Research progress on the interactions between long non-coding RNAs and microRNAs in human cancer (Review)

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Abstract. Numerous types of molecular mechanisms mediate the development of cancer. Non-coding RNAs (ncRNAs) are being increasingly recognized to play important role in mediating the development of diseases, including cancer. Long non-coding RNAs (lncRNAs) and microRNAs (miRNAs) are the two most widely studied ncRNAs. Thus far, lncRNAs are known to have biological roles through a variety of mechanisms, including genetic imprinting, chromatin remodeling, cell cycle control, splicing regulation, mRNA decay and translational regulation, and miRNAs regulate gene expression through the degradation of mRNAs and lncRNAs. Although ncRNAs account for a major proportion of the total RNA, the mechanisms underlying the physiological or pathological processes mediated by various types of ncRNAs, and the specific interaction mechanisms between miRNAs and lncRNAs in various physiological and pathological processes, remain largely unknown. Thus, further research in this field is required. In general, the interaction mechanisms between miRNAs and lncRNAs in human cancer have become important research topics, and the study thereof has led to the recent development of related technologies. By providing examples and descriptions, and performing chart analysis, the present study aimed to review the interaction mechanisms and research approaches for these two types of ncRNAs, as well as their roles in the occurrence and development of cancer. These details have far-reaching significance for the utilization of these molecules in the diagnosis and treatment of cancer.

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Abbreviations: ncRNA, non-coding RNA; lncRNA, long non-coding RNA; miRNA, microRNA; AGO, argonaute; RISC, RNA-induced silencing complex; 3'UTR, 3'untranslated region; 5'UTR, 5'untranslated region; ceRNA, competing endogenous RNA; MRE, microRNA response element; HAT, histone acetylation

Key words: lncRNA, miRNA, cancer, molecular mechanisms, research methods

Contents

1. Introduction

In 1993, Lee *et al* (1) discovered the first microRNA (miRNA), lin-4, which by repressing the lin-14 gene is essential for controlling the timing of *Caenorhabditis elegans* larval development. In 2000, the miRNAlet-7 was discovered to repress lin-41 to promote a later developmental transition in *C. elegans* (2). Since then, a number of evolutionarily conserved miRNAs have been identified, from plants and fungi to humans, and have been shown to play various roles in biological and pathophysiological processes. To date, thousands of studies on miRNAs using well-developed methods which are now performed routinely (3). Mature miRNAs are short, single-stranded RNA molecules,~22 nucleotides in length, processed from well-characterized precursors through a highly accurate pathway involving a fold-back hairpin structure (4). The majority of miRNA genes are located in intergenic regions; however, a small portion are located in intron and exon sequences. miRNAs function via their seed sequence (5'-end 2-8 nucleotide sequence), which is completely complementary or partially complementary to the 3'untranslated region (3'UTR), or even the coding sequence and 5'UTR, of the target gene. A ribonucleoprotein complex, named the RNA-induced silencing complex (RISC), is involved in regulating diverse biological processes, with argonaute (AGO) being the catalytic component (5). Gene silencing occurs either through RNA cleavage promotion or translational inhibition. In addition, some miRNAs do not inhibit target gene expression, but rather bind to the 5'UTR of ribosomal protein mRNA and promote ribosomal protein synthesis (6).

The discovery of long non-coding RNAs (lncRNAs) occurred earlier than that of miRNAs: The first lncRNA,

H19, was discovered by Brannan *et al* (7) in 1990. However, defining lncRNAs based simply on the size and the absence of protein-coding capability is insufficient. Thus far, miRNAs which greatly expand the functional genome from a large-scale regulatory network are well understood, while the lncRNA counterpart of the transcriptome has been relatively neglected. Nonetheless, the evolution and functions of lncRNAs have recently piqued interest among researchers due to the availability of sensitive detection techniques. lncRNAs are most commonly defined as non-protein-coding RNA molecules (>200 nucleotides) transcribed by RNA polymerase that may or may not be polyadenylated, and can be present within the nucleus or cytoplasm (8). lncRNAs share a similar conserved structure with mRNAs (9,10) and are considered sense, antisense, bidirectional, intronicor intergenic mRNAs, according to their location in the gene sequence. Some lncRNAs tend to be transcribed away from the 5' or the 3'ends of the gene and are concentrated near promoters. The initial exons and introns of these genes suggest that the transcription of these lncRNAs comprises a potential regulatory aspect (11). ncRNAs also participate in a wide variety of biological processes (12,13), such as post-transcriptional regulation (14). In general, weak conservation of lncRNAs exists due to evolution, and due to selective pressure, several local highly conserved sequences are often distributed in fragile chromosome sites. A number of studies on lncRNAs have focused on their regulation of protein-coding genes, and little is known about interactions between RNA classes. In addition, recent reports (15) suggest that lncRNAs may interact with other RNA classes, including miRNAs. Thus, non-coding RNAs (ncRNAs) are not mere evolutionary relics; rather, they provide a 'Rosetta Stone', facilitating the interpretation of much of the genomic repertoire of non-coding transcripts.

2. Interactions between lncRNAs and miRNAs

With the development of gene networks, and differential expression and pathway analyses, lncRNAs are emerging as important regulators implicated in various biological processes (16). However, our understanding of the impact of miRNA-lncRNA regulatory networks remains limited.

'*Sponge effect' of lncRNAs on miRNAs*. Competing endogenous RNAs (ceRNAs) and microRNA response elements (MREs), two important components involved in the 'sponge effect', can act in almost all interaction mechanisms as lncRNAs and miRNAs (Fig. 1). ceRNAs were first proposed by Salmena *et al* (17), who hypothesized molecular regulation patterns, such as an lncRNA that competes with a miRNA to release the inhibition of other genes; this lncRNA was called a ceRNA. Lewis *et al* (18) described more fully the concept of an MRE in 2004; an MRE (miRNA response element) is a seed region that comprises nucleotides 2-8 of the 5'portion of the miRNA and is particularly crucial for mRNA recognition and silencing or interaction with ncRNAs. Moreover, MREs and ceRNAs play an irreplaceable role in the 'sponge effect' of lncRNAs and miRNAs. The characteristics of this 'sponge effect' can be observed via the following aspects.

At present, there are two modes used to describe the 'sponge effect' of lncRNAs and miRNAs, namely complete complementary mode and partial complementary mode. miRNAs that bind to target gene sequences are partially complementary, and this process is mediated by MREs that harbor conserved target sites. In 2009, Seitz (19) proposed that miRNA-binding sites identified via bioinformatics can titrate miRNAs and thereby impair their activity. Such ceRNAs regulate MREs on their targets, and thus play an important role in post-transcriptional regulation. When the sponging effect of an lncRNA and a miRNA occurs, it is usually complete complementation. However, when an miRNA negatively controls an lncRNA, the mature lncRNA usually has a hat and a poly5-A tail, that is, a 5'UTR and a 3'UTR. Therefore, miRNAs can also have partial complementation with an lncRNA, similar to an mRNA (11).

In general, an lncRNA has multiple MREs, and the more it has, the more the lncRNAs and miRNAs communicate with each other. This has an important effect indifferent physiological and pathological conditions. For instance, lncRNA-BGL3 functions as a ceRNA for miR-17, miR-93, miR-20a, miR-20b, miR-106a and miR-106b to prevent repression of the mRNA for phosphatase and tensin homolog (20). lncRNAs that share multiple MREs will crosstalk effectively, which is also of great significance in a variety of biochemical processes (21).

Moreover, the same MREs on a ceRNA are not equal. For miRNA, all lncRNAs that do not contain an MRE will have a sponging effect with the corresponding miRNA, exhibiting a preference when several miRNAs are present at the same time (22). For instance, the lncRNA BC032469 contains elements complementary to the miR-1207-5p and miR-1266 seed regions; however, BC032469 functions as a ceRNA by impairing only miR-1207-5p-dependent target gene downregulation (23). It is proposed that the primary targets of a certain miRNA are preferentially affected, whereas the remainder are less affected Moreover, previous studies (24,25) have suggested that MREs in lncRNAs show a positional preference for the AGO binding sites in mid-regions and at the 3'ends of the lncRNAs (11). These sites harbor a possible pattern of regulatory elements across transcripts.

In addition, the overall influence of the sponging effect depends on the specific spatial-temporal distribution. For example, during embryonic development, an miRNA has been proven to be an important post-transcriptional regulator that can promote the rapid clearance of core transcription factors (TFs) during human embryonic stem cell (hESC) differentiation (26). Long intergenic non-coding RNA, regulator of reprogramming (Linc-RoR) can serve as the endogenous 'sponge' for differentiation-related miRNAs. In hESC self-renewal, Linc-RoR suppresses miRNAs at a certain stage when highly expressed or under treatment with various agents. However, in hESCs with strong differentiation ability, the relevant miRNA is highly transcribed, and Linc-RoR levels decrease. Linc-RoR is important for suppressing miRNA expression in the early stage of hESC differentiation, which may facilitate further hESC differentiation (26). Moreover, these results may provide an insight into miRNA-lncRNA interactions occurring in multiple stem cells.

In summary, the sponging effect is the basis of the molecular mechanism of the network involved in various biochemical processes mediated by miRNAs, lncRNAs and related molecules.

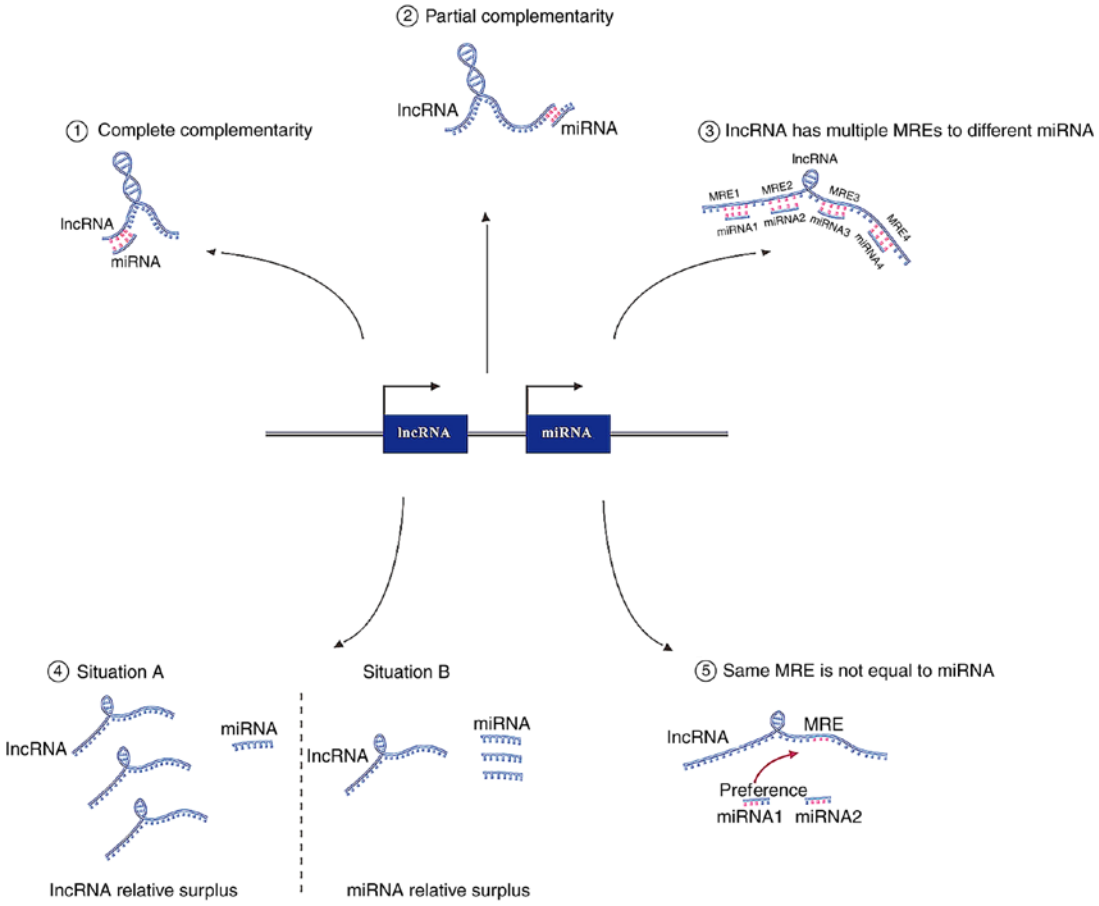

Figure 1. Different 'Sponge' effect of lncRNAs on miRNAs. (1) Complete complementarity between lncRNAs and miRNAs. (2) Partial complementarity between lncRNAs and miRNAs. (3) lncRNAs can have multiple MREs for different miRNAs. (4) The overall influence of the sponging effect depends on the specific spatial-temporal distribution. (5) For different miRNAs containing the same MRE, lncRNAs will give priority to one of these miRNAs for binding. lncRNA, long non-coding RNA; miRNA, microRNA; MRE, microRNA response element.

Main mechanisms of regulation between lncRNAs and miRNAs. There are two aspects of regulatory factors and regulatory targets: One is the regulation of lncRNAs by miRNAs, and the other is the regulation of miRNAs by lncRNAs (Fig. 2). Regarding the former, miRNAs can indirectly regulate the expression of lncRNAs. lncRNAs and miRNAs interact to form the transcriptome of regulatory networks, an interaction that is sometimes similar to an enhancer function, influencing the expression of flanking genes (27). An interesting example of the interaction between an miRNA and an lncRNA is the DLK1-MEG3 imprinted domain, which includes the tumor suppressor factor MEG3 lncRNA, and an miRNA, such as miR-29, which is involved in a number of cancer types (28). miR-29 negatively regulates DNA methylase and indirectly regulates the expression of MEG3 in liver cancer. In addition, miRNAs degrade lncRNAs in an AGO-dependent manner. Within the RISC, miRNA binds to the target lncRNA 3'UTR, leading to full mRNA degradation or blockade of the ribosomal machinery, both of which result in gene silencing (29). lncRNAs also regulate miRNAs in further ways. The most common involves lncRNA-mediated inhibition of miRNA expression via the sponging effect. lncRNAs can be used as precursors of miRNAs to directly affect miRNA regulation; some differences between the two sequences may exist (30). Guo *et al* (31) examined H19 and the product of miR-675 sequencing analysis, and found that the H19 main base is G, with miR-675 having a G or C. These two types of mature miRNA sequences are reversed inmiR-675-3p/5p, and this structure ensures the stability of the pre-miRNA stem-loop structure. Differences in nucleotide composition tend to indicate that different lengths are required for functioning. Although miR-675 and H19 belong to the ncRNA family, they exhibit different conservation and nucleotide mutation frequencies. Additionally, lncRNAs bind competitively with miRNA targets (some mRNAs), and lncRNAs compete with the 3'UTR of the target mRNA, which indirectly inhibits the negative regulation of the target mRNA by the miRNA (18,31). For example, lncRNA FEZF1-AS1 can competitively inhibit miRNA-30a, leading to Nanog silencing in breast cancer (32). lncRNAs also bind to several proteins in complex to regulate miRNA expression, such as H19, which can act on PCAF/hnRNPU/Pol RNA II and enhance the histone acetylation of the region upstream of miR-200 (33), and lncRNAs can affect the expression of miRNAs via other chromatin modifications (34).

miRNAs and lncRNAs constitute a negative feedback loop. Another important mechanism of interaction between miRNAs and lncRNAs is that they can function together to form a negative feedback regulation pathway. A relatively

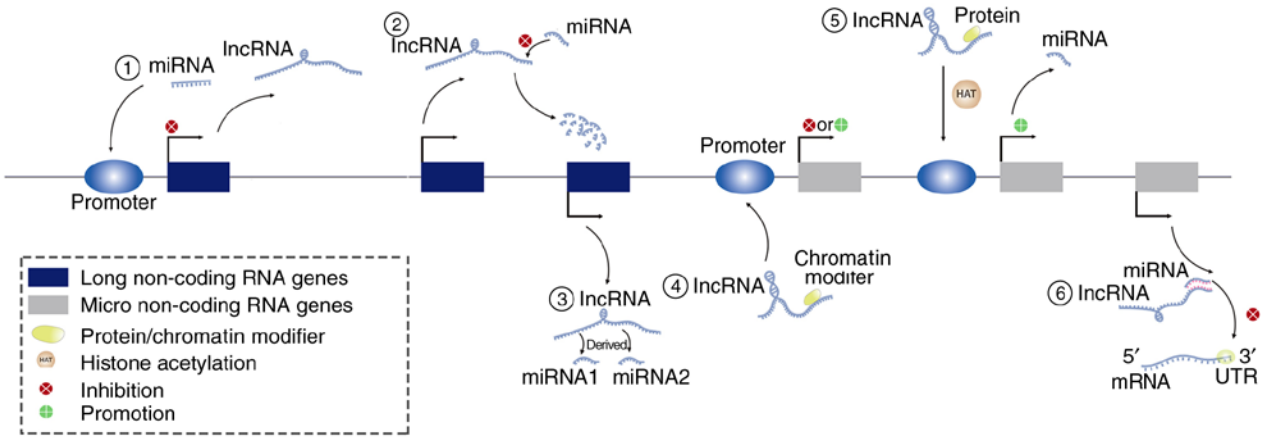

Figure 2. Main mechanisms of regulation between lncRNAs and miRNAs. (1) miRNAs can affect the expression of lncRNA genes through DNA methylation. (2) miRNAs can degrade lncRNAs in an argonaute-dependent manner. (3) lncRNAs can serve as precursors of miRNAs to directly affect the regulation of miRNAs. (4) lncRNAs can bind with some proteins to act as a complex which enhances acetylation of the upstream region of the miRNA gene. (5) lncRNA can bind with some proteins to act as a complex which regulates the expression of the miRNA gene. (6) lncRNAs can act as a sponge of miRNAs, thereby inhibiting the degradation of mRNAs targeted by miRNAs. lncRNA, long non-coding RNA; miRNA, microRNA; HAT, histone acetylation.

simple example is that miRNA-200a and histone deacetylase4 (HDAC4) can form a negative feedback regulation loop in hepatocellular carcinoma; that is, HDAC4 overexpression can inhibit miR-200a (33). Other studies have confirmed that HDAC4 overexpression also inhibits H19, indicating that H19, miR-200A and HDAC4 together constitute a negative feedback regulation loop (33,35). Another example involves the tumor formation process, whereby the enhancer of zeste homolog 2 (EZH2) gene participates in polycomb complex 2 core subunit inhibition, with epigenetic modification playing a crucial role. EZH2 has been confirmed to interact with a variety of miRNAs and has been accepted as a negative regulator of miRNAs (36). Some miRNAs can bind directly to the 3'UTR of EZH2, and EZH2 regulates miRNA expression at two transcriptional levels. By interacting with EZH2, miRNAs can affect H3K27 methylation and regulate cellular processes. Thus, miRNAs and EZH2 constitute an important regulatory and feedback pathway in which EZH2 is a stable factor. In addition, miR-26a-2 forms a negative feedback loop with miR-101 and EZH2 and is under the negative regulation of MYC and HIF-1a/1b (36,37). EZH2 inhibits cell cycle regulatory factors and the tumor suppressor gene Rap1GAP, and participates in the epithelial-mesenchymal transition process via molecules such as E-cadherin (36). Moreover, EZH2 and lncRNAs are closely related, affecting both each other and the expression of target genes. Therefore, miRNA-101, miR-26a, EZH2 and HOTAIR lncRNA also comprise a negative feedback loop (38). Furthermore, lncRNAs and related molecules can form other negative feedback loops. In addition, MIR100HG, miR-100 and miR-125b overexpression has been observed in cetuximab-resistant colorectal cancer, head and neck squamous cell cancer cell lines, as well as in tumors from patients with colorectal cancer whose disease progressed on cetuximab, and miR-100 and miR-125b have been observed to coordinately repress five Wnt/β-catenin negative regulators (mitochondrial genome maintenance exonuclease 1, Dbf4-dependent kinase 3, ring finger protein 4, cell division cycle 27 and nuclear factor, erythroid 2 like 2). These results describe a double-negative feedback loop between MIR100HG and the TF GATA binding protein 6 (GATA6): GATA6 represses MIR100HG; however, this repression is relieved through targeting of GATA6 by miR-125b, which results in increased Wnt signaling, and Wnt inhibition in cetuximab-resistant cells restores cetuximab responsiveness (39). Thus, the lncRNA MIR100HG, miR-100, miR-125b and GATA6 form a double-negative feedback loop. These examples also indicate that lncRNAs and miRNAs may be involved in the diversity of the negative feedback loop (Fig. 3).

3. Methods of research into lncRNAs and miRNAs

Databases for studying interactions between miRNAs and lncRNAs. In recent years, a number of lncRNA/miRNA-related databases have been established by researchers in combination with bioinformatics technology (Table I) (40-50). The establishment of these databases not only provides comprehensive information on various types of lncRNAs, but also a very important platform for studying the regulatory relationship between lncRNAs and miRNAs. Three representative databases (44,46,50) are discussed below. The DIANA-LncBase database (http://www.microrna.gr/LncBase) is a tool developed by the DIANA Laboratory for researchers to explore potential interactions between miRNAs and lncRNAs. The DIANA-LncBase database offers detailed information for each miRNA-lncRNA pair, such as graphical plots of the genomic location of the transcript, a representation of binding sites, lncRNA tissue expression, and MRE conservation and prediction scores. The CHIP database (http://rna.sysu.edu.cn/chipbase/) is an open database developed by Zhongshan University (Guangzhou, China). The CHIP database is mainly used for comprehensive annotation of ncRNAs, including TF binding sites and motifs, and for decoding the transcriptional regulatory networks of lncRNAs, miRNAs, other ncRNAs and protein-coding genes based on chromatin immunoprecipiation-sequencing (seq) data. By integrating experimental and predicted ncRNA-disease associations from manual literature curation and other resources under one common framework, the MNDR v2.0

Table I. Related databases for the study of interactions between miRNAs and lncRNAs.

Author, year	Database	Website	Applicable ncRNA	(Refs.)
Erdmann *et al*, 2000	Non-codingRNA database	http://biobases.ibch.poznan.pl/ncRNA	lncRNA/miRNA	(40)
Mituyama *et al*, 2009	fRNAdb	http://www.ncRNA.org/frnadb	lncRNA/miRNA	(41)
Dinger *et al*, 2009	NERD	http://jsm-research.imb.uq.edu.au/NRED	lncRNA	(42)
Amaral *et al*, 2011	lncRNAdb	http://www.lncrnadb.org/	lncRNA	(43)
Yang *et al*, 2013	ChipBase v2.0	http://rna.sysu.edu.cn/chipbase/	lncRNA/miRNA	(44)
Volders *et al*, 2013	LNCipedia	http://www.lncipedia.org	lncRNA	(45)
Paraskevopoulou *et al*, 2013	DIANA-LncBase	http://www.microrna.gr/LncBase	lncRNA/miRNA	(46)
Cook *et al*, 2011	RBPDB	http://rbpdb.ccbr.utoronto.ca/	lncRNA/miRNA	(47)
Li *et al*, 2014	lncRNABase(starBase) v2.0	http://starbase.sysu.edu.cn/	lncRNA	(48)
Hsu *et al*, 2006	miRNAMap	http://mirnamap.mbc.nctu.edu.tw	miRNA	(49)
Cui *et al*, 2018	MNDR v2.0	http://www.rna-society.org/mndr/index.html	lncRNA/miRNA	(50)

miRNA, microRNA; lncRNA, long non-coding RNA; ncRNA, non-coding RNA.

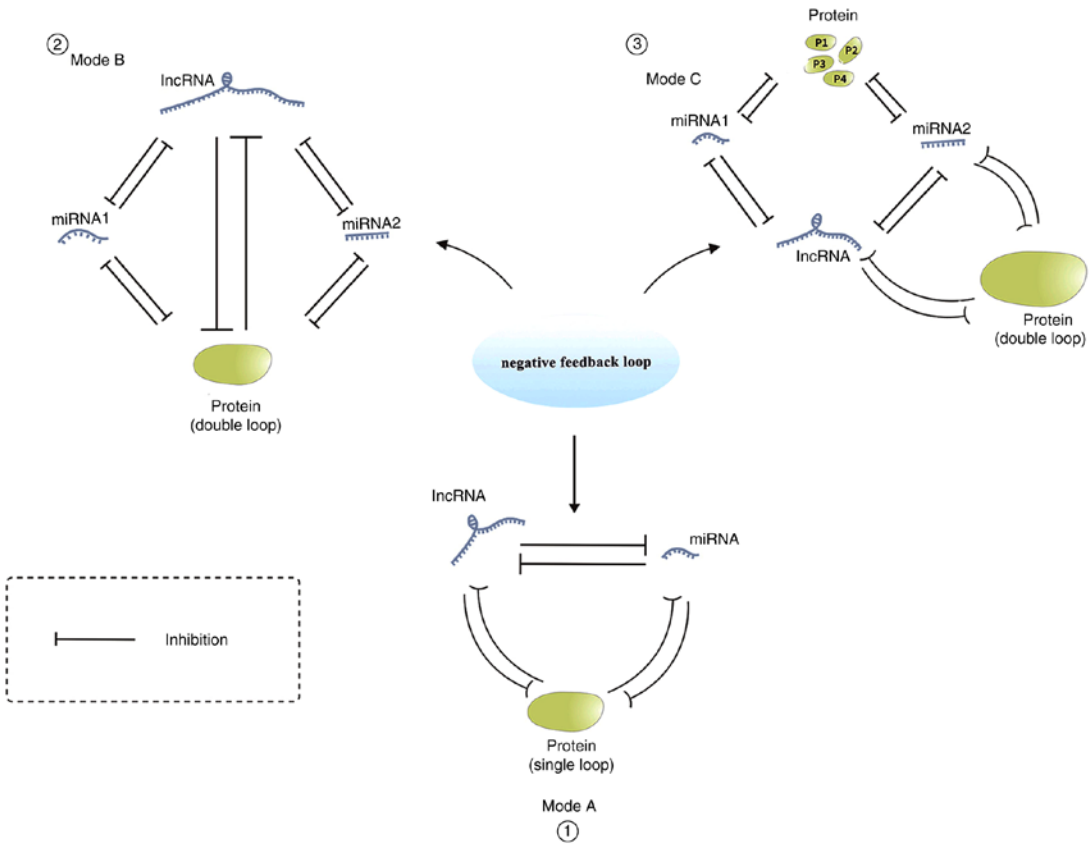

Figure 3. Three common types of negative feedback loops composed of miRNAs and lncRNAs. (1) lncRNA, miRNA and a protein constitute a single-negative feedback loop. (2) lncRNA, two miRNAs and a protein constitute a double-negative feedback loop. (3) lncRNA, two miRNAs and multiple proteins constitute a double-negative feedback loop. miRNA, microRNA; lncRNA, long non-coding RNA.

database (http://www.rna-society.org/mndr/index.html) was developed by Harbin Medical University (Harbin, China) for ncRNAs and related diseases.

Research technology for lncRNAs and miRNAs. As lncRNAs/miRNAs have various functions through numerous types of mechanisms, the establishment and application of

molecular biology research methods has a very important role in investigating lncRNA/miRNA functions (Table II). At present, there are several well-developed research methods for qualitative and quantitative analysis of ncRNAs. Microarray, RNA-seq, northern blotting, reverse transcription-quantitative polymerase chain reaction (RT-qPCR) and fluorescence *in situ* hybridization (FISH) have been used for such analyses of ncRNAs (51). Indeed, Ørom *et al* (52) observed the expression of 3,019 types of lncRNAs in a variety of human cell lines through microarray detection spectrum analysis. Using RNA-seq technology from induced pluripotent stem cells of human neurons, Lin *et al* (53) found that a number of lncRNAs are involved in the development of nervous system diseases. Northern blotting (54) and RT-qPCR (55) assays have been employed to examine the expression of ncRNAs, and to verify the authenticity of the results of microarray experiments. In addition to FISH technology, combined knockdown and localization of ncRNAs (c-KLAN) can be used to analyze the localization of non-coding RNAs in cells or tissues (56). Subcellular fractionation (57), which is a process used to separate cellular components while preserving the individual functions of each component, is has also been applied to the study of ncRNA localization. The main technologies currently being used in research into ncRNA function, in terms of silencing ncRNA gene expression, include RNA interference (RNAi; small interfering or short hairpin RNA) (48), locked nucleic acids (58) and clustered regularly interspaced short palindromic repeats (CRISPR) (59). As another approach to the study of ncRNA functions, the target ncRNA gene can be overexpressed by a plasmid or lentiviral vector, followed by the observation of changes in cell phenotype. Among these techniques, RNAi has been widely employed to examine a specific lncRNA (60), and RNA binding protein immunoprecipitation (RIP) has been widely used for examining the mechanism of ncRNA action. RIP is also used to screen proteins related to lncRNA binding. With the development of molecular biology technologies, researchers have combined RIP with microarrays to develop a new technology, RIP-Chip (61), and the combination of RIP and RNA-seq has resulted in another technology, RIP-seq (62). With regards to bioinformatics research methods for ncRNAs, numerous new approaches have been reported, such as catRAPID [fast predictions of RNA and protein interactions and domains; (63)], which is being used in the rapid prediction of RNA and protein interactions (thepredictive function can provide guidance for finding the lncRNA target). Capture long-read sequencing (CLS), a new technology for accelerating lncRNA annotation developed by the GENCODE alliance, combines targeted RNA capture with the third generation of long read sequencing. The full-length transcriptional model produced by CLS is superior to that of the existing short-reading technology, revealing the genomic features of lncRNAs, including promoter and gene structure, and protein coding potential (64). Chromatin conformation capture (3C technology) is another technology that implements quantitative or semi-quantitative methods to assess changes in the interactions between the three-dimensional structures of genomic regions (65). In recent years, 4C-seq (66), 5C-seq (67) and Hi-C (68) have been derived from next-generation sequencing. With the increase in the number of lncRNAs involved in chromatin conformation interactions, this technology is also used to study lncRNA-mediated chromatin interactions (65-68). The results of ncRNA research technology have recently aided in the development of the new technique of frozen electron microscopy, which analyzes the structure of nucleic acids (including ncRNAs/proteins and their complexes), providing a more thorough understanding of their functions (69). Moreover, the rapid amplification of cDNA ends technique is used to study the function of ncRNAs for loss-of-function studies, as well as the cellular localization of lncRNAs, starting from a known cDNA fragment and extending through the ends to obtain the complete 3'and 5'ends and, subsequently, the full-length lncRNA sequence (70). The development of new technologies in functional areas is helpful for discovering the biological functions of lncRNAs, their molecular mechanisms, and the pathological mechanisms involved in the development of tumors.

4. lncRNAs and miRNAs in cancer

Overall, miRNAs and lncRNAs have important roles in the diagnosis and treatment of cancer. Recent studies have indicated that specific lncRNAs and miRNAs related to cancer can be detected in blood and serum samples (71,72). For example, lncRNA GHET1 is overexpressed in various cancers, which can predict unfavorable survival and clinical parameters in patients (73). Recent literature has shown that miR-20a is overexpressed in colon cancer and acts as a diagnostic and prognostic biomarker (74). lncRNAs and miRNAs can also be combined for the diagnosis of cancer. Permuth *et al* (75) reported on the use of eight lncRNAs (C00472, MEG3, PANDA, PVT1, UCA1, ANRIL, GLIS3-AS1, and ADARB2-AS1) for the diagnosis of pancreatic ductal carcinoma (PDAC), and Li *et al* (76) found that miRNA1209 in the serum of patients with PDAC has a higher diagnostic accuracy than CA-199. In recent years, the mechanisms by which lncRNAs and miRNAs mediate cancer progression have been gradually studied (Table III) (77-86), and the main mechanisms involved are epigenetic regulation, transcriptional and post-transcriptional regulation, and ceRNAs. The knowledge on these mechanisms can be useful in the treatment and diagnosis of tumors. In China, ncRNAs have been used for cancer diagnosis in the form of diagnostic kits. Qadir *et al* (87) attempted to summarize the emerging field of ncRNAs and their role in different diseases, including cancer, their modes of action, and their potential in target identification and therapeutic drug development. In addition, some gene editing techniques have been used for cancer treatment, such as CRISPR. Although, at present, there is no systematic evaluation of the clinical prognosis of ncRNA-mediated tumors, more clinical diagnoses and treatments of tumors could be explored, according to the interaction mechanisms of different ncRNAs in the processes of tumorigenesis and development. It is worth noting that in recent years, some other types of ncRNA have been involved in the development of diseases including cancer, such as circular RNAs(circRNAs) and PIWI-interacting RNAs (piRNAs). circRNA is a novel form of RNA which is distinct from the traditional linear RNA. circRNA has a strong cyclic structure, species conservation and tissue specificity, and it is not readily cleaved by nucleases (88,89). piRNAs, ncRNAs of 25-33 nt in length, function by interacting with the PIWI protein (90,91). Thus, various ncRNAs involved in the regulation of the occurrence and development of cancer still need further study.

Table II.Related technology for the study of interactions between miRNAs and lncRNAs.

Author, year	Technology	Function	Significance	Applicable ncRNA	(Refs.)
Yan *et al*, 2012	Microarray	Qualitativeand quantitative research on ncRNAs	Detection spectrum analysis of lncRNAsin a variety of cell lines	lncRNA/miRNA	(51)
Yan *et al*, 2012	RNA-seq	Qualitative and quantitative research on ncRNAs	Analysis of the sequence and expression level of target ncRNAs in cells	lncRNA/miRNA	(51)
Yan *et al*, 2012	Northern blotting; RT-qPCR	Quantitative study of target ncRNA	Analysis of the expression level of ncRNAs in cells or tissues	lncRNA/miRNA	(51)
Yan *et al*, 2012	FISH	Quantitative study on the location of target ncRNA	Analysis of the location and expression level of ncRNAs in cells or tissues	lncRNA/miRNA	(51)
Chakraborty *et al*, 2012; Alberts *et al*, 2002	c-KLAN; subcellular fractionation	Study on the location of target ncRNA	Clarification on the site of action of ncRNAs	lncRNA/miRNA	(56,57)
Keene *et al*, 2006	RIP-Chip	Study on the composition of complex compound with ncRNA	Provides guidance on the changes in the expression levels of target RNA in cancer or other diseases.	lncRNA/miRNA	(61)
Bellucci *et al*, 2011	catRAPID	Predictions of RNA and fast interactions and domains	Provides positive guidance for finding ncRNA targets, and it can be used to detect the interaction between RNA and DNA/protein	lncRNA/miRNA	(63)
Lagarde *et al*, 2017	CLS	Accelerating lncRNA annotations	To articulate the genome features of lncRNAs, including promoter and gene structure, and protein coding potential	lncRNA	(64)
Olivarius *et al*, 2009	RACE	Rapidly amplifying the 5' and 3' ends of cDNA from low abundance transcripts based on PCR	To obtain the full-length lncRNA sequence for research	lncRNA	(65)
Yan *et al*, 2012; Koshkin *et al*, 1998; Zhang *et al*, 2014	RNAi/CRISPR/LNA	Interfering with the expression of ncRNA in varying degrees	Study of the function of ncRNAs by cell phenotype	lncRNA/miRNA	(51,58,59)
Tanizawa *et al*, 2012; Splinter *et al*, 2012; Dostieand Dekker, 2007; Belton *et al*, 2012	3C/4C/5C/Hi-c technology	Study on the changes in the interaction between the three dimensional structural changes between genomic regions	Used for lncRNA-mediated chromatin interaction	lncRNA	(65-68)

miRNA, microRNA; lncRNA, long non-coding RNA; ncRNA, non-coding RNA.

Table III. lncRNAs and miRNAs associated with molecular mechanisms in human cancer.

Author, year	ncRNAs	Expression		Mechanism	Outcomes	Cancer	(Refs.)
		Upregulated	Downregulated				
Yang *et al*, 2019	lncRNA00173, miRNA182-5p	miRNA182-5pl	lncRNA00173	Sponge effect	Facilitate cell proliferation, migration and apoptosis	Non-small cell lung cancer	(77)
Li *et al*, 2019	lncRNA XIST, miR-497-5p	miR-191	lncRNA XIST	Sponge effect	Facilitate cell proliferation, migration	Hepatocellular carcinoma	(78)
Zhang *et al*, 2019	miR-191	miR-191	-	Regulation of signaling pathway (axis)	Facilitate cell proliferation	Hepatocellular carcinoma	(79)
Hu *et al*, 2016	miRNA 21, lncRNA GAS5	miRNA 21	lncRNA GAS5	Transcriptional regulation	Promote cell migration and invasion	Hepatocellular carcinoma	(80)
Wu *et al*, 2015	lncRNA uc002yug.2	lncRNA uc002yug.2	-	Post-transcriptional regulation	Promote cell proliferation, migration and invasion	Esophageal cancer	(81)
Chen *et al*, 2014; Kang *et al*, 2015	lncRNA ANRIL	-	lncRNA ANRIL	Transcriptional regulation	Promote cell proliferation and anchorage-dependent growth; inhibits apoptosis	Esophageal cancer	(82,83)
Zhang *et al*, 2017	lncRNA CCAT1	lncRNA CCAT1	-	Epigenetic modification	Promote cell growth, migration, tumour occurrence	Esophageal cancer	(84)
Mazzu *et al*, 2019	miRNA 193b	miRNA 193b	-	Epigenetic modification	Facilitate prostate cancer progression	Prostate cancer	(85)
Chen *et al*, 2019	miRNA 31-5p, miRNA 223-3p	miRNA 31-5p, miRNA 223-3p	-	Post-transcriptional regulation	Promote the occurrence of colon cancer	Colitis-associated cancer	(86)

miRNA, microRNA; lncRNA, long non-coding RNA; ncRNA, non-coding RNA.

5. Conclusion

In conclusion, the mechanisms by which miRNAs and lncRNAs mediate the occurrence and development of cancer still need further exploration in order to provide broader prospects for cancer treatment. Currently, the miRNA-lncRNA interaction mechanisms are an important part of research and treatment for most cancer types. However, there are numerous challenges to be addressed, such as the safety of miRNAs for the treatment of tumors. Nonetheless, with additional research on ncRNAs in the field of cancer, it is considered likely that the specific mechanism of ncRNA-mediated tumorigenesis and development will be found, offering accurate entry points for the treatment of tumors. Therefore, exploring miRNA and lncRNA interactions could provide new breakthroughs for the clinical treatment of tumors.

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Authors' contributions

BS and CL wrote the manuscript draft. BS, CL, HL and LZ contributed to the preparation of the manuscript. ML, SL and GL revised the manuscript. BS, CL, ML conceived the design of the figures. All authors read and approved the final manuscript.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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