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Long noncoding RNA turnover

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Abstract

Most RNAs transcribed in mammalian cells lack protein-coding sequences. Among them is a vast family of long (>200 nt) noncoding (lnc)RNAs. LncRNAs can modulate cellular protein expression patterns by influencing the transcription of many genes, the post-transcriptional fate of mRNAs and ncRNAs, and the turnover and localization of proteins. Given the broad impact of lncRNAs on gene regulation, there is escalating interest in elucidating the mechanisms that govern the steady-state levels of lncRNAs. In this review, we summarize our current knowledge of the factors and mechanisms that modulate mammalian lncRNA stability.

1. Introduction

Eukaryotic cells transcribe large numbers of noncoding (nc)RNAs. The Encyclopedia of DNA Elements (ENCODE) project recently revealed that while 2–3% of the mammalian genome is transcribed into protein-coding RNAs (mRNAs), the vast majority of our genome (up to 80%) is transcribed into noncoding (nc)RNAs [1,2]. Some ncRNAs are processed to generate small RNAs [3,4], but most ncRNAs are larger than 200 nucleotides in their mature forms and thus are designated long noncoding (lnc)RNAs [5–8]. LncRNAs are generally a few hundred to a few thousand nucleotides in length, but some very long noncoding RNAs (vlncRNAs) can reach one million nucleotides in length. Mammalian lncRNAs can be expressed from intergenic regions (lincRNAs), from introns of annotated genes (long intronic ncRNAs), from the promoter regions of coding mRNAs (promoter-associated lncRNAs), from the opposite strand of mRNAs (antisense lncRNAs), or from pseudogenes [6]. They can also be generated by the splicing machinery (circular RNAs) [9–11].

The molecular functions of lncRNAs are quite varied. Some nuclear lncRNAs can regulate gene expression epigenetically by recruiting chromatin-modification factors to activate or inactivate different loci [12,13]. LncRNAs can also regulate transcription by assembling transcriptional activators and repressors to modulate the initiation of transcription [14]. They can influence the nuclear architecture and the structure of nuclear speckles, paraspeckles, and interchromatin granules [15]. Additionally, lncRNAs can regulate gene expression post-

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transcriptionally by modulating the translation and/or stability of partially complementary mRNAs and by interfering with RNA-binding proteins to influence splicing and translation [16–20]. Competing endogenous RNAs (ceRNAs) and circular RNAs are stable lncRNAs that accumulate in the cell and modulate gene expression by acting as decoys or sponges for microRNAs [21]. Finally, some lncRNAs function post-translationally to control protein turnover by facilitating ubiquitination [22,23]. Given the recognition that lncRNAs robustly regulate gene expression [14,24], there is mounting interest in understanding how lncRNA expression is regulated.

Like the transcription of protein-coding genes, the transcription of lncRNAs is driven by promoter elements, in some cases by distinct histone modification signatures [25,26]. Akin to mRNAs, lncRNA precursor transcripts are subsequently regulated by splicing, 5′ capping, and 3′ polyadenylation to generate mature lncRNAs which can eventually reside in the nucleus, the cytoplasm, or both of these compartments. Unlike mRNAs, however, cytoplasmic lncRNAs are generally not translated [27,28], even though recent reports have uncovered an association of lncRNAs with ribosomes and have identified small peptides generated from lncRNAs [29–32]. The mechanisms that regulate lncRNA stability are poorly understood. However, since modulating the abundance of a lncRNA is a rapid and effective way to regulate its function, the mechanisms that control lncRNA turnover are attracting much attention. In this review, we discuss our emerging understanding of the mechanisms that influence mammalian lncRNA stability.

2. Mechanisms of RNA decay

2.1. Global lncRNA stability

Recent studies using custom RNA arrays to measure the half-lives of ~800 lncRNAs in mouse Neuro-2a cells revealed that ~29% of lncRNAs were unstable when considering a half-life ($t_{1/2}$) of 2 h or less, compared with 17% of unstable mRNAs [33]. Intergenic, cis-antisense, and spliced lncRNAs were generally more stable than intronic lncRNAs and unspliced lncRNAs comprising a single exon, while cytoplasmic lncRNAs were found to be more stable than nuclear lncRNAs [33]. The regulators of lncRNA turnover have not been identified systematically, but we are beginning to discover that some of the machineries same machineries that control mRNA decay also govern lncRNA decay.

2.2. Decapping, deadenylation, exonucleolytic and endonucleolytic degradation

The control of mRNA stability is a major mechanism of post-transcriptional gene regulation in eukaryotic cells, affecting the abundance of a given mRNA by increasing or decreasing its half-life [34,35]. The canonical mRNA decay follows sequential ribonucleolytic activities although the order of the enzymatic events vary depending on the target mRNA and the specific cellular conditions. Three main mechanisms can trigger mRNA decay: 1) removal of the 3′-polyadenosine [poly(A)] tail by a deadenylase complex initiating 3′-to-5′decay, 2) removal of the ^{7}mGpppG 5′ cap structure by decapping enzymes, inducing 5′-to 3-exoribonucleolytic decay, and 3) endoribonuclease cleavage of a target mRNA in the middle of the transcript. The 3′ deadenylation can be triggered by a multi-subunit complex consisting of poly(A) tail-specific ribonucleases and deadenylases, including PAN2, PAN3,

CNOT6/CCR4A, CNOT6L/CCR4B, PARN and other enzymatic activities (reviewed in [34–36]). Deadenylated mRNA is targeted to the exosome complex, which contains the 3′-to-5′ exonucleases RRP44 and EXOSC10. The deadenylated RNA is also a substrate of 5′ decapping enzymes such as DCP2, followed by 5′-to-3′ exonucleolytic degradation via XRN1 [34,37]. Endonucleases such as RMP1, ZC3H12A and IRE1 cleave in the middle of a transcript, followed by degradation of the resulting fragments via 3′-to-5′exosomal and 5′-to-3′ exoribonucleolytic enzyme activities, respectively [38]. Since many lncRNAs are structurally similar to mRNAs, with 5′ caps and 3′ poly(A) tails, the enzymes that control mRNA decapping, deadenylation, and exo- and endonucleolytic degradation are believed to modulate the turnover of many lncRNAs.

2.3. Translation-associated RNA decay: NMD, SMD, NGD, NSD

mRNA decay is also tightly associated with the translation machinery, serving as a quality-control mechanism to ensure the production of adequate protein products. External stimuli and intrinsic properties in mRNA sequences can block mRNA translation during initiation and elongation. Inhibition of translation initiation leads to the accumulation of 43S preinitiation complex, translation repressors, and mRNA decay enzymes in cytoplasmic granules that contain bulk mRNAs targeted for translation repression and stabilization [39–41]. Nonsense-mediated mRNA decay **(NMD)** is a mechanism that prevents the synthesis of aberrant protein products that can induce cellular toxicity [42]. NMD is triggered by the termination of translation upstream of a splicing-derived exon junction complex (EJC) during a pioneer round of translation. Binding of UPF1 to the EJC triggers UPF1 phosphorylation by SMG1 [34]. The interaction of p-UPF1 and SMG5-7 or SMG-6 ultimately cleaves the RNA with the PTC (premature termination codon) and promotes 5′-to-3′ decay through deadenylation and decapping [43]. STAU1-mediated mRNA decay **(SMD)** degrades mRNAs bearing intra- or inter-molecular double-stranded structures in the 3′UTR [16,44]. After the termination of translation, UPF1 binds to the mRNA-associated STAU1 and triggers mRNA degradation, likely following events similar to those in conventional NMD [44]. Ribosome stalling on the mRNA during elongation triggers no-go mRNA decay **(NGD)** and bypassing a stop codon induces non-stop mRNA decay **(NSD)** which triggers dissociation of ribosomes from mRNA and removes unfavorable mRNA and peptide products [45]. As much of protein-coding mRNA degradation is closely linked to mRNA translation, these decay mechanisms may in principle be distinct from those that govern lncRNA decay, as they do not codify proteins. On the other hand, given the accumulating evidence that ribosomes can bind to some lncRNAs and may generate small peptides [46,47], the full spectrum of translation-independent and -dependent mechanisms control lncRNA decay remains to be elucidated.

2.4. Recruitment of RNA decay machineries by microRNAs and RBPs

The degradation machinery can be recruited to selective groups of mRNAs. This recruitment can be promoted by small RNAs like microRNAs (miRNAs), small interfering RNAs (siRNAs), and PIWI-interacting RNAs (piRNAs), which accelerate target mRNA decay via complementarity sequences within the mRNA 3′UTR [48]. The best-studied small RNAs, microRNAs, associate with several proteins including argonaute 2 (AGO2) to form the RNA-induced silencing complex (RISC), which mediates the decay of the target mRNA.

MicroRNA biogenesis typically begins with the synthesis of a primary miRNA (pri-miRNAs) containing a 5′ cap and a 3′ poly(A) tail. Subsequent 'cropping' of the pri-miRNA by the type III RNase Drosha releases a small stem-loop structure, the precursor miRNA (pre-miRNA). Following export of the pre-miRNA to the cytoplasm by the nuclear exporting factor 5 (EXP5), cytoplasmic pre-miRNA is further processed by another type-III RNase, Dicer. Dicer cleaves the pre-miRNA loop structure and degrades one strand, releasing a ~22 nt-long mature miRNA which is loaded onto AGO1-AGO4 proteins [3]. The mature miRNA directs RISC to a target mRNA, with which it interacts via imperfect base-pairing. This interaction triggers mRNA decay (by promoting deadenylation, decapping, and exonucleolytic degradation), translational repression, or both of these processes [49–52]. The recruitment of mRNAs to the decay machinery can also be modulated through select RNA-binding proteins (RBPs) that associate with specific sequences on the mRNA. Some RBPs enhance the recruitment of target mRNAs to the degradation machinery, as seen for decay-promoting RBPs like tristetraprolin, UPF1, and AUF1; other RBPs prevent this recruitment, as seen for stabilizing RBPs such as members of the Hu/elav family, changing the relative half-life of the mRNA accordingly [53].

Similar to the decay of mRNAs, lncRNA degradation is driven by RBPs and small RNAs that promote or inhibit the interaction of lncRNAs with the decay machinery, via recruitment of decapping enzymes or by mobilization of the mRNA to the exosome. Also similar to mRNA turnover, cis-regulatory elements recognized by microRNAs and by RBPs are present in lncRNAs and influence their rate of decay. Here, we summarize our current understanding of lncRNA degradation pathways.

3. microRNA-triggered lncRNA decay

Several recent reports highlight a role for microRNAs in modulating lncRNA stability, and consequently lncRNA abundance and function.

3.1. Let-7

A recent study revealed that the stability of *LINCRNAP21* is controlled by the microRNA let-7b [18]. Knockdown of AGO2 stabilized human *LINCRNAP21*, while targeted deletion of AGO2 in mouse embryonic fibroblasts (MEFs) increased the abundance of mouse *Lincrnap21*, suggesting that microRNAs were involved in the decay of this lncRNA. Among several miRNAs predicted to target human *LINCRNAP21* (using the software RNA22), microRNA let-7b was shown to regulate its stability. Ectopic expression of let-7b promoted *LINCRNAP21* decay in human cervical carcinoma HeLa cells, while antagonization of let-7b prevented it, indicating that let-7b accelerated *LINCRNAP21* degradation [18]. Interestingly, the RBP HuR promoted *LINCRNAP21* turnover in a let-7b-dependent manner, as the decay of *LINCRNAP21* by overexpression of HuR was rescued by antagonizing let-7b. When *LINCRNAP21* was stabilized, it formed partial hybrids with *CTNNB1* and *JUNB* mRNAs and suppressed their translation.

Let-7 was also found to interact with *HOTAIR*, an antisense lncRNA transcribed from the *HOX* locus, and reduced *HOTAIR* levels [22]. Similar to *LINCRNA21*, *HOTAIR* was destabilized by let-7 (in this case let-7i), and was stabilized when let-7i or AGO2 were

suppressed. Also like *LINCRNAP21* decay, *HOTAIR* degradation occurred when HuR promoted the interaction of let-7i-AGO2 with *HOTAIR*. Accordingly, in cells that expressed low levels of HuR (for example by reaching replicative senescence), *HOTAIR* was stable, accumulated, and served as a scaffold for E3 ubiquitin ligases (as shown for Mex3b and Dzip3) and their respective ubiquitination substrates (Snurportin-1 and Ataxin-1) [22].

Additional lncRNAs are also targeted by the let-7 family. One of the long-known lncRNAs, *H19*, contains RNA sequences targeted by let-7 family microRNAs (let-7a, -b, -g, -i [54]). *H19* levels declined after let-7a overexpression in an AGO2-dependent manner. Although it remains to be determined if microRNAs affect *H19* stability, a reporter construct containing *H19* sequences was selectively inhibited after let-7b overexpression. As a target of let-7, *H19* functions as competing endogenous RNA (ceRNA) of mRNAs encoding proteins that are critical for myotube formation [54].

3.2. miR-9

miR-9 was shown to target *MALAT1* in the human primary glioblastoma cell line U87MG and the human Hodgkin lymphoma cell line L428 [55]. *MALAT1* levels increased when miR-9 was inhibited using an antagomir, while they decreased when miR-9 was overexpressed. Since *MALAT1* is exclusively nuclear, miR-9 may promote *MALAT1* degradation in the nucleus via nuclear decay-promoting factors.

3.3. miR-34a

Very recently, miR-34a was found to lower the stability of *UFC1*, a lncRNA that is more highly expressed in human hepatocellular carcinoma (HCC) than in healthy liver [56]. Interestingly, the lincRNA *UFC1* appeared to export HuR to the cytoplasm, thereby enhancing the stability of the HuR target *CTNNB1* mRNA (encoding β-catenin), in this manner possibly contributing to enhancing tumorigenesis [56].

3.4. miR-211

The lncRNA *LOC285194*, a p53-inducible tumor suppressor, was found to be a target of miR-211 in the human colon cancer cell line HCT-116 [57]. Transfection of a miR-211 precursor reduced the expression of *LOC285194*, although the contribution of *LC285194* destabilization to this reduction was not studied. The lower expression of *LOC285194* in human colon cancer was linked to the accumulation of miR-211 in this cancer type. In this paradigm, an interesting reciprocal regulation of miR-211 was postulated, as *LC285194* reduces steady-state level of mature miR-211 but not pri-miR-211 or pre-miR-211 levels, further implicating *LOC285194* in the regulation of miR-211 stability [57].

3.5. miR-574-5p

miR-574-5p interacts with and lowers the levels of the tumor suppressor lncRNA *PTCSC3* in the human thyroid cancer cell lines BCPAP, FTC133, and 8505C. Ectopic expression of miR-574-5p in these cell lines decreased *PTCSC3* abundance [58]. Since *PTCSC3* arrests cells in G0/G1, miR-574-5p was proposed to enhance cell proliferation by maintaining low levels of *PTCSC3*.

3.6. miR-124

miR-124 binds to and lowers the levels of the retropseudogene *LNCSCA7* [59]. Overexpression of miR-124 in mouse N2A cells decreased *Lncsca7* abundance, whereas introduction of miR-124 antagomir increased it. Analysis of reporter constructs further supported the notion that miR-124 specifically promoted *Lncsca7* decay. Since *Lncsca7* was proposed to function as ceRNA for *Atxn7* mRNA, which encodes a transcriptional repressor of miR-124 itself, this auto-regulatory loop may help to titrate the level of *Lncsca7*, *Atxn7*, and miR-124 during neurodegeneration [59].

4. RBP-mediated lncRNA decay

Several RBPs are involved in lncRNA decay. Through their ability to bind specific RNA sequences, they can promote or inhibit the degradation of lncRNAs. These RBPs include classic ARE-binding proteins, RNA helicases, and RBPs that function in RNA transport from the nucleus.

4.1. HuR

This ubiquitous RBP recognizes AU- or U-rich RNA sequences in many mRNAs and promotes their stability [60]. Interestingly, however, HuR instead lowered the stability of some lncRNAs [18,22]. As mentioned above, HuR promoted the decay of *LINCRNAP21*, a lncRNA present in both the nucleus and the cytoplasm, by promoting its interaction with AGO2-let-7b complexes in HeLa cells. In keeping with this mode of action, HuR overexpression decreased the steady-state levels of *LINCRNAP21*, while a let-7b antagomir rescued the effect of HuR and increased *LINCRNAP21* abundance. Conversely, HuR depletion increased *LINCRNAP21* abundance, and co-expression of let-7b precursor lowered *LINCRNAP21* levels. These results suggest that HuR promotes *LINCRNAP21* decay in let-7b-dependent manner. Similarly, HuR promoted decay of lncRNA *HOTAIR* (also present in both the nucleus and the cytoplasm) by enhancing the recruitment of let-7i-AGO2 to *HOTAIR* [22].

4.2. AUF1

This RBP, which exists in four isoforms (p37, p40, p40, p45), was found to have strong affinity for U- and GU-rich RNAs, and promoted decay of the nuclear lncRNA *NEAT1* [61]. In contrast to HuR, which generally stabilizes mRNA but destabilized lncRNAs, AUF1 displayed the same degradation-promoting influence on lncRNAs as that reported for mRNAs. This influence was evidenced by the fact that silencing AUF1 (all four isoforms) increased the steady-state levels of *NEAT1*. Although NEAT1 is mainly localized in nuclear speckles, it is not known at present whether AUF1 promoted *NEAT1* degradation in the nucleus or the cytoplasm. In turn, the accumulation of nuclear *NEAT1* led to increased non-clustered (random) nuclear speckles and to the retention of *NEAT1* target mRNAs in the nucleus [61].

4.3. HuD

The neuronal RBP HuD associated with *BACE1AS*, an antisense lncRNA which shuttles between the nucleus and the cytoplasm depending on growth conditions, and partly

complements *BACE1* (β-site APP-cleaving enzyme 1) mRNA [17]. HuD was shown to bind 5′ and 3′ segments of *BACE1AS* but not the central double-stranded RNA segment complementary to *BACE1* mRNA [62]. Depletion of HuD in neuroblastoma SK-N-F1 destabilized *BACE1AS* and reduced its steady-state level. As the microRNA miR-485-5p targets *BACE1* mRNA [62], one of the proposed mechanisms through which *BACE1AS* increases BACE1 expression is by blocking the interaction of miR-485-5p with *BACE1* mRNA [63]. A recent study suggests that HuD prevents the interaction of eIF4A with microRNA-RISC [64].

4.4. PABPN1

Poly(A)-binding protein nuclear 1 (PABPN1), an RBP involved in the addition of poly(A) tails to the 3′ end of mRNAs, reportedly protects lncRNAs from degradation [65]. Depletion of PABPN1 in HeLa cells did not affect the steady-state levels of many mRNAs. Interestingly, however, PABPN1 silencing increased the stability and abundance of nuclear lncRNAs *NEAT1*, *SHG60*, and *SHG104*. Moreover, mutation in the AAUAAA sequence, required for polyadenylation, reduced the steady-state level of lncRNA *SHG60*, implicating this sequence in polyadenylation-dependent lncRNA decay. Further analysis revealed that *SHG60* accumulated in human embryonic kidney (HEK)293T cells after silencing RRP40, a protein component of exosome, but not UPF1, a core protein in nonsense-mediated mRNA decay (NMD) [65].

4.5. IGF2BP

Microarray analysis of 60 human hepatocellular carcinoma (HCC) samples found that the lncRNA *HULC* (highly up-regulated in liver cancer) was overexpressed in many HCCs compared to normal liver [66]. *HULC* interacts with several RBPs, including the *IGF2* mRNA-binding protein (IGF2BP) 1, -2, and -3 in the hepatocellular carcinoma cell line HepG2. Notably, depletion of IGF2BP1 (but not IGF2BP2 or -3), stabilized *HULC*, increasing its abundance. Since IGF2BP1 interacts with CNOT1, a core protein of the deadenylase complex, it may recruit CNOT1 to promote *HULC* deadenylation [66].

4.6. UPF1

A recent study using BrU RNA labeling measured lncRNA stability globally in mammalian cells [67]. UPF1 depletion stabilized *GAS5* (growth arrest-specific 5), a lncRNA found in both the nucleus and the cytoplasm, as well as *cIAP2* and *SGK1* mRNAs, which are involved in the glucocorticoid response. Serum depletion increased the stability and abundance of *GAS5*, whereas it decreased the abundance of *cIAP2* and *SGK1* mRNAs. Strikingly, suppression of *GAS5* accumulated *cIAP2* and *SGK1* mRNAs in HEK293T cells, suggesting that *GAS5* may, in turn, promote the degradation of *cIAP2* and *SGK1* mRNAs by interacting with UPF1.

5. Decapping and deadenylation of lncRNA

5.1. XRN1

Mammalian XRN1 can degrade long noncoding RNA generated by arthropod-borne flaviviruses [68]. The Dengue virus 3′UTR is degraded by XRN1, HeLa cell extract, or

mosquito (*Aedes* C6/36) extracts to generate a short noncoding RNA (sfRNA). In turn, accumulation of the sfRNA in mammalian cells inhibits XRN1 function, allowing the accumulation of many cellular mRNAs, including *FOS* and *TUT1* mRNA. These results indicate that inhibition of XRN1 can result in the accumulation of host mRNA as well as long noncoding RNAs.

5.2. CNOT1

As mentioned above, the lncRNA *HULC* is degraded by CNOT1, a core protein component of the mammalian deadenylase complex, as silencing CNOT1 increased *HULC* stability and steady-state levels [66]. The RBP IGF2BP1 interacts with CNOT1 and may recruit it to *HULC* for deadenylation and subsequent degradation. In agreement with this idea, silencing IGF2BP1 stabilizes *HULC*, although deadenylation and IGF2BP1-mediated decay may also occur independently.

6. Cis-regulatory elements in lncRNAs

6.1. 3′ end processing

Although mature *MALAT1* is exclusively nuclear, the 3′end processing product from nascent *MALAT1* resides in the cytoplasm after cleavage by RNases P and Z. The resulting 61 nt-long 3′end product is processed further through the tRNA biogenesis pathway to generate a tRNA-like cytoplasmic RNA called *mascRNA* [69]. Further processing adds CCA to the 3′end of *mascRNA* resulting in its destabilization and export to the cytoplasm [70].

6.2. RNA triple helix

Although mature *MALAT1* lacks a poly(A) tail, it is much more stable than mRNAs. The 3′end of *MALAT1* forms a conserved triple-helix that prevents access of 3′-to-5′ exonucleases [71]. The crystal structure of the human *MALAT1 ENE* (expression and nuclear retention element) A-rich tract reveals a bipartite triple helix [72]. Indeed, mutations that disrupt this blunt-ended triple helix abolish the stability of *MALAT1* in HeLa cells. Similar RNA triple helix characteristics were identified in lncRNA *PAN* (polyadenylated nuclear) from Kaposi's sarcoma-associated herpes virus (KSHV) [73]. Triple helix formation with a poly(A) tail inhibits its rapid decay in the nucleus. Taken together, these studies indicate that evolutionally conserved RNA triple-helix complexes protect lncRNAs from rapid degradation.

7. Concluding remarks and perspectives

LncRNAs regulate mammalian protein expression programs by influencing the transcription of protein-coding transcripts, as well as pre-mRNA splicing, mRNA decay, protein translation, and protein degradation. In order to ensure proper lncRNA function, the levels and localization of lncRNAs must be carefully orchestrated. Here, we have reviewed the mechanisms of lncRNA degradation by focusing on how lncRNA stability is affected by trans-interacting factors (proteins and RNAs) and by cis-elements in the lncRNA.

Although this review focused on mammalian lncRNA turnover, the decay of yeast lncRNAs [74] likely shares many similarities and may guide future studies. In one report, yeast Dcp2

and Xrn1 were found to be necessary for the decay of lncRNAs implicated in the response to galactose availability [75], notably the lncRNA *GAL10*; accordingly, stabilization and accumulation of *GAL10* repressed *GAL1* mRNA transcription via changes in chromatin structure. Whether a similar mechanism operates in mammalian cells is not yet known.

As discussed in this review, lncRNA and mRNA decay pathways share many similarities. The main difference between lncRNA decay and mRNA decay pathways may reside in the fact that mRNA metabolism is closely tied to its interaction with ribosomes for translation. However, recent ribosome density mapping (also called ribosome profiling) revealed that a large proportion (43.1% [30]) of lncRNAs do interact with ribosomes [46,47]. Nonetheless, lncRNAs are ~13-fold less likely to produce peptides than mRNAs, and in the two cell lines analyzed by GENCODE v7, the majority of lncRNAs (~92%) were not translated [27]. Further analysis of a collection of 79,333 peptides revealed only 85 peptides matching to open reading frames in a handful of lncRNAs (<1% of total lncRNAs) [27]. Whether the translation machinery-associated decay pathways differ for coding and noncoding RNAs needs more detailed examination.

With the exception of HuR, which generally promotes mRNA decay but enhances lncRNA decay [18,22], the rest of lncRNA decay mechanisms follow similar rules as mRNAs for decay mediated by *trans*-factor binding. As discussed here, many miRNAs promote lncRNA degradation by seed-dependent complementarity and several RBPs (AUF1, IGF2BP1, and UPF1) promote lncRNA decay [61,66,67]. Likewise, mRNA-stabilizing RBPs such as HuD and PABPN1 also protect lncRNAs from degradation [62,65]. LncRNAs also appear to utilize general mRNA decay factors (Dcp2, Dcp1, Xrn1, and CNOT1) for decapping, deadenylation, and degradation 5′-to-3′ and 3′-to-5′ [66,68,75]. In distinction with mRNAs, however, *cis*-regulatory sequences embedded in lncRNAs can determine their stability by affecting 3′ end processing or by forming RNA triple helices exclusively in lncRNAs, but not mRNAs [70-73].

A comprehensive understanding of the mechanisms that control lncRNAs await much additional work. In the same way that regulation of mRNA decay contributes to the temporal availability of mRNA for translation, modulation of lncRNA decay affects the abundance and distribution of lncRNAs. The local and temporal control of lncRNA abundance can affect chromatin remodeling, target mRNA fate, and protein stability. By changing lncRNA levels, cells may rapidly and effectively titrate the amount of mRNA decay factors, RBPs, and miRNAs. For instance, just as ceRNAs compete with mRNAs for binding miRNAs [76], circular lncRNAs may bind and sequester RBPs [77]. Linear lncRNAs can also interact with decapping enzymes, deadenylases, exoribonucleases, and RBPs, thus modulating their availability in cells [77]. Given the unexpected functions of many lncRNAs, elucidating in full the mechanisms of lncRNA decay will increase our understanding of these regulatory RNAs and unveil new ways in which we can target lncRNAs in order to modulate gene expression patterns.

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Abbreviations

lncRNA	long noncoding RNA
lincRNA	long intergenic noncoding RNA
miRNA	micro RNA
RBP	RNA-binding protein
RISC	RNA-induced silencing complex
UTR	untranslated region

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- LncRNAs control gene expression transcriptionally and posttranscriptionally
- Changes in lncRNA turnover effectively alter mammalian lncRNA abundance
- LncRNA turnover is largely regulated by the general mRNA decay machinery
- RNA-binding proteins interacting with lncRNAs can enhance or lower lncRNA half-life
- MicroRNAs associate with lncRNAs and promote lncRNA degradation

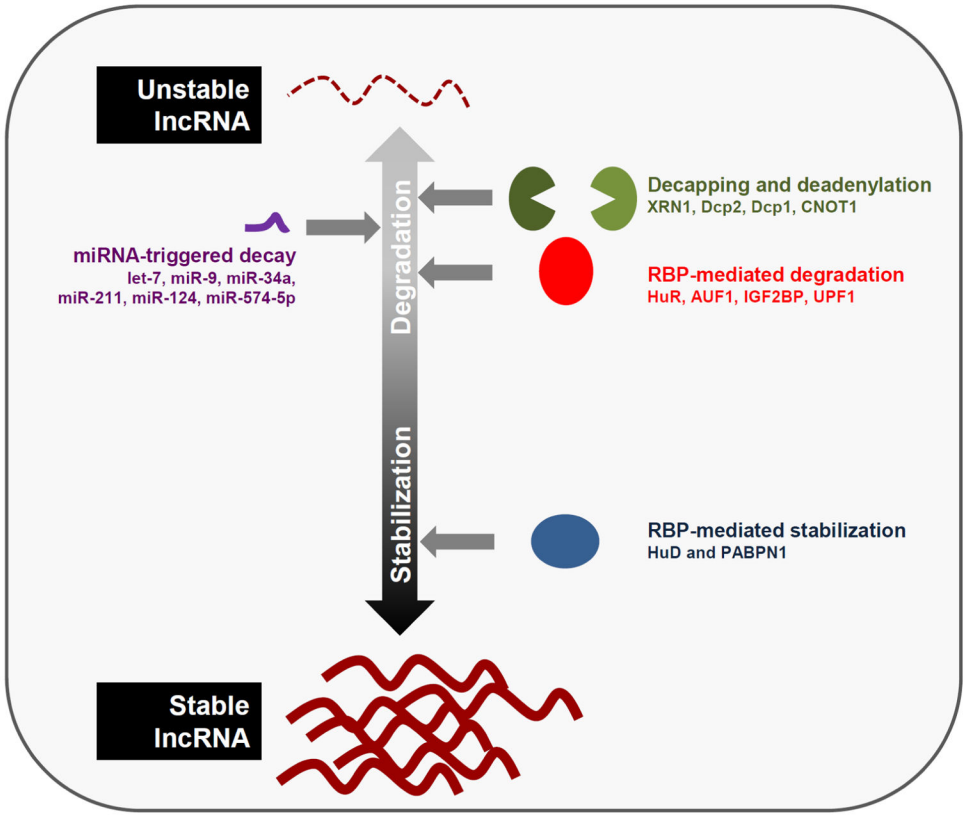

FIGURE 1. Modes of lncRNA degradation

Schematic of the major mechanisms of lncRNA decay. *Top*, LncRNAs are degraded by many miRNAs, decay-promoting RBPs (HuR, AUF1, IGF2BP, and UPF1), and general decapping enzymes and dadenylases (Dcp2, Dcp1, and CNOT1). *Bottom*, lncRNAs are protected from degradation by stabilizing RBPs (HuD and PABPN1).

Table 1
Examples of mammalian lncRNA degradation

Decay factors (column 1) affecting the stability and/or level of lncRNAs (column 2) in various species (column 3). The consequences on lncRNA stability are indicated (column 4).

Turnover Factor	lncRNA	Species	Consequences	References
microRNAs				
let-7b	*LINCRNAP21*	Human, Mouse	Degradation	[18]
let-7i	*HOTAIR*	Human, Mouse	Degradation	[22]
let7a,b,g,i	*H19*	Human, Mouse	Degradation	[54]
miR-9	*MALAT1*	Human	Degradation	[55]
miR-34a	*UFC1*	Human	Degradation	[56]
miR-211	*LOC285194*	Human	Degradation	[57]
miR-574-5p	*PTCSC3*	Human	Degradation	[58]
miR-124	*Lncsca7*	Mouse	Degradation	[59]
RNA-binding proteins				
HuR	*LINCRNAP21*	Human, Mouse	Degradation	[18]
HuR	*HOTAIR*	Human, Mouse	Degradation	[22]
AUF1	*NEAT1*	Human	Degradation	[61]
HuD	*BACE1AS*	Human	Stabilization	[62]
PABPN1	*NEAT1, SHG60, SHG104*	Human	Stabilization	[64]
IGF1BP	*HULC*	Human	Degradation	[66]
UPF1	*GAS5*	Human	Degradation	[67]
Decapping & deadenylation				
XRN1	Dengue virus 3′UTR	Flavivirus hosts	Degradation	[68]
CNOT1	*HULC*	Human	Degradation	[66]
Cis-regulatory elements				
3′end CCA	*mascRNA*	Mouse	Cytoplasmic export	[69]
RNA triple helix	*Malat1*	Mouse	Stabilization	[71,72]
RNA triple helix	*PAN*	KSHV hosts	Stabilization	[73]