein (Carninci et al., 2005; Derrien et al., 2012; Hangauer, Vaughn, & McManus, 2013). Among those noncoding (nc)RNAs, long noncoding (lnc) RNAs are defined as being >200 nt in length and reside throughout the cell. Recently, *de novo* transcriptome assembly of next-generation RNA sequencing (RNA-seq) data collected from various human tissues identified >50,000 lncRNAs present at one copy or more per cell, and transcribed from intergenic regions (lincRNAs) or from introns and/or exons of protein-coding genes in the sense or antisense

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Conflicts of Interest

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direction (Derrien et al., 2012; Montes & Lund 2016). Through their primary sequence and secondary structure, lncRNAs can bind to other nucleic acids and/or proteins to regulate gene expression programs, in turn controlling a growing number of cellular processes, such as cell division, the stress response, differentiation, survival, and senescence (Grammatikakis, Panda, Abdelmohsen, & Gorospe, 2014; Li, Tian, Yang & Gong, 2016; Audas & Lee S, 2016; Chen, Satpathy, & Chang, 2017). By affecting these processes, there is increasing appreciation that lncRNAs have a direct impact on the physiology of tissues and organs, and on a growing number of disease processes (e.g. muscle disease, cancer, and cardiovascular pathologies) (Greco, Gorospe, & Martelli, 2015; Schmitt, & Chang, 2016; Ballarino, Morlando, Fatica, & Bozzoni, 2016; Alvarez-Dominguez, & Lodish. 2017; Wang, Xiao, and Wang; 2017). Despite intense efforts, however, only a small number of lncRNAs have been characterized functionally, while the vast majority of lncRNAs have no known functions at present.

Nuclear lncRNAs and their nuclear functions have been studied quite extensively, revealing a number of nucleus-specific lncRNA functions (i.e. chromosome scaffolding, chromatin remodeling, alternative splicing, epigenetic control of transcription, etc), most often serving key regulatory roles for transcriptional programs and subcellular structures (Derrien et al., 2012; Kugel, & Goodrich, 2012; Tripathi et al., 2013; Hung et al., 2011; Clemson et al., 2009; Zhao, Sun, Erwin, Song, & Lee, 2008; Lee, 2012; Mercer et al., 2011). These structural and functional roles were found to require, almost universally, the interaction of lncRNAs with RNA-binding proteins (RBPs), forming nuclear lncRNA-associated ribonucleoprotein complexes (lncRNPs).

Cytoplasmic lncRNAs, on the other hand, also form complexes with RBPs but are substantially less well understood. Recent studies showed that cytoplasmic lncRNPs can comprise lncRNAs transcribed from nuclear DNA or expressed locally in the cytoplasm (e.g. mitochondrial DNA-encoded lncRNAs) (Mercer et al., 2011). These cytoplasmic lncRNPs can govern cytoplasmic events essential for maintaining cellular structure and functions (Yoon, Abdelmohsen, & Gorospe, 2013; Rashid, Shah, & Shan, 2016), including protein localization and turnover, mRNA translation and stability, availability of cytoplasmic factors, and scaffolding of proteins operating in a shared pathway. In this review, we focus on the major cytoplasmic lncRNPs studied to-date (Table 1), discuss their functions in different cellular contexts (Figure 1), and suggest directions of future research that will advance our knowledge of lncRNP function.

LncRNAs controlling mRNA stability and translation

Cytoplasmic lncRNAs can modulate two cytoplasmic processes closely interconnected that impact profoundly on protein production: the turnover and translation of specific mRNAs. As discussed below, this influence may be elicited through the binding of lncRNAs to mRNAs leading to the recruitment of RBPs that promote decay, RBPs that suppress translation, or factors that initiate translation. It may also be mediated via lncRNA-mRNA complexes that prevent microRNAs from binding the intended target mRNAs. These regulatory paradigms were found to influence specific physiologic processes, including muscle homeostasis, Alzheimer's pathogenesis, and T lymphocyte function. We anticipate

that additional mechanisms of lncRNA-mediated translation and turnover of mRNAs will be elucidated as studies in these areas continue to advance.

1/2-sbsRNAs-STAU1, *TINCR*-STAU1

Intermolecular base-pairing was reported between an Alu element present in a 3′-untranslated region (UTR) and a partially complementary Alu sequence present within a class of lncRNAs named 1/2-sbsRNAs (half STAU1-binding site RNAs). The ensuing double-stranded RNA can recruit the RBP STAU1 (Staufen1), resulting in the degradation of the target mRNAs via a process called STAU1-mediated mRNA decay (SMD, reviewed by Park & Maquat, 2013), which additionally implicates the RNA helicase UPF1. Depletion of 1/2-sbsRNAs led to the upregulation of the respective target mRNAs (Gong & Maquat, 2011).

Terminal differentiation-induced ncRNA (*TINCR*) is another cytoplasmic lncRNA associating directly with STAU1. Recently, the *TINCR*-STAU1 lncRNP complex was found to be necessary for epidermal differentiation (Kretz et al., 2013). *TINCR* interacts with various mRNAs encoding differentiation proteins through a 25-nucleotide 'TINCR box' motif that is highly enriched in such mRNAs, and renders the mRNAs stable. Notably, the lack of change in *TINCR* levels by STAU1 depletion and the direct binding of *TINCR* to STAU1 without other RNAs such as 1/2-sbsRNA indicates that *TINCR* is not a direct degradation target of STAU1 (Kretz et al., 2013). This finding also suggests alternative, UPF1/2-independent ways in which STAU1 regulates mRNAs, possibly involving *TINCR*-STAU1 lncRNP complexes in the cytoplasm.

Recently, Ravel-Chapuis et al. suggested novel rescue functions for STAU1 in myotonic dystrophy type 1 (DM1). Overexpressed STAU1 was found to induce the nuclear export and translation of mRNAs bearing expanded CUG repeats (CUG^{exp}) in noncoding segments, and it rescued the alternative splicing of insulin receptor (IR) pre-mRNA, both of which provide beneficial effects to DM1 (Ravel-Chapuis et al., 2012). Additional transcriptome-wide studies are needed to understand the mechanisms whereby STAU1 affects the fate of coding and noncoding RNAs.

LincRNA-p21-HuR

Although nuclear *lincRNA-p21* had been shown to regulate transcription (Huarte et al., 2010; Dimitrova et al. 2014), Yoon et al. reported a model of translational suppression mediated by *lincRNA-p21*. Cytoplasmic *lincRNA-p21* was found to bind the RBP HuR [human antigen R, also known as ELAV-like protein (ELAVL)1] and this interaction led to the recruitment of microRNA let-7 along with the RNA-induced silencing complex (RISC) onto *lincRNA-p21*, triggering its degradation. In the absence of HuR, *lincRNA-p21* was stable, accumulated in the cytoplasm, and was proposed to form partial hybrids through multiple regions of complementarity with target mRNAs including *CTNNB1* mRNA [encoding CTNNB1 (β-catenin)] and *JUNB* mRNA (encoding the transcription factor JUNB). These regions of partial base-paring at coding and noncoding mRNA segments led to the recruitment of translational suppressors RCK/p54 and FMRP and lowered the translation of CTNNB1 and JUNB (Chu & Rana, 2006; Yoon et al., 2012).

BACE1-AS-HuD

BACE1 [β-site amyloid precursor protein (APP)-cleaving enzyme 1] is a crucial enzyme in the pathophysiology of Alzheimer's disease (AD), as it cleaves APP to generate the toxic peptide Aβ, which can then lead to the formation of amyloid plaques that are the hallmark of AD (Faghihi, Mottagui-Tabar, &Wahlestedt, 2004). As reported earlier, the cytoplasmic function of lncRNA *BACE1-AS* (BACE1 antisense) is to enhance the stability of *BACE1* mRNA through a region of partial complementarity, following exposure to various cell stressors including Aβ42 (Faghihi et al., 2008). Kang and colleagues subsequently found that the cytoplasmic RBP HuD (ELAVL4) (Kasashima, Terashima, Yamamoto, Sakashita, & Sakamoto, 1999), increased the stability of *BACE1-AS*, as well as the stabilities of *BACE1* and *APP* mRNAs, thereby coordinating several steps that converge on the generation of amyloidogenic Aβ in the AD brain (Kang et al., 2014). Faghihi and coworkers discovered that the base-pairing between *BACE1* mRNA and *BACE1-AS* resulted in the masking of a binding site for miR-485-5p, which would otherwise suppress BACE1 biosynthesis (Faghihi et al., 2010). Together, these findings indicate that the mRNP and lncRNP complexes involving HuD (with *APP* mRNA, *BACE1* mRNA, and *BACE1-AS*) jointly regulate the processing of APP to Aβ.

GAS5-eIF4E

The cytoplasmic lncRNA *GAS5* was previously known to be upregulated in human T cells in response to the mTOR antagonist rapamycin (Mourtada-Maarabouni, Hasan, Farzaneh, & Williams, 2010). Considering the crucial role of mTOR in protein translation, this finding suggested that *GAS5* might affect gene expression at the translational level.

GAS5 was subsequently found to regulate negatively the translation of the protein MYC (c-Myc) without affecting the levels of *MYC* mRNA or the stability of MYC protein. The authors reported that *GAS5* was recruited to the translation initiation complex via direct binding to eIF4E. The direct interaction between *MYC* mRNA and *GAS5* in the non-polysomal fraction suggested that *GAS5* might decrease the efficiency of the initiation of *MYC* mRNA translation (Hu, Lou, & Gupta, 2014).

Uchl1-AS1-Uchl1 mRNA

The antisense lncRNA *Uchl1-AS1* is predominantly nuclear, but shuttles to the cytoplasm under stress conditions to bind the first 73 nt in the 5′UTR of *Uchl1* mRNA. This interaction triggers increased translation of the protein UCHL1 (Carrieri et al., 2012). However, it is not clear if specific RBPs are involved in either the export of *Uchl1-AS1* to the cytoplasm or the enhanced *Uchl1* mRNA translation.

LncRNAs regulating protein stability

Cytoplasmic lncRNAs may also influence protein expression programs by controlling protein degradation pathways, notably by hindering or enhancing access to the ubiquitin/proteasome machinery. As discussed in this section, examples of processes modulated by lncRNA-regulated protein stability include cellular senescence, the hypoxia response, and viral replication.

LincRNA-p21-HIF-1α

In addition to its function in repressing translation of partially complementary mRNAs (as mentioned above; Yoon et al., 2012), *lncRNA-p21* elevation by hypoxic conditions contributed to hypoxia-enhanced glycolysis. Yang and colleagues found that the hypoxia-induced protein HIF1A (HIF-1α) transcriptionally activated *lncRNA-p21*, which in turn bound to both HIF1A and the von Hippel-Lindau (VHL) protein, thereby preventing VHL-mediated HIF1A ubiquitination and allowing HIF1A to accumulate. They suggested that a positive feedback loop between HIF1A and *lincRNA-p21* promoted glycolysis under hypoxia (Yang, Zhang, Mei, & Wu, 2014).

HOTAIR-Snurportin-1, *HOTAIR*-Ataxin-1

Similar to the above-mentioned mechanisms whereby HuR binding to *lncRNA-p21* led to the recruitment of let-7/RISC, HuR binding to the lncRNA *HOTAIR*, a lncRNA that resides both in the nucleus and the cytoplasm, also led to let-7/RISC-mediated degradation of *HOTAIR*.[38] In conditions of low HuR abundance in cells (e.g., during senescence), *HOTAIR* was stable and accumulated in the cytosol, serving as a physical substrate for other proteins, including two ubiquitin ligases (DZIP3 and MEX3B) and their respective substrates [Snurportin 1 (SNUPN) and Ataxin-1 (ATXN1)]. Accordingly, when *HOTAIR* levels were high, SNUPN and ATXN1 were ubiquitinated and degraded, while reductions in *HOTAIR* allowed SNUPN and ATXN1 to accumulate in human fibroblasts and cancer cells (Yoon et al., 2013).

NRON-CUL4B, *NRON*-PSMD11

Recently, Li et al. reported that the cytoplasmic lncRNA *NRON* controlled HIV latency by suppressing the activation of the HIV-1 promoter. However, the authors also found that *NRON* interacted with the HIV protein Tat and promoted its degradation by recruiting the ubiquitin/proteasome components CUL4B (Cullin 4B) and PSMD11 (Proteasome 26S Subunit, Non-ATPase 11), which also associate with *NRON*. By forming the lncRNP complex *NRON*-CUL4B-PSMD11-Tat, *NRON* promotes the degradation of the essential HIV-1 regulatory protein Tat via the ubiquitin/proteasome system (Li et al., 2016).

LncRNAs regulating RBP availability

Accumulating evidence suggests that cytoplasmic lncRNAs can also serve as ‘decoys’ for RBPs, dissociating RBPs from target mRNAs, and thereby influencing the abundance and translation of such mRNAs. In some cases, the sequestration of RBPs by lncRNAs in the cytoplasm affected the actions of such RBPs in other locales (e.g., transcription in the nucleus). LncRNAs that modulate the molecular and spatial availability of RBPs were found to affect the cell division cycle, the cellular response to damaging agents, the oncogenic response, and the process of muscle differentiation.

gadd7-TDP-43

The lncRNA *gadd7* (growth arrest- and DNA damage-inducible gene 7) was first identified in mammalian cells responding to growth inhibition and different types of damage (Fornace, Alamo, & Hollander, 1988; Hollander, Alamo, & Fornace, 1996; Brookheart, Michel,

Listenberger, Ory, & Schaffer, 2009). *Gadd7* binds TAR DNA-binding protein 43 (TDP-43), an RBP involved in mRNA transcription, processing, and stabilization (Buratti, & Baralle, 2008). Induction of *gadd7* in Chinese hamster ovary (CHO)-K1 cells following ultraviolet light irradiation increased *gadd7*-TDP-43 complexes, in turn preventing the binding of TDP-43 to cyclin-dependent kinase 6 (*Cdk6*) mRNA and triggering *Cdk6* mRNA decay (Liu, Li, Zhang, Guo, & Zhan, 2012).

OIP5-AS1-HuR

OIP5-AS1 (*OIP5 antisense RNA 1*) is a mammalian lncRNA spanning ~1.9 kb that is abundant in the cytoplasm (van Heesch et al., 2014). First identified as *Cyrano* in zebrafish, this lncRNA was found to be involved in brain and eye development (Ulitsky, Shkumatava, Jan, Sive, & Bartel, 2011). Recently, Kim et al. found that *OIP5-AS1* interacted with cytoplasmic HuR in human cervical carcinoma cells. The authors uncovered a possible sponging function for *OIP5-AS1*, as it prevented HuR binding to target mRNAs (including those that encode proteins CCNA2, CCND1, and SIRT1), and thus suppressed the HuR-elicited proliferative phenotypes (Kim et al., 2016). In addition, *OIP5-AS1* was found to interact with *GAK* mRNA, promoting *GAK* mRNA decay and hence reducing GAK protein levels and lowering cell proliferation (Kim et al., 2017). These findings indicate that *OIP5-AS1*, in HuR-dependent and -independent ways, is capable of regulating the levels of target mRNAs, and thus suppresses cell division.

7SL-HuR

The noncoding RNA *7SL* is an essential component of the signal recognition particle (SRP) which transports proteins for secretion or membrane insertion (Walter, Blobel, 1982). *7SL* interacts with the 3′UTR of the mRNA encoding the transcription factor and tumor suppressor TP53 (p53), thereby preventing HuR binding to *TP53* mRNA and repressing TP53 translation. Downregulation of *7SL* enhanced HuR binding to *TP53* mRNA, leading to increased TP53 translation and hence triggering senescence, autophagy, and cell cycle arrest (Abdelmohsen et al., 2014). This example illustrates a regulatory paradigm whereby noncoding RNAs associate with mRNAs to modulate RBP binding and influence mRNA fate.

LncMyoD-IMP2

As reported recently by Gong and colleagues, murine lncRNA *lncMyoD* was directly activated by its neighboring gene *Myod* and controlled cell-cycle exit during myoblast differentiation. The formation of a novel lncRNP comprised of *lncMyoD* and IMP2 (IGF2-mRNA-binding protein 2) caused a reduction in IMP2-mediated translation of proliferative proteins such as NRAS and MYC (Gong et al., 2015).

GAS5-GR

Besides the aforementioned function as an inhibitor of translation initiation (Hu G, Lou Z, Gupta M, 2014), lncRNA *GAS5* was found to be involved in regulating cell growth by acting as a decoy for glucocorticoid receptor (GR). The transcription factor GR was inhibited through binding to *GAS5* in the cytoplasm, which prevented the mobilization of

GR to the nucleus and suppressed the transcriptional program mediated by GR (Mourtada-Maarabouni, Pickard, Hedge, Farzaneh, & Williams, 2009).

H19-KSRP

The lncRNA *H19* controls imprinting of a conserved cluster of genes that includes *IGF2* (insulin-like growth factor 2), which encodes a protein important for cell proliferation, survival, fat metabolism, and fat deposition (Jones, Levorse, &Tilghman, 2001). A recent study revealed that *H19* interacts with K homology-type splicing regulatory protein (KHSRP or KSRP) in the cytoplasm of mouse C2C12 myoblasts, in turn causing the destabilization of the *Myog* mRNA [encoding the muscle protein myogenin (MYOG)], a labile KSRP-target transcript. This lncRNP complex was dissociated by AKT activation, thereby permitting KSRP to bind and stabilize *Myog* mRNA, and inducing muscle differentiation (Giovarelli et al., 2014).

UCA1-HNRNPI

UCA1 (Urothelial cancer-associated 1) was first identified as an oncogenic lncRNA that was highly expressed in human bladder cancer (Wang et al., 2006). Recently, *UCA1* was found to promote breast cancer cell growth by lowering the expression of the tumor suppressor CDKN1B (p27), a protein that is translationally upregulated by HNRNPI (hnRNP I). The reduction in p27 levels was proposed to be mediated, at least in part, via *UCA1* binding to HNRNPI, as this interaction prevented the binding of HNRNPI to the 5′UTR of *p27* mRNA and suppressed p27 translation. Silencing *UCA1* promoted growth arrest by enabling the restoration of p27 translation by HNRNPI (Huang et al., 2014).

In addition, many other lncRNPs modulate the activity of the RBPs in the complex, and thus indirectly affect the outcome of the mRNAs that are targets of such RBPs. For example, Gumireddy and colleagues identified a translational repressor RNA (‘treRNA’) that reduced E-cadherin (CDH1) translation via the actions of three proteins (hnRNPK, FXR1, and FXR2) (Gumireddy et al, 2013). The authors postulated that *treRNA* was instrumental in assembling these three proteins on the 3′UTR of *E-cadherin* mRNA, thereby reducing E-cadherin translation, even though treRNA and *E-cadherin* mRNA did not interact. In another example, Tichon and colleagues linked the actions of lncRNA *NORAD* (Lee et al., 2016) to the half-lives of mRNAs which are targets of PUM1 and PUM2; the observed effects appeared mediated via the classic mRNA decay-promoting function of Pumilio proteins, and only indirectly by *NORAD* (Tichon et al., 2016).

LncRNAs as microRNA decoys

Cytoplasmic lncRNAs may also function broadly as competing endogenous (ce)RNAs. By sequestering miRNAs, they reduce their availability to AGO2/RISC and hence to target mRNAs. In this manner, cytoplasmic lncRNAs can relieve numerous instances of miRNA-mediated translational repression. LncRNAs that modulate the availability of microRNAs have been implicated in carcinogenesis and in differentiation programs including myogenesis.

HULC

The lncRNA *HULC* ('highly upregulated in liver cancer') is processed like mRNA as it undergoes splicing and polyadenylation (Panzitt et al., 2007). The microRNA miR-372 is known to bind to *PRKACB* (protein kinase cAMP-activated catalytic subunit beta) mRNA and repress its translation. *HULC* acts as a microRNA decoy or sponge for miR-372 and thereby enhances *PRKACB* mRNA translation. Interestingly, PRKACB phosphorylates and activates the transcription factor CREB (cAMP-responsive element-binding protein), which promotes the transcription of *HULC* (Wang et al., 2010).

LincRNA-RoR

LincRNA-RoR also functions as a microRNA sponge in embryonic stem cells, controlling the levels of miR-145 available to repress production of the transcription factors and regulators of differentiation NANOG, OCT4, and SOX2 (Loewer et al., 2010; Wang et al., 2013).

H19

Besides binding RBPs, as mentioned in the previous section (Giovarelli et al., 2014), *H19* acts as a sponge for microRNA let-7 in HEK293 cells, and was thus proposed to be pro-oncogenic. Accordingly, depleting *H19* increased let-7 activity and muscle differentiation in C2C12 cells (Kallen et al., 2013). Interestingly, *H19* is also the host of microRNA miR-675, which suppresses the production of the tumor suppressor PTEN, further enhancing the oncogenic function of *H19* (Cai & Cullen, 2007).

Linc-MD1

The cytoplasmic, muscle-specific lncRNA *linc-MD1* was previously known to act as a competitor endogenous (ce)RNA for miR-133 and miR-135; miR-133 reduces the levels of the protein mastermind-like-1 (MAML1), miR-135 lowers the abundance of myocyte-specific enhancer factor 2C (MEF2C). In this paradigm, expression of *linc-MD1* increased the levels MAML1 and MEF2C through the inhibition of microRNA activity (Cesana et al., 2011). Recently, Legnini et al. proposed a novel feedforward regulatory mechanism involving HuR and *linc-MD1* in early phases of muscle differentiation. Intriguingly, HuR was found to interact with both *linc-MD1* and miR-133b and was proposed to recruit miR-133b onto *linc-MD1* in the cytoplasm. This paradigm was further complicated by the repression of HuR production by miR-133. Cytoplasmic HuR increased the sponging activity of *linc-MD1* and inhibited the generation of miR-133b from a precursor sequence embedded in *linc-MD1* by interfering with the access of DROSHA, an RNase involved in processing microRNAs. In later differentiation stages, HuR levels declined as miR-133 levels rose, triggering its exit from the regulatory circuit (Legnini, Morlando, Mangiavacchi, Fatica, & Bozzoni, 2014).

PTENP1

LncRNA *PTENP1*, expressed from a *PTEN* pseudogene, is a well-recognized sponge of several microRNAs, including miR-21, miR-20a, miR-214, miR-19b, miR-26a, and miR-499-5p. As reviewed by Tang, Ning, Zeng, & Li (2016), these microRNAs also target

the *PTEN* 3′UTR and repress production of the tumor suppressor PTEN. By sponging this group of microRNAs, lncRNA *PTENP1* derepresses PTEN production and enables its tumor suppressor function.

Subcellular mobilization of lncRNAs

LncRNAs can shuttle to various subcellular locations, sometimes leading to their accumulation in specific cellular compartment (van Heesch et al. 2014; Cabili et al. 2015). The studies discussed in this section reveal that the local interaction of lncRNAs with RBPs is critical for retaining structural and functional integrity of subcellular organelles such as mitochondria, as well as for T cell function.

NRON-NFAT

A decade ago, Willingham et al. suggested a novel function for a cytoplasmic lncRNA (now named *NRON*) that regulated the nuclear translocation of nuclear factor of activated T cells (NFAT) and involved importin-β (Willingham et al. 2005). This example was among the first to illustrate the shuttling of lncRNAs among subcellular compartments. As mentioned above, *NRON* was subsequently implicated in HIV replication (Li et al., 2016).

MALAT1-HNRNPC

Recent efforts to create a ‘subcellular atlas’ have made it possible to classify a number of lncRNAs according to their subcellular localization. *MALAT1* was known to be predominantly nuclear, but *MALAT1* transcripts were recently found to enter the cytoplasm in the G2/M phase. In this regard, the RBP HNRNPC was found to form a lncRNP with *MALAT1* that mediated its cytoplasmic translocation during the G2/M phase transition (Yang, Yi, Ha, Du, & Liang, 2013), providing an example of lncRNPs that promote the timely mobilization of lncRNAs and RBPs to elicit appropriate cellular functions.

RMRP-HuR, *RMRP*-GRSF1

In another recent study, Noh et al. reported two RBPs that contributed to the subcellular mobilization of the organelle-specific localization of lncRNP complexes. A lncRNA abundant in the nucleus, *RMRP* (an RNA component of the mitochondrial RNA-processing endoribonuclease) associated with the RBP HuR in the nucleus, and the resulting lncRNP was mobilized into the cytoplasm through CRM1 (chromosome region maintenance 1)-dependent nuclear export. This exported *RMRP* was selectively targeted to the innermost compartment of mitochondria (the matrix), where the mitochondria resident protein GRSF1 (G-rich RNA sequence-binding factor 1) associated with *RMRP* and formed a mitochondrial lncRNP complex, *RMRP*-GRSF1, which was proposed to contribute to the maintenance of mitochondrial structure as well as functions such as oxidative phosphorylation and mitochondrial DNA replication (Noh et al., 2016).

RMRP-PNPASE, *RPPH1*-PNPASE

The protein PNPASE, which resides in the mitochondrial intermembrane space (IMS), was found to mobilize noncoding RNAs such as *RPPH1* and *RMRP*, encoded by nuclear DNA but found in mitochondria (Mercer et al., 2011). PNPASE recognized a particular stem-loop

structure embedded in *RPPH1* and *RMRP* and promoted RNA import into the mitochondrial matrix (Wang et al., 2010). It is still unclear what factors mediate the physical import of RNA through the inner membrane (IM), but PNPASE was proposed to capture RNAs in the IMS and transferred them to complexes that delivered RNAs through the IM into the matrix.

LncRNAs modulating signaling pathways

Cytoplasmic lncRNAs capable of modulating signal transduction pathways by binding specific signaling molecules and/or altering their phosphorylation status are also beginning to be recognized. Although the proteins implicated in these regulatory paradigms notably lack canonical RNA-binding domains (RBDs), they can play prominent functions in physiological and pathological conditions. Their functions have been studied primarily in the immune and inflammatory responses, as well as in cancer.

LINK-A-BRK and *LINK-A*-LRRK2

A novel function was recently proposed for the cytoplasmic lncRNA *LINK-A* (long intergenic non-coding RNA for kinase activation) in the signal transduction triggered by heparin-binding epithelial growth factor (HB-EGF). *LINK-A* recruited the breast tumor kinase BRK to the dimer EGFR-GPNMB (EGF receptor-transmembrane glycoprotein NMB), helping to activate BRK. *LINK-A* also interacted with the kinase LRRK2, in turn triggering the conformational change, phosphorylation, and activation of BRK; these changes subsequently led to normoxic HIF1A stabilization in triple-negative breast cancer cells (Lin et al., 2016).

Lnc-DC-STAT3

Wang et al. reported a novel lncRNP complex that affected cytoplasmic signaling. The lncRNA *lnc-DC*, which is essential for the differentiation of dendritic cells, directly bound to cytoplasmic STAT3 (signal transducer and activator of transcription 3) and promoted phosphorylation of STAT3 by preventing the inhibitory function of SHP1 [tyrosine phosphatase Src-homology 2 domain (SH2)-containing PTP-1] (Wang et al., 2014).

NKILA-NF-κB, *Lethe*-NF-κB

The NF-κB pathway is essential for the transcriptional induction of several mRNAs encoding proteins involved in inflammation and cell survival. Liu et al. reported a novel cytoplasmic lncRNA, *NKILA* (NF-κB-interacting long noncoding RNA), which is upregulated by inflammatory cytokines and by NF-κB activity in tumor cells. They also found that *NKILA* negatively regulated NF-κB signaling by associating with the NF-κB/IκB complex, masking the phosphorylation sites of IκB and preventing NF-κB signaling (Liu et al., 2015). Another lncRNA called *Lethe* was found to bind RELA (a member of the NF-κB/Rel family), which inhibited RELA binding to DNA, thus reducing the transcriptional activity of RELA (Rapicavoli et al., 2013). These findings indicate that several lncRNAs can interfere with the NF-κB pathway and thus influence gene expression in inflammation and carcinogenesis.

Remaining challenges in cytoplasmic lncRNA biology

Despite much progress in elucidating the constituents and functions of cytoplasmic lncRNPs, major questions remain. In this section, we point to key emerging areas of lncRNP biology awaiting in-depth study.

LncRNAs associated with ribosomes

A number of lncRNAs (e.g. *H19* and *TUG1*) have been found enriched in the polysomal fraction.[45] For example, the *C. elegans* lncRNA *tts-1* (transcribed telomeric sequence 1) was found to extend the life span of the long-lived *daf-2* mutant (reviewed by Kenion, 2010) in a manner dependent on its ribosome-binding activity (Essers et al., 2015), and Ingolia and co-workers found many lncRNAs directly associated with the translation machinery in mammalian cells (Ingolia, Lareau, Weissman, 2011). Subsequent studies similarly identified lncRNAs associated with ribosomes and likely to be translated into short peptides (van Heesch et al., 2014;. Bazzini et al., 2014; Ruiz-Orera, Messeguer, Subirana, & Alba, 2014; Ingolia et al., 2014). Carlevaro-Fita and colleagues recently identified ~70% of cytoplasmic lncRNAs in polysomes, ~30% in the free cytoplasmic fraction (Carlevaro-Fita et al., 2016). They also found that the presence of exonic transposable elements (TEs) in cytoplasmic lncRNAs correlates with their ribosome-free localization, supporting previous observations that TEs are functional lncRNA sequences (Carlevaro-Fita et al., 2016; Kelley & Rinn, 2012; Johnson & Guigo R; 2014). It will be important to identify systematically the lncRNAs associated with polysomes, elucidate the lncRNA regions that control these associations, and assess systematically whether they are translated and/or have other functions.

Circular RNAs

In eukaryotes, numerous circular (circ)RNAs have been identified, many of them derived from back-spliced exons (Ebbesen, Kjems, & Hansen, 2016), capable of binding cytoplasmic molecules including RBPs and microRNAs. For example, *CircPABPN1* was a strong target of the RBP HuR; accordingly, high levels of *CircPABPN1* reduced HuR's ability to bind *PABPN1* mRNA, in turn lowering PABPN1 expression in cancer cells (Abdelmohsen et al., 2017). Although the exact mechanisms governing these interactions are not known, *CircPABPN1* originates from exon 6 of *PABPN1* mRNA and the sequence similarity might be linked to their competitive binding (Abdelmohsen et al., 2017). In another example, circRNA *ciRS-7*, which contains ~70 sites of interaction with miR-7, sponged and suppressed miR-7 function in brain and islet cells (Memczak et al., 2013; Xu, Guo, Li, & Yu, 2015). Similarly, circRNA *Sry* (sex-determining region Y) was found to sponge miR-138, suppressing miR-138 effect on target mRNAs (Hansen et al., 2013).

Examples are also emerging of circRNAs that originate from linear lncRNAs. For instance, *CircPVT1*, generated from the oncogenic lncRNA *PVT1*, was recently identified as a senescence-associated circular RNA (SAC-RNA). *CircPVT1* was low in senescent WI-38 human fibroblasts, and its high abundance in proliferating WI-38 cells was linked to the binding and hence the functional suppression of let-7, the inhibition of cell senescence, and the enhancement of cell division (Panda et al., 2017). *CircPVT1* also regulates chondrocyte

apoptosis in osteoarthritis by acting as a sponge for miR-488-3p (Li, Li, Luo, Liu, & Yu, 2017).[87] Given the important functions elicited by circRNAs, building a complete catalog of circRNPs will be critical towards a fuller understanding of lncRNP biology.

Dynamic, tissue-specific maps of lncRNPs

Similar to the proposal by Batista and Chang that lncRNAs are key components of nuclear architecture and function (Batista and Chang, 2013), spatio-temporal changes of cytoplasmic lncRNAs are essential for regulating various cellular events. As summarized above, many cytoplasmic lncRNAs function by interacting with RBPs, indicating that their various cytoplasmic roles are mostly attributed to lncRNP activity. However, the complete catalogs of RBPs interacting with each lncRNA, and their competitive, cooperative, or sequential binding to form diverse lncRNPs, are unknown. Considering that the functions of most lncRNAs are not yet known, creating a comprehensive inventory of lncRNAs and RBPs that constitute cytoplasmic lncRNPs will critically advance our knowledge of the cytoplasmic lncRNA functions.

Resources to study lncRNP identity and function

Even though mRNA-RBP interactions (mRNPs) have been identified for decades (Gerstberger, Hafner, & Tuschl, 2014), comprehensive maps of lncRNPs will require advances in both wet-lab and computational methods. Crosslinking and immunoprecipitation (CLIP, including its variants HITS-CLIP, PAR-CLIP, iCLIP, eCLIP, etc), followed by RNA-seq analysis, allows state-of-the-art mapping transcriptome-wide RNA-binding sites of an RBP of interest (Konig, Zarnack, Luscombe, & Ule, 2011). Large CLIP-derived datasets were generated recently from over 100 RBPs (http://clipdb.ncrnalab.org) (Licatalosi et al., 2008; Hafner et al., 2010; Konig et al., 2010; Yang et al., 2015). For example, TARDBP (TAR DNA-binding protein 43, TDP-43), a DNA/RNA-binding protein associated with the neurodegenerative diseases amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) (Onesto et al., 2016), showed increased disease-associated localization in mitochondria and strong binding to mitochondrial *ND3* and *ND6* mRNAs, suppressing their expression and causing disassembly of the mitochondrial complex I. The authors proposed that interfering with the mitochondrial localization of TDP-43 could have therapeutic benefit in neurodegeneration (Wang et al., 2016). Together with other CLIP datasets it is clear that under certain conditions, TDP-43 can interact with cytoplasmic lncRNAs, with nucleus-retained lncRNAs (e.g., *MALAT1* and *NEAT1*), and with mRNAs encoding neurodegeneration-associated proteins (e.g., FUS, progranulin) (Tollervey et al., 2011; Polymenidou et al., 2011).

Individual lncRNPs can be identified experimentally, but this is still a costly proposition and depends on the availability of good antibodies. To identify lncRNPs computationally, many databases have been developed to provide information on RBP target RNAs and RNA-binding motifs using validated protein-RNA interactions (Cook, Kazan, Zuberi, Morris, & Hughes, 2011; Giulietti et al., 2013; Ray et al., 2013; Park, Yu, Choi, Kim, & Lee, 2014; Giudice, Sanchez-Cabo, Torroja, & Lara-Pezzi E, 2016). A recent attempt to construct a global lncRNA-protein network (LPN) based on experimentally verified functional interactions among lncRNAs and interacting RBPs revealed that lncRNA-binding proteins

have distinct topological properties (Shang et al., 2015). We propose that developing accurate computational algorithms to predict lncRNP interactions will greatly enhance our understanding of cytoplasmic lncRNA functions systematically.

Subcellular detection of endogenous lncRNAs

Eukaryotic cells have evolved many cellular domains and compartments, including membrane-enclosed cytoplasmic organelles. Given that RNA functions are closely linked to their subcellular localization, it is critical to investigate their subcellular distribution. Recent advances in fractionation and RNA-seq technologies have uncovered vast numbers of lncRNAs in specific cellular compartments, suggesting that lncRNAs may be mobilized into different cytoplasmic regions, including structured subcellular organelles (e.g. ribosomes, endoplasmic reticulum, exosomes, mitochondria, etc.) and more dynamic domains such as processing bodies or stress granules (Mercer et al., 2011; Guttman, & Rinn, 2012; Guttman, Russell, Ingolia, Weissman, & Lander, 2013; Halic et al., 2004; Rackham et al., 2011; Turner, Galloway, & Vigorito, 2014).

However, the accurate localization of cytoplasmic lncRNAs requires *in situ* detection methods. Nelles et al. detected endogenous RNAs by using a nuclease-inactive CRISPR/Cas9 system that comprised an RNA-directed Cas9 (RCas9) and an RNA-specific guide RNA (sgRNA) that tracked endogenous mRNAs (Nelles et al., 2016). Compared with earlier methods that employed genetically manipulated aptamers such as MS2-MCP (MS2-coat protein; reviewed by Weil, Parton, & Davis, 2010), RCas9 has the advantage of tracking ‘tag-less’ endogenous RNAs. It remains to be seen whether this method can detect low-abundance lncRNAs and whether it is superior for live-cell imaging compared with conventional RNA FISH or tagged RNA detection. An alternative form of RNA tagging was recently suggested by using another partner of CRISPR, Cas13a (Abudayyeh et al., 2016; East-Seletsky, O’Connell, Burstein, Knott, & Doudna, 2017; Gootenberg et al., 2017). Considering that its major advantage over RCas9 is that the Cas13a system does not require the additional oligonucleotide ‘PAMmer’, Cas13a appears likely to become a powerful tool for targeting and detecting endogenous lncRNAs.

Subcellular and suborganellar distribution of lncRNPs

An earlier study revealed that all organisms can import tRNAs from the cytoplasm to mitochondria (Rubio et al., 2008). tRNAs appeared to be actively delivered to the mitochondrial surface instead of passively reaching mitochondria after being released into the cytoplasm (Yoshihisa, Yunoki-Esaki, Ohshima, Tanaka, & Endo, 2003). A recent proteomic analysis of tRNA export to the cytosol identified sets of proteins necessary for mediating the nuclear export and mitochondrial import of tRNAs, including nuclear export machineries, actin cytoskeleton components, and mitochondrial outer membrane proteins (Wu, Bao, Chatterjee, Wan, & Hopper, 2015). For lncRNAs, it is still unknown what RBPs might mobilize them out of the nucleus and onto the surface of organelles such as mitochondria, or into organelles. The specific lncRNA sequences required for subcellular transport are also unknown.

Exosomes are small vesicles, with diameters of 30–120 nm, secreted by most cell types and present in all body fluids. They have been found to carry lncRNAs, proteins, DNA, microRNAs, and other molecules (Nolte-‘t Hoen et al., 2012; Gezer, Ozgur, Cetinkaya, Isin, & Dalay, 2014; Ahadi, Brennan, Kennedy, Hutvagner, & Tran, 2016). Although it is not yet known how the contents of this membrane-enclosed structure are loaded, specific RBPs are believed to form lncRNPs in order to deliver cytoplasmic lncRNAs to exosomes.

As we gain more information about the specific cellular distribution of lncRNAs, we will be able to integrate and predict the functions of specific lncRNPs. Guo et al. assembled all the known public databases for protein subcellular location (Guo, Liu, Ju, Wang, & Wang, 2016), and Itzhak et al. proposed a ‘global dynamic map’, which included physical distribution and movement of proteins in cells. This proteomic view of the cell, which includes large protein complexes (ribosomes and proteasome) and cellular organelles (e.g. membrane, ER, Golgi apparatus, endosome, lysosome, peroxisome and mitochondria) (Itzhak, Tyanova, Cox, & Borner, 2016), can guide our efforts to map cellular lncRNPs in dynamic spaces.

Structural and chemical aspects of lncRNAs

The secondary and tertiary structures of lncRNAs are more highly conserved than their primary sequence, and thus they are considered to be more relevant to lncRNA biological function (Johnsson, Lipovich, Grander, & Morris, 2014; Mercer, & Mattick, 2013). Once mobilized to the cytoplasm, structural changes in lncRNAs may affect their function and/or binding to target proteins. Therefore, analyzing their structures in each compartment appears to be essential for understanding lncRNA function. Some computational methods have been developed to predict RNA secondary (or tertiary) structure (Yan et al., 2016), and experimental techniques have been designed to probe RNA structures in the whole transcriptome (i.e., the ‘RNA structurome’) (Wan, Kertesz, Spitale, Segal, & Chang, 2011; Ding et al., 2014; Novikova, Dharap, Hennelly, & Sanbonmatsu, 2013. As we use this approach to study lncRNPs, we should be mindful of post-transcriptional modifications of RNAs. For example, a recent report uncovered that N^6-methyladenosine (m^6A) altered the local structure of mRNA and lncRNA globally, thereby modifying their interaction with an RBP, HNRNPC (Liu et al., 2015).

Closing remarks

Several thousand human lncRNAs have been identified, but their potential roles and subcellular localizations are largely unknown. Many studies in recent years have solidified the idea that nuclear lncRNPs function as ‘localization elements’ to define nuclear domains with key roles in maintaining structural and functional integrity of the nucleus. As discussed above, these concepts can be extended to cytoplasmic lncRNA functions, such as maintaining cytoplasmic structure, defining cytoplasmic domains, and promoting organelle activity. In other words, the distribution of cytoplasmic lncRNPs may be controlled dynamically in time and space, with lncRNPs delivered to specific cytoplasmic locations requiring certain enzymatic activities and/or structural platforms.

A comprehensive understanding of the composition and localization of cytoplasmic lncRNPs will set the stage for exploring the biological functions of cytoplasmic lncRNAs. As we understand the cellular processes controlled by lncRNAs, we can begin to devise strategies to intervene therapeutically in pathological situations in which such processes become impaired.

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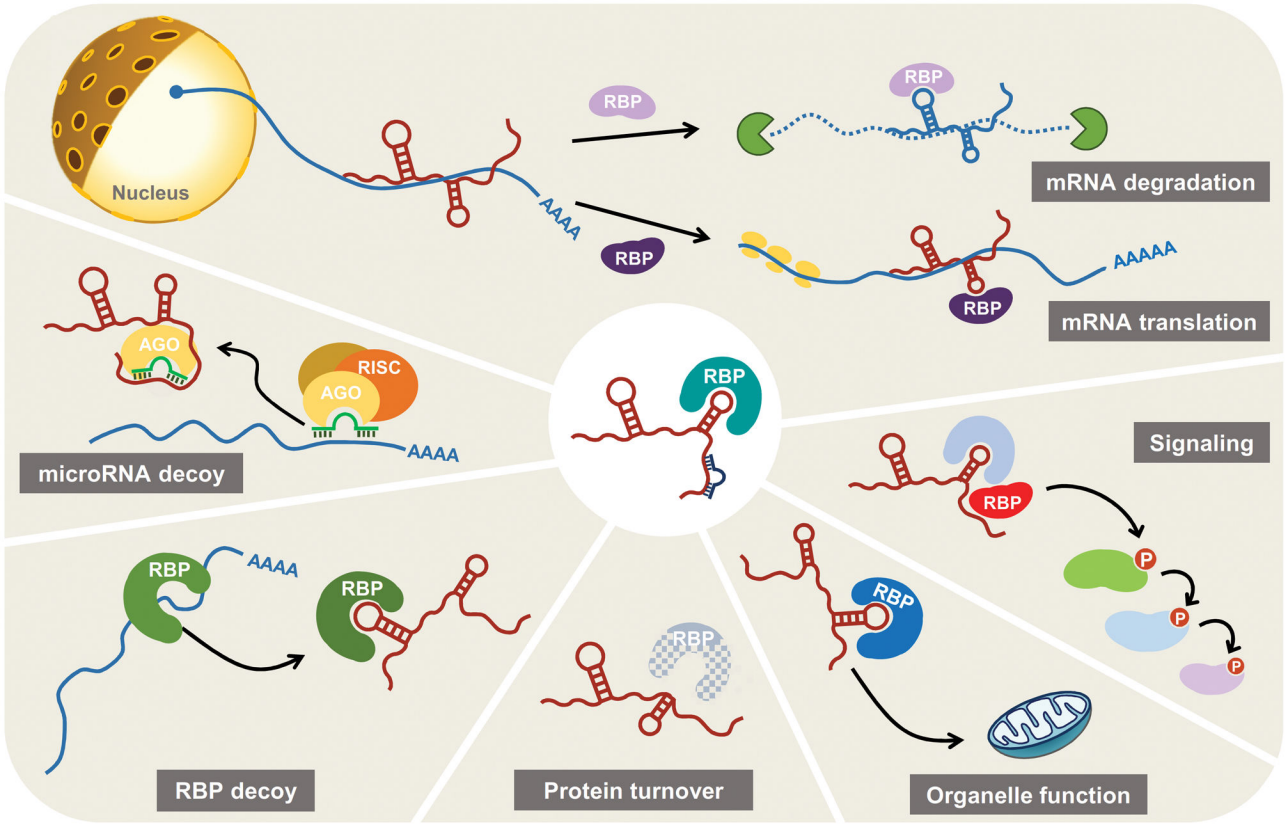

Figure 1. Different levels of regulation of gene expression by cytoplasmic lncRNAs

(Clockwise). Top, following export to the cytoplasm, lncRNAs can associate with RNA-binding proteins (RBPs) or with partially complementary mRNAs to regulate the stability and/or translation of specific mRNAs. *Signaling*, association of RBPs with lncRNAs can lead to conformational changes that activate signaling molecules (e.g., kinases). *Organelle function*, RBPs can chaperone the mobilization of lncRNAs to cellular organelles where they carry out specific functions. *Protein stability*, lncRNAs can serve as platforms that facilitate the presentation of specific RBPs to the protein degradation machinery. *RBP decoy* and *microRNA decoy*, lncRNAs binding to RBPs and microRNAs can reduce the availability of these factors to mRNAs, in turn modulating mRNA fate. See text and Table 1 for details.

Table 1

Cytoplasmic lncRNAs, interacting factors, and function of lncRNA complexes

Table includes the functions of the cytoplasmic lncRNAs reviewed (column 1), the lncRNAs (column 2) and interacting RBPs and RNAs (column 3), and the function of the ensuing complexes (column 4).

Functional Category	Long noncoding RNAs (lncRNAs)	Interacting Factors	Function	Refs.
mRNA turnoverand translation	**1/2-sbsRNAs**	STAU1	Degradation of 1/2-sbsRNA target mRNAs	Gong & Maquat, 2011
	TINCR	STAU1	Stabilization of epidermal differentiation mRNAs	Kretz et al., 2013
	CUG^{exp} (CUG repeats)	STAU1	Induction of translation of mRNAs bearing CUG^{exp}	Ravel-Chapuis et al., 2012
	LincRNA-p21	HuR	Degradation of *lincRNA-p21*, suppression of TNNB1 and JUNB translation	Chu & Rana, 2006; Yoon et al., 2012
	BACE1AS	HuD	Stabilization of *BACE1* and *APP* mRNAs	Kang et al., 2014
	GAS5	eIF4E	Suppression of MYC translation	Hu, Lou, & Gupta, 2014
	Uchl1-AS1	*Uchl1* 5′UTR	Induction of UCHL1 translation	Carrieri et al., 2012
Protein turnover	***LincRNA-p21***	HIF1A	Prevention of VHL-mediated HIF1A ubiquitination	Yang, Zhang, Mei, & Wu, 2014
	HOTAIR	DZIP3, MEX3B	Degradation of Snurportin-1 and Ataxin-1	Yoon et al., 2013
	NRON	CUL4B, PSMD11	Degradation of HIV protein Tat	Li et al., 2016
RBPdecoy	***Gadd7***	TDP-43	Degradation of *Cdk6* mRNA	Buratti & Baralle, 2008; Liu, Li, Zhang, Guo, & Zhan, 2012
	OIP5-AS1	HuR	Prevent HuR binding to targets (*CCNA2*, *CCND1*, *SIRT1* mRNAs)	Kim et al., 2016
	OIP5-AS1	*GAK* mRNA	Degradation of *GAK* mRNA	Kim et al., 2017
	7SL	*TP53* mRNA	Repression of TP53 translation	Abdelmohsen et al., 2014
	LncMyoD	IMP2	Reduction of NRAS and MYC protein	Gong et al., 2015
	GAS5	GR	Prevention of GR mobilization to the nucleus	Mourtada-Maarabouni et al., 2009
	H19	KSRP (KHSRP)	Destabilization of *Myog* mRNA	Giovarelli et al., 2014
	UCA1	HNRNPI	Prevention of HNRNPI binding to *p27* mRNA, repression of p27 translation	Huang et al., 2014
MicroRNA decoy	***HULC***	miR-372	Induction of PRKACB translation	Wang et al., 2010
	lincRNA-RoR	miR-145	Derepression of NANOG, OCT, SOX2 production	Loewer et al., 2010; Wang et al., 2013
	H19	let-7	Interference with let-7 activity	Kallen et al., 2013

Functional Category	Long noncoding RNAs (lncRNAs)	Interacting Factors	Function	Refs.
	Linc-MD1	HuR, miR-133b	Inhibition of miR-133b generation	Cesana et al., 2011; Legnini et al., 2014
	PTENP1	miR-21,-20a,-214,-19b,-26a,-499-5p	Derepression of PTEN production	Tang, Ning, Zeng, & Li, 2016
LncRNP mobilization	***NRON***	NFAT	NFAT nuclear translocation	Willingham et al., 2005
	MALAT1	HNRNPC	Cytoplasmic translocation of *MALAT1* during G2/M transition	Yang, Yi, Han, Du, & Liang, 2013
	RMRP	HuR, GRSF1	Transport of *RMRP* to cytoplasm, maintenance of mitochondrial function	Noh et al., 2016
	RMRP, RPPH1	PNPASE	Transport of *RMRP* and *RPPH1* through mitochondrial inner membrane	Wang et al., 2010
Cellular signaling	***LINK-A***	BRK	Activation of kinase BRK	Lin et al., 2016
	LINK-A	LRRK2	Modification of BRK, normoxic HIF1A stabilization	Lin et al., 2016
	Lnc-DC	STAT3	Promotion of STAT3 phosphorylation	Wang et al., 2014
	NKILA	NF-κB/IκB complex	Inhibition of NF-κB signaling	Liu et al., 2015
	Lethe	RELA	Reduction in RELA transcriptional activity	Rapicavoli et al., 2013

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