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REVIEW

Post-transcriptional regulation of long noncoding RNAs in cancer

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Abstract It is a great surprise that the genomes of mammals and other eukaryotes harbor many thousands of long noncoding RNAs (lncRNAs). Although these long noncoding transcripts were once considered to be simply transcriptional noise or cloning artifacts, multiple studies have suggested that lncRNAs are emerging as new players in diverse human diseases, especially in cancer, and that the molecular mechanisms of lncRNAs need to be elucidated. More recently, evidence has begun to accumulate describing the complex post-transcriptional regulation in which lncRNAs are involved. It was reported that lncRNAs can be implicated in degradation, translation, pre-messenger RNA (mRNA) splicing, and protein activities and even as microRNAs (miRNAs) sponges in both a sequence-dependent and sequence-independent manner. In this review, we present an updated vision of lncRNAs and summarize the mechanism of post-transcriptional regulation by lncRNAs, providing new insight into the functional cellular roles that they may play in human diseases, with a particular focus on cancers.

Keywords Long noncoding RNA · Mechanism · Post-transcriptional regulation · Cancer

Abbreviations

lncRNAs	Long noncoding RNAs
miRNA	MicroRNA
ceRNA	Competitive endogenous RNA
siRNAs	Small interfering RNAs
piRNAs	Piwi-associated RNAs
Xist	X inactive specific transcript
HOTAIR	Hox transcript antisense intergenic RNA
MREs	MicroRNA response elements
HULC	Highly upregulated in liver cancer
HCC	Hepatocellular carcinoma
PTCSC3	Papillary thyroid carcinoma susceptibility candidate 3
PTC	Papillary thyroid carcinoma
snRNPs	Small nuclear ribonucleoproteins
hnRNPs	Heterogeneous nuclear ribonucleoproteins
MALAT1	Metastasis-associated lung adenocarcinoma transcript 1
NAT	Natural antisense transcript
UTR	Untranslated region
EMT	Epithelial–mesenchymal transition
CHO	Chinese hamster ovary
Cdk6	Cyclin-dependent kinase 6
SMD	Staufen 1-mediated mRNA decay
1/2-sbsRNAs	Half-STAU1-binding site RNAs

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TINCR	Terminal differentiation-induced ncRNA
RPA	RNase protection assay
Uchl1	Ubiquitin carboxyterminal hydrolase L1
treRNA	Translational regulatory lncRNA
RNP	Ribonucleoprotein
lncRNA-LET	LncRNA Low Expression in Tumor
H19	H19, imprinted maternally expressed transcript
PTENP1	Phosphatase and tensin homolog pseudogene 1

Introduction

Historically, both proteins and protein-coding RNAs have tended to dominate our view of the cell and the human diseases because of their abundance and the relative ease with which protein-coding genes and their gene products can be identified and studied [1]. However, this paradigm has been undermined in recent years with the development of whole genome and transcriptome sequencing technologies. It is estimated that less than 2 % of the total human genomic sequence codes for proteins [2, 3], although over 70 % of the human genome is capable of being transcribed [4, 1, 5]. Therefore, the majority of the genome gives rise to non-protein-coding RNAs (ncRNAs), which exert their function directly as RNA molecules. These ncRNAs can be broadly grouped into two major classes. The small ncRNAs class includes microRNAs (miRNAs), small interfering RNAs (siRNAs), tiny RNAs, Piwi-associated RNAs (piRNAs), and cryptic unstable transcripts, and the more recently described long noncoding RNAs (lncRNAs) class contains RNAs that are longer than 200 nucleotides [4, 6, 7]. Although studies of small regulatory RNAs, in particular miRNAs, have dominated the field of RNA biology during the past decade [8, 9], a surprisingly broad spectrum of biological processes is also associated with lncRNAs [7, 10, 11]. Thus, the focus of scientists is now shifting to one of the most poorly understood yet most common products of transcription from genomes: lncRNAs [1].

Even though many lncRNAs have small open reading frames, they lack protein-coding capability [12–14]. Many identified lncRNAs undergo 5′-end capping and 3′-end polyadenylation in a process analogous to messenger RNAs (mRNAs) [15, 16]. Furthermore, they may be located within cytosolic or nuclear fractions [17]. In addition, several lncRNAs show clear evolutionary conservation and are often expressed in developmental stage-, tissue-, and organ-specific patterns [18–21]. Over the past several years, accumulated data have begun to advance the idea that lncRNAs are not just transcriptional noise or cloning artifacts but important supplements to proteins and other effectors in complex regulatory networks [7]. In fact, multiple lines of evidence demonstrate that a number of characterized lncRNAs are implicated in a spectrum of biological processes and that misregulated lncRNA expression can cause various human diseases and cancers [6, 22]. Furthermore, lncRNAs have been reported to regulate gene expression at both the post-transcriptional and transcriptional level [15]. Transcriptional regulation could occur via lncRNA interaction with chromatin-modifying enzymes, resulting in gene activation or silencing either in *cis* or in *trans* [10]. For example, during X chromatin dosage compensation in mammals, the lncRNA X inactive specific transcript (Xist) recruits the chromatin-modifying complex PRC2 to the transcription site, leading to stable epigenetic silencing of normally widespread gene expression from the X chromosome [23]. Another important lncRNA, Hox transcript antisense intergenic RNA (HOTAIR), can alter and regulate epigenetic states in cells through interaction with PRC2 in *trans* [24, 10].

Despite the well-established function of lncRNAs in epigenetic and transcriptional gene regulation, the role of lncRNAs in other aspects of gene expression regulation is still largely unknown. Of late, a number of lncRNAs, in particular antisense transcripts, have been reported to affect various processes of post-transcription, such as splicing, transport, translation, and degradation (Table. 1). In this review, we will attempt to organize some of the rapidly expanding information, with a focus on post-transcriptional gene regulation by lncRNAs. Additionally, we will highlight their functional role in human cancers.

LncRNAs and ceRNA language

MicroRNAs are small ncRNAs, approximately 22 nucleotides long, that post-transcriptionally regulate gene expression by destabilizing target mRNAs in a sequence-dependent manner [25, 26]. They can pair with microRNA response elements (MREs) on target RNA transcripts and accomplish a key role in many biological processes, such as animal development [27, 28], programmed cell death [29, 30], tumor suppression [31, 32], and hematopoietic cell fate decisions [33, 34]. In addition, recent theoretical and experimental studies have shown that the target RNA transcripts are similarly able to affect microRNA availability [35]. The competitive endogenous RNAs (ceRNAs), which contain shared MREs, could compete for microRNA binding and impact the activity of microRNAs [36]. In this way, MREs become a novel RNA-based regulatory mechanism for modulating miRNA action [37]. More importantly, these ceRNAs, including pseudogenes, protein-coding genes, and long noncoding RNAs, can crosstalk with each other through their ability to compete for microRNA binding, thereby creating an additional level of post-transcriptional regulation (Fig. 1a, b) [38–41].

Table 1 LncRNAs are involved in the complex post-transcriptional regulation

Post-transcription process	LncRNAs	Disease/process	Mechanism	Ref.
I. ceRNA language	HULC	Hepatocellular carcinoma (HCC), hepatic colorectal metastasis	Inhibits the expression and activity of miR-372, resulting in translational derepression of PRKACB and inactivation of CREB	[43, 44, 42]
	PTCSC3	Papillary thyroid carcinoma (PTC)	"sponges" miR-574-5p	[46, 45]
	LOC285194	Osteosarcoma and colorectal cancer	Spongs miR-211 within exon 4	[47, 48]
	OCT4-pg4	Hepatocellular carcinoma (HCC)	Upregulates the corresponding OCT4 protein level by acting as a microRNA decoy for miR-145	[51]
	PTENP1	Prostate cancer melanoma	Competes with the PTEN RNA for miRNA binding sites and modulates the cellular abundance of PTEN mRNA	[40, 50, 49]
II. Pre-mRNA Splicing	NATs	Snail1-induced epithelial-mesenchymal transition	Prevents the splicing of the IRES from the pre-mRNA, leading to increasing the levels of Zeb2 protein and decreasing E-cadherin mRNA and protein	[78]
	MALAT1	Colon, prostate, liver, osteosarcoma, breast, lung, uterus, pancreas, neuroblastoma, cervix tumor	Affects alternative splicing of pre-mRNAs by modulating distribution and activity of SR splicing factors	[105, 69, 60]
III. mRNA stability	aHIF	Breast cancer	1. 3′aHIF-1a is implicated in increasing instability of HIF-1a mRNA via an exposition of AU-rich elements in the HIF-1a mRNA 3′ UTR 2. 5′ aHIF-1a plays a role in nuclear membrane trafficking	[81]
	gadd7	NA	Binds to TAR DNA-binding protein (TDP-43) directly, and then interferes with the interaction between TDP-43 and Cdk6 RNA, generating Cdk6 mRNA degradation	[84, 85, 83]
	1/2-sbsRNAs	NA	Can imperfectly base-pair with another Alu element in 3′UTR of an mRNA forming STAU1-binding sites, and then degrading target mRNAs via SMD	[89, 88]
IV. mRNA translation	LincRNA-p21	Colorectal cancer	Associates with CTNNB1 and JUNB mRNAs, repressing JunB and β-catenin translation through a mechanism that includes reduced polysome sizes	[106, 98, 97]
	Antisense Uchl1 RNA	NA	Promotes the formation of active polysomes on Uchl1 mRNA and hence its translation	[99]
	treRNA	Breast cancer primary and lymph-node metastasis	Influences the distribution of E-cadherin mRNA in HMW and LMW polysomes, resulting in inhibiting the translation of the E-cadherin mRNA	[102]
V. Others	lncRNA-LET	Hepatocellular carcinomas	Affects the stability of nuclear factor 90 protein and HIF-1a mRNA leading to tumor metastasis	[104]
	H19	Bladder, lung, liver, breast, prostate, colorectal tumor	Serves as the precursor for miR-675, which is specifically expressed in the placenta from time of gestation and can act to moderate cell growth	[107]

lncRNAs long noncoding RNAs, *HULC* highly upregulated in liver cancer, *HCC* hepatocellular carcinoma, *PTCSC3* papillary thyroid carcinoma susceptibility candidate 3, *PTC* papillary thyroid carcinoma, *MALAT1* metastasis-associated lung adenocarcinoma transcript 1, *NAT* natural antisense transcript, *Cdk6* cyclin-dependent kinase 6, *SMD* Staufen 1-mediated mRNA decay, *1/2-sbsRNAs* half-STAU1-binding site RNAs, *lncRNA-LET* lncRNA low expression in tumor, *treRNA* translational regulatory lncRNA, *H19* H19 imprinted maternally expressed transcript, *PTENP1* phosphatase and tensin homolog pseudogene 1,

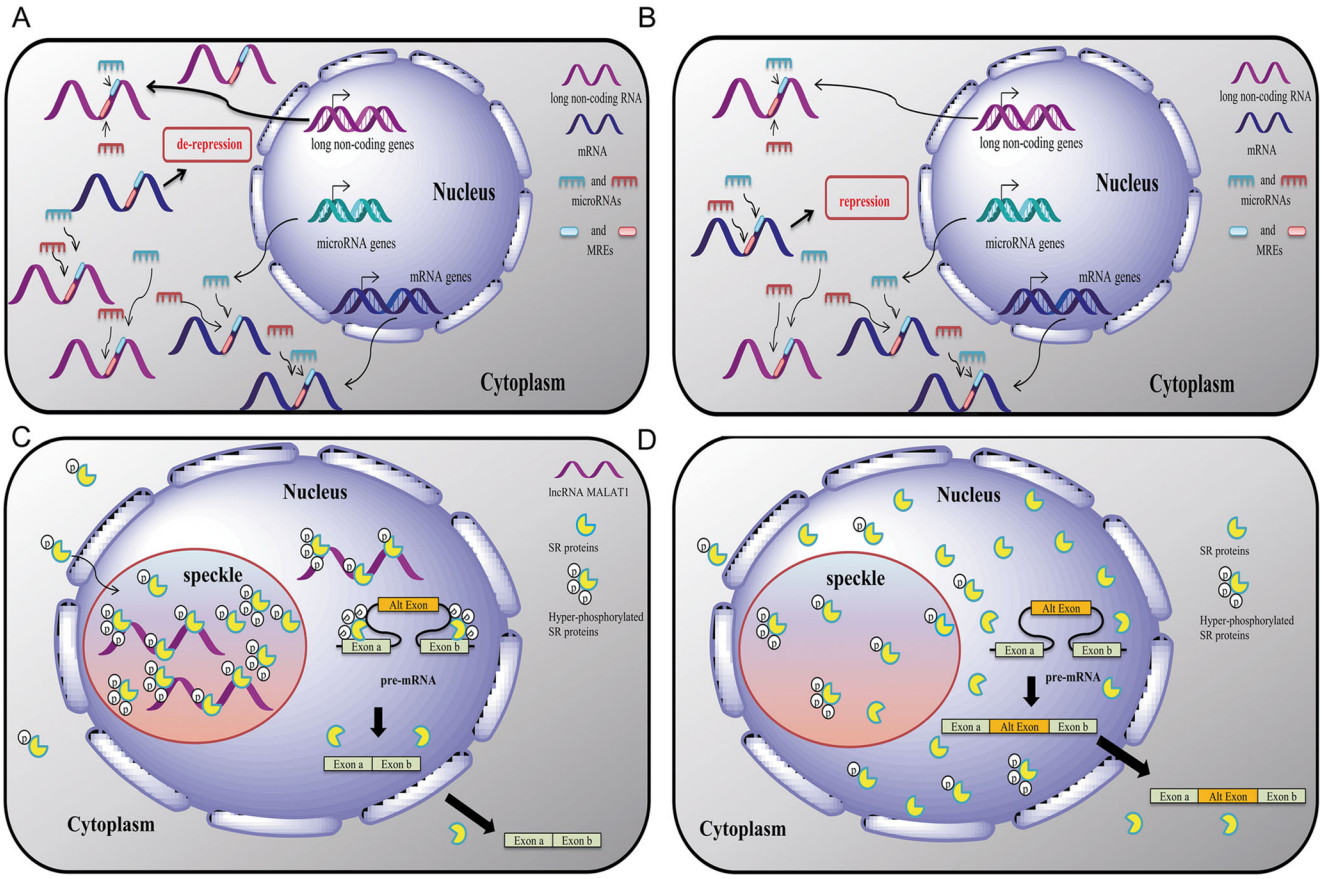

Fig. 1 LncRNAs participate in ceRNA network and pre-mRNA splicing. **a**, **b** The competitive endogenous RNA transcripts, including pseudogenes, protein-coding genes, and long noncoding RNAs, can harbor MREs for the same microRNA. They can crosstalk with each other through their ability to compete for microRNA binding. In this framework, overexpression of lncRNAs increases cellular concentrations of certain MREs, which can lead to the derepression of mRNAs that contain the same MREs. **c**, **d** In cells, lncRNAs can interact with several pre-mRNA splicing factors and modulate distribution and activity of SR splicing factors. Such changes influence alternative splicing of pre-mRNAs and result in corresponding diversification of particular proteins

In this framework, perturbations in the expression levels of a given ceRNA, especially a noncoding ceRNA, result in an associated disturbance of the ceRNA network, which may also contribute to pathologies [41].

Highly upregulated in liver cancer (HULC) is the first lncRNA shown to have highly specific upregulation in hepatocellular carcinoma (HCC) and hepatic metastases from colorectal cancer [42, 43]. Subsequent studies performed by Wang and colleagues indicated that HULC is able to inhibit the expression and activity of miR-372 by acting as an endogenous sponge, resulting in translational derepression of PRKACB. PRKACB induces the phosphorylation and activation of CREB, which allows lncRNA HULC to further increase its own expression levels [44]. In addition, papillary thyroid carcinoma susceptibility candidate 3 (PTCSC3) is another newly identified lncRNA that is downregulated in papillary thyroid carcinoma (PTC) tissues and cell lines [45]. The significant inverse correlation between PTCSC3 and miR-574-5p both in silico and in biological analyses demonstrates that PTCSC3 may regulate cell growth and apoptosis in thyroid cancer by sponging miR-574-5p [46]. Similarly, loc285194 functions as a potential tumor suppressor in osteosarcoma and colorectal cancer through the ceRNA network [47, 48]. Both in vivo and in vitro, overexpression of loc285194 can inhibit tumor cell growth by sponging miR-211 within exon 4. Of particular interest, ectopic expression of miR-211 can also decrease the loc285194 expression level, forming a reciprocal repression feedback loop [47].

In addition to lncRNAs, pseudogenes are also a dramatic example of ceRNA regulation as they probably possess many or all of the same MREs that are harbored on their ancestral genes and thus can serve as perfect sponges [41]. In the case of phosphatase and tensin homolog (PTEN), the processed pseudogene phosphatase and tensin homolog pseudogene 1 (PTENP1) can regulate the interaction between PTEN-targeting microRNAs and PTEN mRNA, thereby affecting PTEN mRNA stability [49, 50, 40]. Because the sequence of PTENP1 is extensively similar to the sequence of PTEN, PTENP1 competes for miRNA binding with authentic PTEN RNA and protects PTEN mRNA from microRNA-mediated degradation. Therefore, PTENP1 is also a bona fide tumor suppressor gene in many human tumors [50, 40]. Analogous

to PTENP1, it is recently reported that a pseudogene of OCT4, OCT4-pg4, is able to upregulate the corresponding OCT4 protein level in HCC by acting as a microRNA decoy for tumor-suppressive miR-145, which promotes growth and tumorigenicity of HCC cells [51]. Importantly, a high expression level of OCT4-pg4 is significantly correlated with poor prognosis of HCC patients [51].

Overall, RNA molecules are core nodes in the intracellular signal transmission and biological processes, including protein translation and amino acid transport in the cytoplasm. Protein translation is an essential biochemical reaction for maintenance of biological function. The mechanism by which miRNA-mediated RNA crosstalk through the ceRNA network, in which MREs serve as letters of a new language, is poised to become a fundamental post-transcriptional gene regulatory pathway for this process. If expression levels of miRNAs or lncRNAs are misregulated, it may result in disorder of the buffer system composed of RNAs and lead to disease. Although the role of lncRNAs in this complex ceRNA network and the underlying mechanism remain largely undefined, these results may provide insight into the functional interactions of the components of ceRNA networks. A better knowledge of the ceRNA language will allow us to promote the understanding of the development of human tumors and, importantly, may shed new light on the therapies.

LncRNAs participate in pre-mRNA splicing

It has recently been estimated that approximately 95 % of the multiexon human pre-mRNAs undergo alternative splicing; therefore, the correct alternative splicing of pre-mRNAs is considered to be a key step in mRNA translation as well as regulation of gene function in higher eukaryotes [52–56]. Because errors can have deleterious consequences and may lead to developmental defects and disease, alternative splicing is precisely regulated by *trans*-acting protein factors, including small nuclear ribonucleoproteins (snRNPs), the heterogeneous nuclear ribonucleoproteins (hnRNPs), the serine/arginine-rich (SR) family of nuclear phosphoproteins (SR proteins), and SR-related proteins [53, 57]. Recent work has shown that lncRNAs can interact with several important protein factors and function as novel regulators of alternative splicing [58].

Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) is highly conserved among mammals and predominantly localizes to nuclear speckles, a subnuclear domain [59–61]. There is overwhelming evidence suggesting that MALAT1 plays a pivotal role in alternative splicing regulation [59, 62, 63, 61]. In human cells, MALAT1 can interact with several pre-mRNA splicing factors and affect alternative splicing of pre-mRNAs by modulating distribution and activity of SR splicing factors (Fig. 1c, d) [64–68, 61]. Therefore, the deregulation of MALAT1 has been correlated with a distinct pathological event, especially as observed in various cancers [60, 69–71]. More importantly, it can serve as an independent prognostic marker for survival in the early stages of non-small cell lung cancer [72]. Moreover, a recent study proposed a role for MALAT1 in cell cycle progression through modulation of the expression and/or pre-mRNA processing of cell cycle-regulated transcription factors [73]. Tripathi et al. found that MALAT1-depleted cells not only display a reduced expression of a large number of genes involved in mitotic progression but also showed changes in alternative splicing of B-MYB and CENPE transcripts that resulted from altered binding of splicing factors on pre-mRNA. These findings further supported the involvement of MALAT1 in tumorigenesis.

Natural antisense transcript (NAT) refers to any RNA transcript that is complementary to the exonic regions of an endogenous mRNA transcript, which may lead to post-transcriptional gene silencing [74–77]. Of considerable interest, the mechanism by which NATs regulate splicing of overlapping sense transcripts through base pairing has been observed in the case of alternative processing of Zeb2/Sip1, a transcriptional repressor of E-cadherin [78]. The expression of the Zeb2 protein correlates with the conservation of a long 5′-untranslated region (UTR) that contains an internal ribosome entry site (IRES) and is upregulated after Snail1-induced epithelial-mesenchymal transition (EMT). Beltran and colleagues found a NAT that overlaps the 5′ splice site containing the IRES and is transcribed during EMT. Subsequently, this NAT prevents splicing of the IRES from the pre-mRNA, leading to increasing the levels of Zeb2 protein and decreasing E-cadherin mRNA and protein [78].

As is known, sort bases are the foundation of correct protein translation, and accurate mRNA alternative splicing determines the mature mRNA sort bases. Therefore, the sequences of mRNA will be inconsistent when their splicing is changed, and lncRNAs could regulate this process just as a tailor sews different clothes. Although an increasing number of lncRNAs that are involved in alternative splicing regulation have been identified, our understanding about their relevance and underlying mechanism is only the tip of the iceberg. It will therefore be crucial to unravel the functions of additional alternative splicing-related lncRNAs that are buried within the complex mine of the human genome.

LncRNAs affect mRNA stability

In addition to established roles in ceRNA language and control of alternative pre-mRNA splicing, lncRNAs are involved in another layer of post-transcriptional processing through their modulation of mRNA half-life. Although microRNAs and RNA-binding proteins are major factors that affect the stability of mRNAs, lncRNAs are recognized as a prominent class of

ncRNAs that can base-pair with target mRNAs to trigger their degradation. This is particularly true for antisense transcripts.

The first example of a lncRNA involved in lncRNA-mediated mRNA degradation was the antisense transcript of the hypoxia inducible factor a, which contains 5′aHIF-1a and 3′aHIF-1a [79]. Although both are activated in response to different types of stress and can serve as a marker of poor prognosis in human breast cancer [79, 80], Bertozzi found that the two antisense RNAs are involved in different regulatory mechanisms. The 3′aHIF-1a, which is known to lack a 5′cap and a poly (A+) tail, is implicated in increasing instability of HIF-1a mRNA via an exposition of AU-rich elements in the HIF-1a mRNA 3′ UTR [81]. Conversely, the function of 5′ aHIF-1a, which has a 5′ cap and a poly (A+) tail, is more complex and diverse. LncRNA growth arrest and DNA-damage-inducible lncRNA7 (gadd7), a 754 nt polyadenylated lncRNA, is another example involved in regulating mRNA decay. The cDNA of gadd7 was originally isolated from Chinese hamster ovary (CHO) cells on the basis of its increased mRNA expression levels in response to UV radiation [82–84]. Zhan and Liu found that gadd7 regulates the cell cycle G1/S checkpoint upon DNA damage by binding to TAR DNA-binding protein (TDP-43) directly. This interferes with the interaction between TDP-43 and cyclin-dependent kinase 6 (Cdk6) mRNA, which promotes Cdk6 mRNA degradation [85].

Staufen 1 (STAU1)-mediated mRNA decay (SMD) is also a critical way of decreasing the stability of mRNAs. STAU1 is a double-stranded (ds) RNA-binding protein, and many the target mRNAs of Staufen 1 contain Alu elements instead of having obvious double-stranded RNA structures [86, 87]. Recently, a new group of lncRNAs that harbor the Alu element has been identified by Gong and Maquat in 2011 [88, 89]. The Alu element in this new group of lncRNAs can imperfectly base-pair with another Alu element in 3′UTR of an mRNA forming STAU1-binding sites. This binding promotes degradation of translationally active target mRNAs via SMD (Fig. 2a, b). Therefore, Gong and Maquat named this group of lncRNAs half-STAU1-binding site RNAs (1/2-sbsRNAs) [88, 89]. In addition to the Alu element, lncRNA–mRNA interaction can occur through other elements, such as the ‘TINCR box’ motif. Most recently, Siprashvili et al. found that terminal differentiation-induced ncRNA (TINCR) interacts with a range of differentiation mRNAs and prolongs the half-life of key differentiation mRNAs through a 25-nucleotide TINCR box motif [90].

In the context of correct mRNA sort bases, the RNA stability determines the protein levels through translation of mature mRNA. In addition to affecting mRNA alternative splicing, lncRNAs can also regulate mRNA stability via binding to specific protein complexes such as STAU1 and promoting mRNA decay. This evidence furthers our understanding about the regulators that are involved in regulating target mRNA stability; however, many more lncRNAs that participate in this biological process need to be investigated and documented in the future.

LncRNAs involved in mRNA translation

Another fundamental biological process in which all mRNAs are engaged is translation [91]. More specifically, translation initiation is a key determining factor of eukaryotic gene expression and thereby the control of cell proliferation, differentiation, and survival [92]. Consequently, abnormal translation can cause various human diseases [93–95]. Although lncRNAs had not been predicted to participate in translation, recent advances have revealed that some lncRNAs are associated with mRNA translation and additional cytoplasmic functions will likely emerge as we understand more about post-transcriptional regulation.

In 2010, it was reported that lincRNA-p21, a 2-kb-long noncoding RNA, can physically associate with hnRNP-K and modulate the genomic localization of repressive complexes to sets of previously active genes, ultimately generating apoptosis [96]. Therefore, in response to DNA damage, lincRNA-p21 serves as key regulatory hub in the nucleus during induction of apoptosis in cells. However, this is far from the end of the story for this lncRNA. Most recently, Yoon and colleagues demonstrated an additional function for lincRNA-p21 as a modulator of translation [97]. They found that the RNA-binding protein HuR can destabilize lincRNA-p21 via the recruitment of let-7/Ago2. In the absence of HuR, lincRNA-p21 is stable and elevated, resulting in increased association of lincRNA-p21 with CTNNB1 and JUNB mRNAs, as well as repression of JunB and β-catenin translation through a mechanism that includes reduced polysome sizes (Fig. 2c, d) [98, 97]. Therefore, the authors have uncovered a vital role for this lncRNA as an agent of post-transcriptional translation inhibition.

Translation mediated by antisense lncRNAs may be another mechanism that affects synthesis of proteins. An elegant study recently published in *Nature* by Carrieri et al. has highlighted the function of a nuclear-enriched antisense lncRNA that is transcribed in the opposite strand of the mouse ubiquitin carboxyterminal hydrolase L1 (Uchl1) gene [99]. They demonstrated that rapamycin can trigger the shuttling of antisense Uchl1 RNA from the nucleus to the cytoplasm, where it post-transcriptionally regulates UCHL1 protein levels by promoting the formation of active polysomes on Uchl1 mRNA. It is intriguing that the activity of antisense Uchl1 only requires the presence of a 5′ overlapping sequence (73 nt) and an embedded inverted SINEB2 sequence. Because the SINEB2 family of repeats constitutes approximately 0.7 % of total mouse genomic DNA and is at low abundance in humans [100], this mechanism may be common to other sense–antisense pairs.

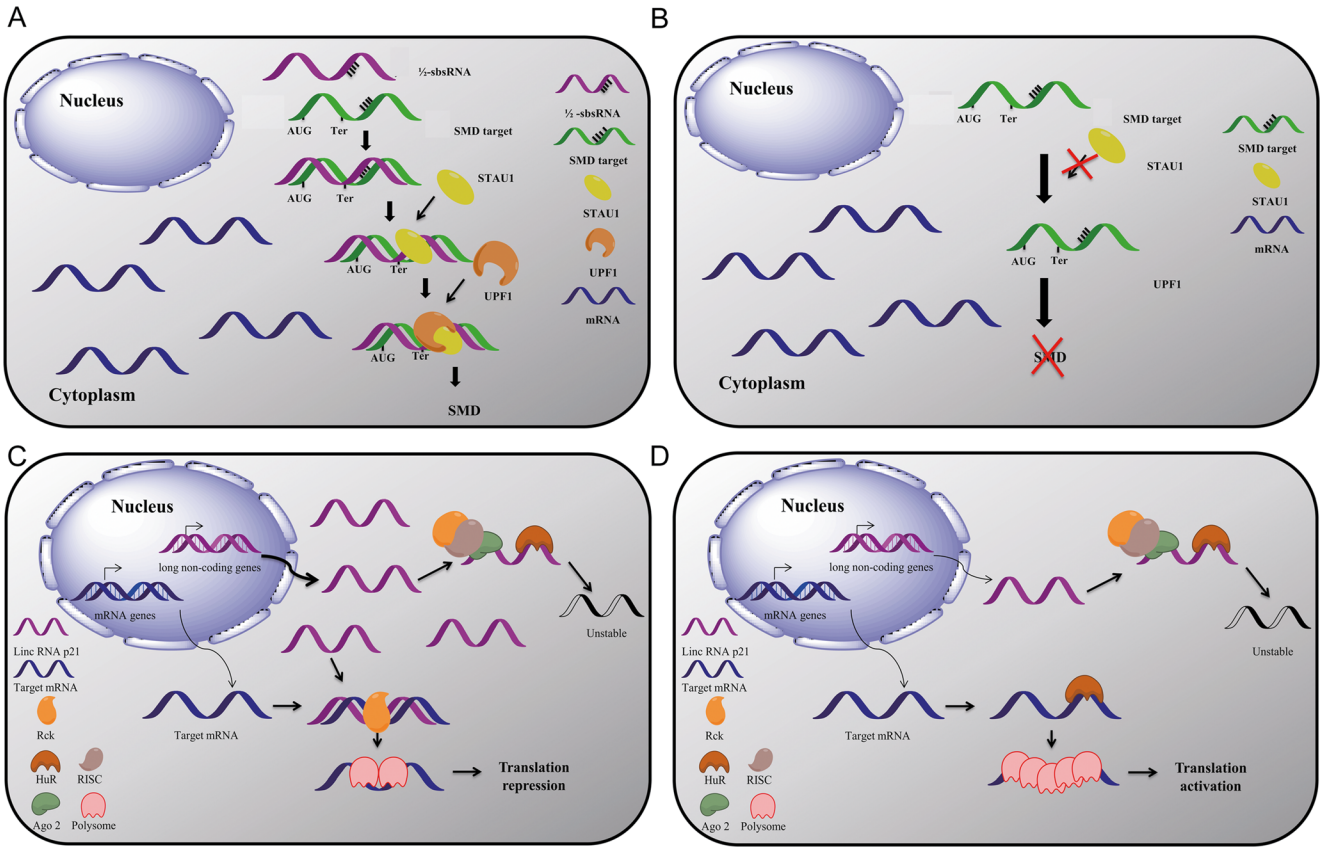

Fig. 2 LncRNAs participate in Staufen 1 (STAU1)-mediated mRNA decay (SMD) and mRNA translation. **a**, **b** STAU1-binding sites can be formed by imperfect base pairing between an Alu element within the 3′ UTR of an SMD target and another Alu element with in a lncRNA. Therefore, a functional SBS is formed. The STAU1-bound SBS interacts with UPF1, which triggers SMD. **c**, **d** The interaction between RNA-binding protein HuR and lincRNA-p21 destabilizes lincRNA-p21 via the recruitment of let-7/Ago2. When the expression level of lincRNA-p21 is elevated, the increase in association of lincRNA-p21 with target mRNAs by base pairing can repress their translation

A lncRNA named translational regulatory lncRNA (treRNA) was identified through a genome-wide computational analysis by Orom et al. in 2010 [101]. With increasing recognition that lncRNAs employ various molecular mechanisms at multiple steps to regulate gene expression, Huang and colleagues found that treRNA can also decrease the expression level of the epithelial marker protein E-cadherin through inhibition of translation of the E-cadherin mRNA, in addition to enhancing the expression of neighboring genes in the nucleus [102, 101]. However, unlike lincRNA-p21, it is likely that treRNA elicits its effects through a novel ribonucleoprotein (RNP) complex which consists of RNA-binding proteins (FXR1, FXR2, and hnRNP K), SF3B3, and PUF60 [102]. Furthermore, treRNA can influence the distribution of E-cadherin mRNA in HMW and LMW polysomes.

Taken together, these findings provide novel insight into the understanding of the translational functions of lncRNAs. With rapidly emerging evidence that increasingly supports the view that lncRNAs play a pivotal role in human disease processes [103], more critical proteins that are post-transcriptionally regulated by the orchestrated effect of lncRNAs and RNA-binding proteins are likely to emerge.

Others

With all of the diverse and powerful functions of lncRNAs, it is perhaps unsurprising that they have been involved in protein stability. A recent study conducted by Sun et al. revealed that the expression of the lncRNA low expression in tumor (lncRNA-LET) was reduced in hypoxic microenvironments as hypoxia-induced histone deacetylase 3 decreased the histone acetylation-mediated modulation of the lncRNA-LET promoter region [104]. Intriguingly, downregulation of lncRNA-LET may increase the stability of nuclear factor 90 protein, leading to hepatocellular carcinoma metastasis. Together, these results broaden our horizons of the role of lncRNAs as post-transcriptional regulators of gene expression and provide new avenues for effective therapy against tumor progression.

Concluding remarks and perspectives

In general, it has become increasingly clear that misexpression of lncRNAs is recognized as a hallmark feature in human disease, importantly in cancers. However, there are still many

gaps in our current understanding of the functional roles for the vast majority of these unique lncRNAs. Therefore, future studies are needed to elucidate the molecular mechanisms by which lncRNAs fulfill a critical function in the regulation of gene expression. In this review, we highlighted some exciting experimental evidence supporting the functionality of lncRNAs that are involved in diverse methods of post-transcriptional regulation, as well as described their potential roles in human cancer-associated processes. It is important to emphasize that lncRNAs have been associated with a broad spectrum of post-transcriptional biological processes, such as mRNA stability, translation, alternative pre-mRNA splicing, nuclear import, and protein activities, and even as regulators of mRNA decay. Given the versatile, critical, and surprising regulatory functions of lncRNAs uncovered so far, forming a better understanding of the precise molecular mechanisms by which lncRNAs function in various diseases and cancers will be an exciting journey and also critical for exploring new potential strategies for early diagnosis and therapy.

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Authors' contributions YS conceived of the review and participated in its design. XFS and MS drafted the manuscript. YW drafted Table 1. LW and YWY drafted the figures and the figure legends. HBL, DMY, and CHL participated in the design of the study and helped to draft the manuscript. All authors read and approved the final manuscript.

Conflicts of interest None

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