Received: 13 September 2020 | Revised: 12 December 2020 | Accepted: 2 February 2021

DOI: 10.1002/cac2.12146

CANCER COMMUNICATIONS Open Access

REVIEW

Involvement of long non-coding RNAs in the progression of esophageal cancer

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Abstract

Esophageal cancer (EC) is one of the most common malignant tumors of the digestive system with high incidence and mortality rate worldwide. Therefore, exploring the pathogenesis of EC and searching for new targeted therapies are the current research hotspot for EC treatment. Long non-coding RNAs (lncRNAs) are endogenous RNAs with more than 200 nucleotides, but without protein-coding function. In recent years, lncRNAs have gradually become the focuses in the field of non-coding RNA. Some lncRNAs have been proved to be closely related to the pathogenesis of EC. Many lncRNAs are abnormally expressed in EC and participate in many biological processes including cell proliferation, apoptosis, and metastasis by inhibiting or promoting target gene expression. LncRNAs can also regulate the progression of EC through epithelial-mesenchymal transformation (EMT), which is closely related to the occurrence, development, and

List of Abbreviations: EC, esophageal cancer; ESCC, esophageal squamous cell carcinoma; lncRNA, long non-coding RNA; HOTAIR, HOX transcript antisense RNA; MEG3, maternal expressed gene 3; UCA1, urothelial cancer associated factor 1; CASC9, cancer susceptibility candidate 9; SNHG6, small nucleolar RNA host gene 6; PVT1, plasmacytoma variant translocation 1; HOTTIP, HOXA transcript at the distal tip; UTR, untranslated region; ceRNA, competitive endogenous RNA; EZH2, enhancer of zeste homolog 2; PDCD4, programmed cell death 4; Bcl-2, B-cell lymphoma-2; mTOR, mammalian target of rapamycin; MEG3, maternally expressed gene 3; HOTTIP, HOXA transcripts at the distal tip; CDKN1A, cyclin-dependent kinase inhibitor 1A; MDM2, murine double minute 2; MMP-2, matrix metalloproteinase-2; SNHG6, small nuclear RNA host gene 6; hTERT, human telomerase reverse rranscriptase; siRNA, small interfering RNA; ZEB1, Zinc finger E-box binding homeobox-1; DNMT1, ubiquitination of DNA methyltransferase 1; WIF-1, WNT inhibitory factor 1; PRC2, polycomb repressive complex 2; EZR, ezrin; SMYD3, SET and MYND domain-containing protein 3; EMT, epithelial-mesenchymal transition; 5-FU, fluorouracil; P-gp, P-glycoprotein; MRP1, multidrug resistance protein 1; MRP2, multidrug resistance protein 2; BCRP, breast cancer resistance protein; STAT1, signal transducer and activator of transcription 1

prognosis of EC. In this article, we review and discuss the involvement of lncRNAs in the progression of EC.

KEYWORDS
apoptosis, biomarker, diagnosis, drug resistance, esophageal cancer, long non-coding RNA, metastasis, prognosis, proliferation

1 | INTRODUCTION

Esophageal cancer (EC) is one of the most common malignant tumors in the world and the fourth leading cause of all cancer deaths in China [1, 2]. In China, the main type of EC is esophageal squamous cell carcinoma (ESCC), accounting for about 90% of all cases of EC, and the remaining cases are esophageal adenocarcinoma [3]. In recent decades, EC has brought severe challenges to medical services and public health and its prevention and control has aroused widespread concern [4]. Routine treatments for EC include surgery, radiotherapy and chemotherapy. Despite advances in diagnostic techniques, the incidence and mortality of EC in China are still high, and the prognosis of a large number of patients is poor [5, 6]. The 5-year overall survival rate is still less than 30% [7], part of the reason may be related to the late diagnosis of most patients with EC [8]. Lacking of specific symptoms and effective treatment goals has created obstacles to the development of new treatment regimens and the improvement of patients' prognosis. Therefore, a deeper understanding of the molecular mechanism of EC tumorigenesis and identification of new biomarkers are essential to improve the diagnosis and treatment of EC.

The results of the Human Genome Project showed that only 2% of the RNA sequences in the normal human genome could encode proteins, most of which are transcribed into non-coding RNA, including long non-coding RNAs (lncRNAs) and microRNAs [9]. lncRNAs are a kind of non-coding RNAs whose transcriptional length is more than 200 nucleotides. lncRNAs can be divided into sense, antisense, bidirectional, intragenic, and intergenic lncRNAs according to the anatomical characteristics of gene loci. Initially, lncRNAs were regarded as a transcriptional "noise" and were not considered to have biological functions, but then found that they were involved in the regulation of protein coding genes at both transcriptional and epigenetic level [10]. Up to now, more and more evidences have shown that lncRNAs are widely expressed in most organs and tissues, and participate in various cellular biological processes, including regulating transcription and protein activity, exertion of structural or histological roles, altering RNA processing and expression regulation as precursors of microRNAs, and participating in chromosomal silencing and modification, etc., which mediate the growth of cancer cells reproductive, invasive and apoptotic processes [11–14]. HOX transcript antisense RNA (*HOTAIR*) [15], maternal expressed gene 3 (*MEG3*) [16], urothelial cancer associated factor 1 (*UCA1*) [17], cancer susceptibility candidate 9 (*CASC9*) [18], small nucleolar RNA host gene 6 (*SNHG6*) [19], plasmacytoma variant translocation 1 (*PVT1*) [20], and HOXA transcript at the distal tip (*HOTTIP*) [21] were all confirmed to be abnormally expressed in EC. Furthermore, the biological functions of lncRNAs are closely related to microRNAs. MicroRNAs are special non-coding RNA that can be widely observed in eukaryotic organisms. They are ~19-25 nucleotides in length. MicroRNAs are involved in the regulation of cell cycle, differentiation, development, metabolism and aging. At present, there are more than 2,000 specific microRNAs in the human genome. Although they do not have open reading frames and encode proteins, they can complement and pair with the base of the 3' untranslated region (UTR) of the RNA, which inhibits their translation and regulates the sequential expression of genes in organisms at the transcriptional and post-transcriptional levels, thus, exerting their biological effects [22]. Some lncRNAs can regulate the activity of microRNAs by "sponge" adsorption, thereby affecting the transcription and expression of downstream target genes and participating in the occurrence and development of malignant tumors. These lncRNAs are also known as competitive endogenous RNA (ceRNA).In recent years, some scholars have sorted out the role and application of lncRNAs in EC. Huang *et al.* [23] summarized the function of lncRNA in EC, focusing on the lncRNA-mediated regulatory mechanism that affects the biological characteristics of EC. Su *et al.* [24] focused on the regulatory mechanism of lncRNAs in EC and discussed their potential clinical applications as diagnostic and prognostic biomarkers. Yu *et al.* [25] discussed the role of competitive endogenous RNA networks in ESCC and identified several meaningful lncRNAs related to the prognosis of ESCC. These published literature articles provide basic materials and ideas for the development of this review. However, with the increasing number of studies on lncRNAs-mediated EC, it is necessary to summarize

the latest research results and further sort out and summarize them. In this review, we intend to review and discuss the involvement of lncRNAs in the progression of EC.

2 | INVOLVEMENT OF lncRNAs IN THE GROWTH OF EC

Escaping proliferation inhibition, resisting apoptosis are the most common biological characteristic of EC cells. Studies have found that abnormal expression of lncRNAs is closely related to the biological behavior of EC cells, such as proliferation, apoptosis and cell cycle abnormalities (Table 1).

2.1 | Promoting proliferation

The growth of normal cells depends on the regulation of growth factors, but EC cells can maintain their ability to continue to proliferate with little or no growth factors, Chen *et al.* [26] found that the expression of lncRNA SBF2-AS1 was significantly up-regulated in ESCC cells, and the proliferation ability of ESCC was significantly reduced after silencing lncRNA SBF2-AS1. Therefore, lncRNA SBF2-AS1 is considered as a new biomarker in ESCC and potential therapeutic target. Liu *et al.* [27] found that lncRNA DUXAP8 can promote the proliferation of EC cells and may be an important regulator of EC. In order to determine the biological role of lncRNA DLX6-AS1 in ESCC cells, Tian *et al.* [28] carried out *in vitro* functional loss experiments. The transfection of lncRNA DLX6-AS1 targeting oligonucleotides (si-dlx6-as1) was found to hinder the expression of lncRNA DLX6-AS1 in EC9706 and KYSE-520 cells Compared with negative control group, cell counting kit-8 (CCK-8) assay and colony formation analysis showed that the silencing of lncRNA DLX6-AS1 could significantly inhibit the proliferation of ESCC cells and reduce the number of colony formation, respectively. These results suggested that lncRNA DLX6-AS1 could accelerate the proliferation of ESCC cells *in vitro*, suggesting that lncRNA DLX6-AS played an important role in ESCC. Wu *et al.* [18] demonstrated that lncRNA CASC9 promoted the proliferation of EC cells by recruiting enhancer of zeste homolog 2 (*EZH2*) and subsequently changes H3K27me3 level to negatively regulate programmed cell death 4 (*PDCD4*) expression for the first time. As carcinogenic genes, lncRNA SBF2-AS1, lncRNA DUXAP8, lncRNA DLX6-AS1 and lncRNA CASC9 may be biomarker with diagnostic or prognostic value in ESCC.

2.2 | Inhibiting proliferation

LncRNA LET, also known as NPTN intron transcript 1, is 2606 nucleotides in length and located on chromosome 15q24.1. As the latest identified lncRNA, lncRNA LET is under-expressed in several cancers and used as a tumor inhibitor [29, 30]. Chen *et al.* [31] investigated the expression, clinical significance and biological role of microRNAs-548k and lncRNA LET in ESCC. Bioinformatics analyses and cell experiments showed that lncRNA LET could inhibit the proliferation of ESCC cells, was a direct target of microRNA-548k, and mediated the carcinogenic effect of microRNA-548k in ESCC. These data indicated that the regulation axis of microRNA-LET could be used as a potential biomarker and therapeutic target in ESCC.

2.3 | Inhibiting apoptosis

Apoptosis is a process of cell death caused by endogenous and exogenous factors triggering the intracellular death program. The infinite growth of EC cells is related to the inhibition of apoptosis, so the apoptosis disorder is closely related to the occurrence of EC. Fan *et al.* [32] confirmed that lncRNA SNHG6 significantly inhibited ESCC apoptosis. The overexpression of lncRNA PLncRNA-1 was related to the stage of advanced tumors and lymph node metastasis, and it could be a potential prognostic marker and therapeutic target of ESCC. Wang *et al.* [33] confirmed that lncRNA PLncRNA-1 could inhibit the apoptosis of ESCC cells. In a study by Tian *et al.* [28], the authors examined the expression and biological role of lncRNA DLX6-AS1 in EC and found that the down-regulation of DLX6-AS1 could accelerate the apoptosis of ESCC cells and affect the expression of apoptosis-related protein B-cell lymphoma-2 (*Bcl-2*). Moreover, bioinformatics predictions showed that DLX6-AS1 had a binding site of microRNA-99a/100, while microRNA-99a/100 had a mammalian target of rapamycin (*mTOR*) targeting site. Another study confirmed that microRNA-99a/100 promoted apoptosis by targeting *mTOR* in human ESCC. [34]. Yoon *et al.* [35] reported that lncRNA LUCAT1 promoted tumorigenesis by controlling ubiquitination and stability of DNA methyltransferase 1 in ESCC. In conclusion, these data suggested that lncRNA DLX6-AS1 and lncRNA lucat1 acted as an oncogene by inhibiting the apoptosis of EC cells.

2.4 | Inducing apoptosis

Contrary to lncRNA and lncRNA LUCAT1, some lncRNAs can induce apoptosis in EC. Huang *et al.* [36] detected the

TABLE 1 The expression status, functions, molecular mechanisms, and clinic-pathological and prognosis correlations of lncRNA in EC

LncRNA	Pathological type	Sample type	Expression level	Function	Molecular mechanism	Clinic-pathological correlation	Prognosis correlation	Reference
91H	ESCC	Cell, Tissue	↓	Inhibit invasion	Associate with *H19* methylation and inhibit *IGF2* expression	Negatively correlate with depth of invasion, neoplastic grading and TNM	Positive correlation	[59]
AFAP1-AS1	EAC, ESCC	Cell, Tissue	↑	Promote proliferation, growth, invasion, migration and chemoradiotherapy resistance; inhibit apoptosis	NA	Positively correlate with lymph node metastasis, distant metastasis, advanced clinical stage and response to radiotherapy	Negative correlation	[51, 60]
AK001796	ESCC	Cell,Tissue	↑	Promote growth, influence cell cycle	Rregulate *MDM2/p53* signal pathway	NA	NA	[40]
ATB	ESCC	Cell, Tissue	↑	Promote proliferation and migration	Dysregulate miR-200b/K2 signaling	NA	Negative correlation	[42, 61]
BC032469	ESCC	Cell, Tissue	↑	Promote proliferation, migration, and invasion; influence cell cycle; inhibit apoptosis.	Regulate *HTERT* expression	Positively correlate with lymph node metastasis, TNM stage and tumor size	Negative correlation	[38]
BC200	ESCC	Tissue	↑	NA	NA	NA	Negative correlation	[62]
BDNF-AS	EC	Cell, Tissue	↓	Inhibit proliferation, migration, invasion, EMT	Target miR-214	NA	NA	[63]
CASC2	ESCC	Cell	↓	Enhance antitumor activity of cisplatin	Inhibiting miR-181a	NA	NA	[17]

(Continues)

TABLE 1 (Continued)

LncRNA	Pathological type	Sample type	Expression level	Function	Molecular mechanism	Clinic-pathological correlation	Prognosis correlation	Reference
CASC9	ESCC	Cell, Tissue	↑	Promote proliferation, migration, invasion; influence cell cycle; inhibit apoptosis	Modulate expression levels of EMT markers; negatively regulate *PDCD4* expression	Positively correlate with tumor size, tumor stage, lymph nodes metastasis, and clinical stage	Negative correlation	[18, 41, 62, 64-66]
CCAT1	ESCC	Cell	↑	Promote proliferation, migration and adhesion	Regulate miR-7/*HOXB13* axis	NA	NA	[67]
CCAT2	ESCC	Tissue	↑	NA	NA	Correlate with lymph node metastasis, advanced TNM stages	Negative correlation	[68]
CDKN2B-AS1	EC	Cell	↑	Promote proliferation	Inhibit *HTERT* expression	NA	NA	[69]
DANCR	ESCC, EC	Cell, Tissue	↑	Promote proliferation, migration, invasion; inhibit apoptosis	NA	NA	NA	[70]
DUXAP8	EC	Cell,Tissue	↑	Promote proliferation, invasion	NA	NA	NA	[27]
ECM	ESCC	Cell, Tissue	↑	Promote invasion and metastasis	Regulate *ICAM-1*	Positively correlate with lymph node metastasis	NA	[48, 71]
ENST00000508406.1	ESCC	Tissue	↑	NA	NA	Positively correlate with TNM stages	NA	[72]
ESCCAL-1	ESCC	Tissue	↑	Promote invasion; inhibit apoptosis	NA	NA	NA	[43, 64]
EZR-AS1	ESCC	Cell, Tissue	↑	Promote migration	Upregulate *EZR* expression by causing *SMYD3* Redistribution	NA	NA	[44]
FAM201A	ESCC	Tissue	↑	Reduce radiosensitivity	Regulate *ATM* and *mTOR* Expression via miR-101	NA	Negative correlation	[73]

(Continues)

TABLE 1 (Continued)

LncRNA	Pathological type	Sample type	Expression level	Function	Molecular mechanism	Clinic-pathological correlation	Prognosis correlation	Reference
FOXCUT	ESCC	Cell, Tissue	↑	Promote proliferation, Colony formation, migration, invasion	Modulate *FOXC1*	Positively correlate with poor Differentiation, advanced lymph node classification and metastasis	Negative Correlation	[74]
GAS5	ESCC	Tissue, Serum	↓	Inhibit proliferation, migration and invasion	Inactivate the *PI3K/PKB/mTOR* pathway; feedback loop between *GAS5* and the interferon signaling pathway; induce cell cycle arrest at G2/M stage; Influence the expression of EMT-associated proteins	Positively correlate with stage of primary tumor	NA	[39-41, 75-77]
H19	ESCC, EC	Cell, Tissue	↑	Promote proliferation and metastasis	Regulate G0/G1 phase and epithelial marker; induce EMT	Positively correlate with tumor depth, clinical stage and lymph node metastasis	Negative correlation	[48, 78]
HNF1A-AS1	ESCC, EAC	Cell, Tissue	↑	Promote growth, proliferation, metastasis migration, invasion and angiogenesis; inhibit cell apoptosis	Sponge miR-214 to upregulate the expression of *SOX-4*; modulate chromatin and nucleosome assembly	NA	NA	[30, 31, 79, 80]

(Continues)

TABLE 1 (Continued)

LncRNA	Pathological type	Sample type	Expression level	Function	Molecular mechanism	Clinic-pathological correlation	Prognosis correlation	Reference
HOTAIR	EC, ESCC	Cell,Tissue, Serum	↑	Promote proliferation, invasion, migration and EMT; reduce radioresistance	Regulate miR-125/*HK2* and miR-143/*HK2* axis, miR-148a/*Snail2* axis, miR-1/*CCND1* axis; mediate gene regulation; inhibit *WIF-1* expression and activate *WNT* pathway	Positively correlate with TNM stage	Negative correlation	[32-37, 43, 81–86]
HOTTIP	ESCC	tissue, cell	↑	promote proliferation, Migration and invasion	Induce EMT	NA	NA	[21]
LET	ESCC	Tissue,Cell	↓	Inhibit migration and invasion; promote apoptosis	regulate *p53* expression	Positively correlate with clinical features	NA	[87]
LINC00173	ESCC	Cell	↓	Inhibit proliferation and cell cycle	NA	NA	NA	[88]
linc00460	ESCC, EC	Cell, Tissue	↑	Promote growth, proliferation; inhibit Apoptosis	NA	Positively correlate with TNM stage, lymph node metastasis	Negative correlation	[27, 45, 46, 89]
LINC01234	EC	Cell	↑	Promote proliferation, migration and invasion, inhibit apoptosis	NA	NA	NA	[90]
LINC01296	ESCC	Cell,Tissue	↑	Promote proliferation, colony formation, migration and invasion	Suppress *KLF2* expression via interacting *EZH2*	Positively correlate with TNM stage, lymph node metastasis	Negative correlation	[91]
LINC01419	ESCC	Cell,Tissue	↑	Promote proliferation, inhibit apoptosis, reduce sensitivity to 5-FU	Promote *GSTP1* methylation	NA	NA	[86]

(Continues)

TABLE 1 (Continued)

LncRNA	Pathological type	Sample type	Expression level	Function	Molecular mechanism	Clinic-pathological correlation	Prognosis correlation	Reference
LINC01503	ESCC	Cell, Tissue	↑	Promote proliferation, colony formation, migration and invasion	Activate *ERK* signaling via MAPK and increase *AKT* signaling	NA	NA	[92]
LncRNA625	ESCC	Cell,Tissue	↑	Promote proliferation, Invasion, migration	Upregulate oncogenes and downregulate tumor Suppressor genes	Positively correlate with clinical stages, lymph node metastasis	Negative correlation	[93]
LOC285194	ESCC	Tissue	↓	Reduce chemoradiotherapy resistance	NA	Positively correlate with tumor size, TNM stage, lymph node metastases and distant Metastases	NA	[54]
MALAT1	ESCC	Tissue, Cell	↑	Promote proliferation, cell cycle, migration and Invasion	Upregulate *p21* and *p27* expression, Posttranscriptional regulation	Positively correlate with clinical stages, primary tumor size, and lymph node Metastasis	Negative correlation	[39, 94, 95]
NEAT1	ESCC	Tissue, Cell	↑	Promote proliferation, foci formation, viability, migration, and invasion	Regulate miR-129/*CTBP2* axis	Positively correlate with tumor size, lymph node metastasis and clinical stage	Negative correlation	[47, 48, 96, 97]
NMR	ESCC	Tissue, Cell	↑	Promote migration and invasion; inhibit apoptosis; Increase drug resistance	Interact with *BPTF* and recruits it to chromatin, Upregulate expression of *MMP-3* and *MMP-10* via *ERK1/2* activation	Positively correlate tumor metastasis	Negative correlation	[98]
NR_037652.1	ESCC	Tissue	↑	NA	NA	Positively correlate with TNM stage	NA	[72]

(Continues)

TABLE 1 (Continued)

LncRNA	Pathological type	Sample type	Expression level	Function	Molecular mechanism	Clinic-pathological correlation	Prognosis correlation	Reference
PART1	ESCC	Cell	↑	Reduce gefitinib resistance	Through miR-129/*Bcl-2* pathway	NA	NA	[57]
PAX9	ESCC	Tissue	↓	NA	NA	NA	positive correlation	[99]
PCAT-1	ESCC	Tissue	↑	NA	NA	Positively correlate with clinical stage, tumor invasion, lymph node metastasis	Negative correlation	[100]
POU5F1B	EC	Cell	↑	Reduce radiosensitivity	NA	NA	NA	[101]
PVT1	EC	Cell	↑	Promote invasion and metastasis	Induce EMT by regulating expression of *EMT* markers	Positively correlate with tumor stage and metastasis	NA	[20]
SBF2-AS1	ESCC	Tissue, Cell	↑	Promote proliferation and invasion	Bind with *PRC2* and guide *PRC2* to the promoter of *CDKN1A* and decrease *CDKN1A* expression	Positively correlate with tumor size and TNM stage	NA	[26, 49]
SNHG1	ESCC	Tissue, Cell	↑	Promote proliferation, invasion and EMT	Down-regulate E-cadherin and up-regulate Vimentin and N-cadherin	Positively correlate with TNM stage, depth of invasion, lymph node metastasis	NA	[102]
SNHG6	ESCC	Tissue, Cell	↑	Promote proliferation, migration and invasion	NA	Positively correlate with TNM stage, lymph node metastasis, distant metastasis	Negative correlation	[102, 103]

(Continues)

TABLE 1 (Continued)

LncRNA	Pathological type	Sample type	Expression level	Function	Molecular mechanism	Clinic-pathological correlation	Prognosis correlation	Reference
SOX2OT	ESCC	Tissue, Cell	↑	Promote growth, proliferation; antagonize Effect of DDP	NA	NA	NA	[38, 104]
SPRY4-IT1	ESCC	Tissue, Cell	↑	Promote growth, proliferation, invasiveness and migration	NA	Positively correlate with clinical stage	Negative correlation	[105]
TTN-AS1	ESCC	Cell,Tissue	↑	Promote proliferation and Metastasis	Promote expression of Snail1 by binding miR-133b, result in EMT cascade, induce *FSCN1* expression by sponging miR-133b and regulate of mRNA-stabilizing protein	NA	Negative correlation	[49]
TUG1	ESCC	Tissue, Cell	↑	Promote cisplatin resistance	NA	NA	Negative correlation	[44]
TUSC2P	ESCC	Tissue	↓	Inhibit proliferation, invasion; promote apoptosis	Alter expression of *TUSC2*	NA	Positive correlation	[106]
TUSC7	ESCC	Cell, Tissue	↓	Inhibit proliferation, colony formation; promote apoptosis and chemotherapy Resistance	Downregulate miR-224	NA	Positive correlation	[107]
UCA1	ESCC, EC	Cell,Tissue	↑	Promote proliferation, migration and invasion	Regulate miR-204/*Sox4* axis	Positively correlate with clinical stage	Negative correlation	[16, 21, 50, 51, 108, 109]
ZEB1-AS1	ESCC	Tissue	↑	NA	NA	Positively correlate with tumor grade, invasion depth and lymph node metastasis	Negative correlation	[110]

Abbreviations: lncRNA, long non-coding RNA; ESCC, esophageal squamous cell carcinoma; EC, esophageal cancer; EAC, esophageal adenocarcinoma; NA, not available; ↑, upregulation; ↓, downregulation; EMT, epithelial–mesenchymal transition; 5-FU, fluorouracil; DDP, cisplatin.

expression level of lncRNA MEG3 in 28 cases of ESCC and adjacent tissues, and found that the expression of maternally expressed gene 3 (*MEG*3) in cancer tissues was significantly reduced. Further studies showed that *MEG3* could induce the apoptosis of cancer cells. Lv *et al.* [37] reported that the expression of lncRNA MEG3 was down-regulated in ESCC, which could activate p53 and induce the apoptosis of cancer cells. It can be seen that lncRNA MEG3 is involved in regulating the apoptosis of EC cells.

2.5 | Affecting cell cycle

Abnormal regulation of tumor cell proliferation is the result of disordered control of cell cycle correction points. This disorder is secondary to abnormalities in genes that regulate cell cycle correction points or mutations or abnormal expression of oncogenes or tumor suppressor genes that encode proteins in the transmembrane signal transduction pathway that control cell proliferation. Lu *et al.* [38] reported that the knockout of lncRNA BC032469 in TE13 and ECA109 cells could induce cell cycle arrest at the G0/G1 phase. Cell cycle analysis showed that inhibiting the expression of lncRNA CASC9 resulted in cell cycle arrest in G1 phase of cancer cells KYSE450 and KYSE150 and decrease in the proportion of S phase cells [18]. In view of the fact that lncRNA MALAT1 significantly promotes ESCC cell growth *in vitro* and *in vivo*, Hu *et al.* [39] confirmed that inhibiting lncRNA MALAT1 might activate *ATM-CHK2* pathway in EC cells and ultimately led to G2/M stagnation in EC. There are growing evidence that HOXA transcripts at the distal tip (*HOTTIP*) of the 5'end are dysfunctional in various cancers. Chen *et al.* [26] found that lncRNA SBF2-AS1 could be related to the cell cycle of EC and could affect the G2 phase transition of ECA109 cells through reducing the expression of cyclin-dependent kinase inhibitor 1A (*CDKN1A*). It can be seen from the above research that lncRNAs mediate the abnormal cycle of EC cells.

3 | THE INVOLVEMENT OF lncRNAs IN THE INVASION AND METASTASIS OF EC

3.1 | Promoting invasion and metastasis

Tumor cell invasion and metastasis is a complex process, which is affected by many factors, such as microenvironment, host cells, genes, signal molecules and so on. Liu *et al.* [40] found that lncRNA AK001797 could regulate ESCC cell growth and cell cycle by activating murine double minute 2 (*MDM2*)/p53 signal, significantly increased the proportion of S-phase ESCC cells and reduced the proportion of G2/M phase ESCC cells. Pan *et al.* [41] studied the expression and function of lncRNA CASC9 in ESCC. They found that the expression of lncRNA CASC9 was significantly up-regulated in ESCC tissues. In addition, the knockout of lncRNA CASC9 significantly inhibited the migration and invasion of ESCC cells, suggesting that lncRNA CASC9 might be a new marker of poor prognosis of EC and a potential therapeutic target for intervention of EC. Tian *et al.* [28] conducted the experiments to explore the effect of lncRNA DLX6-AS1 on the invasion of ESCC cells. Transwell invasion experiment showed that the number of invasive cells in the lncRNA DLX6-AS1 knockout group was lower than that in the control group in ESCC cell lines (EC9706 and KYSE-520). Western blot analysis showed that the levels of *mTOR*, *Bcl-2* and matrix metalloproteinase-2 (*MMP-2*) in ESCC cell lines were lower than those in the control group. Therefore, these data suggested that lncRNA DLX6-AS1 could promote the invasion of ESCC cells. In order to study the biological function of lncRNA SNHG6 in ESCC, Zhang *et al.* [19] introduced si-SNHG6 into EC109 and EC1 cells to inhibit the expression of lncRNA SNHG6. The results showed that the expression of small nuclear RNA host gene 6 (*SNHG6*) significantly decreased after transfection with si-SNHG6-1 and si-SNHG6-2. The silencing efficiency in EC109 was 75.4% and 77.3%, respectively, and in EC1 was 80.8% and 79.4%, respectively. The transwell assay result showed that lncRNA SNHG6 could enhance the migration ability of EC109 and EC1 cells. Compared with the si-NC group, the numbers of migrating cells in the si-SNHG6-1 and si-SNHG6-2 groups were significantly decreased. At the same time, compared with the si-NC group, the invasive ability of the si-SNHG6-1 and si-SNHG6-2 groups was significantly inhibited. These results suggested that lncRNA SNHG6 might play a carcinogenic role in ESCC. Lu *et al.* [38] used real-time quantitative reverse transcription-polymerase chain reaction to detect the specific differential expression of lncRNA BC032469 in ESCC and evaluated the role of lncRNA BC032469 in the occurrence and development of EC by silencing and overexpressing lncRNA *in vitro* and *in vivo*. The results showed that the expression level of lncRNA BC032469 in ESCC was higher than that in corresponding non-cancerous tissues, while knockout of low lncRNA BC032469 inhibited the migration and invasion of EC cells. Western blotting analysis showed that lncRNA BC032469 could regulate the expression of human telomerase reverse transcriptase (*hTERT*), which is very important for cell invasion and metastasis. In addition, the restored expression of *hTERT* protein could weaken the inhibition of lncRNA BC032469 on ESCC cells. In conclusion, these results showed that lncRNA-BC032469 was a carcinogenic lncRNA that promoted cancer progression. Yoon *et al.* [35] transfected KYSE-30 cells and HCE-4 cells

with si-LUCAT1, and then determined wound healing and invasion. It was noteworthy that si-LUCAT1 significantly inhibited wound closure compared with cells transfected with si-NC. The invasion of KYSE-30 cells and HCE-4 cells was also significantly reduced by transfection with lncRNA LUCAT1 small interfering RNA (si-LUCAT1). These effects of LUCAT1 siRNA were significantly blocked by pcDNA-LUCAT1 transfection. Meanwhile, transfection of si-LUCAT1 reduced the expression of *N-cadherin*, *snail* and Zinc finger E-box binding homeobox-1 (*ZEB1*), while the expression of *E-cadherin* increased. Overexpression of lncRNA LUCAT1 could reverse these changes suggesting that lncRNA LUCAT1 was involved in the invasion and migration of EC cells. Further studies have shown that this was related to the ubiquitination of DNA methyltransferase 1 (*DNMT1*) regulated by lncRNA LUCAT1.

LncRNA HOTAIR is a 2158 NT long lncRNA in the human genome. It is located between HoxC11 and HoxC12 genes on chromosome 12 and regulates the *Hox* gene family [42]. It has been reported that lncRNA HOTAIR can also inhibit the expression of WNT inhibitory factor 1 (*WIF-1*) in ESCC by binding with polycomb repressive complex 2 (*PRC2*) complex, and then activate histone and *Wnt/β-catenin* pathways in H3K27 promoter region [43]. Chen *et al*. [15] also reported that the expression of lncRNA HOTAIR was significantly higher in EC than in adjacent non-cancerous tissues band multivariate analysis showed that the expression of lncRNA HOTAIR was an independent prognostic factor for lymph node metastasis. It can be seen from the above that lncRNA AK001797, lncRNA CASC9, lncRNA DLX6-AS1 and other lncRNAs promote the invasion and metastasis of EC cells through different mechanisms.

3.2 | Inhibiting invasion and metastasis

Metastasis and spread are one of the reasons why EC is difficult to cure, and certain lncRNAs can effectively inhibit the invasion and metastasis of EC cells. Zhang *et al*. [44] showed that antisense lncRNA EZR-AS1 was positively correlated with ezrin (*EZR*) expression in ESCC tissues and cell lines. LncRNA EZR-AS1 promotes cell migration by up-regulating *EZR* expression. In mechanism, antisense lncRNA EZR-AS1 forms a complex with RNA polymerase II to activate *EZR* transcription. In addition, lncRNA EZR-AS1 can also recruit SET and MYND domain-containing protein 3 (*SMYD3*) to binding sites in GC-rich regions downstream of *EZR* promoter to promote their binding. The interaction between lncRNA EZR-AS1 and SMYD3 can further enhance the transcription and expression of *EZR*, suggesting that lncRNA EZR-AS1, as a member of RNA polymerase complex, plays an important role in inhibiting the invasion of EC cells by inhibiting *SMYD3*-dependent *H3K4* methylation. These results showed that lncRNAs inhibited EC cells invasion and metastasis through affecting related gene expression.

3.3 | Epithelial-mesenchymal transition (EMT)

EMT plays an important role in the invasion of various types of cancer by transforming adherent and polarized epithelial cells into invasive and active mesenchymal cells [45]. Transcription factors, such as *Twist* and *Snail* in EMT, can increase the expression level of interstitial markers and decrease the expression of epithelial markers. The rupture of tight junctions can lead to the loss of epithelial markers and the acquisition of mesenchymal markers [46].The expression level of lncRNA FAL1 in ESCC cell lines was found to increase abnormally. Knockout of lncRNA FAL1 inhibited cell invasion and EMT by affecting related genes, while overexpression of lncRNA FAL1 had the opposite effect, suggesting that lncRNA FAL1 could promote the invasion of EC cells [47]. Huang *et al*. [48] found that lncRNA H19 might be involved in the regulation of EMT marker expression in EC cell lines. Lin *et al*. [49] studied the role of lncRNA HOTTIP in ESCC and observed that lncRNA HOTTIP was up-regulated in ESCC and promoted cell metastasis *in vivo* and *in vitro*. Interestingly, as a molecular sponge, lncRNA HOTTIP has the binding site of microRNA-30b, which can regulate the level of microRNA-30b in nucleus and cytoplasm, thus mediating the inhibition of HOXA13. In addition, lncRNA HOTTIP upregulates *Snail* 1 through competitively binding to microRNA-30b, and then promotes EMT and invasion. Therefore, one of the pathways of lncRNAs mediated the development of EC is to affect the EMT process.

4 | THE INVOLVEMENT OF lncRNAs IN THE DRUG RESISTANCE OF EC

Chemoradiotherapy is an important method for the treatment of EC. However, with the prolongation of treatment time, EC cells could become less sensitive to chemoradiotherapy, and even develop resistance to drugs or radiotherapy schemes. This phenomenon is called drug resistance, including primary and acquired resistance, is one of the most difficult and complex problems in the treatment of malignant tumors.Lin *et al*. [50] reported that lncRNA LINC0261 could induce the chemosensitivity of EC cells to fluorouracil (5-FU) by regulating methylation-dependent inhibition of dihydropyrimidine dehydrogenase in human EC. But there are many other studies have confirmed that

most of the lncRNA could enhance the resistance of EC to radiotherapy and chemotherapy. Zhou *et al*. [51] reported that the expression of lncRNAs AFAP1-AS1, UCA1 and HOTAIR in cisplatin -resistant EC cells was imbalanced compared with their parent cells. Jiang *et al*. [52] found that the expression level of lncRNA TUG1 in ESCC tissues was significantly higher than that of matched adjacent normal tissues, and the high expression of lncRNA TUG1 was significantly correlated with chemotherapy resistance. Subsequent survival analysis showed that the prognosis of patients with high expression of lncRNA TUG1 was poor, especially for well-differentiated and moderate, ulcerative, small size and chemo-sensitive tumors. Compared with normal adjacent tissues, the expression of lncRNA PCAT-1 was higher in EC, especially in secondary EC. Overexpression of lncRNA PCAT-1 could increase the proliferation rate and growth of EC cells, and reduce the chemical sensitivity of cells to cisplatin, which showed that lncRNA PCAT-1 promoted the development of EC and inhibited the sensitivity of EC to cisplatin [53]. Tong *et al*. [54] used quantitative real-time polymerase chain reaction to detect the expression of lncRNA LOC285194 in biopsy specimens and matched normal tissues of ESCC patients who underwent surgery or resection after preoperative radiotherapy. Then, the relationship between the expression of lncRNA LOC285194 and clinicopathological features and prognosis was analyzed. The data showed that the expression of lncRNA LOC285194 in ESCC tumors was significantly lower than that in adjacent normal tissues. The complete remission rate was 57% in the group with high expression of lncRNA LOC285194 and 15% in the group with low expression of lncRNA LOC285194. Univariate analyses showed that low expression of lncRNA LOC285194 was significantly correlated with the response to radiotherapy and chemotherapy. In addition, Kaplan-Meier survival analysis showed that the disease-free survival rate and overall survival rate of patients with low expression of lncRNA LOC285194 decreased. Multivariate analysis further confirmed that the low expression of lncRNA LOC285194 was an independent prognostic factor for chemoradiotherapy. Drug transporter-mediated drug resistance is one of the mechanisms of drug resistance. Excitatory transporters are highly expressed in most drug-resistant cells, such as P-glycoprotein (*P-gp*), multidrug resistance protein 1 (*MRP1*), multidrug resistance protein 2 (*MRP2*), breast cancer resistance protein (*BCRP*) and more. They can excrete different kinds of chemotherapeutic drugs from cells, resulting in the reduction of intracellular drug concentration, thereby reducing the toxicity of drugs to cancer cells [55, 56]. At present, resistance to gefitinib and other anti-tyrosine kinase inhibitors has become a major obstacle to improve the clinical prognosis of patients with advanced metastasis of ESCC. Although lncRNA can regulate the biological behavior of EC cells, the role of lncRNA on drug efflux transporters in cells has not been fully elucidated. Therefore, Kang *et al*. [57] studied the potential role of LncRNA in the formation of chemoresistance in human EC. They found that compared with parental ESCC cells, LncRNA PART1 up-regulated signal transducer and activator of transcription 1 (*STAT1*) in gefitinib-resistant cells, in which *STAT1* could bind to the promoter region of lncRNA PART1, leading to its activation. Inhibition of lncRNA PART1 effectively promotes gefitinib-induced cell death, while increase of lncRNA PART1 promotes gefitinib resistance and *Bcl-2* expression in EC cells by competitive binding to microRNA-129[57]. In addition, extracellular lncRNA PART1 was shown to incorporate exosomes and enhance the resistance of other cells to gefitinib. Chen *et al*. [58] found that the high expression of lncRNA VLDLR and lncRNA ABCG2 genes affected the formation of drug resistance in EC. Extracellular vesicles released by drug-resistant cells can up-regulate the expression of lncRNA ABCG2 in EC cells, thus regulating the drug resistance of EC cells. These results suggested that the abnormal expression of lncRNAs was associated with chemosensitivity of EC and may be helpful to predict the poor prognosis of EC.

5 | CONCLUSION

In conclusion, the abnormal expressions of lncRNAs affect the proliferation, apoptosis, invasion, metastasis, and drug resistance of EC cells through related genes or signaling pathways, which provides new approaches for the diagnosis, targeted therapy and evaluation of therapeutic effect of EC (Table 1). However, the research on lncRNA is still lacking in depth. With the continuous application of new technologies, the understanding of the mechanism of lncRNAs in EC will become more and more complete and accurate. Just as lncRNAS play multiple roles in EC, lncRNAs are expected to become a new diagnostic, drug resistance and prognostic indicator of EC.

DECLARATIONS

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

COMPETING INTERESTS

The authors declare that they have no competing interests.

FUNDING

This study was supported by the Natural Science Foundation of Henan Province of China (202300410460); Henan Province Medical Science and Technology Research Project Joint Construction Project (Grant No. LHGJ20190003, LHGJ20190055); the National Natural Science Foundation of China (Grant No. 31670895).

AUTHORS' CONTRIBUTIONS

WHX, YYZ and ZBS contributed substantially to the conception of the review. WHX, LFL and ZJZ searched for document materials and extract information. WHX, WBW, YKZ and ZRF wrote the original draft. JZ, QCK and YKZ revised the manuscript. All authors read and approved the final manuscript.

ACKNOWLEDGEMENTS

Not applicable.

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How to cite this article: Xue W, Zheng Y, Shen Z, et al. Involvement of long non-coding RNAs in the progression of esophageal cancer. *Cancer Commun*. 2021;1-18. https://doi.org/10.1002/cac2.12146