HHS Public Access

Author manuscript

Wiley Interdiscip Rev RNA. Author manuscript; available in PMC 2022 May 01.

Published in final edited form as:

Wiley Interdiscip Rev RNA. 2021 May ; 12(3): e1625. doi:10.1002/wrna.1625.

One locus with two roles: microRNA-independent functions of microRNA-host-gene locus-encoded long noncoding RNAs

Qinyu Sun[1], **You Jin Song**[1], **Kannanganattu V. Prasanth**[1,2]

[1]Department of Cell and Developmental Biology, University of Illinois at Urbana-Champaign, Urbana, Illinois

[2]Cancer Center at Illinois, University of Illinois at Urbana-Champaign, Urbana, Illinois

Abstract

Long noncoding RNAs (lncRNAs) are RNA transcripts longer than 200 nucleotides that do not code for proteins. LncRNAs play crucial regulatory roles in several biological processes via diverse mechanisms and their aberrant expression is associated with various diseases. LncRNA genes are further subcategorized based on their relative organization in the genome. MicroRNA (miRNA)-host-gene-derived lncRNAs (lnc-*MIRHG*s) refer to lncRNAs whose genes also harbor miRNAs. There exists crosstalk between the processing of lnc-*MIRHG*s and the biogenesis of the encoded miRNAs. Although the functions of the encoded miRNAs are usually well understood, whether those lnc-*MIRHG*s play independent functions are not fully elucidated. Here, we review our current understanding of lnc-*MIRHG*s, including their biogenesis, function, and mechanism of action, with a focus on discussing the miRNA-independent functions of lnc-*MIRHG*s, including their involvement in cancer. Our current understanding of lnc-*MIRHGs* strongly indicates that this class of lncRNAs could play important roles in basic cellular events as well as in diseases.

Keywords

cancer; long noncoding RNA; microprocessor; microRNA; splice site-overlapping miRNA

1 | INTRODUCTION

1.1 | Introduction of long noncoding RNA

The fraction of noncoding (nc) regions in the genome increases over the course of evolution. In humans, ~98% of the genome produces nc transcripts, which include small ncRNAs (20–50 nt), mid-size ncRNAs (50–200 nt) (Boivin, Faucher-Giguere, Scott, & Abou-Elela,

Correspondence: Kannanganattu V. Prasanth, Department of Cell and Developmental Biology, University of Illinois at Urbana-Champaign, Urbana, IL. kumarp@illinois.edu.

AUTHOR CONTRIBUTIONS

Qinyu Sun: Conceptualization; data curation; formal analysis; investigation; methodology; resources; visualization; writing-original draft; writing-review and editing. **You Jin Song:** Conceptualization; data curation; methodology; resources; writing-original draft; writing-review and editing. **Kannanganattu Prasanth:** Conceptualization; funding acquisition; project administration; supervision; writing-original draft; writing-review and editing.

CONFLICT OF INTEREST

The authors have declared no conflicts of interest for this article.

2019), and long nc RNAs (lncRNAs) (>200 nt). Most lncRNAs are transcribed by RNA polymerase II and contain normal 5′-caps and 3′ poly-A tails (Marchese, Raimondi, & Huarte, 2017). The expression of lncRNAs is less conserved compared to mRNA genes. In addition, lncRNAs display cell line-, tissue-, or development-specific expression (Cabili et al., 2011; Ulitsky, 2016).

The annotation of lncRNAs is increasing at a rapid rate due to the advances in sequencing and computational technologies. Different databases use independent analyses or curation methods to annotate novel lncRNAs and make huge contributions to our understanding of the lncRNA repertoire. For instance, the GENCODE database uses RNA Capture Long Seq method to accurately annotate lncRNAs (Lagarde et al., 2017). Both LNCipedia and NONCODE databases integrate data from different individual resources. The number of lncRNA genes/transcripts reported in several major databases with the latest releases are summarized in Table 1. It is important to note that genes that are categorized as other types in these databases could also be lncRNAs. For example, GENCODE release 33 has reported 14,768 pseudogenes from which lncRNAs could be derived (Milligan & Lipovich, 2014).

Based on mechanistic studies of a small group of lncRNAs, we have learned that human lncRNAs play crucial roles in multiple biological events, including cell cycle, development, immune response, apoptosis, and disease development (Y. G. Chen, Satpathy, & Chang, 2017; Y. Fang & Fullwood, 2016; Flynn & Chang, 2014; Huarte, 2015; Kitagawa, Kitagawa, Kotake, Niida, & Ohhata, 2013; J. Li, Tian, Yang, & Gong, 2016; Schmitt & Chang, 2016). LncRNAs regulate molecular processes in nuclear and cytoplasmic compartments via various types of molecular mechanisms. In general, nuclear lncRNAs play either *cis*-acting or *trans*-acting functions to modulate chromatin, regulate gene transcription or processing, and/or organize nuclear structures (Q. Sun, Hao, & Prasanth, 2018). Cytoplasmic lncRNAs are known to regulate RNA stability, protein translation, and signal transduction (Noh, Kim, McClusky, Abdelmohsen, & Gorospe, 2018). Mechanistically, lncRNAs can behave as scaffolds for proteins, serve as microRNA (miRNA) sponges, interact with other RNA molecules, or bind to DNA elements such as enhancer elements (Y. Li, Syed, & Sugiyama, 2016; Marchese et al., 2017; Noh et al., 2018; Q. Sun, Hao, et al., 2018; K. C. Wang & Chang, 2011).

1.2 | Introduction to miRNA

miRNAs (or miRs) were initially discovered back in 1993, by Lee and colleagues, in *Caenorhabditis elegans* (Lee, Feinbaum, & Ambros, 1993; Wightman, Ha, & Ruvkun, 1993) and later found to exist in many species, including mammals, plants, and even viruses. They are short nc RNAs that are ~22 nt long and regulate post-transcriptional gene expression. As reported by miRbase database release 22, the human genome contains 1917 miRNA genes (1917 annotated hairpin precursors and 2654 mature miRNA sequences) (Kozomara, Birgaoanu, & Griffiths-Jones, 2019). Mean-while, GENCODE database (release 33) reported 1881 miRNA genes (Frankish et al., 2019). Most miRNA genes are transcribed by RNA Polymerase II (Pol II). Similar to other mRNA genes, the expression of miRNAs is specifically regulated based on cell type, development stage, or disease situation (Ha & Kim, 2014). The aberrant expression levels/copy numbers of miRNAs and mutations in miRNAs

are commonly associated with genetic diseases, including cancer (Baumann & Winkler, 2014; Czubak et al., 2015). Hence, miRNAs are used as diagnosis or prognosis markers for various diseases. Several miRNA-based treatment strategies have already been used in clinical applications (Baumann & Winkler, 2014; Farazi, Spitzer, Morozov, & Tuschl, 2011; Reddy, 2015).

miRNA–mRNA interaction results in post-transcriptional regulation of the target mRNAs, most commonly by inhibiting mRNA translation or regulating mRNA stability (Bartel, 2009; Gebert & MacRae, 2019; Treiber, Treiber, & Meister, 2019). The inhibition of translation is mediated by the release of eukaryotic initiation factor proteins from the target mRNA. miRNAs can also cause mRNA degradation by triggering poly-A shortening, followed by decapping of the target mRNAs (Gebert & MacRae, 2019). miRNAs play a huge role in regulating biological processes, including cell cycle, differentiation, development, immune response, and diseases (Bushati & Cohen, 2007; N. Li, Long, Han, Yuan, & Wang, 2017; Mehta & Baltimore, 2016; Saliminejad, Khorram Khorshid, Soleymani Fard, & Ghaffari, 2019). More than 60% of protein-coding genes in humans contain one or more miRNA target sites (Friedman, Farh, Burge, & Bartel, 2009). In addition, a single miRNA may target several mRNAs, and one mRNA can be targeted by different miRNAs.

2 | LNC-*MIRHG*S FORM AN IMPORTANT BUT UNDER-STUDIED CLASS OF LncRNAs

miRNAs are initially transcribed from the genome as primary miRNAs (pri-miRNAs), which have a unique structure. A pri-miRNA contains a terminal loop, stem (including upper stem and lower stem), and single-stranded overhangs on both the 5′ and 3′ ends of the stem (Ha & Kim, 2014; Treiber et al., 2019). To exert the gene silencing function, miRNA need to be processed from pri-miRNA by several discrete steps, following the canonical or non-canonical miRNA biogenesis pathways.

2.1 | Canonical miRNA biogenesis

Canonical miRNA biogenesis includes three major steps. The first step to generate precursor miRNAs (pre-miRNAs) from pri-miRNA occurs in the nucleus, executed by the microprocessor complex: Drosha/DGCR8 (Gregory et al., 2004). The pri-miRNA is recognized by the microprocessor complex, consisting of DGCR8 dimer and Drosha (Nguyen et al., 2015). DGCR8 (DiGeorge critical region 8) is a double-stranded RNA (dsRNA) binding protein that binds to pri-miRNA as a dimer. Drosha is an RNase III enzyme that cleaves the dsRNA between the upper stem and lower stem, which releases the hairpin-structured pre-miRNA. On the pri-mRNA, the basal junction refers to the junction between the lower stem and the flanking single-stranded RNA segments. The apical junction refers to the junction between the terminal loop and the upper stem. The distance from the Drosha cleavage site to the basal junction is ~11 nt, whereas the distance from the Drosha cleavage site to the apical junction is ~22 nt (Nguyen et al., 2015). The cleavage site of the microprocessor complex is precisely controlled by the structure of the microprocessor protein complex and the sequence elements of pri-miRNA. In particular, several motifs including the CNNC motif and UG motif in the basal junction and the UGUG motif in the

terminal loop are important for pri-miRNA processing (Auyeung, Ulitsky, McGeary, & Bartel, 2013). In addition, both the basal junction and the apical junction play essential roles in the determination of the cleavage sites (Auyeung et al., 2013; Han et al., 2006; Kwon et al., 2019; Ma, Wu, Choi, & Wu, 2013; Zeng, Yi, & Cullen, 2005). Pre-miRNAs are transported to the cytoplasm by Exportin 5 (Exp5) and further cleaved by the RNase III enzyme Dicer (Song & Rossi, 2017). Dicer cuts on the dsRNA region near the terminal loop of pre-miRNAs to liberate a double stranded miRNA with a length of ~21 nt (Ha & Kim, 2014; MacRae, Zhou, & Doudna, 2007; Park et al., 2011).

Finally, the double-stranded miRNA, along with Argonaute (AGO) and associated factors, forms the RNA-induced silencing complex (RISC) (Filipowicz, Jaskiewicz, Kolb, & Pillai, 2005). The double-stranded miRNA is loaded on the AGO to form the pre-RISC, followed by the unwinding of the duplex. Only one strand from the miRNA duplex, called “guide strand”, stays with AGO in the mature RISC while the other strand is degraded. The 2nd nt to the ~7th or 8th nt of the guide strand is referred to as the seed sequence. The seed sequence will lead the RISC to form complementarity with their target mRNAs, usually at their 3′-UTR regions (Bartel, 2009; Gebert & MacRae, 2019). Although the miRNA duplex is able to generate guide miRNAs from both strands, one particular strand serves as the guide miRNA in most cases. Such selection preference is caused by the thermodynamic stability of the two ends: the strand with a less stable 5′ is favored as the guide miRNA (Schwarz et al., 2003).

2.2 | Noncanonical miRNA biogenesis

Instead of the canonical pathway using microprocessors and Dicer, alternative pathways have been reported to synthesize miRNAs, including two major types: microprocessor-independent and Dicer-independent pathways.

A well-studied group of miRNAs that is generated without the use of microprocessors is the “mirtron”, which reside in the intronic regions of other genes (Westholm & Lai, 2011). Mirtrons were first identified in *Drosophila* and *C. elegans* and later also found in several mammalian species (Berezikov, Chung, Willis, Cuppen, & Lai, 2007; Okamura, Hagen, Duan, Tyler, & Lai, 2007; Ruby, Jan, & Bartel, 2007). Some mirtrons are conserved across several mammalian species, including miR-877, miR-1,224, and miR-1,225 (Berezikov et al., 2007). In the case of mirtrons, splicing machinery, instead of microprocessors, is responsible for the cleavage of pri-miRNAs to produce pre-miRNAs. In this case, the pri-miRNAs no longer have the “molecular rulers” (microprocessors) to safeguard the production of the typical 5′ and 3′ ends of pre-miRNAs. Alternative mechanisms are used to remove the extra nucleotides on the pre-miRNAs, including nuclease trimming by exosome exonuclease (Flynt, Greimann, Chung, Lima, & Lai, 2010; Westholm & Lai, 2011). Another microprocessor-independent pathway involves cleavage by transcription termination. A study identified “microprocessor-independent 7-methylguanosine (m7G)-capped pre-miRNAs”, exemplified by pre-miR-320, which are located near the 5’ end of the host transcripts and naturally form hairpin structures (Xie et al., 2013). Transcription termination generates the 3′ end of the pre-miRNA and the intact 5′ cap present in the pre-miRNA facilitates the nuclear export event.

Dicer-independent miRNA biogenesis is relatively less studied. One example is miR-451. The pri-miR-451 undergoes microprocessor-mediated cleavage resulting in a short hairpin, which is further "sliced" by Ago2 and trimmed by the Poly(A) specific ribonuclease, PARN, to form the functional miRNA (Cheloufi, Dos Santos, Chong, & Hannon, 2010; Cifuentes et al., 2010).

2.3 | miRNAs and miRNA host genes (*MIRHG*s)

Only a small fraction (~28%) of miRNAs are transcribed from independent genomic loci (intergenic miRNAs) (Kahl, 2009). Rather, most miRNAs are hosted by the so-called miRNA-host-genes (*MIRHG*s), which include both protein-coding and lncRNA genes. These miRNAs are called "intragenic miRNAs", including intronic, exonic, and splice site overlapping miRNAs (SO-miRNAs) (Mattioli, Pianigiani, & Pagani, 2014) (Figure 1). Intronic miRNAs constitute the largest portion of intragenic miRNAs (55%) (Kahl, 2009).

Several studies have reported correlated expression between miRNAs and their respective *MIRHG*s (Baskerville & Bartel, 2005; B. Liu, Shyr, Cai, & Liu, 2018; Lutter, Marr, Krumsiek, Lang, & Theis, 2010). An evolutionary study suggested that *MIRHG*s may provide increased expression constraints to their intragenic miRNAs during the course of evolution; "older" *MIRHG*s tend to display more correlated expression with the hosted miRNAs (Franca, Vibranovski, & Galante, 2016). Cancer cells epigenetically regulate the expression of *MIRHGs* to alter the levels of miRNAs. Several studies have identified that the promoters of *MIRHG*s showed altered methylation levels in certain cancers. As a result, the miRNAs encoded within these *MIRHG*s show differential expression, and can thus serve as cancer biomarkers. Some of these miRNAs have even been demonstrated to play crucial roles in cancer progression (Augoff, McCue, Plow, & Sossey-Alaoui, 2012; Daniunaite et al., 2017; Grady et al., 2008; Yeung, Tsang, Yau, & Kwok, 2017). Such studies also indicated that the methylation status of *MIRHG* promoters could be used as cancer biomarkers.

However, such co-regulated expression is not observed for all miRNA-*MIRHG* pairs. A significant number of studies have reported a lack of correlation and have shown that most miRNAs use independent promoters (Budach, Heinig, & Marsico, 2016; B. Liu et al., 2018; Steiman-Shimony, Shtrikman, & Margalit, 2018). For example, lncRNA *DLEU2* is down-regulated in some pediatric acute myeloid leukemia patients due to promoter methylation. However, the tumor suppressive miR-15a/16-a, which are embedded within *DLEU2* gene, do not show decreased expression in these patients (Morenos et al., 2014). We will detail several more examples in a later part of this review.

Intragenic miRNAs also exert functional impacts on their host *MIRHGs*. One study predicted that ~1/5 of intragenic miRNAs could target their host mRNA transcripts, suggesting that these miRNAs are part of negative feedback loops to regulate the expression of their host genes (Hinske, Galante, Kuo, & Ohno-Machado, 2010). Additionally, miRNAs also target certain genes, which could in turn regulate the expression of their *MIRHG*s, hence facilitating/antagonizing the function of their *MIRHG* indirectly (Lutter et al., 2010; Steiman-Shimony et al., 2018). Lastly, the miRNAs that regulate the expression of their host *MIRHG*s are more conserved than the ones that impart no functional association with their

host *MIRHGs*. This implies that organisms gain evolutionary advantage by utilizing miRNAs to coordinate the regulatory functions of their host genes (Steiman-Shimony et al., 2018).

2.4 | Crosstalk between intragenic miRNA biogenesis and *MIRHG* splicing

The biogenesis and further processing of intragenic miRNAs and their corresponding *MIRHG*s are highly regulated events. Several studies have reported the interaction between members of the splicing machinery and microprocessors to modulate the syntheses of the miRNA and the mature *MIRHG* (Agranat-Tamir, Shomron, Sperling, & Sperling, 2014; Kataoka, Fujita, & Ohno, 2009). Based on our current knowledge, two major models recognized as the "synergic/cooperative model" and the "competitive model" are in place to explain the crosstalk between splicing and miRNA processing factors.

It has been reported that the cleavage of *MIRHG* transcripts by Drosha, a necessary event in canonical miRNA production, occurs co-transcriptionally and sometimes even before the splicing of introns (Y. K. Kim & Kim, 2007; Morlando et al., 2008). In the synergic/cooperative model, the splicing of *MIRHG*s facilitates the biogenesis of the miRNAs, and/or vice versa (Figure 2a–c). All mirtrons fall into this category, due to their dependence on *MIRHG* splicing as the means to generate pre-miRNAs (Figure 2a) (Berezikov et al., 2007; Westholm & Lai, 2011). Many splicing factors are shown to exert a positive influence on miRNA production (Figure 2b) (Ratnadiwakara, Mohenska, & Anko, 2018). An earlier study reported "mutually cooperative splicing and microprocessor activities" to achieve coordinated splicing and miRNA processing of intronic miRNAs (Janas et al., 2011). U1 snRNP, which recognizes the 5′ splice site of introns, facilitates the recruitment of Drosha to process intronic miR-211. Drosha in turn promotes splicing activity (Janas et al., 2011). In addition, SRSF3 was found to modulate the levels of many miRNAs by regulating splicing (Ajiro, Jia, Yang, Zhu, & Zheng, 2016). Another study reported that SRSF3 facilitates pri- to pre-miRNA processing by recruiting Drosha (K. Kim, Nguyen, Li, & Nguyen, 2018). Interestingly, studies have also identified "splicing-independent" functions of splicing factors in miRNA processing (Figure 2c). In this scenario, the splicing factors do not play their canonical roles to regulate gene splicing. Rather, they directly modulate the binding or activity of the microprocessor complex to regulate miRNA processing. Two proteins that are known to regulate gene splicing, hnRNPA1 and KSRP, have been found to bind to the stem-loop structure of the pri-miRNA to facilitate the microprocessor-mediated miRNA processing (Guil & Caceres, 2007; Trabucchi et al., 2009). SRSF1 (previously known as SF2/ASF) was also reported to promote the maturation of intronic miR-7, not by executing its splicing activity, but by directly regulating the cleavage by Drosha (Wu et al., 2010). Spliceosome-associated ISY1 was found to be required for the processing of the miR17 ~ miR-92 cluster during embryonic stem cell differentiation (P. Du, Wang, Sliz, & Gregory, 2015). Finally, several splicing-related proteins were shown to co-regulate miRNA biogenesis. HnRNPA1, which was introduced above, was found to negatively impact the processing of let-7a by antagonizing the binding of KSRP on pri-let-7a-1 (Michlewski & Caceres, 2010). Such cases, describing the "splicing-independent" function of splicing factors, cannot be identified as examples of the "synergetic model," because of the lack of *MIRHG* splicing events. However, these studies still provide us with key insights into the

molecular interplay between splicing factors and microprocessors in controlling miRNA biogenesis.

On the other hand, several studies have reported data supporting the "competition model" (Figure 2d,e), in which the splicing factors compete with the miRNA-processing complex, especially when the miRNAs are located at the exon–intron junctions of *MIRHG*s (SO-miRNAs). *MCM7* hosts miR-106b-25 in its intron. However, under certain conditions, by using alternative splicing to "transform" the miR-106b-25-containing intronic sequence to an exonic sequence, *MCM7* no longer produces miRNAs from its nascent transcripts (Agranat-Tamir et al., 2014) (Figure 2d, Scenario 1). Other miRNAs that utilize similar mechanisms of biogenesis include mouse miR-412, human miR-202, human miR-34b, human miR-205, and human miR-612 (Mattioli, Pianigiani, & Pagani, 2013; Melamed et al., 2013; Profumo et al., 2019; X. Yang et al., 2018). In the case of mmu-miR-412, the alternative splicing event includes a cassette exon inclusion/exclusion and the miRNA is located at the splice junction (Melamed et al., 2013) (Figure 2d, Scenario 2). Lastly, miR-612 is hosted in the well-studied lncRNA nuclear-enriched abundant transcript 1 (*NEAT1*). A study showed that hepatocellular carcinoma cells can fine-tune the alternative splicing of *NEAT1* to balance the relative concentrations of full-length *NEAT1* and the miR-612, in order to regulate cell proliferation and metastasis (X. Yang et al., 2018).

In addition, the "competition model" also includes an "alternative splicing-independent" scenario (Figure 2e). A recent study from our laboratory has shown that *MIR222HG* nascent transcripts generate a multi-exonic lncRNA by enhancing the nascent RNA splicing during early serum response post-cellular quiescence (Q. Sun et al., 2020). During serum stimulation, the splicing factors compete with the microprocessor complex in order to facilitate the synthesis of the spliced lncRNA over pre-miRNA from the nascent MIR222HG transcripts. Our study found that the inhibition of splicing can increase the miR-222 production. Another study found that the pri- to pre-miRNA processing of several SO-miRNAs is not coupled with alternative splicing (Pianigiani et al., 2018). Both studies observed that the microprocessor cleavage causes the degradation of *MIRHG* transcripts. These findings imply that, in a particular scenario, nascent *MIRHG* transcripts "choose" a fate between gene splicing and SO-miRNA production (Figure 2e).

2.5 | LncRNAs as miRNA host genes

LncRNAs have been sub-categorized based on their function/genomic location/expression patterns/subcellular distribution (St Laurent, Wahlestedt, & Kapranov, 2015). The biogenesis and function of several lncRNAs subtypes, such as antisense lncRNAs, *cis*-lncRNAs, and enhancer lncRNAs, are well explored, (Jadaliha et al., 2018; T. K. Kim, Hemberg, & Gray, 2015; Kopp & Mendell, 2018; Latge, Poulet, Bours, Josse, & Jerusalem, 2018). However, the miRNA-independent roles of the miRNA-host-gene-derived lncRNAs, which generate 17.5% of miRNAs in humans (Dhir, Dhir, Proudfoot, & Jopling, 2015), still remain to be elucidated. In the rest of this review, we use the term "lnc-*MIRHG*" to refer to these mature lncRNAs produced from the miRNA-host-gene loci.

The major question that needs to be addressed is whether lnc-*MIRHG* gene loci are merely serving as primary miRNA units for producing miRNAs, or if they might also generate

mature lnc-*MIRHG*s that have independent roles. One study observed that upon depletion of microprocessors, several lnc-*MIRHG*s fail to terminate their transcription, resulting in the synthesis of nonfunctional and unstable readthrough transcripts. This study suggested that the microprocessor cleavage of lnc-*MIRHG*s causes transcription termination, whereas protein-coding *MIRHGs* use cleavage and polyadenylation-mediated termination (Dhir et al., 2015). Based on this study, the authors argued that lnc-*MIRHG*s merely serve as primary miRNAs and are not functional otherwise.

However, many recent studies from our laboratory as well as other groups have discovered that the mature transcripts produced from lnc-*MIRHG*s, which are fully spliced and polyadenylated, perform miRNA-independent functions. In the next part of this review, we will discuss the recent literature describing the miRNA-independent roles of several lnc-*MIRHG*s. We will also summarize the studies indicating the involvement of lnc-*MIRHG*s in cancer.

3 | miRNA-INDEPENDENT ROLES OF lnc-*MIRHG*

Studies from multiple groups have shown that lnc-*MIRHG*s perform functions that are independent of their role as miRNA precursors. Like other types of lncRNAs, lnc-*MIRHG*s also exert their functions via various mechanisms. Based on the current knowledge, we have summarized their molecular mechanisms into three major categories: “competing endogenous RNA (ceRNAs)”, “DNA interactors”, and “protein interactors” (Table 2, Figure 3). Of note, an individual lnc-*MIRHG* may perform multiple functions through non-overlapping mechanisms.

Some lncRNAs have been reported to serve as ceRNAs by “sponging” certain miRNAs, thereby inhibiting the miRNA function. To be defined as a “ceRNA”, a lncRNA needs to contain one or more miRNA recognition elements to sponge the miRNAs. The luciferase reporter assay is a classic method that is used to confirm the predicted miRNA binding sites on a lncRNA (Jin, Chen, Liu, & Zhou, 2013). In the case of the ceRNA model, the loss of a potential ce-lncRNA will release the “sponged” miRNAs such that these miRNAs will be available to inhibit the expression of their target mRNAs, hence a concomitant decrease in the levels of those target mRNAs would be expected. We summarize the lnc-*MIRGH*s that mechanistically behave as ceRNAs (Table 2, Class 1, Figure 3a). The function of these “ce-lnc-*MIRHG*s” is exerted via a “lnc-*MIRHG*-sponged miRNA-target mRNA” axis.

LncRNAs can also directly interact with DNA elements, such as promoters, to form RNA-dsDNA triplex structures and further recruit protein factors to regulate the DNA activity, such as transcription (Bacolla, Wang, & Vasquez, 2015). Two lnc-*MIRHG*s, *MIR100HG* and *MIR205HG*, fall in this category (Table 2, Class 2, Figure 3b).

LncRNAs can also regulate cellular functions via modulating protein activity (Marchese et al., 2017). In this review, we further categorize the “protein interactors” into several subclasses (Table 2, Class 3, Figure 3c). Subclass 3.1 includes the group of lnc-*MIRHG*s that influence the interacting protein(s) by regulating their modification, stability, or complex assembly (Figure 3ca). Lnc-*MIRHG*s in Subclasses 3.2 and 3.3 function by acting

as a scaffold or by recruiting or titrating the interacting proteins to/from their destinations, in order to regulate transcriptional (Figure 3cb) or post-transcriptional (Figure 3cc) events. Two additional nonoverlapping mechanisms utilized by *NEAT1* are categorized into Subclass 3.4 (*NEAT1*) (Figure 3cd,ce).

Finally, lncRNAs have also been reported to generate short functional peptides (Table 2, Class 4, Figure 3d). *LINC-PINT* is a lnc-*MIRHG* under this category, and will be discussed in detail later.

3.1 | MIR22HG

MIR22HG shows tumor-suppressive roles in multiple cancers (Table 3). In endometrial cancer, it acts as an anti-proliferative ceRNA and sponges miR-141–3p to increase the RNA and protein levels of DAPK1 (Cui et al., 2018). In colorectal cancer, *MIR22HG*, by competitively interacting with SMAD2, disrupts the SMAD2-SMAD4 interaction and thereby perturbs TGFβ signaling pathway (Xu et al., 2020). *MIR22HG* was also shown to interact with HuR to maintain the nuclear localization of HuR. In addition, by competitively interacting with HuR, *MIR22HG* reduced the binding of HuR to several of its oncogenic mRNA targets, including β-catenin, resulting in reduced expression of these oncogenes (D. Y. Zhang, Zhao, et al., 2018). Finally, in lung cancer, *MIR22HG* was found to interact with YBX1 to stabilize YBX1 levels. *MIR22HG*-YBX1 in turn modulates the expression of cancer-associated genes such as MET and p21 (Su et al., 2018).

3.2 | MIR100HG

Our laboratory previously reported that the *MIR100HG* gene locus produces a multi-exonic nuclear lncRNA, which is highly expressed in the G1 phase of the cell cycle in osteosarcoma cells (U2OS). The encoded miRNAs, however, do not display the cell cycle-dependent dynamic expression pattern. *MIR100HG* is required for cell cycle progression in a miRNA-independent manner. Mechanistically, *MIR100HG* contains U-rich sequences that facilitate its interaction with both HuR and several HuR target RNAs. *MIR100HG* serves as a "scaffold" to facilitate HuR-target RNA association, which is required to stabilize the cellular levels of these target RNAs and their corresponding proteins (T. Sun, Du, et al., 2018). Another study showed that *MIR100HG* plays an oncogenic role in breast cancer by directly interacting with the promoter of *CDKN1B* (p27) to form a triplex structure, which attenuates the transcription of *CDKN1B* (S. Wang, Ke, et al., 2018).

3.3 | MIR31HG

MIR31HG is a hypoxia-induced lncRNA that plays crucial roles in the progression of oral squamous cell carcinoma (Shih et al., 2017). *MIR31HG* uses its 5′ terminal region to interact with the PAS-B domain of HIF-1α. This interaction facilitates the assembly of the HIF-1 complex and enhances the chromatin recruitment of HIF-1α and p300 cofactor to their target gene promoters, thereby promoting the HIF-1 transcriptional network. *MIR31HG*, hence, is annotated as "*LncHIFCAR*" (long nc HIF-1a co-activating RNA) in this study. Another study identified *MIR31HG* as a ceRNA of miR-193b in pancreatic ductal adenocarcinoma. In this study, *MIR31HG* was shown to negatively regulate the miR-193b-mediated destabilization of *CCND1* and *KRAS* (H. Yang et al., 2016).

3.4 | MIR205HG/LEADeR

MIR205HG is an intriguing lnc-*MIRHG* that is involved in several diverse functions and molecular mechanisms. In head and neck squamous cell carcinoma and cervical cancer, *MIR205HG* was shown to act as an oncogenic ceRNA. By quenching the cellular pool of miR-590–3p and miR-122–5p, *MIR205HG* enhances the levels of pro-proliferative or oncogenic genes (Di Agostino et al., 2018; Y. Li, Zhou, et al., 2019). *MIR205HG* also negatively regulates the differentiation of prostate cancer cells by suppressing the expression of several genes whose promoters contain Alu elements and inter-feron regulatory factor (IRF) binding sites (Profumo et al., 2019). *MIR205HG* directly binds to the promoters of genes, which contain Alu and IRF binding sites, via Alu-mediated intermolecular interactions. Mechanistically, *MIR205HG* inhibits the binding of IRF to the IRF elements of several target genes, which are required for basal-luminal differentiation, resulting in their transcription repression (Profumo et al., 2019). Finally, another study demonstrated that *MIR205HG* is expressed in regions that specify the anterior pituitary during mouse embryogenesis (Q. Du et al., 2019). During development, *MIR205HG* regulates growth hormone and prolactin production by forming complexes with Pit1 and Zbtb20 transcription factors in order to enhance the transcription of *Prolactin*, *Gh* (growth hormone) and *Pit1* (Q. Du et al., 2019). These studies clearly demonstrate the lncRNA-specific function of the *MIR205HG* locus in cancer differentiation and mouse neuronal development.

3.5 | RMST

RMST is a multi-exonic and conserved lncRNA that harbors miR-1251 and miR-135a2 in its intron. During neuronal differentiation of human embryonic stem cells, the *RMST* level is induced to facilitate the differentiation process via its interaction with SOX2, which is an important transcription factor for neuronal fate determination. Mechanistically, *RMST* promotes the global binding of SOX2 to its target genes, thereby facilitating neuronal differentiation (Ng et al., 2013).

3.6 | CYTOR

CYTOR is a lnc-*MIRHG* that hosts miR-4435–1 and plays oncogenic roles in colorectal cancer. In colorectal cancer, it forms a heterotrimeric complex with Nucleolin and Sam68 via its first exon, and thus facilitates Nucleolin and Sam68 complex assembly. The *CYTOR*-NCL-Sam68 complex promotes the progression of colorectal cancer by activating the downstream NF-κB pathway (X. Wang, Yu, et al., 2018). Another study showed that *CYTOR* promotes the epithelial-mesenchymal transition (EMT) and metastasis in colon cancer. Mechanistically, *CYTOR* interacts with β-catenin to prevent the phosphorylation of cytoplasmic β-catenin by casein kinase 1 (CK1), thereby facilitating its nuclear translocation and transcription promoting activity (Yue et al., 2018).

3.7 | LINC01138

LINC01138, which hosts miR-5087, is transcribed from a frequent DNA-gain region in hepatocellular carcinoma (HCC) (Z. Li et al., 2018). Elevated expression of *LINC01138* promoted cell growth and metastasis of HCC cells and was identified as a prognostic marker of HCC patients. Mechanistically, *LINC01138* interacts with the protein arginine

methyltransferase 5 (PRMT5) to increase the stability of PRMT5 by blocking its ubiquitin/proteasome-dependent degradation. Hence, *LINC01138* is recognized as an oncogenic driver through its role in stabilizing the PRMT5 levels in HCC. It would be important to test if *LINC01138* plays such an oncogenic role in other types of cancer that are sensitive to PRMT5 levels.

3.8 | LINC-PINT

LINC-PINT or *Pint* was initially identified in a mouse study. This lnc-*MIRHG* is induced by p53, hence named "*p*53-*i*nduced *n*on-coding *t*ranscript" (Marin-Bejar et al., 2013). It plays a tumor suppressive role by inhibiting the migration and invasion of colorectal cells *in vitro* and *in vivo* (Marin-Bejar et al., 2017). Mechanistically, *LINC-PINT* has been shown, in both mouse and humans, to interact with PRC2 and mediate PRC2 targeting to different genes for their transcriptional silencing (Marin-Bejar et al., 2013; Marin-Bejar et al., 2017). For example, in colorectal cancer, *LINC-PINT* promotes the PRC2-mediated repression of genes with invasion signature, such as *EGR1* and *FOS* (Marin-Bejar et al., 2017). Another recent study reported that a circular RNA, *CircPINTexon2*, is processed from the second exon of *LINC-PINT* by back-splicing (M. Zhang, Zou, et al., 2018). The cytoplasmic *CircPINTexon2* encodes an 87-amino-acid peptide, PINT87aa, which inhibits the proliferation of glioblastoma cells *in vitro* and *in vivo*. Mechanistic studies revealed that PINT87aa peptide interacts with PAF1 (RNA pol II-associated factor 1) to inhibit the transcriptional elongation of multiple oncogenes, including *CPEB1*, *SOX2*, and *c-Myc*. This is a classic example where a lncRNA and a peptide are synthesized from the same lncRNA locus to play independent activities as tumor suppressors.

3.9 | MIR503HG

MIR503HG was identified as another tumor suppressor lnc-*MIRHG*. A study using the HCC model demonstrated that *MIR503HG* inhibits HCC cell invasion and metastasis *in vitro* and *in vivo* (H. Wang, Liang, et al., 2018). *MIR503HG* interacts with the heterogeneous nuclear ribonucleoprotein A2/B1 (hnRNPA2B1) and facilitates the ubiquitination-mediated degradation of hnRNPA2B1. The *MIR503HG*-mediated degradation of hnRNPA2B1 further results in reduced mRNA stability of *p52* and *p65* as well as protein levels of multiple NF-κB downstream effectors, thereby inhibiting cancer cell metastasis. In triple-negative breast cancer, *MIR503HG* was reported to function as a ceRNA of miR-103 to protect the levels of the miR-103 target tumor suppressor gene, olfactomedin 4 (OLFM4) (Fu et al., 2019). In the case of *MIR503HG*, it modulates the protein stability in one instance, but then performs a completely different function, as a ceRNA in another scenario, indicating that lnc-*MIRHG*s could participate in versatile functions in a tissue or cell-line specific fashion.

3.10 | NEAT1

NEAT1 (Nuclear-enriched abundant transcript 1) is a well-known "structural determinant lncRNA", which maintains the structural integrity of paraspeckles (Clemson et al., 2009). It is also a lnc-*MIRHG* that harbors miR-612. A recent study revealed that paraspeckle structure exhibits phase-separated properties and *NEAT1* is necessary and sufficient for paraspeckle assembly. *NEAT1* contains several domains, within which each domain executes important functions, including RNA stability, isoform switching, and paraspeckle assembly

(Yamazaki et al., 2018). For example, the middle domain of *NEAT1*, which is located within the inner core of the paraspeckle, controls paraspeckle assembly. Hirose and colleagues observed that the middle domain of *NEAT1* recruits NONO protein dimers to initiate assembly of the paraspeckle structure (Yamazaki et al., 2018). The 5′ and 3′ termini are located on the outer shell of the paraspeckle (Souquere, Beauclair, Harper, Fox, & Pierron, 2010). The 3′ terminus of *NEAT1* contains a triple helix structure, which modulates RNA stability, and the 5′ terminal domain functions in regulating the stability and transcription of *NEAT1*. *NEAT1* has also been reported to repress the transcription of several genes, including *ADARB2*. Mechanistically, *NEAT1* sequesters the splicing factor proline/glutamine-rich (SFPQ) away from *ADARB2* promoters to paraspeckles (Hirose et al., 2014).

NEAT1 was also identified as an oncogene or a tumor suppressor gene in a context-dependent manner. Several mechanisms were proposed to address the oncogenic or tumor suppressor activity of *NEAT1* (see reviews Dong et al., 2018; Ghafouri-Fard & Taheri, 2019). For example, *NEAT1* promotes glioblastoma progression by promoting the β-catenin nuclear transport (Q. Chen, Cai, et al., 2018). Recently, the Chen lab reported a novel role for *NEAT1* in modulating the intracellular dynamics of mRNAs coding for mitochondrial proteins (Y. Wang, Hu, et al., 2018). These studies and many others identified *NEAT1* as a lncRNA with versatile functions. *NEAT1* is a widely studied lncRNA implicated in a variety of biological functions and diseases, which are beyond the scope of this review, but numerous excellent reviews on *NEAT1* have already been published covering different aspects of its functions/roles (An, Williams, & Shelkovnikova, 2018; Y. Chen, Qiu,, et al., 2018; Dong et al., 2018; Fox & Lamond, 2010; Ghafouri-Fard & Taheri, 2019; Naganuma & Hirose, 2013; Riva, Ratti, & Venturin, 2016; C. Yang et al., 2017; Yu, Li, Zheng, Chan, & Wu, 2017).

A recent study also recognized *NEAT1* as a pseudo-*MIRHG* (L. Jiang, Shao, et al., 2017). The authors revealed that the cellular level of miR-612, which is harbored within *NEAT1*, is below the detectable level, indicating the inefficient production of miR-612 from the abundant *NEAT1* lnc-*MIRHG* transcripts. This study showed that miR-612 serves as a "pseudo-miRNA" to recruit the microprocessor to *NEAT1*, thereby facilitating the interactions between the microprocessor and the *NEAT1*-bound NONO-PSF (SFPQ) complex. The *NEAT1*-NONO/PSF-microprocessor complex enhances global pri-miRNA processing. This study has brought novel insights into the role of a nuclear domain architectural lnc-*MIRHG* in nuclear miRNA processing.

3.11 | PVT1

PVT1 is a famous oncogenic lncRNA, which is processed from the lnc-*MIRHG* locus that harbors several miRNAs, including miR-1204, -1205, -1206, -1207 (3p and 5p), and -1208. The *PVT1* gene is located in genomic proximity to the *c-Myc* oncogene, and has been shown to positively regulate *c-Myc* expression and activity (Tseng et al., 2014) (Table 3). In addition, *PVT1* was shown to sponge many tumor suppressive miRNAs (see review W. Wang, Zhou, et al., 2019). Finally, *PVT1* inhibits the expression of several tumor suppressor genes, including *LATS2*, *CDKN2B* (p15), *CDKN2A* (p16), and miR-200 genes (Kong et al., 2015; Wan et al., 2016; S. Zhang et al., 2016) by recruiting EZH2 to their promoters to

establish a repressive chromatin mark. All of these studies clearly established *PVT1* as an oncogene (Colombo et al., 2015). However, a recent study from the Dimitrova laboratory identified a DNA damage-induced isoform of *PVT1* (*Pvt1b*) as an inhibitor of *c-myc* transcription (Olivero et al., 2020). The authors observed that p53 induces the expression of the *Pvt1b* isoform during DNA damage or during oncogenic signaling. By utilizing various approaches, the authors demonstrated the tumor suppressor activity of *Pvt1b*, primarily by its role in inhibiting *c-myc* transcription. This study highlights an important idea that different isoforms of a particular lncRNA could perform entirely opposite functions in response to various cellular signals.

3.12 | H19

H19 is the first identified mammalian lncRNA (Brannan, Dees, Ingram, & Tilghman, 1990). It is transcribed from the genomically imprinted *H19*/*IGF2* cluster and displays maternal monoallelic expression. The *H19* gene locus harbors miR-675. A previous study reported that *H19* inhibits the growth of the placenta before birth via modulating the processing of miR-675, whose targets include growth-promoting insulin-like growth factor 1 receptor (*IGF1R*) (Keniry et al., 2012). *H19* is also widely known as an oncogenic lncRNA (Raveh et al., 2015). *H19* adopts a wide spectrum of mechanisms to control gene expression. First, the *H19*-miR-675 axis functions via suppressing different miR-675 mRNA targets, including SMAD and TGFβ1 (Raveh et al., 2015; L. Zhang et al., 2017). H19 also serve as a ceRNA to sponge miRNAs including let-7a and miR-106a (Imig et al., 2015; Kallen et al., 2013). Lastly, *H19*, as reported in different studies, interacts with protein partners, including EZH, MBD1, hnRNPU, and KSRP and influences their activity. The various molecular mechanisms allow *H19* to control multiple biological processes, including those relevant to cancer, such as cell proliferation and EMT. *H19* has been extensively well studied. We recommend two excellent reviews on *H19* lncRNA to learn more about this enigmatic lncRNA (Raveh et al., 2015; L. Zhang et al., 2017).

3.13 | MIR222HG

A previous study has reported that lncRNA *MIR222HG* is upregulated in castration-resistant prostate cancer cells to increase androgen-independent cell growth (T. Sun, Du, et al., 2018). Recently, our laboratory discovered *MIR222HG*'s role in facilitating cell cycle re-entry post-cellular quiescence (Q. Sun et al., 2020). Interestingly, we found that upon early serum-stimulation, diploid fibroblasts enhance the splicing of the host nascent pri-*MIR222HG* transcript dramatically and show increased levels of spliced *MIR222HG*. The pre-mRNA splicing factor SRSF1 associates with the nascent *MIR222HG* transcripts and negatively regulates the miRNA processing of miR-221/222. Mechanistically, the spliced *MIR222HG* lncRNA facilitates cell cycle re-entry by interacting with the ILF3/2 complex and several other RNAs to form an RNP complex. Our study demonstrates that the competition between the splicing and microprocessor machinery fine-tunes the cellular levels of lncRNA *MIR222HG* that dictates cell cycle re-entry.

4 | EMERGING ROLES OF LNC-*MIRHG*S IN CANCER

The last few years have seen a rapid increase in the number of publications demonstrating the involvement of lncRNAs in cancer. The decreased cost of next-generation sequencing, advances in computational and statistical pipelines, and the increased resources of cancer databases have provided us with a great opportunity to identify cancer-related lncRNAs. Many studies have reported aberrant lncRNA expression in tumor or cancer cells. In the clinical setting, lncRNAs have been identified as diagnosis or prognosis markers in patients. LncRNAs also regulate crucial molecular events during cancer cell proliferation or tumor metastasis (Huarte, 2015; Schmitt & Chang, 2016). The discovery of lncRNA function in cancer is important for drug discovery and cancer treatment.

miRNAs are also found to play key roles in cancer. The expression relationship or functional association between miRNA and their host genes in cancer have been studied and summarized by a previous review (B. Liu et al., 2018). In the current review, we only focus on the function of lnc-*MIRHG*s in cancer. Many groups have performed meta-analysis of tumor samples and reported several lnc-*MIRHG*s as biomarkers or prognosis markers of certain cancer types. These studies provide us with great resources to carry on further investigations on the molecular functions of lnc-*MIRHG*s. In this review, we only summarize studies that have included experimentally proven functions of lnc-*MIRHG*s (Table 3).

We have categorized the lnc-*MIRHG*s into oncogenic (Onc) or tumor suppressor (Ts) groups. A typical oncogenic lnc-*MIRHG* shows upregulation in certain tumor/cancer cell lines. Its high expression is typically associated with poor prognosis in patients. Functional assessment in cell lines or animal models further proves the oncogenic activity of the lnc-*MIRHG*, which usually includes one or more of the following: promoting cell proliferation, causing larger tumor size in animal models, and enhancing migration or invasion of cancer cells. A tumor suppressor lnc-*MIRHG* usually displays the opposite features.

Based on the summary in Table 3, one could observe that a particular lnc-*MIRHG* may participate in tumor progression in various cancer types. In addition, several lnc-*MIRHG*s function as an oncogene in one cancer model but demonstrate tumor suppressor activity in another cancer model (including *CCDC26*, *MIR31HG*, *MIR503HG*, *PVT1*, *NEAT1*), implying that they perform cancer-specific functions.

5 | CONCLUSIONS

The human genome contains a large number of genomic loci that could produce multiple transcripts. For example, bifunctional RNAs, or bifRNAs, are RNAs that are functional in the form of both mRNA and nc RNA (lncRNA/snoRNA/miRNA) (Hube & Francastel, 2018). BifRNAs have been identified from bacteria to mammals (Aspden et al., 2014; Gimpel, Heidrich, Mader, Krugel, & Brantl, 2010; Ji, Song, Regev, & Struhl, 2015; Lauressergues et al., 2015). Cells can precisely modulate the functions of the coding and nc portions of the bifRNAs to meet corresponding regulatory needs. However, it has not been thoroughly tested whether the same gene locus can produce two types of functional nc

transcripts, for instance, lncRNAs and miRNAs. These “bifunctional nc RNAs” are the focus of this review.

In this review, we have summarized the current knowledge of lnc-*MIRHG*s. These functional and mechanistic studies have proven that not all lnc-*MIRHG*s are “junk transcripts” (Figure 4a). Rather, the lnc-*MIRHG* loci can produce both functional miRNAs and lncRNAs, which might function synergistically or independently (Figure 4b,c). The studies of *NEAT1* also suggest that the miRNA can be the “pseudo-RNA” while the lncRNA produced from lnc-*MIRHG* gene locus plays the dominant role (Figure 4d). Collectively, the beauty of those lnc-*MIRHG* loci, dictated by their potential dual functions from both the lncRNA and miRNA, strongly suggests that we should pay more attention to this class of lncRNAs. Lnc-*MIRHG*s display a whole spectrum of functions, especially in diseases such as cancer. Having a good understanding of the mechanisms of this lncRNA repertoire will be beneficial for drug design and development.

ACKNOWLEDGMENTS

We thank Ms. Q. Hao and Ms. M. Kovour for proofreading the manuscript. All figures were created using BioRender. com. Work in the Prasanth KV Lab is funded by grants from National Institute of Health (R21AG065748), Cancer Center at Illinois seed grant, and Prairie Dragon Paddlers and NSF (EAGER; MCB1723008).

Funding information

Cancer center at Illinois seed grant and Prairie Dragon Paddlers; National Institute on Aging, Grant/Award Number: R21AG065748; National Science Foundation, Grant/Award Number: MCB1723008

REFERENCES

Agranat-Tamir L, Shomron N, Sperling J, & Sperling R (2014). Interplay between pre-mRNA splicing and microRNA biogenesis within the supraspliceosome. Nucleic Acids Research, 42(7), 4640–4651. 10.1093/nar/gkt1413 [PubMed: 24464992]

Ajiro M, Jia R, Yang Y, Zhu J, & Zheng ZM (2016). A genome landscape of SRSF3-regulated splicing events and gene expression in human osteosarcoma U2OS cells. Nucleic Acids Research, 44(4), 1854–1870. 10.1093/nar/gkv1500 [PubMed: 26704980]

An H, Williams NG, & Shelkovnikova TA (2018). NEAT1 and paraspeckles in neurodegenerative diseases: A missing lnc found? Non-coding RNA Research, 3(4), 243–252. 10.1016/j.ncrna.2018.11.003 [PubMed: 30533572]

Aspden JL, Eyre-Walker YC, Phillips RJ, Amin U, Mumtaz MA, Brocard M, & Couso JP (2014). Extensive translation of small open Reading frames revealed by poly-Ribo-Seq. eLife, 3, e03528. 10.7554/eLife.03528 [PubMed: 25144939]

Augoff K, McCue B, Plow EF, & Sossey-Alaoui K (2012). miR-31 and its host gene lncRNA LOC554202 are regulated by promoter hypermethylation in triple-negative breast cancer. Molecular Cancer, 11, 5. 10.1186/1476-4598-11-5 [PubMed: 22289355]

Auyeung VC, Ulitsky I, McGeary SE, & Bartel DP (2013). Beyond secondary structure: Primary-sequence determinants license pri-miRNA hairpins for processing. Cell, 152(4), 844–858. 10.1016/j.cell.2013.01.031 [PubMed: 23415231]

Bacolla A, Wang G, & Vasquez KM (2015). New perspectives on DNA and RNA triplexes as effectors of biological activity. PLoS Genetics, 11(12), e1005696. 10.1371/journal.pgen.1005696 [PubMed: 26700634]

Bartel DP (2009). MicroRNAs: Target recognition and regulatory functions. Cell, 136(2), 215–233. 10.1016/j.cell.2009.01.002 [PubMed: 19167326]

Baskerville S, & Bartel DP (2005). Microarray profiling of microRNAs reveals frequent coexpression with neighboring miRNAs and host genes. RNA—A Publication of the RNA Society, 11(3), 241–247. 10.1261/rna.7240905

Baumann V, & Winkler J (2014). miRNA-based therapies: Strategies and delivery platforms for oligonucleotide and non-oligonucleotide agents. Future Medicinal Chemistry, 6(17), 1967–1984. 10.4155/fmc.14.116 [PubMed: 25495987]

Berezikov E, Chung WJ, Willis J, Cuppen E, & Lai EC (2007). Mammalian mirtron genes. Molecular Cell, 28(2), 328–336. 10.1016/j.molcel.2007.09.028 [PubMed: 17964270]

Boivin V, Faucher-Giguere L, Scott M, & Abou-Elela S (2019). The cellular landscape of mid-size noncoding RNA. Wiley Interdisciplinary Reviews: RNA, 10(4), e1530. 10.1002/wrna.1530 [PubMed: 30843375]

Brannan CI, Dees EC, Ingram RS, & Tilghman SM (1990). The product of the H19 gene may function as an RNA. Molecular and Cellular Biology, 10(1), 28–36. 10.1128/mcb.10.1.28 [PubMed: 1688465]

Budach S, Heinig M, & Marsico A (2016). Principles of microRNA regulation revealed through modeling microRNA expression quantitative trait loci. Genetics, 203(4), 1629–1640. 10.1534/genetics.116.187153 [PubMed: 27260304]

Bushati N, & Cohen SM (2007). MicroRNA functions. Annual Review of Cell and Developmental Biology, 23, 175–205. 10.1146/annurev.cellbio.23.090506.123406

Cabili MN, Trapnell C, Goff L, Koziol M, Tazon-Vega B, Regev A, & Rinn JL (2011). Integrative annotation of human large intergenic noncoding RNAs reveals global properties and specific subclasses. *Genes &* Development, 25(18), 1915–1927. 10.1101/gad.17446611

Cairns J, Ingle JN, Kalari KR, Shepherd LE, Kubo M, Goetz MP, … Wang L (2019). The lncRNA MIR2052HG regulates ERalpha levels and aromatase inhibitor resistance through LMTK3 by recruiting EGR1. Breast Cancer Research, 21(1), 47. 10.1186/s13058-019-1130-3 [PubMed: 30944027]

Cheloufi S, Dos Santos CO, Chong MM, & Hannon GJ (2010). A dicer-independent miRNA biogenesis pathway that requires Ago catalysis. Nature, 465(7298), 584–589. 10.1038/nature09092 [PubMed: 20424607]

Chen J, Yu Y, Li H, Hu Q, Chen X, He Y, … Sun R (2019). Long non-coding RNA PVT1 promotes tumor progression by regulating the miR-143/HK2 axis in gallbladder cancer. Molecular Cancer, 18(1), 33. 10.1186/s12943-019-0947-9 [PubMed: 30825877]

Chen Q, Cai J, Wang Q, Wang Y, Liu M, Yang J, … Jiang C (2018). Long noncoding RNA NEAT1, regulated by the EGFR pathway, contributes to Glioblastoma progression through the WNT/beta-catenin pathway by scaffolding EZH2. Clinical Cancer Research, 24(3), 684–695. 10.1158/1078-0432.CCR-17-0605 [PubMed: 29138341]

Chen Y, Qiu J, Chen B, Lin Y, Chen Y, Xie G, … Jiang D (2018). Long non-coding RNA NEAT1 plays an important role in sepsis-induced acute kidney injury by targeting miR-204 and modulating the NF-kappaB pathway. International Immunopharmacology, 59, 252–260. 10.1016/j.intimp.2018.03.023 [PubMed: 29669307]

Chen YG, Satpathy AT, & Chang HY (2017). Gene regulation in the immune system by long noncoding RNAs. Nature Immunology, 18(9), 962–972. 10.1038/ni.3771 [PubMed: 28829444]

Cifuentes D, Xue H, Taylor DW, Patnode H, Mishima Y, Cheloufi S, … Giraldez AJ (2010). A novel miRNA processing pathway independent of Dicer requires Argonaute2 catalytic activity. Science, 328(5986), 1694–1698. 10.1126/science.1190809 [PubMed: 20448148]

Clemson CM, Hutchinson JN, Sara SA, Ensminger AW, Fox AH, Chess A, & Lawrence JB (2009). An architectural role for a nuclear noncoding RNA: NEAT1 RNA is essential for the structure of paraspeckles. Molecular Cell, 33(6), 717–726. 10.1016/j.molcel.2009.01.026 [PubMed: 19217333]

Colombo T, Farina L, Macino G, & Paci P (2015). PVT1: A rising star among oncogenic long noncoding RNAs. BioMed Research International, 2015, 304208–304210. 10.1155/2015/304208 [PubMed: 25883951]

Cui Z, An X, Li J, Liu Q, & Liu W (2018). LncRNA MIR22HG negatively regulates miR-141–3p to enhance DAPK1 expression and inhibits endometrial carcinoma cells proliferation. Biomedicine & Pharmacotherapy, 104, 223–228. 10.1016/j.biopha.2018.05.046 [PubMed: 29775889]

Czubak K, Lewandowska MA, Klonowska K, Roszkowski K, Kowalewski J, Figlerowicz M, & Kozlowski P (2015). High copy number variation of cancer-related microRNA genes and frequent amplification of DICER1 and DROSHA in lung cancer. Oncotarget, 6(27), 23399–23416. 10.18632/oncotarget.4351 [PubMed: 26156018]

Daniunaite K, Dubikaityte M, Gibas P, Bakavicius A, Rimantas Lazutka J, Ulys A, … Jarmalaite S (2017). Clinical significance of miRNA host gene promoter methylation in prostate cancer. Human Molecular Genetics, 26(13), 2451–2461. 10.1093/hmg/ddx138 [PubMed: 28398479]

Derderian C, Orunmuyi AT, Olapade-Olaopa EO, & Ogunwobi OO (2019). PVT1 signaling is a mediator of Cancer progression. Frontiers in Oncology, 9, 502. 10.3389/fonc.2019.00502 [PubMed: 31249809]

Dhir A, Dhir S, Proudfoot NJ, & Jopling CL (2015). Microprocessor mediates transcriptional termination of long noncoding RNA transcripts hosting microRNAs. Nature Structural & Molecular Biology, 22(4), 319–327. 10.1038/nsmb.2982

Di Agostino S, Valenti F, Sacconi A, Fontemaggi G, Pallocca M, Pulito C, … Blandino G (2018). Long non-coding MIR205HG depletes Hsa-miR-590–3p leading to unrestrained proliferation in head and neck squamous cell carcinoma. Theranostics, 8(7), 1850–1868. 10.7150/thno.22167 [PubMed: 29556360]

Dong P, Xiong Y, Yue J, Hanley SJB, Kobayashi N, Todo Y, & Watari H (2018). Long non-coding RNA NEAT1: A novel target for diagnosis and therapy in human tumors. Frontiers in Genetics, 9, 471. 10.3389/fgene.2018.00471 [PubMed: 30374364]

Du P, Wang L, Sliz P, & Gregory RI (2015). A biogenesis step upstream of microprocessor controls miR-17 approximately 92 expression. Cell, 162(4), 885–899. 10.1016/j.cell.2015.07.008 [PubMed: 26255770]

Du Q, Hoover AR, Dozmorov I, Raj P, Khan S, Molina E, … van Oers NSC (2019). MIR205HG is a long noncoding RNA that regulates growth hormone and prolactin production in the anterior pituitary. Developmental Cell, 49(4), 618–631 e615. 10.1016/j.devcel.2019.03.012 [PubMed: 30982661]

Emmrich S, Streltsov A, Schmidt F, Thangapandi VR, Reinhardt D, & Klusmann JH (2014). LincRNAs MONC and MIR100HG act as oncogenes in acute megakaryoblastic leukemia. Molecular Cancer, 13, 171. 10.1186/1476-4598-13-171 [PubMed: 25027842]

Fang S, Zhang L, Guo J, Niu Y, Wu Y, Li H, … Zhao Y (2018). NONCODEV5: A comprehensive annotation database for long non-coding RNAs. Nucleic Acids Research, 46(D1), D308–D314. 10.1093/nar/gkx1107 [PubMed: 29140524]

Fang Y, & Fullwood MJ (2016). Roles, functions, and mechanisms of Long non-coding RNAs in cancer. Genomics, Proteomics & Bioinformatics, 14(1), 42–54. 10.1016/j.gpb.2015.09.006

Farazi TA, Spitzer JI, Morozov P, & Tuschl T (2011). miRNAs in human cancer. The Journal of Pathology, 223(2), 102–115. 10.1002/path.2806 [PubMed: 21125669]

Filipowicz W, Jaskiewicz L, Kolb FA, & Pillai RS (2005). Post-transcriptional gene silencing by siRNAs and miRNAs. Current Opinion in Structural Biology, 15(3), 331–341. 10.1016/j.sbi.2005.05.006 [PubMed: 15925505]

Flynn RA, & Chang HY (2014). Long noncoding RNAs in cell-fate programming and reprogramming. Cell Stem Cell, 14(6), 752–761. 10.1016/j.stem.2014.05.014 [PubMed: 24905165]

Flynt AS, Greimann JC, Chung WJ, Lima CD, & Lai EC (2010). MicroRNA biogenesis via splicing and exosome-mediated trimming in Drosophila. Molecular Cell, 38(6), 900–907. 10.1016/j.molcel.2010.06.014 [PubMed: 20620959]

Fox AH, & Lamond AI (2010). Paraspeckles. Cold Spring Harbor Perspectives in Biology, 2(7), a000687. 10.1101/cshperspect.a000687 [PubMed: 20573717]

Franca GS, Vibranovski MD, & Galante PA (2016). Host gene constraints and genomic context impact the expression and evolution of human microRNAs. Nature Communications, 7, 11438. 10.1038/ncomms11438

Frankish A, Diekhans M, Ferreira AM, Johnson R, Jungreis I, Loveland J, … Flicek P (2019). GENCODE reference annotation for the human and mouse genomes. Nucleic Acids Research, 47(D1), D766–D773. 10.1093/nar/gky955 [PubMed: 30357393]

Friedman RC, Farh KK, Burge CB, & Bartel DP (2009). Most mammalian mRNAs are conserved targets of microRNAs. Genome Research, 19(1), 92–105. 10.1101/gr.082701.108 [PubMed: 18955434]

Fu J, Dong G, Shi H, Zhang J, Ning Z, Bao X, … Xiong B (2019). LncRNA MIR503HG inhibits cell migration and invasion via miR-103/OLFM4 axis in triple negative breast cancer. Journal of Cellular and Molecular Medicine, 23(7), 4738–4745. 10.1111/jcmm.14344 [PubMed: 31062436]

Gebert LFR, & MacRae IJ (2019). Regulation of microRNA function in animals. Nature Reviews. Molecular Cell Biology, 20(1), 21–37. 10.1038/s41580-018-0045-7 [PubMed: 30108335]

Ghafouri-Fard S, & Taheri M (2019). Nuclear enriched abundant transcript 1 (NEAT1): A long non-coding RNA with diverse functions in tumorigenesis. Biomedicine & Pharmacotherapy, 111, 51–59. 10.1016/j.biopha.2018.12.070 [PubMed: 30576934]

Gimpel M, Heidrich N, Mader U, Krugel H, & Brantl S (2010). A dual-function sRNA from *B. subtilis*: SR1 acts as a peptide encoding mRNA on the gapA operon. Molecular Microbiology, 76(4), 990–1009. 10.1111/j.1365-2958.2010.07158.x [PubMed: 20444087]

Giovarelli M, Bucci G, Ramos A, Bordo D, Wilusz CJ, Chen CY, … Gherzi R (2014). H19 long noncoding RNA controls the mRNA decay promoting function of KSRP. Proceedings of the National Academy of Sciences of the United States of America, 111(47), E5023–E5028. 10.1073/pnas.1415098111 [PubMed: 25385579]

Grady WM, Parkin RK, Mitchell PS, Lee JH, Kim YH, Tsuchiya KD, … Tewari M (2008). Epigenetic silencing of the intronic microRNA hsa-miR-342 and its host gene EVL in colorectal cancer. Oncogene, 27(27), 3880–3888. 10.1038/onc.2008.10 [PubMed: 18264139]

Gregory RI, Yan KP, Amuthan G, Chendrimada T, Doratotaj B, Cooch N, & Shiekhattar R (2004). The microprocessor complex mediates the genesis of microRNAs. Nature, 432(7014), 235–240. 10.1038/nature03120 [PubMed: 15531877]

Guil S, & Caceres JF (2007). The multifunctional RNA-binding protein hnRNP A1 is required for processing of miR-18a. Nature Structural & Molecular Biology, 14(7), 591–596. 10.1038/nsmb1250

Ha M, & Kim VN (2014). Regulation of microRNA biogenesis. Nature Reviews. Molecular Cell Biology, 15(8), 509–524. 10.1038/nrm3838 [PubMed: 25027649]

Han J, Lee Y, Yeom KH, Nam JW, Heo I, Rhee JK, … Kim VN (2006). Molecular basis for the recognition of primary microRNAs by the Drosha-DGCR8 complex. Cell, 125(5), 887–901. 10.1016/j.cell.2006.03.043 [PubMed: 16751099]

Hinske LC, Galante PA, Kuo WP, & Ohno-Machado L (2010). A potential role for intragenic miRNAs on their hosts' interactome. BMC Genomics, 11, 533. 10.1186/1471-2164-11-533 [PubMed: 20920310]

Hirano T, Yoshikawa R, Harada H, Harada Y, Ishida A, & Yamazaki T (2015). Long noncoding RNA, CCDC26, controls myeloid leukemia cell growth through regulation of KIT expression. Molecular Cancer, 14, 90. 10.1186/s12943-015-0364-7 [PubMed: 25928165]

Hirose T, Virnicchi G, Tanigawa A, Naganuma T, Li R, Kimura H, … Pierron G (2014). NEAT1 long noncoding RNA regulates transcription via protein sequestration within subnuclear bodies. Molecular Biology of the Cell, 25(1), 169–183. 10.1091/mbc.E13-09-0558 [PubMed: 24173718]

Huang PS, Chung IH, Lin YH, Lin TK, Chen WJ, & Lin KH (2018). The Long non-coding RNA MIR503HG enhances proliferation of human ALK-negative anaplastic large-cell lymphoma. International Journal of Molecular Sciences, 19(5). 10.3390/ijms19051463

Huarte M (2015). The emerging role of lncRNAs in cancer. Nature Medicine, 21(11), 1253–1261. 10.1038/nm.3981

Hube F, & Francastel C (2018). Coding and non-coding RNAs, the frontier has never been so blurred. Frontiers in Genetics, 9, 140. 10.3389/fgene.2018.00140 [PubMed: 29720998]

Imig J, Brunschweiger A, Brummer A, Guennewig B, Mittal N, Kishore S, … Hall J (2015). miR-CLIP capture of a miRNA targetome uncovers a lincRNA H19-miR-106a interaction. Nature Chemical Biology, 11(2), 107–114. 10.1038/nchembio.1713 [PubMed: 25531890]

Ingle JN, Xie F, Ellis MJ, Goss PE, Shepherd LE, Chapman JW, … Wang L (2016). Genetic polymorphisms in the long noncoding RNA MIR2052HG offer a pharmacogenomic basis for the

response of breast cancer patients to aromatase inhibitor therapy. Cancer Research, 76(23), 7012–7023. 10.1158/0008-5472.CAN-16-1371 [PubMed: 27758888]

Jadaliha M, Gholamalamdari O, Tang W, Zhang Y, Petracovici A, Hao Q, … Prasanth KV (2018). A natural antisense lncRNA controls breast cancer progression by promoting tumor suppressor gene mRNA stability. PLoS Genetics, 14(11), e1007802. 10.1371/journal.pgen.1007802 [PubMed: 30496290]

Janas MM, Khaled M, Schubert S, Bernstein JG, Golan D, Veguilla RA, … Novina CD (2011). Feed-forward microprocessing and splicing activities at a microRNA-containing intron. PLoS Genetics, 7(10), e1002330. 10.1371/journal.pgen.1002330 [PubMed: 22028668]

Ji Z, Song R, Regev A, & Struhl K (2015). Many lncRNAs, 5'UTRs, and pseudogenes are translated and some are likely to express functional proteins. eLife, 4, e08890. 10.7554/eLife.08890 [PubMed: 26687005]

Jiang L, Shao C, Wu QJ, Chen G, Zhou J, Yang B, … Fu XD (2017). NEAT1 scaffolds RNA-binding proteins and the microprocessor to globally enhance pri-miRNA processing. Nature Structural & Molecular Biology, 24(10), 816–824. 10.1038/nsmb.3455

Jiang N, Wang X, Xie X, Liao Y, Liu N, Liu J, … Peng T (2017). lncRNA DANCR promotes tumor progression and cancer stemness features in osteosarcoma by upregulating AXL via miR-33a-5p inhibition. Cancer Letters, 405, 46–55. 10.1016/j.canlet.2017.06.009 [PubMed: 28642170]

Jin Y, Chen Z, Liu X, & Zhou X (2013). Evaluating the microRNA targeting sites by luciferase reporter gene assay. Methods in Molecular Biology, 936, 117–127. 10.1007/978-1-62703-083-0_10 [PubMed: 23007504]

Kahl G (2009). The dictionary of genomics, transcriptomics and proteomics (5th ed.). Hoboken, NJ: Wiley-Blackwell.

Kallen AN, Zhou XB, Xu J, Qiao C, Ma J, Yan L, … Huang Y (2013). The imprinted H19 lncRNA antagonizes let-7 microRNAs. Molecular Cell, 52(1), 101–112. 10.1016/j.molcel.2013.08.027 [PubMed: 24055342]

Kang X, Kong F, Huang K, Li L, Li Z, Wang X, … Wu X (2019). LncRNA MIR210HG promotes proliferation and invasion of non-small cell lung cancer by upregulating methylation of CACNA2D2 promoter via binding to DNMT1. Oncotargets and Therapy, 12, 3779–3790. 10.2147/OTT.S189468 [PubMed: 31190878]

Kataoka N, Fujita M, & Ohno M (2009). Functional association of the microprocessor complex with the spliceosome. Molecular and Cellular Biology, 29(12), 3243–3254. 10.1128/MCB.00360-09 [PubMed: 19349299]

Keniry A, Oxley D, Monnier P, Kyba M, Dandolo L, Smits G, & Reik W (2012). The H19 lincRNA is a developmental reservoir of miR-675 that suppresses growth and Igf1r. Nature Cell Biology, 14(7), 659–665. 10.1038/ncb2521 [PubMed: 22684254]

Kim K, Nguyen TD, Li S, & Nguyen TA (2018). SRSF3 recruits DROSHA to the basal junction of primary microRNAs. RNA, 24(7), 892–898. 10.1261/rna.065862.118 [PubMed: 29615481]

Kim TK, Hemberg M, & Gray JM (2015). Enhancer RNAs: A class of long noncoding RNAs synthesized at enhancers. Cold Spring Harbor Perspectives in Biology, 7(1), a018622. 10.1101/cshperspect.a018622 [PubMed: 25561718]

Kim YK, & Kim VN (2007). Processing of intronic microRNAs. The EMBO Journal, 26(3), 775–783. 10.1038/sj.emboj.7601512 [PubMed: 17255951]

Kitagawa M, Kitagawa K, Kotake Y, Niida H, & Ohhata T (2013). Cell cycle regulation by long non-coding RNAs. Cellular and Molecular Life Sciences, 70(24), 4785–4794. 10.1007/s00018-013-1423-0 [PubMed: 23880895]

Kong R, Zhang EB, Yin DD, You LH, Xu TP, Chen WM, … Zhang ZH (2015). Long noncoding RNA PVT1 indicates a poor prognosis of gastric cancer and promotes cell proliferation through epigenetically regulating p15 and p16. Molecular Cancer, 14, 82. 10.1186/s12943-015-0355-8 [PubMed: 25890171]

Kopp F, & Mendell JT (2018). Functional classification and experimental dissection of long noncoding RNAs. Cell, 172(3), 393–407. 10.1016/j.cell.2018.01.011 [PubMed: 29373828]

Kozomara A, Birgaoanu M, & Griffiths-Jones S (2019). miRBase: From microRNA sequences to function. Nucleic Acids Research, 47(D1), D155–D162. 10.1093/nar/gky1141 [PubMed: 30423142]

Kwon SC, Baek SC, Choi YG, Yang J, Lee YS, Woo JS, & Kim VN (2019). Molecular basis for the single-nucleotide precision of primary microRNA processing. Molecular Cell, 73(3), 505, e505–518. 10.1016/j.molcel.2018.11.005 [PubMed: 30554947]

Lagarde J, Uszczynska-Ratajczak B, Carbonell S, Perez-Lluch S, Abad A, Davis C, … Johnson R (2017). High-throughput annotation of full-length long noncoding RNAs with capture long-read sequencing. Nature Genetics, 49(12), 1731–1740. 10.1038/ng.3988 [PubMed: 29106417]

Latge G, Poulet C, Bours V, Josse C, & Jerusalem G (2018). Natural antisense transcripts: Molecular mechanisms and implications in breast cancers. International Journal of Molecular Sciences, 19(1). 10.3390/ijms19010123

Lauressergues D, Couzigou JM, Clemente HS, Martinez Y, Dunand C, Becard G, & Combier JP (2015). Primary transcripts of microRNAs encode regulatory peptides. Nature, 520(7545), 90–93. 10.1038/nature14346 [PubMed: 25807486]

Lee RC, Feinbaum RL, & Ambros V (1993). The *C. elegans* heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14. Cell, 75(5), 843–854. 10.1016/0092-8674(93)90529-y [PubMed: 8252621]

Li J, Tian H, Yang J, & Gong Z (2016). Long noncoding RNAs regulate cell growth, proliferation, and apoptosis. DNA Cell Biology, 35(9), 459–470. 10.1089/dna.2015.3187 [PubMed: 27213978]

Li J, Wu QM, Wang XQ, & Zhang CQ (2017). Long noncoding RNA miR210HG sponges miR-503 to facilitate osteosarcoma cell invasion and metastasis. DNA and Cell Biology, 36(12), 1117–1125. 10.1089/dna.2017.3888 [PubMed: 28972855]

Li N, Long B, Han W, Yuan S, & Wang K (2017). microRNAs: Important regulators of stem cells. Stem Cell Research & Therapy, 8(1), 110. 10.1186/s13287-017-0551-0 [PubMed: 28494789]

Li XY, Zhou LY, Luo H, Zhu Q, Zuo L, Liu GY, … Li X (2019). The long noncoding RNA MIR210HG promotes tumor metastasis by acting as a ceRNA of miR-1226–3p to regulate mucin-1c expression in invasive breast cancer. Aging (Albany NY), 11(15), 5646–5665. 10.18632/aging.102149 [PubMed: 31399552]

Li Y, Syed J, & Sugiyama H (2016). RNA-DNA triplex formation by long noncoding RNAs. Cell Chemical Biology, 23(11), 1325–1333. 10.1016/j.chembiol.2016.09.011 [PubMed: 27773629]

Li Y, Wang H, & Huang H (2019). Long non-coding RNA MIR205HG function as a ceRNA to accelerate tumor growth and progression via sponging miR-122–5p in cervical cancer. Biochemical and Biophysical Research Communications, 514(1), 78–85. 10.1016/j.bbrc.2019.04.102 [PubMed: 31023531]

Li Z, Zhang J, Liu X, Li S, Wang Q, Di C, … He X (2018). The LINC01138 drives malignancies via activating arginine methyltransferase 5 in hepatocellular carcinoma. Nature Communications, 9(1), 1572. 10.1038/s41467-018-04006-0

Liu B, Shyr Y, Cai J, & Liu Q (2018). Interplay between miRNAs and host genes and their role in cancer. Briefings in Functional Genomics, 18(4), 255–266. 10.1093/bfgp/elz002 [PubMed: 30785618]

Liu Y, Zhang M, Liang L, Li J, & Chen YX (2015). Over-expression of lncRNA DANCR is associated with advanced tumor progression and poor prognosis in patients with colorectal cancer. International Journal of Clinical and Experimental Pathology, 8(9), 11480–11484. [PubMed: 26617879]

Liu Z, Dou C, Yao B, Xu M, Ding L, Wang Y, … Liu Q (2016). Ftx non coding RNA-derived miR-545 promotes cell proliferation by targeting RIG-I in hepatocellular carcinoma. Oncotarget, 7(18), 25350–25365. 10.18632/oncotarget.8129 [PubMed: 26992218]

Lu KH, Li W, Liu XH, Sun M, Zhang ML, Wu WQ, … Hou YY (2013). Long non-coding RNA MEG3 inhibits NSCLC cells proliferation and induces apoptosis by affecting p53 expression. BMC Cancer, 13, 461. 10.1186/1471-2407-13-461 [PubMed: 24098911]

Lu Y, Zhao X, Liu Q, Li C, Graves-Deal R, Cao Z, … Coffey RJ (2017). lncRNA MIR100HG-derived miR-100 and miR-125b mediate cetuximab resistance via Wnt/beta-catenin signaling. Nature Medicine, 23(11), 1331–1341. 10.1038/nm.4424

Lutter D, Marr C, Krumsiek J, Lang EW, & Theis FJ (2010). Intronic microRNAs support their host genes by mediating synergistic and antagonistic regulatory effects. BMC Genomics, 11, 224. 10.1186/1471-2164-11-224 [PubMed: 20370903]

Ma H, Wu Y, Choi JG, & Wu H (2013). Lower and upper stem-single-stranded RNA junctions together determine the Drosha cleavage site. Proceedings of the National Academy of Sciences of the United States of America, 110(51), 20687–20692. 10.1073/pnas.1311639110 [PubMed: 24297910]

MacRae IJ, Zhou K, & Doudna JA (2007). Structural determinants of RNA recognition and cleavage by Dicer. *Nature Structural &* Molecular Biology, 14(10), 934–940. 10.1038/nsmb1293

Marchese FP, Raimondi I, & Huarte M (2017). The multidimensional mechanisms of long noncoding RNA function. Genome Biology, 18 (1), 206. 10.1186/s13059-017-1348-2 [PubMed: 29084573]

Marin-Bejar O, Marchese FP, Athie A, Sanchez Y, Gonzalez J, Segura V, … Huarte M (2013). Pint lincRNA connects the p53 pathway with epigenetic silencing by the Polycomb repressive complex 2. Genome Biology, 14(9), R104. 10.1186/gb-2013-14-9-r104 [PubMed: 24070194]

Marin-Bejar O, Mas AM, Gonzalez J, Martinez D, Athie A, Morales X, … Huarte M (2017). The human lncRNA LINC-PINT inhibits tumor cell invasion through a highly conserved sequence element. Genome Biology, 18(1), 202. 10.1186/s13059-017-1331-y [PubMed: 29078818]

Mattioli C, Pianigiani G, & Pagani F (2013). A competitive regulatory mechanism discriminates between juxtaposed splice sites and pri-miRNA structures. Nucleic Acids Research, 41(18), 8680–8691. 10.1093/nar/gkt614 [PubMed: 23863840]

Mattioli C, Pianigiani G, & Pagani F (2014). Cross talk between spliceosome and microprocessor defines the fate of pre-mRNA. Wiley Interdisciplinary Reviews: RNA, 5(5), 647–658. 10.1002/wrna.1236 [PubMed: 24788135]

Mehta A, & Baltimore D (2016). MicroRNAs as regulatory elements in immune system logic. Nature Reviews. Immunology, 16(5), 279–294. 10.1038/nri.2016.40

Melamed Z, Levy A, Ashwal-Fluss R, Lev-Maor G, Mekahel K, Atias N, … Ast G (2013). Alternative splicing regulates biogenesis of miRNAs located across exon-intron junctions. Molecular Cell, 50(6), 869–881. 10.1016/j.molcel.2013.05.007 [PubMed: 23747012]

Michlewski G, & Caceres JF (2010). Antagonistic role of hnRNP A1 and KSRP in the regulation of let-7a biogenesis. Nature Structural & Molecular Biology, 17(8), 1011–1018. 10.1038/nsmb.1874

Milligan MJ, & Lipovich L (2014). Pseudogene-derived lncRNAs: Emerging regulators of gene expression. Frontiers in Genetics, 5, 476. 10.3389/fgene.2014.00476 [PubMed: 25699073]

Monnier P, Martinet C, Pontis J, Stancheva I, Ait-Si-Ali S, & Dandolo L (2013). H19 lncRNA controls gene expression of the imprinted gene network by recruiting MBD1. Proceedings of the National Academy of Sciences of the United States of America, 110(51), 20693–20698. 10.1073/pnas.1310201110 [PubMed: 24297921]

Morenos L, Chatterton Z, Ng JL, Halemba MS, Parkinson-Bates M, Mechinaud F, … Wong NC (2014). Hypermethylation and down-regulation of DLEU2 in paediatric acute myeloid leukaemia independent of embedded tumour suppressor miR-15a/16–1. Molecular Cancer, 13, 123. 10.1186/1476-4598-13-123 [PubMed: 24885794]

Morlando M, Ballarino M, Gromak N, Pagano F, Bozzoni I, & Proudfoot NJ (2008). Primary microRNA transcripts are processed co-transcriptionally. Nature Structural & Molecular Biology, 15(9), 902–909.

Naganuma T, & Hirose T (2013). Paraspeckle formation during the biogenesis of long non-coding RNAs. RNA Biology, 10(3), 456–461. 10.4161/rna.23547 [PubMed: 23324609]

Ng SY, Bogu GK, Soh BS, & Stanton LW (2013). The long noncoding RNA RMST interacts with SOX2 to regulate neurogenesis. Molecular Cell, 51(3), 349–359. 10.1016/j.molcel.2013.07.017 [PubMed: 23932716]

Nguyen TA, Jo MH, Choi YG, Park J, Kwon SC, Hohng S, … Woo JS (2015). Functional anatomy of the human microprocessor. Cell, 161(6), 1374–1387. 10.1016/j.cell.2015.05.010 [PubMed: 26027739]

Nie FQ, Ma S, Xie M, Liu YW, De W, & Liu XH (2016). Decreased long noncoding RNA MIR31HG is correlated with poor prognosis and contributes to cell proliferation in gastric cancer. Tumour Biology, 37(6), 7693–7701. 10.1007/s13277-015-4644-z [PubMed: 26692098]

Noh JH, Kim KM, McClusky WG, Abdelmohsen K, & Gorospe M (2018). Cytoplasmic functions of long noncoding RNAs. Wiley Interdisciplinary Reviews: RNA, 9(3), e1471. 10.1002/wrna.1471 [PubMed: 29516680]

Okamura K, Hagen JW, Duan H, Tyler DM, & Lai EC (2007). The mirtron pathway generates microRNA-class regulatory RNAs in Drosophila. Cell, 130(1), 89–100. 10.1016/j.cell.2007.06.028 [PubMed: 17599402]

O'Leary NA, Wright MW, Brister JR, Ciufo S, Haddad D, McVeigh R, … Pruitt KD (2016). Reference sequence (RefSeq) database at NCBI: Current status, taxonomic expansion, and functional annotation. Nucleic Acids Research, 44(D1), D733–D745. 10.1093/nar/gkv1189 [PubMed: 26553804]

Olivero CE, Martinez-Terroba E, Zimmer J, Liao C, Tesfaye E, Hooshdaran N, … Dimitrova N (2020). p53 Activates the Long noncoding RNA Pvt1b to inhibit Myc and suppress tumorigenesis. Molecular Cell, 77(4), 761–774 e768. 10.1016/j.molcel.2019.12.014 [PubMed: 31973890]

Park JE, Heo I, Tian Y, Simanshu DK, Chang H, Jee D, … Kim VN (2011). Dicer recognizes the 5′ end of RNA for efficient and accurate processing. Nature, 475(7355), 201–205. 10.1038/nature10198 [PubMed: 21753850]

Peng W, & Jiang A (2016). Long noncoding RNA CCDC26 as a potential predictor biomarker contributes to tumorigenesis in pancreatic cancer. Biomedicine & Pharmacotherapy, 83, 712–717. 10.1016/j.biopha.2016.06.059 [PubMed: 27470572]

Peng W, Si S, Zhang Q, Li C, Zhao F, Wang F, … Ma R (2015). Long non-coding RNA MEG3 functions as a competing endogenous RNA to regulate gastric cancer progression. Journal of Experimental & Clinical Cancer Research, 34, 79. 10.1186/s13046-015-0197-7 [PubMed: 26253106]

Pianigiani G, Licastro D, Fortugno P, Castiglia D, Petrovic I, & Pagani F (2018). Microprocessor-dependent processing of splice site overlapping microRNA exons does not result in changes in alternative splicing. RNA, 24(9), 1158–1171. 10.1261/rna.063438.117 [PubMed: 29895677]

Profumo V, Forte B, Percio S, Rotundo F, Doldi V, Ferrari E, … Gandellini P (2019). LEADeR role of miR-205 host gene as long non-coding RNA in prostate basal cell differentiation. Nature Communications, 10(1), 307. 10.1038/s41467-018-08153-2

Qian H, Chen L, Huang J, Wang X, Ma S, Cui F, … Zheng G (2018). The lncRNA MIR4435–2HG promotes lung cancer progression by activating beta-catenin signalling. Journal of Molecular Medicine (Berlin, Germany), 96(8), 753–764. 10.1007/s00109-018-1654-5

Qin J, Ning H, Zhou Y, Hu Y, Yang L, & Huang R (2018). LncRNA MIR31HG overexpression serves as poor prognostic biomarker and promotes cells proliferation in lung adenocarcinoma. Biomedicine & Pharmacotherapy, 99, 363–368. 10.1016/j.biopha.2018.01.037 [PubMed: 29367106]

Ratnadiwakara M, Mohenska M, & Anko ML (2018). Splicing factors as regulators of miRNA biogenesis - links to human disease. Seminars in Cell & Developmental Biology, 79, 113–122. 10.1016/j.semcdb.2017.10.008 [PubMed: 29042235]

Raveh E, Matouk IJ, Gilon M, & Hochberg A (2015). The H19 Long non-coding RNA in cancer initiation, progression and metastasis—A proposed unifying theory. Molecular Cancer, 14, 184. 10.1186/s12943-015-0458-2 [PubMed: 26536864]

Reddy KB (2015). MicroRNA (miRNA) in cancer. Cancer Cell International, 15, 38. 10.1186/s12935-015-0185-1 [PubMed: 25960691]

Riva P, Ratti A, & Venturin M (2016). The long non-coding RNAs in neurodegenerative diseases: Novel mechanisms of pathogenesis. Current Alzheimer Research, 13(11), 1219–1231. 10.2174/1567205013666160622112234 [PubMed: 27338628]

Ruby JG, Jan CH, & Bartel DP (2007). Intronic microRNA precursors that bypass Drosha processing. Nature, 448(7149), 83–86. 10.1038/nature05983 [PubMed: 17589500]

Saliminejad K, Khorram Khorshid HR, Soleymani Fard S, & Ghaffari SH (2019). An overview of microRNAs: Biology, functions, therapeutics, and analysis methods. Journal of Cellular Physiology, 234(5), 5451–5465. 10.1002/jcp.27486 [PubMed: 30471116]

Schmitt AM, & Chang HY (2016). Long noncoding RNAs in cancer pathways. Cancer Cell, 29(4), 452–463. 10.1016/j.ccell.2016.03.010 [PubMed: 27070700]

Schwarz DS, Hutvagner G, Du T, Xu Z, Aronin N, & Zamore PD (2003). Asymmetry in the assembly of the RNAi enzyme complex. Cell, 115(2), 199–208. 10.1016/s0092-8674(03)00759-1 [PubMed: 14567917]

Shen Y, Katsaros D, Loo LW, Hernandez BY, Chong C, Canuto EM, … Yu H (2015). Prognostic and predictive values of long non-coding RNA LINC00472 in breast cancer. Oncotarget, 6(11), 8579–8592. 10.18632/oncotarget.3287 [PubMed: 25865225]

Shih JW, Chiang WF, Wu ATH, Wu MH, Wang LY, Yu YL, … Kung HJ (2017). Long noncoding RNA LncHIFCAR/MIR31HG is a HIF-1alpha co-activator driving oral cancer progression. Nature Communications, 8, 15874. 10.1038/ncomms15874

Song MS, & Rossi JJ (2017). Molecular mechanisms of dicer: Endonuclease and enzymatic activity. The Biochemical Journal, 474(10), 1603–1618. 10.1042/BCJ20160759 [PubMed: 28473628]

Souquere S, Beauclair G, Harper F, Fox A, & Pierron G (2010). Highly ordered spatial organization of the structural long noncoding NEAT1 RNAs within paraspeckle nuclear bodies. Molecular Biology of the Cell, 21(22), 4020–4027. 10.1091/mbc.E10-08-0690 [PubMed: 20881053]

St Laurent G, Wahlestedt C, & Kapranov P (2015). The landscape of long noncoding RNA classification. Trends in Genetics: TIG, 31(5), 239–251. 10.1016/j.tig.2015.03.007 [PubMed: 25869999]

Steiman-Shimony A, Shtrikman O, & Margalit H (2018). Assessing the functional association of intronic miRNAs with their host genes. RNA—A Publication of the RNA Society, 24(8), 991–1004. 10.1261/rna.064386.117

Su W, Feng S, Chen X, Yang X, Mao R, Guo C, … Chen G (2018). Silencing of Long noncoding RNA MIR22HG triggers cell survival/death signaling via oncogenes YBX1, MET, and p21 in lung Cancer. Cancer Research, 78(12), 3207–3219. 10.1158/0008-5472.CAN-18-0222 [PubMed: 29669758]

Sun Q, Hao Q, Lin YC, Song YJ, Bangru S, Arif W, … Prasanth KV (2020). Antagonism between splicing and microprocessor complex dictates the serum-induced processing of Lnc-MIRHG for efficient cell cycle re-entry. RNA—A Publication of the RNA Society., rna.075309.120. 10.1261/rna.075309.120

Sun Q, Hao Q, & Prasanth KV (2018). Nuclear long noncoding RNAs: Key regulators of gene expression. Trends in Genetics, 34(2), 142–157. 10.1016/j.tig.2017.11.005 [PubMed: 29249332]

Sun T, Du SY, Armenia J, Qu F, Fan J, Wang X, … Kantoff PW (2018). Expression of lncRNA MIR222HG co-transcribed from the miR-221/222 gene promoter facilitates the development of castration-resistant prostate cancer. Oncogene, 7(3), 30. 10.1038/s41389-018-0039-5

Terashima M, Ishimura A, Wanna-Udom S, & Suzuki T (2018). MEG8 long noncoding RNA contributes to epigenetic progression of the epithelial-mesenchymal transition of lung and pancreatic cancer cells. The Journal of Biological Chemistry, 293(47), 18016–18030. 10.1074/jbc.RA118.004006 [PubMed: 30262664]

Terashima M, Tange S, Ishimura A, & Suzuki T (2017). MEG3 Long noncoding RNA contributes to the epigenetic regulation of epithelial-mesenchymal transition in lung Cancer cell lines. The Journal of Biological Chemistry, 292(1), 82–99. 10.1074/jbc.M116.750950 [PubMed: 27852821]

Trabucchi M, Briata P, Garcia-Mayoral M, Haase AD, Filipowicz W, Ramos A, … Rosenfeld MG (2009). The RNA-binding protein KSRP promotes the biogenesis of a subset of microRNAs. Nature, 459(7249), 1010–1014. 10.1038/nature08025 [PubMed: 19458619]

Treiber T, Treiber N, & Meister G (2019). Regulation of microRNA biogenesis and its crosstalk with other cellular pathways. Nature Reviews. Molecular Cell Biology, 20(1), 5–20. 10.1038/s41580-018-0059-1 [PubMed: 30228348]

Tseng YY, Moriarity BS, Gong W, Akiyama R, Tiwari A, Kawakami H, … Bagchi A (2014). PVT1 dependence in cancer with MYC copy-number increase. Nature, 512(7512), 82–86. 10.1038/nature13311 [PubMed: 25043044]

Ulitsky I (2016). Evolution to the rescue: Using comparative genomics to understand long non-coding RNAs. Nature Reviews. Genetics, 17 (10), 601–614. 10.1038/nrg.2016.85

Volders PJ, Anckaert J, Verheggen K, Nuytens J, Martens L, Mestdagh P, & Vandesompele J (2019). LNCipedia 5: Towards a reference set of human long non-coding RNAs. Nucleic Acids Research, 47(D1), D135–D139. 10.1093/nar/gky1031 [PubMed: 30371849]

Wan L, Sun M, Liu GJ, Wei CC, Zhang EB, Kong R, … Wang ZX (2016). Long noncoding RNA PVT1 promotes non-small cell lung Cancer cell proliferation through epigenetically regulating LATS2 expression. Molecular Cancer Therapeutics, 15(5), 1082–1094. 10.1158/1535-7163.MCT-15-0707 [PubMed: 26908628]

Wang AH, Jin CH, Cui GY, Li HY, Wang Y, Yu JJ, … Tian XY (2020). MIR210HG promotes cell proliferation and invasion by regulating miR-503–5p/TRAF4 axis in cervical cancer. Aging (Albany NY), 12(4), 3205–3217. 10.18632/aging.102799 [PubMed: 32087604]

Wang F, Yuan JH, Wang SB, Yang F, Yuan SX, Ye C, … Sun SH (2014). Oncofetal long noncoding RNA PVT1 promotes proliferation and stem cell-like property of hepatocellular carcinoma cells by stabilizing NOP2. Hepatology, 60(4), 1278–1290. 10.1002/hep.27239 [PubMed: 25043274]

Wang H, Liang L, Dong Q, Huan L, He J, Li B, … He X (2018). Long noncoding RNA miR503HG, a prognostic indicator, inhibits tumor metastasis by regulating the HNRNPA2B1/NF-kappaB pathway in hepatocellular carcinoma. Theranostics, 8(10), 2814–2829. 10.7150/thno.23012 [PubMed: 29774077]

Wang H, Wu M, Lu Y, He K, Cai X, Yu X, … Teng L (2019). LncRNA MIR4435–2HG targets desmoplakin and promotes growth and metastasis of gastric cancer by activating Wnt/beta-catenin signaling. Aging (Albany NY), 11(17), 6657–6673. 10.18632/aging.102164 [PubMed: 31484163]

Wang KC, & Chang HY (2011). Molecular mechanisms of long noncoding RNAs. Molecular Cell, 43(6), 904–914. 10.1016/j.molcel.2011.08.018 [PubMed: 21925379]

Wang L, Liu D, Wu X, Zeng Y, Li L, Hou Y, … Liu Z (2018). Long non-coding RNA (LncRNA) RMST in triple-negative breast cancer (TNBC): Expression analysis and biological roles research. Journal of Cellular Physiology, 233(10), 6603–6612. 10.1002/jcp.26311 [PubMed: 29215701]

Wang S, Ke H, Zhang H, Ma Y, Ao L, Zou L, … Jiao B (2018). LncRNA MIR100HG promotes cell proliferation in triple-negative breast cancer through triplex formation with p27 loci. Cell Death & Disease, 9(8), 805. 10.1038/s41419-018-0869-2 [PubMed: 30042378]

Wang S, Zuo H, Jin J, Lv W, Xu Z, Fan Y, … Zuo B (2019). Long noncoding RNA Neat1 modulates myogenesis by recruiting Ezh2. Cell Death & Disease, 10(7), 505. 10.1038/s41419-019-1742-7 [PubMed: 31243262]

Wang W, Zhou R, Wu Y, Liu Y, Su W, Xiong W, & Zeng Z (2019). PVT1 promotes cancer progression via MicroRNAs. Frontiers in Oncology, 9, 609. 10.3389/fonc.2019.00609 [PubMed: 31380270]

Wang X, Yu H, Sun W, Kong J, Zhang L, Tang J, … Zhang H (2018). The long non-coding RNA CYTOR drives colorectal cancer progression by interacting with NCL and Sam68. Molecular Cancer, 17(1), 110. 10.1186/s12943-018-0860-7 [PubMed: 30064438]

Wang Y, Hu SB, Wang MR, Yao RW, Wu D, Yang L, & Chen LL (2018). Genome-wide screening of NEAT1 regulators reveals cross-regulation between paraspeckles and mitochondria. Nature Cell Biology, 20(10), 1145–1158. 10.1038/s41556-018-0204-2 [PubMed: 30250064]

Westholm JO, & Lai EC (2011). Mirtrons: microRNA biogenesis via splicing. Biochimie, 93(11), 1897–1904. 10.1016/j.biochi.2011.06.017 [PubMed: 21712066]

Wightman B, Ha I, & Ruvkun G (1993). Posttranscriptional regulation of the heterochronic gene lin-14 by lin-4 mediates temporal pattern formation in *C. elegans*. Cell, 75(5), 855–862. 10.1016/0092-8674(93)90530-4 [PubMed: 8252622]

Wu H, Sun S, Tu K, Gao Y, Xie B, Krainer AR, & Zhu J (2010). A splicing-independent function of SF2/ASF in microRNA processing. Molecular Cell, 38(1), 67–77. 10.1016/j.molcel.2010.02.021 [PubMed: 20385090]

Xie M, Li M, Vilborg A, Lee N, Shu MD, Yartseva V, … Steitz JA (2013). Mammalian 5′-capped microRNA precursors that generate a single microRNA. Cell, 155(7), 1568–1580. 10.1016/j.cell.2013.11.027 [PubMed: 24360278]

Xu J, Meng Q, Li X, Yang H, Xu J, Gao N, … Chen R (2019). Long noncoding RNA MIR17HG promotes colorectal cancer progression via miR-17–5p. Cancer Research, 79(19), 4882–4895. 10.1158/0008-5472.CAN-18-3880 [PubMed: 31409641]

Xu J, Shao T, Song M, Xie Y, Zhou J, Yin J, … Zhang J (2020). MIR22HG acts as a tumor suppressor via TGFbeta/SMAD signaling and facilitates immunotherapy in colorectal cancer. Molecular Cancer, 19(1), 51. 10.1186/s12943-020-01174-w [PubMed: 32127004]

Yamazaki T, Souquere S, Chujo T, Kobelke S, Chong YS, Fox AH, … Hirose T (2018). Functional domains of NEAT1 architectural lncRNA induce Paraspeckle assembly through phase separation. Molecular Cell, 70(6), 1038–1053 e1037. 10.1016/j.molcel.2018.05.019 [PubMed: 29932899]

Yang C, Li Z, Li Y, Xu R, Wang Y, Tian Y, & Chen W (2017). Long non-coding RNA NEAT1 overexpression is associated with poor prognosis in cancer patients: A systematic review and meta-analysis. Oncotarget, 8(2), 2672–2680. 10.18632/oncotarget.13737 [PubMed: 27926523]

Yang H, Liu P, Zhang J, Peng X, Lu Z, Yu S, … Chen J (2016). Long noncoding RNA MIR31HG exhibits oncogenic property in pancreatic ductal adenocarcinoma and is negatively regulated by miR-193b. Oncogene, 35(28), 3647–3657. 10.1038/onc.2015.430 [PubMed: 26549028]

Yang X, Qu S, Wang L, Zhang H, Yang Z, Wang J, … Dou K (2018). PTBP3 splicing factor promotes hepatocellular carcinoma by destroying the splicing balance of NEAT1 and pre-miR-612. Oncogene, 37(50), 6399–6413. 10.1038/s41388-018-0416-8 [PubMed: 30068940]

Ye Y, Yang S, Han Y, Sun J, Xv L, Wu L, … Ming L (2018). Linc00472 suppresses proliferation and promotes apoptosis through elevating PDCD4 expression by sponging miR-196a in colorectal cancer. Aging (Albany NY), 10(6), 1523–1533. 10.18632/aging.101488 [PubMed: 29930217]

Yeung CL, Tsang TY, Yau PL, & Kwok TT (2017). Human papillomavirus type 16 E6 suppresses microRNA-23b expression in human cervical cancer cells through DNA methylation of the host gene C9orf3. Oncotarget, 8(7), 12158–12173. 10.18632/oncotarget.14555 [PubMed: 28077801]

Yoshimura H, Matsuda Y, Yamamoto M, Kamiya S, & Ishiwata T (2018). Expression and role of long non-coding RNA H19 in carcinogenesis. Frontiers in Bioscience (Landmark Edition), 23, 614–625. 10.2741/4608 [PubMed: 28930564]

Yu X, Li Z, Zheng H, Chan MT, & Wu WK (2017). NEAT1: A novel cancer-related long non-coding RNA. Cell Proliferation, 50(2), e12329. 10.1111/cpr.12329

Yue B, Liu C, Sun H, Liu M, Song C, Cui R, … Zhong M (2018). A positive feed-forward loop between LncRNA-CYTOR and Wnt/-beta-catenin signaling promotes metastasis of colon cancer. Molecular Therapy, 26(5), 1287–1298. 10.1016/j.ymthe.2018.02.024 [PubMed: 29606502]

Zeng Y, Yi R, & Cullen BR (2005). Recognition and cleavage of primary microRNA precursors by the nuclear processing enzyme Drosha. The EMBO Journal, 24(1), 138–148. 10.1038/sj.emboj.7600491 [PubMed: 15565168]

Zhang DY, Zou XJ, Cao CH, Zhang T, Lei L, Qi XL, … Wu DH (2018). Identification and functional characterization of long non-coding RNA MIR22HG as a tumor suppressor for hepatocellular carcinoma. Theranostics, 8(14), 3751–3765. 10.7150/thno.22493 [PubMed: 30083257]

Zhang L, Zhou Y, Huang T, Cheng AS, Yu J, Kang W, & To KF (2017). The interplay of LncRNA-H19 and its binding partners in physiological process and gastric carcinogenesis. International Journal of Molecular Sciences, 18(2). 10.3390/ijms18020450

Zhang M, Zhao K, Xu X, Yang Y, Yan S, Wei P, … Zhang N (2018). A peptide encoded by circular form of LINC-PINT suppresses oncogenic transcriptional elongation in glioblastoma. Nature Communications, 9(1), 4475. 10.1038/s41467-018-06862-2

Zhang P, Cao L, Zhou R, Yang X, & Wu M (2019). The lncRNA Neat1 promotes activation of inflammasomes in macrophages. Nature Communications, 10(1), 1495. 10.1038/s41467-019-09482-6

Zhang S, Zhang G, & Liu J (2016). Long noncoding RNA PVT1 promotes cervical cancer progression through epigenetically silencing miR-200b. APMIS, 124(8), 649–658. 10.1111/apm.12555 [PubMed: 27272214]

Zhao Q, Li T, Qi J, Liu J, & Qin C (2014). The miR-545/374a cluster encoded in the Ftx lncRNA is overexpressed in HBV-related hepatocellular carcinoma and promotes tumorigenesis and tumor progression. PLoS One, 9(10), e109782. 10.1371/journal.pone.0109782 [PubMed: 25299640]

Zhao W, Ma X, Liu L, Chen Q, Liu Z, Zhang Z, … Wu J (2019). SNHG20: A vital lncRNA in multiple human cancers. Journal of Cellular Physiology, 234, 14519–14525. 10.1002/jcp.28143

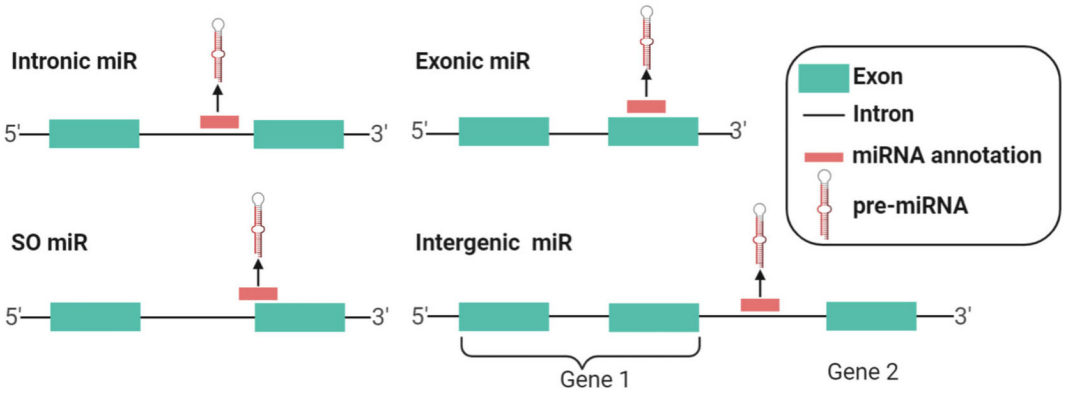

FIGURE 1.
Categorization of miRNAs with respect to their relationship with miRNA-host-genes (*MIRHG*s)

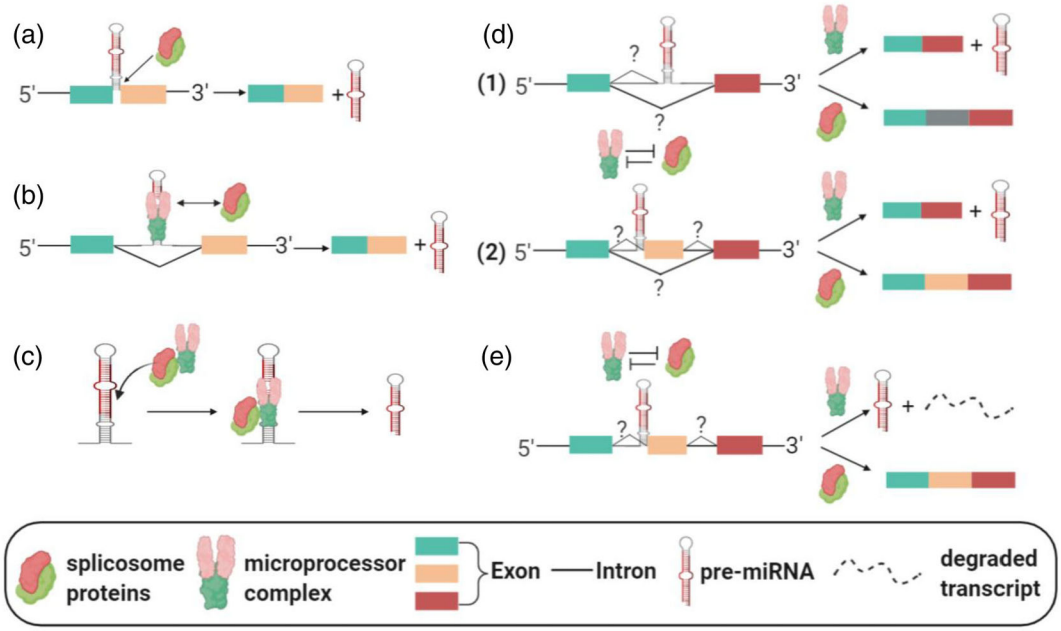

FIGURE 2.

Different models of *MIRHG* splicing and intragenic miRNA biogenesis. (a–c) Synergetic model. (a) Mirtron. (b) Splicing machinery and microprocessors facilitate each other. (c) Splicing factors facilitate miRNA production in a splicing-independent manner. (d,e) Competition model. (d) Alternative-splicing-mediated miRNA production. Two scenarios of alternative splicing are depicted. (e) Nonalternative-splicing-mediated miRNA production

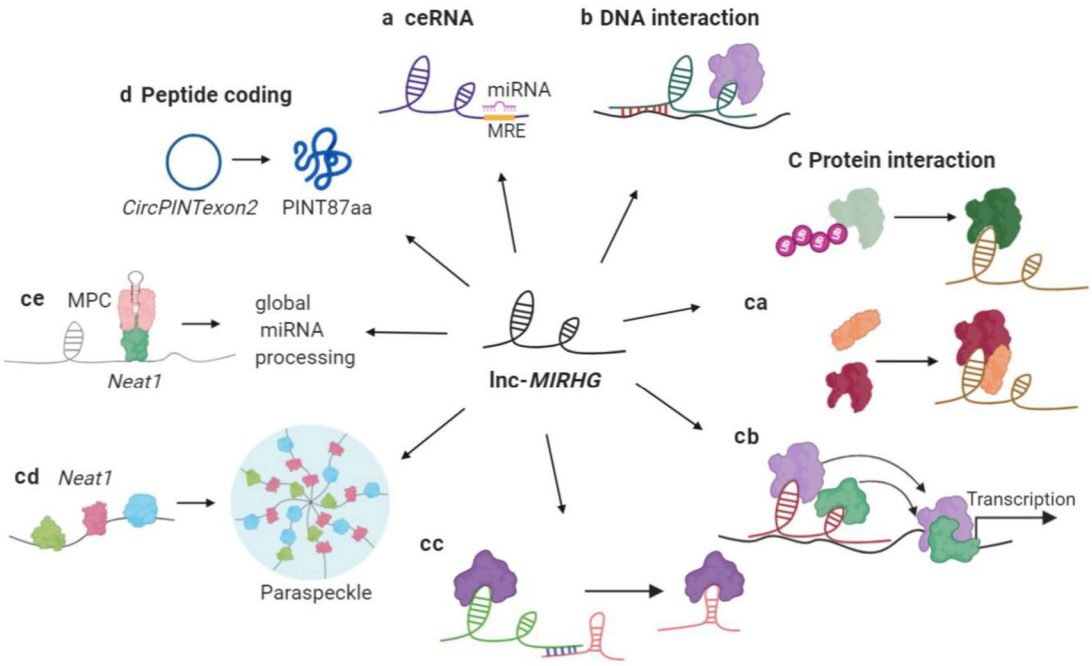

FIGURE 3.

Molecular mechanisms of lnc-*MIRHG*s. (a) ceRNA. (b) Interacting with DNA elements. (c) Interacting with proteins. (ca) Regulating the interacting protein(s). Top: stabilizing the interacting protein. Bottom: mediating protein–protein interaction. (cb) Recruiting/titrating protein factors to regulate transcription. (cc) Recruiting/titrating protein factors to regulate post-transcriptional regulation. (cd) Global regulation of primary RNA processing (*NEAT1*). (ce) Maintaining nuclear structure (*NEAT1*).(d) Peptide encoding. Example is the circular *LINC-PINT*

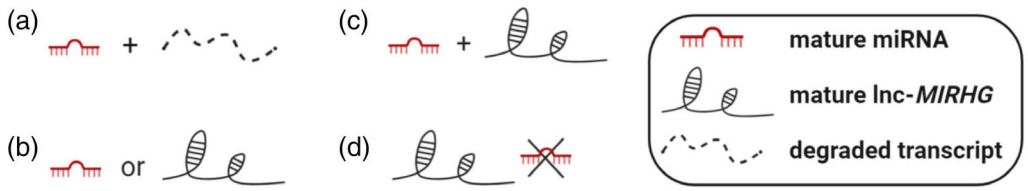

FIGURE 4.

Summary of lnc-*MIRH*G loci outcome. (a) Only generates miRNA; the lnc-*MIRH*G nascent transcript degrades quickly. (b) The loci only produces one type of ncRNA: either miRNA or lnc-*MIRH*G can be generated. (c) The loci can produce both miRNA and lnc-*MIRH*G. (d) The loci exerts low miRNA production efficiency and only produces lnc-*MIRH*G (*NEAT1* example)

TABLE 1

Number of human long noncoding RNAs (lncRNAs) in the latest releases of different databases

Database	*lncRNA* gene	lncRNA transcript	Version
GENCODE (Frankish et al., 2019)	17,952 genes	48,438	Release 33 (GRCh38.p13)
NCBI Refseq (O'Leary et al., 2016)	–	27,381	Release 109. 20200228
LNCipedia (Volders et al., 2019)	56,946	127,802	Version 5
NONCODE (S. Fang et al., 2018)	96,308	172,216	v5.0

TABLE 2

Molecular mechanisms of lnc-*MIRHG*s

Class 1: Competing endogenous RNA (ceRNA)

Lnc-*MIRHG*	Encoded miRNA	sponged_miRNA
DANCR	miR-4449	miR-33a-5p (N. Jiang, Wang, et al., 2017)
H19	miR-675	miR-106a (Imig et al., 2015), let-7 (Kallen et al., 2013), review (Raveh, Matouk, Gilon, & Hochberg, 2015; L. Zhang et al., 2017)
LINC00472	miR-30c2, -30a	miR-196a (Ye et al., 2018)
MEG3	miR-2392, -770	miR-181a (Peng et al., 2015)
MIR17HG	miR-17, -18a, -19a, -20a, -19b1, -92a1	miR-375 (Xu et al., 2019)
MIR205HG	miR-205	miR-590-3p (Di Agostino et al., 2018), miR-122-5p (Y. Li, Wang, & Huang, 2019)
MIR210HG	miR-210	miR-503 (J. Li, Wu, Wang, & Zhang, 2017; A. H. Wang et al., 2020), miR-1226-3p (X. Y. Li, Zhou, et al., 2019)
MIR22HG	miR-22	miR-141-3p (Cui, An, Li, Liu, & Liu, 2018)
MIR31HG	miR-31	miR-193b (H. Yang et al., 2016)
MIR503HG	miR-503	miR-103 (Fu et al., 2019)
NEAT1	miR-612	ceRNA (several, see review) (Dong et al., 2018; Ghafouri-Fard & Taheri, 2019)
PVT1	miR-1204, -1205, -1206, -1207	miR-143 (J. Chen et al., 2019), review (W. Wang, Zhou, et al., 2019)

Class 2: DNA binding

Lnc-*MIRHG*	Encoded miRNA	Interacting DNA elements
MIR100HG	miR-125b1, -let7a2, -100	DNA interaction (p27 promoter) (S. Wang, Ke, et al., 2018)
MIR205HG	miR-205	Alu with nearby IRF binding site (Profumo et al., 2019)

Class 3: Protein-interaction

Subclass 3.1: Directly modulating the activity of interacting protein(s)

Lnc-*MIRHG*	Encoded miRNA	Interacting protein and the corresponding impact
CYTOR/Linc00152	miR-4435-1	NCL and Sam68 (facilitate their association) (X. Wang, Yu, et al., 2018), β-catenin (blocks phosphorylation and change localization) (Yue et al., 2018)
LINC01138	miR-5087	PRMT5 (enhance stability) (Z. Li et al., 2018)
MIR22HG	miR-22	YBX1 (enhance stability) (Su et al., 2018), HuR (regulate localization) (D. Y. Zhang, Zou, et al., 2018)
MIR4435-2HG	miR-4435-2	β-Catenin (enhance stability) (Qian et al., 2018)
MIR503HG	miR-503	hnRNPA2/B1 (promote degradation) (X. Wang, Yu, et al., 2018)
NEAT1	miR-612	inflammasomes proteins (facilitate assembly) (P. Zhang, Cao, Zhou, Yang, & Wu, 2019)
PVT1	miR-1204, -1205, -1206, -1207	NPO2 (enhance stability) (F. Wang et al., 2014)

Subclass 3.2: Transcriptional regulatory effect via interacting proteins

Lnc-*MIRHG*	Encoded miRNA	Interacting protein and the effect on transcription
H19	miR-675	Several, including EZH, MBD1 (Monnier et al., 2013), hnRNPU (Raveh et al., 2015; L. Zhang et al., 2017)
LINC-PINT	miR-29b1	PRC2 (Marin-Bejar et al., 2013; Marin-Bejar et al., 2017)
MEG3	miR-2392, -770	JARID2 and EZH2 (Terashima, Tange, Ishimura, & Suzuki, 2017)
MEG8	miR-370, -379, -411, -299, -380, -1,197, -323a, -758, -329–1, -329-2, -494, -1193, -543, -495	EZH2 (Terashima, Ishimura, Wanna-Udom, & Suzuki, 2018)

MIR2052HG	miR-2052	EGR1 (Cairns et al., 2019)
MIR205HG	miR-205	Pit1, Zbtb20 (Q. Du et al., 2019), IRF (Profumo et al., 2019)
MIR210HG	miR-210	DNMT1 (Kang et al., 2019)
MIR31HG	miR-31	HIF-1α (Shih et al., 2017)
NEAT1	miR-612	EZH2 (Q. Chen, Cai, et al., 2018; S. Wang, Zuo, et al., 2019), SFPQ (Hirose et al., 2014)
PVT1	miR-1204, -1205, -1206, -1207	EZH2 (Kong et al., 2015; Wan et al., 2016; S. Zhang, Zhang, & Liu, 2016)
RMST	miR-1251, -135a2	SOX2 (Ng, Bogu, Soh, & Stanton, 2013)

Subclass 3.3: Post-transcriptional regulatory effect via interacting proteins

Lnc-*MIRHG*	**Encoded miRNA**	**Interacting protein and the corresponding impact**
H19	miR-675	KSRP (increase KSRP-RNA interaction) (Giovarelli et al., 2014)
MIR100HG	miR-125b1, -let7a2, -100	HuR (increase HuR-target RNA interaction) (Q. Sun, Hao, et al., 2018)
MIR22HG	miR-22	SMAD2 (decrease SMAD2-SMAD4 interaction) (Xu et al., 2020), HuR (decrease HuR-target RNA interaction) (D. Y. Zhang, Zou, et al., 2018)
MIR222HG	miR-221, miR-222	ILF3/ILF2 (maintains *DNM3OS* stability) (Q. Sun et al., 2020)

Subclass 3.4: Other roles via interacting proteins

Lnc-*MIRHG*	**Encoded miRNA**	**Interacting protein and corresponding impact**
NEAT1	miR-612	NONO-SFPQ (global regulation of pri-miRNA processing (L. Jiang, Shao, et al., 2017) 1, NONO and other proteins (initiates paraspeckle assembly (Yamazaki et al., 2018)

Class 4: *Lnc-MIRHGs* exerts function by producing small peptides

Lnc-*MIRHG*	**Encoded miRNA**	**Peptide information**
LINC-PINT	miR-29b1	PINT87aa encoded by *CircPINTexon2* (M. Zhang et al., 2018)

TABLE 3

Function of lnc-*MIRHG*s in different types of cancer

Lnc-*MIRHG*	Encoded miRNA	Cancer	Oncogenic (Onc) or tumor suppressor (Ts)
CCDC26	miR-3686	Childhood acute myeloid leukemia (Hirano et al., 2015), pancreatic cancer (Peng & Jiang, 2016)	Onc (Hirano et al., 2015; Peng & Jiang, 2016), Ts (Hirano et al., 2015)
CYTOR/ Linc00152	miR-4435-1	colorectal cancer (X. Wang, Yu, et al., 2018), Colon Cancer (Yue et al., 2018)	Onc
DANCR	miR-4449	Osteosarcoma (N. Jiang, Wang, et al., 2017), Colorectal Cancer (Y. Liu, Zhang, Liang, Li, & Chen, 2015)	Onc
FTX	miR-421, -374a, -374b, -545	Hepatocellular carcinoma (Z. Liu et al., 2016; Q. Zhao, Li, Qi, Liu, & Qin, 2014)	Onc
H19	miR-675	Multiple cancer (Raveh et al., 2015; Yoshimura, Matsuda, Yamamoto, Kamiya, & Ishiwata, 2018; L. Zhang et al., 2017)	Onc
LINC00472	miR-30c2, -30a	Breast cancer (Shen et al., 2015), colorectal cancer (Ye et al., 2018)	Ts
LINC01138	miR-5087	Hepatocellular carcinoma (Z. Li et al., 2018)	Onc
LINC-PINT	miR-29b1	Colorectal cancer, lung adenocarcinoma (Marin-Bejar et al., 2017), glioblastoma (circular form, peptide encoding) (M. Zhang, Zhao, et al., 2018)	Ts
MEG3	miR-2392, -770	Non-small cell lung cancer (K. H. Lu et al., 2013), gastric cancer (Peng et al., 2015)	Ts
MEG8	miR-370, -379, -411, -299, -380, -1197, -323a, -758, -329-1, -329-2, -494, -1193, -543, -495	Pancreatic cancer, lung cancer (Terashima et al., 2018)	Onc
MIR100HG	miR-125b1, -let7a2, -100	Colorectal cancer (Y. Lu et al., 2017), breast cancer (S. Wang, Ke, et al., 2018), acute megakaryoblastic leukemia (Emmrich et al., 2014), osteosarcoma (Q. Sun, Hao, et al., 2018)	Onc
MIR17HG	miR-17, -18a, -19a, -20a, -19b1, -92a1	Colorectal cancer (Xu et al., 2019)	Onc
MIR2052HG	miR-2052	Breast cancer (Cairns et al., 2019; Ingle et al., 2016)	Onc
MIR205HG	miR-205	Head and neck squamous cell carcinoma (Di Agostino et al., 2018), cervical cancer (Y. Li, Wang, & Huang, 2019)	Onc
MIR210HG	miR-210	Osteosarcoma (J. Li, Wu, et al., 2017), cervical cancer (A. H. Wang et al., 2020), breast cancer (X. Y. Li, Zhou, et al., 2019), lung cancer (Kang et al., 2019)	Onc
MIR222HG	miR-221, 222	prostate cancer (T. Sun, Du, et al., 2018)	Onc
MIR22HG	miR-22	Lung cancer (Su et al., 2018), hepatocellular carcinoma (D. Y. Zhang, Zou, et al., 2018), endometrial cancer (Cui et al., 2018), colorectal cancer (Xu et al., 2020),	Ts
MIR31HG	miR-31	Oral squamous cell carcinoma (Shih et al., 2017), lung adenocarcinoma (Qin et al., 2018), pancreatic ductal adenocarcinoma (H. Yang et al., 2016), gastric cancer (Nie et al., 2016)	Onc (Qin et al., 2018; Shih et al., 2017; H. Yang et al., 2016) Ts (Nie et al., 2016)
MIR4435-2HG	miR-4435-2	Lung cancer (Qian et al., 2018), gastric cancer (H. Wang, Wu, et al., 2019)	Onc
MIR503HG	miR-503	Hepatocellular carcinoma (H. Wang, Liang, et al., 2018), breast cancer (Fu et al., 2019), anaplastic large-cell lymphoma (Huang et al., 2018)	Onc (Huang et al., 2018), Ts (Fu et al., 2019; H. Wang, Liang, et al., 2018)

Lnc-*MIRHG*	Encoded miRNA	Cancer	Oncogenic (Onc) or tumor suppressor (Ts)
MIR99AHG/ MONC	miR-99A, -let7c, -125b2	Leukemia (Emmrich et al., 2014)	Onc
PVT1	miR-1204, -1205, -1206, -1207	Multiple cancers (J. Chen et al., 2019; Colombo, Farina, Macino, & Paci, 2015; Derderian, Orunmuyi, Olapade-Olaopa, & Ogunwobi, 2019; Kong et al., 2015; Olivero et al., 2020; Tseng et al., 2014; Wan et al., 2016; F. Wang et al., 2014; W. Wang, Zhou, et al., 2019; S. Zhang et al., 2016)	Onc and Ts
RMST	miR-1251, -135a2	Triple-negative breast cancer (L. Wang, Liu, et al., 2018)	Ts
SNHG20	miR-6516	Multiple cancers (W. Zhao et al., 2019)	Onc
NEAT1	miR-612	Multiple cancers (Dong et al., 2018; Ghafouri-Fard & Taheri, 2019)	Onc and Ts