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Functional interactions among microRNAs and long noncoding RNAs

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Abstract

In mammals, the vast majority of transcripts expressed are noncoding RNAs, ranging from short RNAs (including microRNAs) to long RNAs spanning up to hundreds of kb. While the actions of microRNAs as destabilizers and repressors of the translation of protein-coding transcripts (mRNAs) have been studied in detail, the influence of microRNAs on long noncoding RNA (lncRNA) function is only now coming into view. Conversely, the influence of lncRNAs upon microRNA function is also rapidly emerging. In some cases, lncRNA stability is reduced through the interaction of specific miRNAs. In other cases, lncRNAs can act as microRNA decoys, with the sequestration of microRNAs favoring expression of repressed target mRNAs. Other lncRNAs derepress gene expression by competing with miRNAs for interaction with shared target mRNAs. Finally, some lncRNAs can produce miRNAs, leading to repression of target mRNAs. These microRNA-lncRNA regulatory paradigms modulate gene expression patterns that drive major cellular processes (such as cell differentiation, proliferation, and cell death) which are central to mammalian physiologic and pathologic processes. We review and summarize the types of microRNA-lncRNA crosstalk identified to-date and discuss their influence on gene expression programs.

1. Introduction

In mammalian cells, the vast majority of transcribed RNAs are noncoding [1–4]. Many of them are processed to generate small RNAs, including microRNAs, the best-known class of small RNAs, but also small interfering (si)RNAs, Piwi-interacting (pi)RNAs, transcription initiation (ti)RNAs, tRNA-derived stress-induced RNAs, and small nucleolar (sno)RNAs [5,6]. Other transcripts (long noncoding RNAs or lncRNAs) remain larger than 200 nucleotides in their mature form [7–9]. Through their interaction with DNA, RNA, and proteins, ncRNAs affect all levels of gene regulation, including chromatin remodeling, transcription, pre-mRNA splicing, mRNA turnover, mRNA translation, and protein stability [10–13]. It has recently become apparent that there is interesting cross-regulation between

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microRNAs and lncRNAs. In this review, we describe and discuss the mutual regulatory influence of mammalian microRNAs and lncRNAs.

1.1. MicroRNA biogenesis and function

The expression of microRNAs begins through transcription of a primary miRNA (pri-miRNA) that harbors the microRNA. The pri-miRNA is processed by a nuclear complex known as a microprocessor, which includes the DiGeorge syndrome critical region 8 (DGCR8) and the ribonuclease Drosha, to generate a miRNA precursor (pre-miRNA). After pre-miRNAs are exported to the cytoplasm, they are cleaved by the ribonuclease Dicer, yielding ~22-nt duplex RNAs; one strand of each duplex is loaded into the miRNA-containing ribonucleoprotein (RNP) complex RISC (RNA-induced silencing complex), which contains Argonaute (Ago) proteins [5,14]. Each of these complexes then targets a specific mRNA, generally (but not exclusively) at the mRNA 3′-untranslated region (UTR), forming a partial hybrid with the miRNA ‘seed’ region (nucleotides 2–7) or other regions of the miRNA [10,15,16]. MicroRNAs regulate the pattern of expressed proteins via a number of proposed mechanisms, most of them repressive. They can modulate gene transcription rates, inhibit the initiation and elongation of translation of target mRNAs, promote target mRNA decay, and reduce the stability of proteins newly synthesized from target mRNAs. They can also sequester target mRNAs in cytoplasmic regions (P-bodies) where translation and stability are diminished [11,17–21].

1.2. LncRNA biogenesis and function

The expression of lncRNAs is largely regulated like that of coding RNAs. LncRNAs are subject to transcriptional regulation, and some lncRNAs (although not all) are further regulated via splicing, processing at the 5′ and 3′ ends, and export to the cytoplasm [22,23]. Some lncRNAs can produce small peptides, but the vast majority of lncRNAs are not translated [24,25]. Their function has been tied to their modular structure, which permits them to interact specifically with proteins, DNA, and RNA [26]. Studies on the influence of lncRNAs on the patterns of expressed genes have revealed increasing richness and complexity of mechanisms through which lncRNAs control gene expression, at both transcriptional and post-transcriptional levels, as explained below.

The roles of lncRNAs in regulating gene transcription have been studied extensively. Since the early finding that chromatin was purified with extensive amount of RNAs [27], many lncRNAs have been found to interact with chromatin-modifying enzymes and to modulate the transcriptional activation or silencing of genes [28]. For example, the lncRNA *XIST*, expressed from one X chromosome, inactivates the other X chromosome via mechanisms that include, but are not restricted to, recruitment of PRC2 (Polycomb repressive complex) [29]. In mammalian cells, the lncRNA *HOTAIR* represses target gene expression by associating with PRC2 and LSD1 and triggering genome-wide histone H3 lysine-27 trimethylation (H3K27me3) and lysine 4 demethylation (H3K4me2), while a lncRNA transcribed from the *CEBPA* (CCAAT/enhancer binding protein α) locus activates *CEBPA* mRNA transcription by inhibiting DNMT1 (DNA cytosine-5-methyltransferase 1) [30–34]. In addition, p53-regulated lncRNAs (*lincRNA-p21, PANDA, lincRNA-PINT*) suppress target gene transcription by interacting with transcription factors (hnRNPK and NF-YA) or PRC2

[35–37]. The complete spectrum of mechanisms of through which lncRNAs affect transcription is not fully known.

Some lncRNAs have also been found to regulate gene expression post-transcriptionally [13]. Examples of this regulation include the lncRNA *MALAT1* (metastasis-associated long adenocarcinoma transcript 1), which sequesters SR (Serine/Arginine) proteins to modulate pre-mRNA alternative splicing [38], and lncRNAs 1/2-sbsRNAs (half-Staufen 1-binding site RNAs), which promote target mRNA degradation by partial complementarity with target mRNAs and subsequent recruitment of Staufen 1 [39]. In contrast, perfect complementarity between an mRNA and its antisense lncRNA [β amyloid-cleaving enzyme (*BACE*)*1* mRNA and *BACE1AS* (*BACE1* antisense)] protects *BACE1* mRNA from RNase cleavage and degradation [40]. LncRNAs have also been found to repress translation globally in neurons and germ cells (e.g., lncRNA *BC1* [41]) or that of specific target mRNAs (*lincRNA-p21*, [42]). A translation-enhancing function was also reported for *AS Uchl1* (ubiquitin carboxyl-terminal esterase L1 ubiquitin thiolesterase) through its complementarity with target *Uchl1* mRNA and embedded SINEB2 repeat [43]. The post-transcriptional functions of lncRNAs are quickly coming to light.

A number of studies over the past decade have also begun to uncover the interaction among mammalian lncRNAs and miRNAs. LncRNAs are targeted by miRNAs to reduce lncRNA stability (section 2). LncRNAs can also function as molecular decoys or sponges of microRNAs, as proposed by the Pandolfi Group [44] and reported in a few circular RNAs studies (section 3). In addition, lncRNAs can also compete with miRNAs for binding to shared target mRNAs (section 4) and are precursors for the generation of miRNAs to silence target mRNAs (section 5). In this review, we summarize the recent progress in understanding the interplay between lncRNAs and miRNAs.

2. microRNA-triggered lncRNA decay

The abundance of numerous lncRNAs is controlled by microRNAs (Figure 1A). Since many of these lncRNAs affect different cell functions (proliferation, differentiation, senescence, apoptosis, transformation), changes in their abundance directly alter the cellular response in physiologic and pathologic processes.

LincRNA-p21

A recent report uncovered that the stability of *lincRNA-p21*, a lncRNA transcriptionally activated by p53, was regulated by changes in its turnover rate. The RNA-binding proteins (RBP) HuR and Ago2 (Argonaute 2, a component of the RISC), and the miRNA let-7b, all contributed to lowering *lincRNA-p21* stability in human cervical carcinoma cells. HuR depletion stabilized *lincRNA-p21*, whereas let-7b overexpression facilitated *lincRNA-p21* degradation; moreover, the HuR-mediated lowering of *lincRNA-p21* half-life required the recruitment of let-7/Ago2 to the lncRNA, suggesting a cooperative mechanism of *lincRNA-p21* repression by HuR and let-7b. The accumulation of *lincRNA-p21* under reduced HuR or let-7b levels enhanced the formation of partially complementary hybrids with *JUNB* and *CTNNB* mRNAs, causing the repression of JunB and β-catenin translation [42].

HOTAIR

The recruitment of let-7 by HuR also caused decreased stability of another lncRNA, *HOTAIR* [45], suggesting that the mechanism of lncRNA decay through HuR-enhanced microRNA interactions may be widespread. This recruitment model remains to be elucidated in detail, but it may be linked to the ability of HuR to binds several miRNAs, including members of the let-7 family, and to promote the interaction between Ago2 and let-7b [45,46]. Under conditions of high abundance, *HOTAIR* functioned as a platform to foment the interaction of associated RBPs, as shown for two pairs of proteins: Ataxin-1 and Snurportin-1, the substrates of E3 ligases Dzip3 and Mex3b. With *HOTAIR* serving as a scaffold, the increased interaction of these pairs of proteins led to enhanced ubiquitination of Ataxin-1 and Snurportin-1. In addition, microRNA miR-34a was also shown to lower the stability of *HOTAIR* in the human prostate cancer cell lines PC3 and DU145 [47].

MALAT1

MALAT1 is also targeted by microRNA-Ago2-RISC in the human primary glioblastoma cell line U87MG and the human Hodgkin cell line L428 [48]. Silencing Ago2 or antagonizing miR-9 increased the steady state level of *MALAT1*, whereas miR-9 overexpression decreased it. Interestingly, the lowering of *MALAT1* stability by miR-9 was mainly elicited in the nucleus, highlighting a nuclear decay-promoting function for this miRNA.

LOC285194

One of the p53-inducible lncRNAs, the tumor suppressor transcript *LOC285194* is the target of Ago2 and miR-211 in the colon cancer cell line HCT-116 [49]. The downregulation of *LOC285196* in colon cancer specimens was proposed to be triggered by miR-211, which shows enhanced levels in colon cancer. A reciprocal negative regulation of *LOC285194* upon the levels of mature miR-211 was also hypothesized, perhaps with *LOC285194* acting as a ‘sponge’ (below).

PTCSC3

Another cancer-related lncRNA, the tumor suppressor *PTCSC3*, is targeted by miR-574-5p. In thyroid cancer cell lines (BCPAP, FTC133, and 8505C), miR-574-5p overexpression reduced *PTCSC3* expression levels [50]. Given that *PTCSC3* overexpression arrests cells in G0/G1 and induces apoptosis, reduction in *PTCSC3* levels by miRNAs might directly affect cell proliferation and tumorigenesis.

H19

One of the classic lncRNAs, *H19* is predicted to have 4 let-7 target sites (let7a, let-7b, let-7g, let-7i) [51]. The findings that overexpressing let-7 in C2C12 myoblasts promoted myotube formation while depleting *H19* increased it suggested that let-7 and *H19* have opposite functions in myoblast differentiation [51].

LincRNA-RoR

LincRNA-RoR is also targeted by many miRNAs in human embryonic stem cells [52]. Among the putative regulators, overexpression of miR145-5p, miR-181a-5p or miR-99b-3p specifically decreased the activity of a reporter containing *lincRNA-RoR* sequences [52].

3. lncRNAs as miRNA sponges/decoys

The reciprocal influence, lncRNAs affecting the levels and function of microRNAs (Figure 1B), has also emerged in recent years. In particular, it has been proposed that the concentration of microRNAs in the cytoplasm (and likely the nucleus) can be titrated by the abundant lncRNAs that harbor similar microRNA target sequences and hence can sequester microRNAs away from mRNAs, as first described in plants [54]; these lncRNAs are known as competing endogenous (ce)RNAs [44,53,55]. As a group, mammalian lncRNAs antagonize miRNA function by titrating miRNAs for target mRNA binding during processes that include muscle differentiation and stem cell self-renewal.

PTENP1

The first example of ceRNAs was described by Poliseno and colleagues [56], who found that expression of the tumor suppressor PTEN (phosphatase and tensin homolog) was dependent on the expression levels of the transcript encoded by pseudogene *PTENP1*. The *PTENP1* RNA elicited this influence by acting as a decoy for *PTEN* mRNA-targeting microRNAs. Accordingly, the *PTENP1* locus is lost in many human cancers.

Linc-MD1

A muscle-specific lncRNA, *linc-MD1* modulates muscle differentiation by competing with miRNAs for target mRNA binding [57]. Overexpression of *linc-MD1* in mouse accelerated muscle differentiation whereas its depletion prevented it. Moreover, in keeping with the ceRNA mechanism of regulation, *linc-MD1* enhanced expression of *MAML1* and *MEF2C* mRNAs by reducing the availability of miR-133 and miR-135, respectively, from binding to target mRNAs in mouse and human myoblasts. Recently, a feed-forward regulatory loop was described for the RNA-binding protein HuR, a target of repression by miR-133. High levels of *linc-MD1* in early stages of myogenesis sponges miR-133 away from HuR, allowing HuR to accumulate in cells and establish a myogenic gene expression program [58].

Circular RNAs

This class of long noncoding RNAs was first identified in adult mouse testis [59] but their function was unknown. Recent advances in high-throughput RNA sequencing (RNA-seq) technology characterized a variety of circular RNAs with the same sequence information in many model organisms and cell types. Circular RNAs are mainly generated as by-products of pre-mRNA splicing intermediates, although their biogenesis is not limited to protein-coding RNAs [60–63]. Once generated, these transcripts are strongly resistant to exonuclease digestion and to microRNA-mediated decay, suggesting that they collectively have very high stabilities, although circRNAs can be degraded by the presence of a perfectly matched miRNA target site [64]. One of the functions currently proposed for circular RNAs

is the sequestration of miRNAs away from target mRNAs, thereby derepressing mRNAs that bear miRNA target sequences. Such function was reported for the human circRNA *CDR1as* (antisense to the cerebellar degeneration-related protein 1 transcript), which harbors a strikingly high number (greater than 70) of conserved binding sites for miR-7 [62], while the testis-specific circRNA *Sry* (sex-determining region Y) serves as a sponge for miR-138, prompting the hypothesis that circular RNAs might serve as efficient miRNA sponges [59]. Other potential functions of circular RNAs, as proposed by Hentze and Preiss [65], include serving as vehicles for miRNAs or RBPs, RBP sponges, assembly platforms for RBPs that have shared functions, allosteric regulators of RBPs, modulators of mRNA expression, and templates for translation.

LincRNA-RoR

In human embryonic stem cells, *lincRNA-RoR* was downregulated under differentiation conditions like the triggering of embryonic body formation, the removal of fibroblast growth factor (bFGF), and treatment with bone morphogenetic protein (BMP) 4 [52]. Under these conditions, *lincRNA-RoR* is not present in enough abundance to sequester miR-145-5p, a microRNA that targets mRNAs encoding the pluripotency proteins Nanog, Oct4, and Sox2. Interestingly, Nanog, Oct4, and Sox2 activate *lincRNA-RoR* transcription, so that human embryonic stem cells maintain their pluripotency through this self-regulatory loop [52].

H19

As indicated above, *H19* also functions as an antagonist of let-7 during muscle differentiation [51]. *H19* displays sequences partially complementary with let-7e, let-7g, and let-7i and is downregulated by these miRNAs. During differentiation of the mouse myoblast cell line C2C12, the steady state levels of *H19* and let-7 increase along with those of myogenic factors MHC (myosin heavy chain) and Myogenin. Interestingly, *H19* depletion or let-7 overexpression increased the levels of *MHC* mRNA, *Myog* mRNA, and Igf2, in turn promoting myotube formation.

4. lncRNAs competing with miRNAs for interaction with mRNAs

In addition to functioning as ceRNAs, lncRNAs can also compete with miRNAs for binding to target mRNAs (Figure 1C).

BACE1AS

The lncRNA *BACE1AS*, partially antisense to *BACE1* mRNA (encoding the β-site amyloid precursor protein cleaving enzyme 1) promoted the stabilization of *BACE1*, which bears a miR-485-5p site [66]. In the human embryonic kidney HEK-293 cells, miR-485-5p overexpression reduced *BACE1* mRNA levels; this decline was rescued by overexpressing *BACE1AS*, which is complementary to *BACE1* mRNA in a region that includes the *BACE1* mRNA miR-485-5p site. This finding suggests that *BACE1AS* protects *BACE1* mRNA by preventing access of miR-485-5p for miRISC-mediated degradation.

ncNRFR

The tumor-promoting lncRNA *ncNRFR* (non-coding Nras functional RNA) contains a 22-nt sequence which is identical to let-7a and differs with other microRNAs (let-7b, let-7c, let-7d, let-7e, let-7f, let-7g, let-7i, and miR-98) by 1–4 nucleotides [67]. Overexpression of *ncNRFR* in the colonic epithelial cell line YAMC increased the activity of a heterologous reporter bearing a let-7 target site, suggesting that *ncNRFR* lowered let-7 function. However, the authors did not elucidate the underlying mechanism, nor did they find evidence that *ncNRFR* affected *Nras* mRNA abundance. Interestingly, YAMC cells overexpressing *ncNRFR* displayed higher levels of let-7 target mRNAs and were highly invasive when injected into nude mice, further suggesting that the tumorigenic function of *ncNRFR* was linked to its ability to suppress let-7 actions upon endogenous target mRNAs [67].

5. lncRNAs generating miRNAs

Finally, some lncRNAs are processed to generate miRNAs (Figure 1D). *Linc-MD1* generates miR-206 and miR-133b from an intron and an exon, respectively, indicating additional regulatory mechanisms by *linc-MD1* in muscle differentiation and muscle dystrophy [57]. LncRNA *H19* can also generate miR-675, a process that is repressed by HuR [68], in turn suppressing translation of the Insulin Growth Factor Receptor (*Igf1r*) mRNA in mouse. Very recently, *H19* knockdown in myoblasts was reported to decrease myogenesis; interestingly, this inhibition was attributed to the loss of miR-675, since ectopic restoration of miR-675 rescued muscle cell differentiation [69]. In addition, the RNA component of RNase MRP (*RMRP*), a lncRNA localized in mitochondria, also produces two miRNAs, RMRP-S1 and RMRP-S2; these microRNAs are putative regulators of *PTCH2* and *SOX4* mRNAs, encoding proteins that are linked to the human disease Cartilage Hair Hypoplasia (CHH) [70].

In sum, an expanding body of evidence reveals that lncRNAs and miRNAs work jointly to control gene expression via a number of complex post-transcriptional mechanisms (Figure 1). More examples of lncRNAs eliciting post-transcriptional actions by competing or cooperating with small RNAs are expected to emerge. Together, microRNAs and lncRNAs contribute to a robust and dynamic control of expressed proteins.

6. Concluding remarks and perspectives

MicroRNAs and lncRNAs regulate gene expression on all levels – transcriptional, post-transcriptional, and post-translational. Through this multi-leveled influence on protein expression patterns, these vast families of noncoding RNAs affect all aspects of cell metabolism, including cell division, senescence, differentiation, stress response, immune activation, and apoptosis. Here, we have reviewed the regulation of lncRNA expression and function by microRNAs, and vice versa. The examples described underscore the rich and complex regulation of gene expression resulting from the reciprocal regulation of ncRNAs.

The effects of microRNAs on lncRNAs (for example, in reducing lncRNA stability) were not entirely unexpected, since lncRNAs resemble mRNAs in many respects. Whether microRNAs also modulate the transcription or splicing of lncRNAs has not been reported. In

addition, while lncRNAs are believed not to be translated, they are often found associated with polysomes [25,42,71,72]; whether or not microRNAs affect these interactions also warrants further study.

Further investigation of the effects of lncRNAs on microRNA levels, localization, and function promises to be particularly exciting. In addition to the mechanisms already recognized (e.g., lncRNA sponging microRNAs, serving as microRNA precursors, and competing with microRNAs for binding to mRNAs), one can envision many other functions for lncRNAs as modulators of microRNA biology. For example, lncRNAs could serve as platforms for presentation of microRNAs to RBPs or mRNAs, as means of intracellular microRNA transport, and even as vehicles for transport outside of the cell or between cells. In this regard, it is important to be reminded that some lncRNA functions are tied to their great stability (circular RNAs, for example) and in some cases their high abundance.

Another immediate consequence of the microRNA-lncRNA interplay is that one must consider additional layers of regulation by lncRNAs and microRNAs. Besides their direct actions upon target complementary mRNAs, pre-mRNAs, and DNA, indirect actions need to be carefully evaluated. For example, a microRNA that appears to repress transcriptionally the levels of an mRNA lacking a microRNA target site may in fact be lowering the abundance of a lncRNA required for the transcriptional activation of the mRNA in question. In another scenario, a lncRNA that appears to enhance the stability of a given mRNA may function indirectly by sponging a microRNA that would otherwise accelerate the decay of that mRNA. As many other mechanisms of indirect impact are possible, we should use extreme care and rigor when interpreting the consequences of lncRNA and microRNA actions on gene expression.

A full elucidation of the complex ncRNA regulatory circuits will require a great deal of additional work. Future studies must focus on lncRNA-microRNA interactions in animal models, on the joint consideration of lncRNA-microRNA when establishing linkages to disease, as well as on the analysis of other lncRNAs (e.g., very long lncRNAs, pseudogenes, antisense RNAs) and other small RNAs (e.g., piRNAs, siRNAs, snoRNAs). Given the unexpected consequences from lncRNA-miRNA interactions identified to-date, future studies of crossregulation among ncRNAs promises to be a thrilling journey.

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Abbreviations

ceRNA	competing endogenous RNAs
lncRNA	long noncoding RNA
lincRNA	large intergenic noncoding RNA
miRNA	micro RNA

RBP	RNA-binding protein
UTR	untranslated region

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Highlights

- LncRNA stability and function can be potently regulated by miRNAs
- LncRNAs can function as miRNA decoys, derepressing miRNA target mRNAs
- LncRNAs can compete with miRNAs for degradation of target mRNAs
- LncRNAs can give rise to miRNA

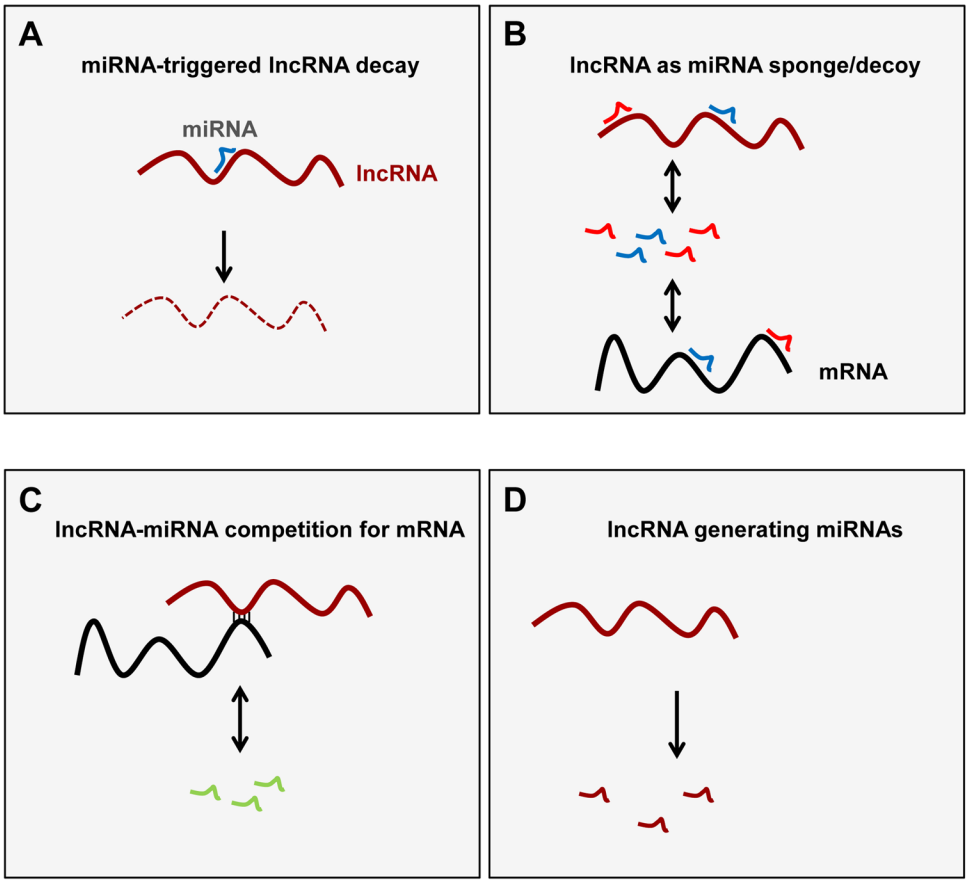

FIGURE 1. Modes of direct post-transcriptional interaction among lncRNAs and miRNAs

Schematic of the major forms of interplay among lncRNAs and miRNAs. **(A)** Some lncRNAs are degraded by miRNAs, as described for *lincRNA-p21* (degraded by let-7), *HOTAIR* (by let-7), *MALAT1* (by miR-9), *LOC285194* (by miR-211), *PTCSC3* (by miR-574-5p), *H19* (by let-7), and *lincRNA-RoR* (by miR145-5p and miR-181a-5p). **(B)** Other lncRNAs can serve as sponges/decoys for microRNAs, as described for *linc-MD1* (sequestering miR-133 and miR-135), circular RNAs (sequestering miR-7, although many more examples are predicted to occur), *lincRNA-RoR* (miR-145-5p), and *H19* (let-7). **(C)** A few examples of lncRNAs that compete with miRNAs for binding to mRNAs have also been reported, including *BACE1 AS*, which competes with miR-485-5p for binding to *BACE1* mRNA, and *ncNRFR*, which competes with let-7 to derepress let-7 site-bearing mRNAs to promote carcinogenesis. **(D)** Several lncRNAs also produce microRNAs and other small RNAs, as shown for *linc-MD1*, which generates miR-206 and miR-133b, *H19* (generates miR-675), and *RMRP* (generates miRNAs RMRP-S1 and RMRP-S2). See text for details.

Table 1

Examples of direct cross-regulation among lncRNAs and miRNAs

LncRNAs (column 1) affecting the levels and/or activity of microRNAs (column 2) and vice versa are summarized (column 3); if known, the consequences on gene expression are also indicated (column 4).

lncRNA	microRNA	Interplay	Consequences	References
lincRNA-p21	let-7b	lncRNA decay	Translational repression of *JUNB* and *CTNNB* mRNAs	[42]
HOTAIR	let-7i	lncRNA decay	Ataxin-1 and Snurportin-1 ubiquitination	[45]
	miR-34a	lncRNA decay	Tumorigenesis	[47]
MALAT1	miR-9	lncRNA decay	Repression of *MALAT1*	[48]
LOC285194	miR-211	lncRNA decay	Tumorigenesis	[49]
PTCSC3	miR-574-5p	lncRNA decay	Tumorigenesis Proliferation	[50]
H19	let7a,b,g,i	lncRNA decay, decoy	Decay of let-7 target mRNAs in muscle cells	[51]
	miR-675	miRNA production	Proliferation, myogenesis	[67,69]
lincRNA-RoR	miR145-5p miR-181a-5p miR-99b-3p	lncRNA decay miRNA competition lncRNA decay lncRNA decay	Stability of *Nanog*, *Oct4*, and *Sox2* mRNAs	52]
Linc-MD1	miR-133 miR-135 miR-206 miR-133b	miRNA competition miRNA competition miRNA production miRNA production	Muscle differentiation, and abundance of *MAML1* and *MEF2C* mRNAs	[57]
CDR1as/ciRS-7	miR-7	miRNA sponge	Neuronal function	[60]
Sry	miR-138	miRNA sponge		[59]
BACE1AS	miR-485-5p	miRNA competition	Brain	[66]
ncNRFR	let-7b,c,d,e,f,g,i miR-98	miRNA competition miRNA competition	Tumorigenesis	[67]
RMRP	RMRP-S1 RMRP-S2	miRNA production miRNA production	CHH (Cartilage-hair hypoplasia) disease	[70]