Review Article

The roles and mechanisms of the lncRNA-miRNA axis in the progression of esophageal cancer: a narrative review

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Background and Objective: Esophageal cancer is one of the most common malignant digestive tract tumors. Despite various treatment methods, the prognosis of patients remains unsatisfactory, largely due to an insufficient understanding of the mechanisms involved in the pathogenesis and progression of esophageal cancer. More than 98% of the nucleotide sequences in the human genome do not encode proteins, and their transcription products are noncoding RNAs (ncRNAs), mainly long noncoding RNAs (lncRNAs) and microRNAs (miRNAs). Experiments have shown that lncRNAs and miRNAs play crucial roles in the occurrence and progression of various human malignancies. These ncRNAs influence the progression of esophageal cancer through an intricate regulatory network. We herein summarized the roles and mechanisms of the lncRNA-miRNA axis in esophageal cancer cell proliferation, apoptosis, epithelial-mesenchymal transition (EMT), invasion and metastasis, drug resistance, radiotherapy resistance, and angiogenesis. This review provides a rationale for anticancer therapy that targets the lncRNA-miRNA axis in esophageal cancer.

Methods: Related articles published in the PubMed database between 05/30/2008 to 09/10/2022 were identified using the following terms: "lncRNA AND miRNA AND esophageal cancer", "lncRNA AND miRNA AND cell proliferation", "lncRNA AND miRNA AND apoptosis", "lncRNA AND miRNA AND EMT", "lncRNA AND miRNA AND invasion and metastasis", "lncRNA AND miRNA AND drug resistance", and "lncRNA AND miRNA AND radiotherapy resistance". Published articles written in English available to readers were considered.

Key Content and Findings: We summarized the roles of the lncRNA-miRNA axis in the progression of esophageal cancer, including cell proliferation, apoptosis, EMT, invasion and metastasis, drug resistance, radio resistance, and other progressions, and determined that the lncRNA-miRNA axis may serve as a potential clinical treatment target for esophageal cancer.

Conclusions: The lncRNA-miRNA axis is closely related to the progression of esophageal cancer and may act as a potential biological target for the clinical treatment of patients with esophageal cancer.

Keywords: Long noncoding RNA (lncRNA); microRNA (miRNA); sponging; esophageal cancer; malignant progression

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Introduction

Esophageal cancer is one of the most aggressive malignant tumors of the digestive system, with high morbidity and mortality, and poor prognosis. It is the 8th most common malignant tumor globally, and according to the global statistical report of the International Agency for Research on Cancer (IARC), there were 604,000 new esophageal cancer cases worldwide in 2020 (1). Despite significant research in the field of esophageal cancer, the precise causes and molecular mechanisms involved in the occurrence, development, metastasis, and recurrence of esophageal cancer, and that of treatment failure (radiotherapy and chemotherapy) remain unclear. In recent years, with the emergence and rapid development of bioinformatics, the role of long noncoding RNAs (lncRNAs) in malignant tumors has received extensive attention. Numerous studies have reported that lncRNAs are closely related to the malignant progression of esophageal cancer (2-4). MicroRNA (miRNA) is another noncoding RNA (ncRNA) that plays an essential role in the lncRNA-mediated regulation of esophageal cancer progression. Indeed, lncRNAs and miRNAs may be potential diagnostic markers and novel therapeutic targets for esophageal cancer (5).

At present, the summary of lncRNA-miRNA axis has not been reported in esophageal cancer, this article reviewed the roles and mechanisms of the lncRNA-miRNA axis in regulating the progression of esophageal cancer. We present the following article in accordance with the Narrative Review reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1449/rc).

Methods

The narrative review was conducted by searching relevant scientific literature published from 05/30/2008 to 09/10/2022 in the PubMed database. The following search terms were used: "lncRNA AND miRNA AND esophageal cancer", "lncRNA AND miRNA AND cell proliferation", "lncRNA AND miRNA AND apoptosis", "lncRNA AND miRNA AND EMT", "lncRNA AND miRNA AND invasion and metastasis", "lncRNA AND miRNA AND drug resistance", and "lncRNA AND miRNA AND radiotherapy resistance". Research articles with outcomes available to readers written in English were considered. The selection process is illustrated in *Table 1*.

Overview of lncRNAs and miRNAs

LncRNAs

LncRNAs are RNA molecules longer than 200 nucleotides that lack open reading frames and has no protein-coding function. LncRNAs are mainly transcribed by RNA polymerase II (RNA pol II) and are highly conserved in tissues and organs of the same species. Still, their expression levels vary in different developmental stages (6). Generally, lncRNA can be divided into five main types, including sense lncRNA, antisense lncRNA, bidirectional lncRNA, intronic lncRNA and intergenic lncRNA (7). LncRNAs are

Table 1 A summary of the literature search strategy

Items	Specification
Date of search	September 10, 2022
Databases and other sources searched	PubMed
Search terms used	"LncRNA AND miRNA AND esophageal cancer", "lncRNA AND miRNA AND cell proliferation", "lncRNA AND miRNA AND apoptosis", "lncRNA AND miRNA AND EMT", "lncRNA AND miRNA AND invasion and metastasis", "lncRNA AND miRNA AND drug resistance", and "lncRNA AND miRNA AND radiotherapy resistance"
Timeframe	05/30/2008–09/10/2022
Inclusion and exclusion criteria	Research articles with outcomes available to readers written in English were considered
Selection process	Two authors reviewed the full text of the relevant and sophisticated literatures to reach a consensus and discussion were conducted if necessary

LncRNA, long noncoding RNA; miRNA, microRNA; EMT, epithelial-mesenchymal transition.

long in length, with a complex spatial structure and diverse mechanism of action. It is primarily divided into the following aspects: epigenetic regulation, transcriptional regulation, and post-transcriptional regulation. In epigenetic regulation, the normal expression of downstream genes can be affected by DNA methylation (8), chromatin remodeling (9) and histone modification (10). In terms of transcription, the lncRNAs generated by the transcription of the coding gene in the promoter region can play a homeopathic role to interfere with the transcription of downstream genes, and then the transcription of genes (11). Similarly, lncRNAs can directly bind to transcription factors to reduce their activity and binding to target gene promoters, thereby affecting messenger RNA (mRNA) production (12). Post-transcriptionally, lncRNAs bind to and pair with the pre-miRNAs of miRNAs to form double-stranded complexes, which regulate the expression of target genes by affecting their splicing, nuclear transport, and degradation (13).

MiRNAs

MiRNAs are a class of evolutionarily conserved endogenous non-coding single-stranded RNA molecules containing about 19–23 nucleotides and are important regulators of gene expression. Like lncRNAs, it does not participate in the translation of proteins. The vast majority of miRNAs bind incompletely to the 3'-untranslated region (3'-UTR) site of their target gene mRNAs, inhibiting the translation process. Most mature miRNAs bind to the human protein AGO2 and can generate a gene silencing complex [RNA induced silencing complex (RISC)] (14). RISC specifically binds to the 3'-UTR of the target mRNA through the nucleotide sequence at the 5' end of the miRNA, which can prevent the translation of the target gene or directly degrade the target gene. There are also a few mature miRNAs that promote protein synthesis by binding to the 5'-UTR of ribosomal protein mRNAs instead of repressing mRNA translation (15,16).

Targeted drugs for esophageal cancer

At present, the main clinical treatments for esophageal cancer are surgical resection, chemotherapy and radiotherapy. However, the recurrence after surgery, the emergence of chemotherapeutic drug resistance, and the reduction of radiotherapy sensitivity are the main reasons for treatment failure. Targeted therapy has been proved to play an important role in the treatment of esophageal cancer.

In clinical trials, targeted drugs for esophageal cancer are mainly targeted at epidermal growth factor receptor (EGFR) pathway, human epidermal growth factor receptor 2 (HER2) pathway, and vascular endothelial growth factor (VEGF) pathway. The EGFR (also known as ERBB1) is ErbB family of receptor tyrosine kinases (RTKs), and is a transmembrane protein receptor. The drugs targeting EGFR include cetuximab (a monoclonal antibody against EGFR) (17), nimotuzumab (a recombinant human monoclonal antibody) (18), and the efficient inhibitors of EGFR, icotinib (19), and gefitinib (20). HER2 is a member of the EGFR family and a tyrosine kinase, which is involved in a variety of biological progress of tumor cells. The experiment shows that HER2/neu is highly expressed in esophageal cancer, and itraconazole (21) and trastuzumab (22) are its main targeted drugs. VEGFs play an important role in inducing the proliferation of vascular endothelial cells and the formation of new blood vessels. At present, many drugs are used to inhibit angiogenic factors, such as bevacizumab (23), ramusirumab (24), apatinib (25), sorafenib (26). In addition, according to basic and clinical experiments, there are also everolimus (27) targeting mammalian target of rapamycin (mTOR) related pathway and rilotumumab (28) targeting c-Met pathway in esophageal cancer.

These drugs can be used alone or in combination with other treatments, which can further improve the therapeutic effect of esophageal cancer and improve the prognosis of patients.

Discussion

LncRNAs and miRNAs are interconnected and work synergistically in the occurrence and progression of esophageal carcinogenesis. Specifically, they can regulate gene expression through the lncRNA-miRNA axis. We herein summarize the regulatory effects and mechanisms of the lncRNA-miRNA axis on cell proliferation, apoptosis, epithelial-mesenchymal transition (EMT), invasion and metastasis, drug resistance, radiotherapy resistance, and another progression in esophageal cancer (*Figure 1*).

The lncRNA-miRNA axis in esophageal cancer

The lncRNA-miRNA axis regulates cell proliferation

Cell proliferation is an essential process of growth and

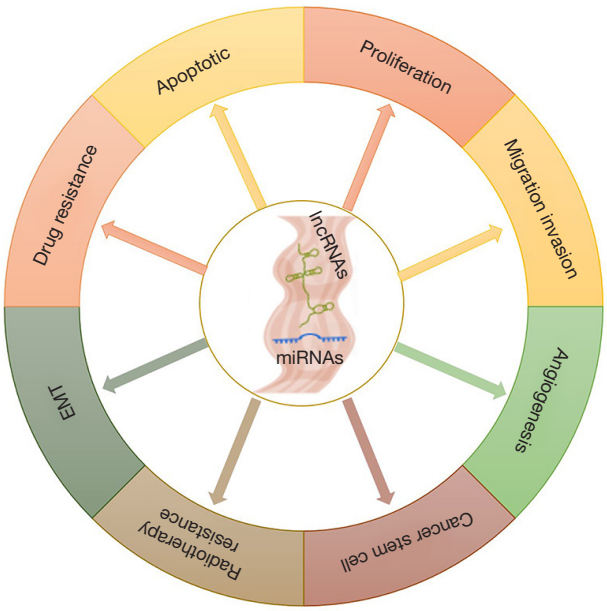

Figure 1 The role of the lncRNA-miRNA axis in regulating esophageal cancer progression. EMT, epithelial-mesenchymal transition; lncRNA, long noncoding RNA; miRNA, microRNA.

development. Due to the imbalance of the cell cycle, cancer cells in the division cycle are not controlled by the normal growth regulatory system, and caused proliferate indefinitely. Accumulating evidence suggests that the lncRNA-miRNA axis plays an important role in the regulation of cell proliferation.

Multiple studies have shown that lncRNA dysregulation is associated with the control of esophageal cancer cell proliferation. The exosomal lncRNA ZFAS1 is highly expressed in esophageal cancer tissues and promotes proliferation by up-regulating the expression of STAT3 after down-regulating the expression of miR-124. At the same time, *in vivo* experiments have showed that elevated ZFAS1 promoted tumor growth in nude mice (29). Similarly, linc00511 was significantly overexpressed in esophageal cancer tissues and enhanced the proliferation of esophageal cancer cell. Cell proliferation was reversed after transfection with miR-150-5p, indicating that linc00511 interacts with miR-150-5p to advance the proliferation of esophageal cancer cells (30). The lncRNA SNHG17 is also significantly upregulated in esophageal squamous cell carcinoma (ESCC) and acted as an endogenous "sponge" that competed with miR-338-3p to regulate the expression of SOX4. Intracellular knockdown of SNHG17 significantly inhibited the proliferation of ESCC (31). Another lncRNA, linc00467, acts as an oncogene in ESCC and is highly expressed in esophageal cancer. By binding to miR-485-5p, it negatively regulates the target protein DPAGT1. Recovery experiments found that overexpression of DPAGT1 can restore the effects of cell proliferation caused by the reduction of linc00467 (32). The lncRNA GAS5 is thought to be closely related to the progression of various cancers, and a new study demonstrated that GAS5 expression was increased in esophageal cancer cells (ECA109, TE-1, TE-3, and EC9706), and revealed that GAS5-miR-301a-CXCR4-Wnt/β-catenin/NF-κB regulatory network promotes cell proliferation, in which GAS5 acts as an endogenous sponge to regulate miR-301a expression, thereby promoting CXCR4 expression, as well as Wnt/β-catenin and NF-κB signaling inactivation of the pathway (33). In addition, the expressions of lncRNA DDX11-AS1, lncRNA FOXD2-AS1 and lncRNA DRAIC are significantly upregulated in esophageal cancer tissues and promote the proliferation of esophageal cancer cells through the DDX11-AS1/miR-514b-3p/RBX1 axis, the FOXD2-AS1/miR-145-5p/CDK6 axis, and the DRAIC/miR-149-5p/NFIB axis (34-36).

Some studies have reported that the expression of lncRNAs in esophageal cancer tissue is down-regulated and inhibit the proliferation of esophageal cancer cells. Yan *et al.* found that the expression of lncRNA HAND2-AS1 was downregulated in the tumor tissue of ESCC patients, and the overexpression of HAND2-AS1 led to the downregulation of miRNA-21 in ESCC cells and inhibited cell proliferation. Overexpression of miRNA-21 failed to affect the HAND2-AS1 expression, but significantly attenuated the inhibitory effect of HAND2-AS1 overexpression on cancer cell proliferation, suggesting that HAND2-AS1 inhibits cancer cell proliferation in ESCC by regulating miRNA-21 (37). Similarly, the lncRNA TMEM161B-AS1 is also downregulated in esophageal cancer cells, and regulates HIF1AN expression by competitively sponging miR-23a-3p, and inhibits cell proliferation through the TMEM161B-AS1/miR-23a-3p/HIF1AN axis (38). The lncRNA WDFY3-AS2 is often downregulated in ESCC tissues and cells, and its expression is linked to TNM staging, lymph node metastasis, and poor prognosis in ESCC patients. In one study, upregulation of WDFY3-AS2 significantly inhibited cell proliferation in ESCC cells. Mechanistically, WDFY3-AS2 acts on miR-2355-5p as a competing endogenous RNA (ceRNA), which further lead to the upregulation of its target gene *SOCS2*, which subsequently inhibits the JAK2/Stat5 signaling

pathway, thereby inhibiting ESCC cell proliferation (39). In another study, the lncRNA PART1 was shown to play an important role in the proliferation of ESCC, with PART1 overexpression inhibiting cell proliferation, while PART1 downregulation promoted ESCC cell proliferation. PART1 acts as a ceRNA by sponge miR-18a-5p, resulting in upregulation of the downstream target gene SOX6 and inactivation of the β-catenin/c-Myc signaling axis, thereby inhibiting ESCC cell proliferation (40).

Some lncRNA-miRNA axes also have diametrically opposite results on the proliferation of esophageal cancer cells due to different target genes. The lncRNA TUG1 functions as an oncogene in many cancers, and two studies have found that in esophageal cancer, TUG1 binds to its target miRNA-498 to regulate esophageal cancer proliferation. Jin's team found that TUG1 promoted ESCC cell proliferation *in vitro* by targeting miR-498 to upregulate XBP1. In contrast, Wang and colleagues found that TUG1 downregulated CDC42 expression by binding to miR-498 in ESCC cells, thereby inhibiting cell proliferation (41,42).

The lncRNA-miRNA axis regulates cell apoptosis

One of the main functional activities of cells is apoptosis, also known as programmed cell death. It is a process of active cell death that involves synthesizing special proteins by triggering the pre-existing death program in cells by various factors inside and outside the body (43). Related studies have reported that the lncRNA-miRNA axis plays a part in the regulation of apoptosis in esophageal cancer cells. The lncRNA PVT1 is a tumor regulator in many cancers. PVT1 binds to miR-145 and regulates its expression. In esophageal cancer tissue, FSCN1 acts as a target gene of miR-145, and downregulated PVT1 can promote the expression of miR-145 and promote apoptosis by inhibiting FSCN1. *In vivo* results also showed that silencing of lncRNA PVT1 resulted in reduced tumor growth in nude mice (44). The lncRNA NRON has been demonstrated to promote bladder cancer and inhibit liver cancer. In esophageal cancer, cisplatin promotes NRON expression, NRON overexposure reduces the expression of miR-31, suggesting that NRON regulates cisplatin-induced apoptosis by downregulating miR-31 in ESCC (45).

It has been reported that the long intergenic ncRNA linc-ROR is involved in the occurrence and development of various tumors. In esophageal cancer, upregulated linc-ROR expression inhibits apoptosis. Mechanistically, linc-ROR acts as a molecular sponge for miR-204-5p to positively regulate MDM2 expression. Meanwhile, overexpression of linc-ROR enhanced the ubiquitination level of p53, suggesting that linc-ROR regulates ESCC apoptosis by targeting miR-204-5p/MDM2 to regulate p53 ubiquitination (46). In addition, lncRNA-IUR expression is downregulated in ESCC, and low levels of IUR predict poor survival in ESCC patients. *In vitro*, IUR can act as a sponge for miR-21 to upregulate PTEN, thereby promoting ESCC apoptosis (47).

Exosomal lncRNA ZFAS1 promotes the proliferation of esophageal cancer cells and also regulate esophageal cancer apoptosis through the ZFAS1/miR-124/STAT3 axis. In esophageal cancer, increase of STAT3 and decreased of miR-124 inhibited apoptosis (29). Similarly, the linc00467/miR-485-5p axis inhibits apoptosis while promoting the proliferation of esophageal cancer cells (32).

The lncRNA-miRNA axis regulates EMT

EMT is a classic developmental phenotypic plasticity program that refers to the phenotypic transformation of epithelial cells to acquire a mesenchymal-like phenotype. This process is accompanied by the gradual loss of epithelial markers (such as E-cadherin and zonula occludens-1) and the gradual expression of mesenchymal markers (such as fibronectin, vimentin, and N-cadherin) (48). The EMT phenomenon helps tumor cells acquire the ability to invade and spread to distant sites through EMT-related transcription factors (including Snial, slug, ZEB1, and Twist) (49). LncRNAs have been confirmed to play an important role in regulation of EMT in esophageal cancer, and multiple lncRNAs function as ceRNAs, targeting miRNAs and regulating EMT in esophageal cancer.

The lncRNA HAGLR plays a crucial regulatory role in the progression and development of human cancers. Yang and colleagues demonstrated that HAGLR can competitively bind miR-143-5p, and miR-143-5p targets LAMP3. Inhibiting HAGLR results in dysregulation of miR-143-5p and increases the expression of E-cadherin, and significantly reduces the expression of LAMP3, N-cadherin, vimentin, Twist1, and Snail1. HAGLR as a ceRNA for miR-143-5p, can increase the expression of LAMP3 and promote EMT in esophageal cancer cells (50). Hypoxia induce EMT in cells, and propofol negatively regulates its expression by upregulated lncRNA TMPO-AS1, acting as a sponge for miR-498 and suppressing hypoxia-induced EMT in esophageal cancer (51). Studies have confirmed elevated expression of lncRNA linc00460 in ESCC, and wound

healing assay, transwell assay and Western blot analyses have all shown that downregulation of linc00460 significantly inhibited the EMT of ESCC. Since miR-1224-5p directly binds linc00460, decreased expression of miR-1224-5p partially eliminated the effect of linc00460 on EMT (52). In another study, *in vitro* experiments revealed that lncRNA-HOTAIR positively regulates Snail2 expression by acting as a miR-148a sponge to promote EMT and regulate the expression of marker proteins (E-cadherin, N-cadherin, and vimentin) in esophageal cancer (53).

The lncRNA DDX11-AS1 has also been shown to promote cellular EMT process *in vitro*, and mechanistically, DDX11-AS1 acts as a ceRNA to upregulate the expression of EMT-transcription factors SNAI1 and ZEB2 by sponging miR-30d-5p. Meanwhile, overexpression of DDX11-AS1 caused activation of Wnt/β-catenin signaling pathway by targeting miR-30d-5p (54). Likewise, linc00886 was downregulated after TGF-β1 treatment of cells and was involved in the EMT process by regulating EMT-related genes, especially ZEB1 and ZEB2. ELF3 is a downstream target gene of linc00886, and its expression is inhibited by linc00886 through interacting with and recruiting SIRT7 to reduce the acetylation level of H3K18 in the promoter region of ELF3. Linc00886, as a tumor suppressor gene in ESCC, promotes the EMT process through epigenetic mechanisms and the SIRT7/ELF3/miR-144 pathway (55). In addition to the above lncRNA-miRNA axis, lncRNA UCA1/miRNA-498/ZEB2 axis (56), LOC440173/miR-30d-5p/HDAC9 axis (57), and HNF1A-AS1/miR-298/TCF4 axis (58) also regulate EMT of esophageal cancer cells.

The lncRNA-miRNA axis regulates invasion and metastasis

Patients with malignant tumors have unsatisfactory prognoses due to the invasion and metastasis of tumor cells. The invasion and metastasis of tumor cells is a complex process, and the lncRNA-miRNA axis has been confirmed to play an important role in this process. The expression of lncRNA EIF3J-AS1 is altered in a variety of tumors, including esophageal carcinoma, and its expression correlated with advanced TNM stage, depth of invasion, and positive lymph node metastasis. Functional experiments showed that downregulation of EIF3J-AS1 expression inhibited esophageal cancer invasion *in vitro* and *in vivo*. Mechanistically, EIF3J-AS1/miR-373-3p/AKT1 established a ceRNA network involved in regulating cell invasion (59). Inhibition of lncRNA SNHG1 expression can inhibit cell invasion and metastasis by targeting Cdc42 by sponge miR-195 (60). In esophageal cancer, linc00963 acts as a sponge for miR-214-5p to bind to RAB14, thereby regulating its expression, Reduced of Reduced expression of linc00963 decreases cell proliferation and invasion *in vitro* through the miR-214-5p/RAB14 axis, and reduces tumor growth *in vivo* (61).

A previous investigation demonstrated that the lncRNAs EGFR-AS1 and ROCK1 are upregulated and positively correlated in ESCC, and bioinformatics analysis showed that miR-145 binds to EGFR-AS1. Furthermore, EGFR-AS1 and ROCK1 overexpression mediated ECSS cell invasion and increased mobility, whereas overexpression of miR-145 had the opposite effect and attenuated the effect of EGFR-AS1 overexpression. Therefore, EGFR-AS1 may unregulated ROCK1 by sponging miR-145 to promote ESCC cell invasion and migration (62). LncRNA NEAT1 is highly expressed in esophageal cancer and regulates cell invasion through the miR-129/CTBP2 axis (63). Linc00662 has been shown to promote cell metastasis by upregulating HOXB2 through sponging miR-340-5p. In this process, linc00662 acts as a sponge for miR-340-5p, which directly targets HOXB2, whose expression can be positively controlled by linc00662 (64).

MALAT1 is a highly conserved lncRNA. MALAT1 is highly expressed in esophageal cancer, and inhibition of MALAT1 hinders cell migration and invasion, and this change was linked to upregulation of miR-1-3p levels and inhibition of CORO1C/TPM3 activity. Moreover, the dual luciferase assay results showed that MALAT1 directly binds to the seed sequence of miR-1-3p, downregulating the levels of miR-1-3p, inducing the activity of CORO1C/TPM3 signaling, and upregulating the expression of MALAT1, suggesting a mutual relationship between MALAT1 and miR-1-3p in the invasion and metastasis of esophageal cancer cells (10,65). In addition, miR-101 and miR-217 have also been shown to affect the expression of MALAT1 and regulate cell invasion and metastasis by affecting the expression of downstream genes (*MIA2*, *HNF4G*, *ROBO1*, *CCT4*, and *CTHRC1*) (66).

In the study by Xu and colleagues, the exosomal lncRNA linc01711 was identified as a ceRNA, and elevated expression of linc01711 was detected in ESCC tissues. Linc01711 upregulated FSCN1 by inhibiting miR-326 expression promotes invasion (67). Similarly, lncRNA ROR also governs the expression of FSCN1. The expression of ROR in esophageal cancer tissue is much higher than that in adjacent healthy tissue. Experiments confirmed that

overexpression of ROR downregulates the expression of miR-145. Western blotting analysis revealed that FSCN1 is a downstream target of ROR/miR-145. ROR acts as a ceRNA for miR-145 in ESCC and promotes cell metastasis and invasion by regulating FSCN1 (68). In addition, another exosomal lncRNA ZFAS1, promotes proliferation and migration, as well as metastasis through the miR-124/STAT3 axis (29). In a recent study, quantitative real-time polymerase chain reaction (qRT-PCR) detected an increased expression of lncRNA TRPM2-AS in both esophageal cancer tissues and cell lines. Silencing TRPM2-AS by small interfering (si)RNA inhibited the migration and invasion of esophageal cancer cells while promoting expression of miR-1291, miR-6852-5p and miR-138-5p. This suggested that the upregulation of TRPM2-AS promotes invasion and metastasis by interacting with miR-1291, miR-6852-5p and miR-138-5p (69). The lncRNA TTTY15 acts as a sponge for miR-337-3p to upregulate the expression of JAK2 and promote cell metastasis (70).

Downregulation of lncRNA CAR4 has been reported to effectively inhibited invasion and migration *in vitro* and reduce tumorigenesis in nude mice *in vivo*. BCAR4 acts as a sponge for miR-181c-5p to upregulate LASP1, knockdown of BCAR4 and overexpression of miR-181c-5p inhibited the activation of STAT3/COX2 signaling, which was reversed after LASP1 overexpression (71). Xu *et al.* demonstrated that lncRNA-HOTAIR was highly expressed in esophageal cancer and acted as a miR-148a sponge to positively regulate Snail2 expression and promote EMT in cells (53). Meanwhile, Wang and colleagues discovered that miR-204 is another target of HOTAIR, and HOTAIR regulates the invasion and migration of esophageal cancer cells through the ceRNA of miR-204 (72).

The lncRNA-miRNA axis not only regulates cell proliferation, but also plays a significant role in regulating the invasion and metastasis of esophageal cancer cells. It has been reported that LncRNA WDFY3-AS2 (39), LINC00511 (30), SNHG17 (31), PART1 (40), HAND2-AS1 (37), TUG1 (41,42), FOXD2-AS1 (35), TMEM161B-AS1 (38), and GAS5 (33) be used as ceRNAs of related miRNAs to regulate the invasion and metastasis of esophageal cancer. The specific mechanisms are shown in *Table 2*.

Table 2 The lncRNA-miRNA axis in esophageal cancer

LncRNA	Expression	MiRNA	Functions	References
ZFAS1	↑	MiR-124	Enhances proliferation, invasion and migration; inhibits apoptosis	(29)
LINC00511	↑	MiR-150-5p	Enhances proliferation, migration and invasion	(30)
SNHG17	↑	MiR-338-3p	Enhances proliferation and invasion	(31)
LINC00467	↑	MiR-485-5p	Enhances proliferation; inhibits apoptosis	(32)
GAS5	↑	MiR-301a, miR-21	Enhances proliferation, migration and invasion; promotes radiotherapy resistance	(33,73)
DDX11	↑	MiR-514b-3p	Enhances proliferation, invasion	(34)
FOXD2-AS1	↑	MiR-145-5p, miR-195	Enhances proliferation, invasion; promotes drug resistance	(35,74)
DRAIC	↑	MiR-149-5p	Enhances proliferation, invasion	(36)
HAND2A-S1	↓	MiRNA-21	Inhibits proliferation, invasion and migration	(37)
TMEM161B-AS1	↓	MiR-23a-3p	Inhibits proliferation, invasion	(38)
WDFY3-AS2	↓	MiR-2355-5p	Inhibits proliferation, invasion	(39)
PART1	↓	MiR-18a-5p	Inhibits proliferation, invasion	(40)
TUG1	↑	MiR-498, miR-144-3p	Enhances proliferation, migration (XBP1); inhibits proliferation, invasion (CDC42); miR-144-3p	(41,42,75)
PVT1	↑	MiR-145, miR-128	Enhances migration and invasion; inhibits apoptosis; predicts poor prognosis	(44,76)

Table 2 (*continued*)

Table 2 (*continued*)

LncRNA	Expression	MiRNA	Functions	References
NRON	↑	MiR-31	Inhibits apoptosis	(45)
Linc-ROR	↑	MiR-204-5p	Inhibits apoptosis	(46)
IUR	↓	MiR-21	Enhances apoptosis	(47)
HAGLR	↑	MiR-143-5p	Induces EMT	(50)
TMPO-AS1	↑	MiR-498	Suppresses EMT	(51)
Linc00460	↑	MiR-1224-5p	Induces EMT	(52)
DDX11-AS1	↑	MiR-30d-5p	Induces EMT	(54)
LINC00886	↓	MiR-144	Suppresses EMT	(55)
UCA1	↑	MiRNA-498	Induces EMT; enhances proliferation, invasion	(56)
LOC440173	↑	MiR-30d-5p	Induces EMT	(57)
HNF1A-AS1	↑	MiR-298	Induces EMT; enhances stemness	(58)
EIF3J-AS1	↑	MiR-373-3p	Enhances invasion	(59)
SNHG1	↑	MiR-195	Enhances migration and invasion	(60)
LINC00963	↑	MiR-214-5p	Enhances invasion; predicts poor prognosis	(61)
EGFR-AS1	↑	MiR-145	Enhances migration and invasion	(62)
NEAT1	↑	MiR-129	Enhances invasion	(63)
LINC00662	↑	MiR-340-5p	Enhances migration	(64)
MALAT1	↑	MiR-1-3p	Enhances migration	(65)
Linc01711	↑	MiR-326	Enhances migration	(67)
ROR	↑	MiR-145	Enhances migration and invasion	(68)
TRPM2-AS	↑	MiR-1291, miR-6852-5p, miR-138-5p	Enhances migration	(69)
TTTY15	↑	MiR-337-3p	Enhances migration	(70)
CAR4	↑	MiR-181c-5p	Enhances proliferation, invasion and migration	(71)
HOTAIR	↑	MiR-148a, miR-204	Induces EMT; enhances invasion and migration	(53,72)
NORAD	↑	MiR-224-3p, miR-199a-5p	Promotes drug resistance; promotes radiotherapy resistance	(77,78)
CCAT1	↑	MiR-143	Promotes drug resistance	(79)
EMS	↑	MiR-758-3p	Promotes drug resistance	(80)
TUSC7	↓	MiR-224	Suppresses drug resistance	(81)
CCAT2	↑	MiR-145	Promotes radiotherapy resistance	(82)
HCP5	↑	MiR-216a-3p	Promotes radiotherapy resistance	(83)
LINC00473	↑	MiR-374a-5p, MiR-497-5p	Promotes radiotherapy resistance	(84,85)
SNHG16	↑	MiR-802	Enhances proliferation and self-renewal	(86)
MEG3	↓	MiR-149-3p, miR-4261	Inhibits immune escape predicts poor prognosis	(87,88)
FAM225A	↑	MiR-206	Promotes angiogenesis	(89)

↑ means upregulation; ↓ means downregulation. LncRNA, long noncoding RNA; miRNA, microRNA; EMT, epithelial-mesenchymal transition.

The lncRNA-miRNA axis regulates drug resistance

Chemotherapy is currently one of the most important means of treating malignant tumors. However, the long-term use of chemotherapeutic drugs and the changes of related mechanisms in tumor cells eventually make some malignant tumors resistant to chemotherapeutic drugs, resulting in reduced or lack of chemotherapeutic effects.

Accumulating evidence suggests that the lncRNA-miRNA axis is involved in the regulation of drug resistance in esophageal cancer cells. In one study, the expression of lncRNA NORAD in cisplatin-resistant ESCC tissues and cells was higher than that in cisplatin-sensitive tissues and cells, and NORAD expression was negatively correlated with postoperative prognosis of ESCC patients receiving cisplatin chemotherapy. The combined results of bioinformatic analysis, qRT-PCR and AGO2-RIP experiments indicated that NORAD is a sponge of miR-224-3p and promotes the nuclear accumulation of β-catenin through the NORAD/miR-224-3p/MTDH axis to promote cisplatin resistance in ESCC cells (77). Meanwhile, upregulation of lncRNA FOXD2-AS was detected in cisplatin-resistant esophageal cancer cells (TE-1/DDP), and knockdown of FOXD2-AS1 significantly inhibited Akt in cisplatin-resistant ESCC cells *in vitro*. Bioinformatic analysis and experimental validation revealed that FOXD2-AS1 regulates the Akt/mTOR axis by acting as a ceRNA for miR-195 and plays a key role in regulating cisplatin resistance in ESCC cells (74).

Recent studies have reported that lncRNA CCAT1 is highly expressed in esophageal cancer and is closely associated with drug resistance. The expression of CCAT1 was positively correlated with drug resistance, and CCAT1 knockdown and miR-143 overexpression inhibited cell resistance to cisplatin. CCAT1 enhances drug resistance of esophageal cancer cells by regulating the miR-143/PLK1/BUBR1 signaling axis *in vitro* and *in vivo* (79). Hypoxia has a significant impact on the development of drug resistance in many malignancies, including esophageal cancer. Hypoxia induces the expression of lncRNA EMS and WTAP and reduces the expression of miR-758-3p in ECA-109 cells. Furthermore, hypoxia-induced cell resistance to cisplatin required the involvement of EMS and WTAP, and overexpression of miR-758-3p reversed the resistance. Targeted knockout of EMS and WTAP significantly attenuated tumor resistance to cisplatin therapy in a xenograft mouse model. This study demonstrated the involvement of the EMS/miR-758-3p/WTAP axis in regulating hypoxia-mediated cisplatin resistance in esophageal cancer (80). In addition, Chang's study found that TUSC7 is downregulated in ESCC tissues and cells, and modulates chemoresistance to cisplatin or 5-fluorouracil (5-FU) through miR-224 regulation of the DESC1/EGFR/AKT pathway (81).

The lncRNA-miRNA axis regulates radiotherapy resistance

Radiation therapy is another important and widely used cancer regimen. Despite the successful results in the treatment of ESCC, some patients still relapse due to treatment failure. One of the reasons is radiotherapy resistance (90). LncRNAs can often enhance or limit radiosensitivity in different ways.

The lncRNA CCAT2 is aberrantly expressed in various types of malignant tumors and is considered an oncogene. In a study on esophageal cancer, CCAT2 was shown to be highly expressed in tissues and cells, and was negatively correlated with the efficacy of radiation therapy in patients with esophageal cancer. *In vitro*, X-ray treatment increased the expression of Bax/Bcl2 and active caspase three and enhanced apoptosis. Meanwhile, CCAT2 negatively regulates the expression of miR-145 and p70S6K1, and CCAT2 promotes the radioresistance of cells by negatively regulating miR-145/p70S6K1 axis (82). Guo *et al.* analyzed The Cancer Genome Atlas (TCGA) database and found that the lncRNA HCP5 was upregulated in esophageal cancer, and knockdown of HCP5 abolished radioresistance by regulating the miR-216a-3p/PDK1 axis and inhibiting AKT activation. Rescue experiments indicated that reducing miR-216a-3p expression attenuated the inhibitory effect of HCP5 knockdown on radiotherapy (83).

Overexpression of linc00473 in esophageal cancer plays a role in the radioresistance of ESCC cells. In one study, knockdown of linc00473 enhanced the sensitivity of ESCC cells to radiation *in vitro*, and mechanistically, there was mutual inhibition between linc00473 and miR-374a-5p. SPIN1 was confirmed to be a downstream target of miR-374a-5p, and linc00473 upregulated the expression of SPIN1 by negatively regulating the expression of miR-374a-5p to promote radioresistance (84). Meanwhile, another study also found that linc00473 regulates radioresistance through different targets, and linc00473 reduces radiosensitivity of ESCC cells by regulating the miR-497-5p/CDC25A axis (85).

The lncRNA NORAD regulates drug resistance and

radioresistance in esophageal cancer. NORAD promotes radioresistance in ESCC through EEPD1/ATR/Chk1 signaling and inhibition of pri-miR-199a1 processing and exosome transfer of miR-199a-5p (78). In addition, lncRNA GAS5 and TUG1 not only regulate cell proliferation, invasion and metastasis of esophageal cancer, but also participate in the regulation of radioresistance. The lncRNA GAS5 enhances cellular radiosensitivity by downregulating miR-21 and upregulating RECK expression (73). The lncRNA TUG1 enhances the radioresistance of ESCC by reducing miR-144-3p levels and modulating the MET/EGFR/AKT axis (75).

The lncRNA-miRNA axis regulates other types of cancer cell progression

In the previous section, we summarized the regulatory roles and mechanisms of the lncRNA-miRNA axis in esophageal cancer cell proliferation, apoptosis, EMT, invasion and metastasis, drug resistance and radiotherapy resistance. Recently, some studies have found that the lncRNA-miRNA axis can also regulate other types of esophageal cancer cell progression, such as stemness, immune escape and angiogenesis. A bioinformatic analysis found that lncRNAs were closely related to the stemness of esophageal cancer (91). The lncRNA HNF1A-AS1 promotes the stemness of ESCC by regulating the miR-298/TCF4 axis (58). Meanwhile, SNHG16 act as a sponge of miR-802 to upregulate PTCH1 and activate the Hedgehog pathway, thereby promoting self-renewal of esophageal cancer cells (86). LncRNA MEG3 mediates the miR-149-3p/FOXP3 axis by reducing p53 ubiquitination to suppress immune escape in esophageal cancer (87). For the regulation of angiogenesis, in one study, exosomal lncRNA FAM225A accelerated angiogenesis in esophageal squamous cell carcinoma by up-regulating NETO2 and FOXP1 expression via spongy miR-206 (89).

Conclusions

Esophageal cancer is one of the top ten malignant tumors in the world and one of the most common malignant tumors of the digestive system, with an extremely poor prognosis (92). Existing evidence indicates that ncRNAs play a central role in the regulation of gene expression in esophageal cancer and influence the various progression of esophageal cancer. The regulatory network between ncRNAs and genes is intricate, and the regulation of the lncRNA-miRNA axis is only a simple pattern in the regulatory network. Through in-depth research, various types of lncRNAs with altered expression levels have been found in various tumor tissue cells, but the expression is tissue-cell-specific. This may be related to the regulation of the corresponding miRNA expression by lncRNAs, which are competitively bound through the ceRNA mechanism, changes the expression of miRNA, thereby changing the expression of its downstream target genes, and further promotes tumor progression (93). In this review, we summarize the effects of the lncRNA-miRNA axis on the progression of esophageal cancer, including cell proliferation, apoptosis, EMT, invasion and metastasis, resistance to chemotherapy and radiotherapy, and describe the molecular mechanisms involved. This provides an exact and reliable scientific basis for a full understanding of the lncRNA-miRNA axis regulating esophageal cancer progression.

A new method of tumor treatment—ncRNA therapeutics. In recent years, therapeutic methods based on lncRNAs and miRNAs have been studied and applied in clinical research. However, only some reports have shown good efficacy. At present, the ncRNA therapeutics has the following key challenges. First, the hurdle of immunogenicity, although achievements have been made on the immunogenicity of ncRNA, it has not been completely overcome and still needs to be further resolved. Secondly, the problem of specificity. The effect of ncRNA therapeutics depends on its targeting specificity. In terms of specificity, there are mainly unexpected off target effects and unexpected on target effects, which will be the key question about specificity. Finally, it is the delivery of ncRNA. NcRNA is required to pass through the cell membrane to perform its intracellular functions. At present, many strategies have been adopted, for instance lipid nanoparticles (LNPs), polymers (synthetic or naturally based), and virus-based approaches. More effective and stable delivery methods are established in the future.

Some studies have confirmed that the lncRNA-miRNA axis be invoked as a marker of poor prognosis in patients with esophageal cancer and predict the prognosis of patients with esophageal cancer. For example, the lncRNA PVT1/miR-128/ZEB1 axis (76), the Linc00963/miR-214-5p/RAB14 axis (61), the lncRNA RMRP/miR-613/NRP2 axis, and the lncRNA MEG3-miR-4261-DKK2-Wnt/β-catenin axis (88) all predicts the poor prognosis of esophageal cancer. With the advancement of detection technology, there are more and more detection methods for lncRNA

and miRNA, with improved precision. Both miRNA and lncRNA can be detected in human body fluids as they are not degraded in the bodily fluid environment. Therefore, they may be potential biomarkers for disease diagnosis and prognosis (94-96). Further in-depth research will further clarify the role of lncRNA-miRNA axis in the occurrence, development, and prognosis of esophageal cancer. Indeed, the lncRNA-miRNA axis may be an important target for the treatment of esophageal cancer, the development of targeted drugs will provide more options for the clinical management of patients with esophageal cancer.

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