Non-coding RNA: A promising diagnostic biomarker and therapeutic target for esophageal squamous cell carcinoma (Review)

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Abstract. Esophageal cancer (EC) is a common form of malignant tumor in the digestive system that is classified into two types: Esophageal squamous cell carcinomas (ESCC) and esophageal adenocarcinoma. ESCC is known for its early onset of symptoms, which can be difficult to identify, as well as its rapid progression and tendency to develop drug resistance to chemotherapy and radiotherapy. These factors contribute to the high incidence of disease and low cure rate. Therefore, a diagnostic biomarker and therapeutic target need to be identified for ESCC. Non-coding RNAs (ncRNAs) are a class of molecules that are transcribed from DNA but do not encode proteins. Initially, ncRNAs were considered to be non-functional segments generated during transcription. However, with advancements in high-throughput sequencing technologies in recent years, ncRNAs have been associated with poor prognosis, drug resistance and progression of ESCC. The present study provides a comprehensive overview of the biogenesis, characteristics and functions of ncRNAs, particularly focusing on microRNA, long ncRNAs and circular RNAs. Furthermore, the ncRNAs that could potentially be used as diagnostic biomarkers and therapeutic targets for ESCC are summarized to highlight their application value and prospects in ESCC.

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Contents

1. Introduction

Esophageal cancer (EC), which can be divided into esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC), is a common malignancy of the digestive tract (1). In 2020, ~604,000 new cases were reported and ~544,000 EC-associated mortalities were reported worldwide (2). EAC occurs mostly in North America and Western Europe, while ESCC occurs mostly in China (3,4). ESCC is usually caused by smoking, alcohol intake, poor diet, viral infection or genetic factors (5). Surgical resection, chemotherapy and radiotherapy are the primary therapeutic strategies of ESCC. Since ESCC is mostly asymptomatic in the early stages, patients often miss the optimal therapeutic opportunity (6). In addition, the therapy for ESCC is often ineffective due to metastasis and medication resistance (7). Therefore, the identification of promising diagnostic biomarkers and the development of effective therapeutic strategies are crucial in combatting ESCC.

Non-coding RNAs (ncRNAs) encompass a range of types of RNA, with microRNAs (miRNAs/miRs), long ncRNAs (lncRNAs) and circular RNAs (circRNAs) being the most well-known. They are transcribed from DNA but lack the ability to encode proteins and were previously considered to be 'transcriptional waste' (8-10). However, with the advent of high-throughput sequencing technology, recent research has revealed that ncRNAs constitute >90% of the human genome (11). By contrast, protein-coding genes make up <2% of the genome (12-14).

NcRNAs are widely involved in various cellular processes, such as cell proliferation, differentiation, aging, apoptosis and immune responses (15-18). Furthermore, extensive research has highlighted the significant dysregulation of expression of numerous ncRNAs in ESCC cells and tissues. This dysregulation is closely linked to ESCC progression, drug resistance and unfavorable patient prognosis (19-22). The present review provides a comprehensive overview of the functions of miRNAs, lncRNAs and circRNAs in ESCC, and investigates their roles as diagnostic biomarkers and potential therapeutic targets for ESCC treatment. This information highlights novel ideas and strategies for the early diagnosis and potential therapeutic targets for ESCC.

2. Characteristics of ncRNAs

The generation of ncRNAs is a multifaceted and intricate process that involves several sequential stages. In the subsequent sections, we provide a comprehensive and detailed explanation of the formation mechanisms that underlie miRNAs, lncRNAs and circRNAs (Fig. 1).

Characteristics of miRNAs. MiRNAs are a category of endogenous and highly conserved small ncRNAs that consist of ~22 nucleotides (23,24). Processing involves two stages. In the first stage, RNA polymerase II catalyzes DNA fragments in the nucleus to produce primary miRNA (pri-miRNA) (25); subsequently, a microprocessor complex, consisting of Drosha, an RNase type III protein and DiGeorge syndrome critical region gene 8, recognizes and cleaves the stem strand on the pri-miRNA hairpin to form pre-miRNA (26). Thereafter, Ran guanosine triphosphate-Exportin 5 facilitates pre-miRNA transfers from the nucleus to the cytoplasm (27,28). In the second stage, a mature double-stranded miRNA is generated after pre-miRNA is identified by Dicer with trans-activation response RNA-binding protein/protein activator of the interferon-induced protein kinase (28,29). The stem-loop structure is then cleaved and modified in the cytoplasm (30,31). The guide strand attaches to the RNA-induced silencing complex and targets the 3'-untranslated Region (3'-UTR) of the mRNA via base complementary pairing when the mature miRNA unwinds (32). The passenger strand is degraded in the cytoplasm (33). Complete base-pair complementation between miRNA and mRNA then causes cleavage of mRNA. An incomplete match can inhibit protein translation of mRNA, which is the most common mode of action of miRNA (34-37).

Characteristics of lncRNAs. LncRNAs are a particular subtype of ncRNAs that are longer than 200 nucleotides and are produced by RNA polymerase II or RNA polymerase III (38,39). They are composed of multiple exons and have a structure similar to mRNA. However, lncRNA transcripts have fewer exons, lower overall expression levels and poorer sequence conservation compared with mRNA (40,41). LncRNAs can be divided into six types: i + ii) Bidirectional and intergenic lncRNAs; iii) sense and iv) antisense exonic lncRNAs; and v) sense and vi) antisense intronic lncRNAs, and they are able to regulate different stages of transcription (42,43).

In pre-transcription, lncRNAs participate in the regulation of histone acetylation and DNA methylation (44,45). They also play a regulatory role during transcription (46). In addition, lncRNAs are directly involved in post-transcriptional regulation of mRNA. Some lncRNAs that contain miRNA complementary sites can change the effect of miRNA by binding to the mRNA via a competing endogenous RNA (ceRNA) mechanism (47). LncRNAs can also regulate RNA editing (48). It is clear that lncRNAs have multiple functions and are crucial for the control of transcription.

Characteristics of circRNAs. CircRNAs are covalently closed, single-stranded ncRNAs formed by back-splicing of precursor mRNA (pre-mRNA) (49). CircRNAs lack 5' caps and 3' poly (A) tails and are classified into three types: i) Exonic circRNAs (EciRNA); ii) intronic circRNAs (ciRNA); and iii) exon-intron circRNAs (EIciRNA) (50,51). They are highly conserved, diverse and widely expressed in different cells and tissues at various stages of development (52-54). The closed-loop structure and the absence of a 5' cap or 3' poly (A) tail in circRNAs also make them less susceptible to exonuclease R compared with linear RNA (55).

CircRNAs can competitively bind to proteins, serving as miRNA decoys or protein scaffolds (56). EciRNAs can control the levels of targeted genes by acting as miRNA sponges, due to their numerous miRNA binding sites in the cytoplasm (57,58). CiRNAs and EIciRNAs have few binding sites with miRNA in the nucleus; however, they can regulate gene transcription in the nucleus (59-61). Moreover, some circRNAs contain extensive N6-methyladenosine (m6A) modification sites and can translate proteins after m6A modification (62). Studies have shown that a single m6A site is sufficient to drive the initiation of translation (63,64). This m6A-driven translation requires the involvement of eukaryotic translation initiation factor 4 gamma 2 (eIF4G2) and m6A reader YTH m6A RNA binding protein (YTHDF)3. It is also enhanced by methyltransferase like 3/14 methyltransferase, inhibited by fat mass and obesity-associated protein (FTO) demethylase and upregulated upon heat shock (65,66). Insulin-like growth factor 2 mRNA-binding protein 1 facilitates circMAP3K4 peptide translation and then promotes hepatocellular carcinoma progression, which is driven by m6A modification (67). In addition, accumulating evidence suggests that several circRNAs are related to polysomes, and they contain an AUG initiation codon and putative open reading frames of optimal length (65,68). This indicates an unexpected potential for protein coding by these circRNAs.

3. Role of ncRNAs in ESCC

The pathogenesis of ESCC involves dysregulation, activation, inactivation and mutation of multiple genes, with the exact mechanisms still not fully understood (69). Recent studies emphasize the critical role of ncRNAs in ESCC development (70-72) (Fig. 2). Cui *et al* (73) revealed that m6A-mediated epigenetic modification of lncRNA is closely associated with ESCC tumorigenesis. The FTO m6A demethylase can mediate the demethylation of lncRNA LINC00022 in a YTHDF2-dependent manner, promoting its accumulation in cells. Elevated levels of LINC00022 can bind specifically to the p21 protein and promote its ubiquitination-mediated degradation, thereby upregulating the levels of cyclin dependent kinase 2 and cyclin E1 proteins (73).

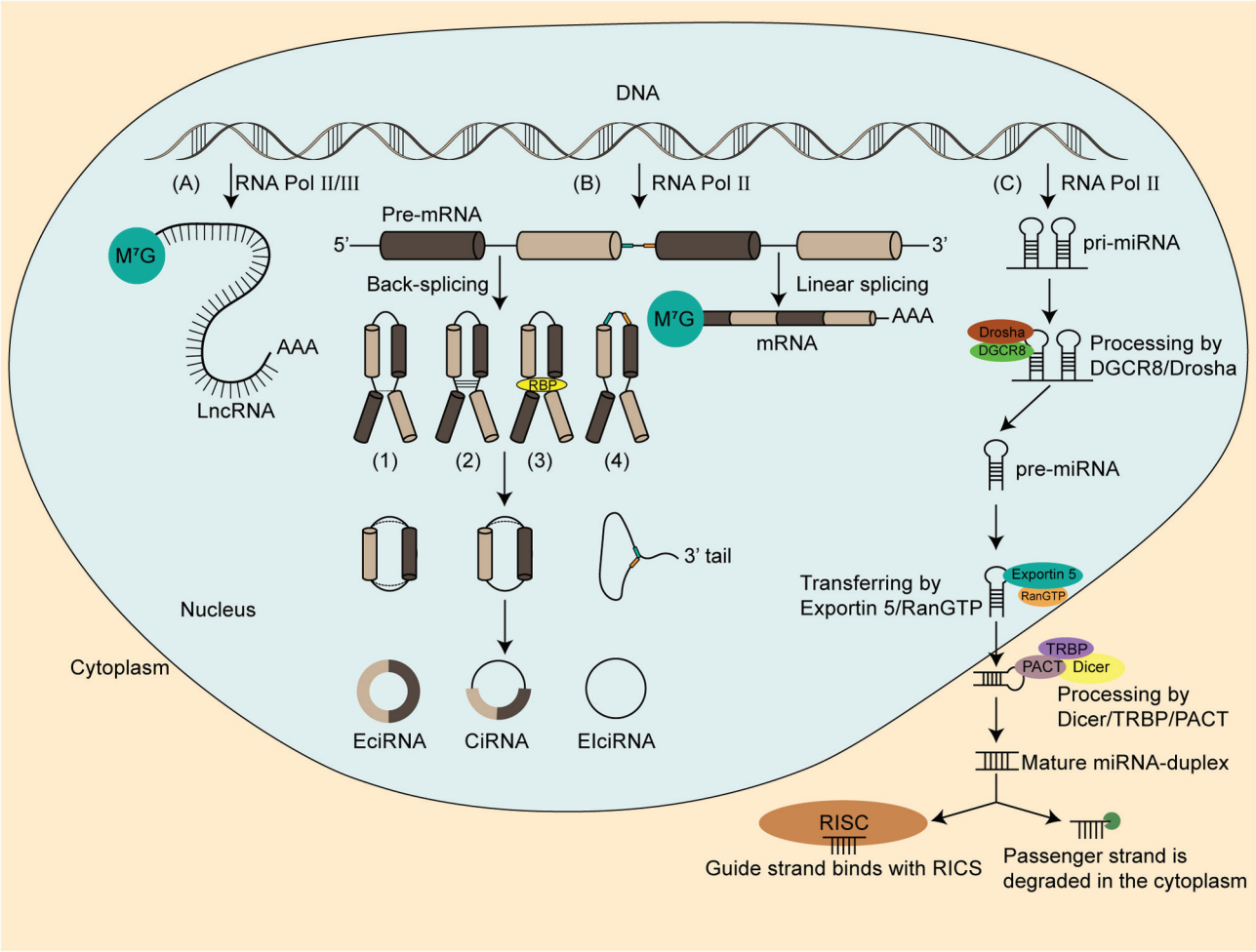

Figure 1. Biogenesis mechanism of ncRNAs. (A) LncRNAs can be transcribed by RNA polymerase II or III. (B) CircRNAs can be formed by back-splicing of pre-mRNA, which mainly includes exon-skipping driven circularization and RBP-driven circularization. (1) Exon-skipping driven circularization: During transcription, pre-mRNA partially folds, allowing the 5' splice donor and 3' splice acceptor sites from non-adjacent exons to join, forming a 3',5'-phosphodiester bond and creating a loop. Subsequent splicing events lead to the formation of circRNA. (2) Intron-pairing-driven circularization: The introns of pre-mRNA directly form loops through base-pairing interactions. (3) RBP-driven circularization: RBPs can bind introns via complementary base pairing, bringing the introns on either side of the exons closer together, facilitating their circularization. (4) Some introns contain specific sequences and form loops, during reverse splicing, which are resistant to degradation. Further processing results in the generation of ciRNA. (C) MiRNAs are transcribed by RNA pol II and are transported to the cytoplasm after a series of processes in the nucleus form the mature chain. RBP, RNA-binding protein; ncRNA, non-coding RNA; lncRNA, long ncRNA; circRNA, circular RNA; ciRNA, intronic circRNAs; pol, polymerase; EciRNA, Exonic circRNAs; EIciRNA, exon-intron circRNAs; miRNA, microRNA.

This leads to a shortened G_0/G_1 phase and prolonged G_2/M phase in the cells, thus driving ESCC development (73). In addition, a study found that the lncRNA HOX transcript antisense RNA can promote ESCC tumorigenesis by binding to miR-1 and upregulating cyclin D1 expression, thereby regulating changes in the cell cycle (74). These findings emphasize the critical role of ncRNAs in ESCC pathogenesis. Current research predominantly explores how ncRNAs promote ESCC progression by regulating cell proliferation, metastasis and therapy resistance (21,75,76). Therefore, this article focuses on elucidating the specific mechanisms and current research status of ncRNAs in regulating ESCC cell proliferation, metastasis, and therapy resistance, alongside their potential as diagnostic markers for ESCC.

NcRNAs regulate proliferation and apoptosis of ESCC cells. Tumor cells exhibit unlimited proliferation and anti-apoptotic capabilities (77). The main challenge in treating tumors lies in controlling the unbridled proliferation of tumor cells *in vivo*. Prior research has demonstrated that miRNAs, lncRNAs and circRNAs have the ability to regulate the proliferation and death of tumor cells, hence limiting or promoting the development and growth of tumors (78,79).

The miR-106b-5p oncogene is commonly upregulated in various malignancies, such as ESCC (80,81). In patients with ESCC, elevated miR-106b-5p levels are associated with decreased expression of the 15-hydroxyprostaglandin dehydrogenase (HPGD) tumor suppressor gene (82). Dual luciferase reporter assays have confirmed HPGD as a direct target of miR-106b-5p, and miR-106b-5p expression is inversely correlated with HPGD levels (82). Overexpression of miR-106b-5p promotes tumor cell proliferation and inhibits apoptosis, while upregulation of HPGD reverses these effects (82).

The levels of miR-497 have been found to be lower in ESCC tissues and cells when compared with normal tissues (83). An increase in miR-497 expression suppresses ESCC cell growth,

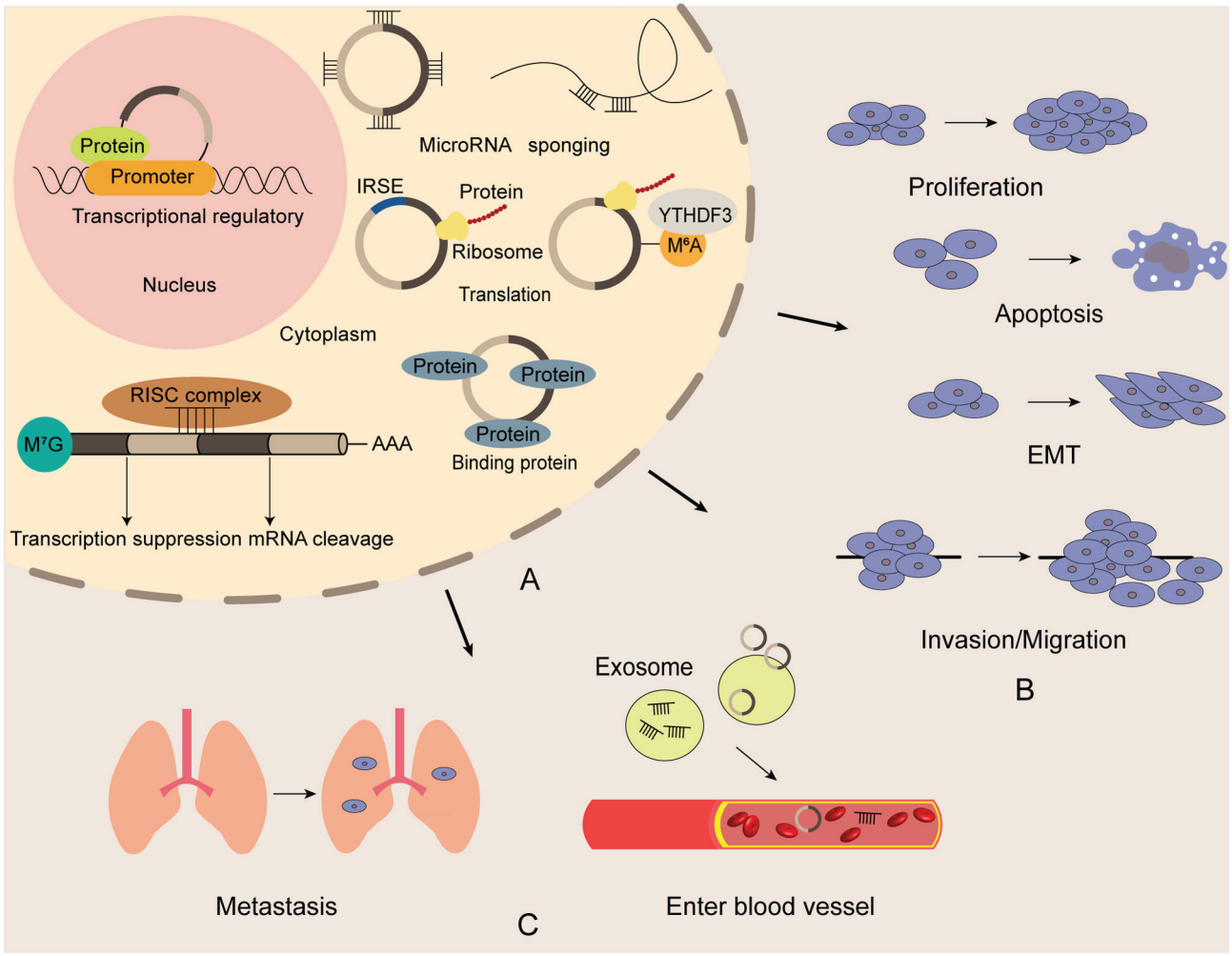

Figure 2. Progression of ESCC is associated with ncRNAs. (A) NcRNAs regulate downstream gene expression by modulating transcription in the nucleus and through various mechanisms in the cytoplasm, such as competing endogenous RNA, binding, encoding proteins and regulating translation. (B) NcRNAs regulate the proliferation, apoptosis, EMT, invasion and migration of ESCC cells. (C) NcRNAs can be transported into the peripheral blood via exosome transport and accelerate the lung metastasis of ESCC. ESCC, Esophageal squamous cell carcinomas; ncRNA, non-coding RNA; EMT, epithelial-mesenchymal transition; M6A, N6-methyladenosine; YTHDF3, YTH m6A RNA binding protein 3.

while a reduction in miR-497 expression promotes ESCC cell proliferation (83). Furthermore, overexpression of miR-497 in ESCC cells injected into BALB/c nude mice results in a decreased level of proliferating cell nuclear antigen, increased cleaved caspase-3 expression and inhibited tumor growth (83). Mechanistically, it has been revealed that the YY1 protein can inhibit HIF2α expression by binding to the HIF2α promoter region, and miR-497 upregulates YY1 protein expression (83).

Furthermore, He *et al* (84) showed that miR-377 may control the chromobox protein homolog 3 (CBX3)/P53/P21 axis, which impacts the ability of ESCC stem cells to proliferate. Overexpression of miR-377 downregulates the level of CBX3 but increases P21 protein levels and phosphorylation of P53 protein. Consequently, expression of the CD133 and CD13 ESCC stem cell markers, plus the Nanog transcription factor, Y-Box 2 sex determining region and octamer-binding transcription factor 4, is reduced (84). In addition, the proliferation, sphere formation and tumorigenicity of ESCC stem cells are significantly inhibited. Conversely, miR-377 inhibitor treatment results in the opposite trend (84).

The regulatory impacts of lncRNAs on the progression of ESCC have been shown in several studies. For example, the lncRNA small nucleolar RNA host gene 16 (SNHG16) oncogene is upregulated in the early stages of ESCC (85). It can enhance the stability of Ras homologue family member U and promote the proliferation of ESCC cells by recruiting the EIF4A3 RNA binding protein-eukaryotic translation initiation factor (85). When cells that overexpress SNHG16 are injected into mice, tumor growth is accelerated (85). Similarly, lncRNA GK intronic transcript 1 can competitively bind to mitogen-activated protein kinase 1 (MAPK1). This prevents its interaction with dual specificity phosphatase 6 and inhibits transmission of the extracellular signal-regulated kinase/MAPK1 signaling pathway, which is mediated by dual specificity phosphatase 6 (86). This facilitates growth and suppresses apoptosis of ESCC cells (86).

Xue *et al* (87) revealed that elevated lncRNA LINC00680 levels in ESCC may promote ESCC cell proliferation and it regulates a ceRNA interaction network known as the LINC00680/miR-423-5p/p21-activated kinase 6 (PAK6) axis. Knockdown of LINC00680 suppresses ESCC cell growth

by increasing miR-423-5p expression and decreasing PAK6 expression (87). These effects can be reversed by a miR-423-5p inhibitor or upregulation of PAK6 expression. This suggests that LINC00680 promotes ESCC progression by upregulating PAK6 levels by acting as a sponge for miR-423-5p (87).

CircRNAs that are aberrantly expressed have been found to facilitate the proliferative ability of ESCC cells. Xiong *et al* (88) demonstrated that circNELL2 can activate the translation of cell division cyclin-6 by acting as a sponge for miR-127-5p, which in turn encourages the growth of ESCC cells. MiR-124 has been demonstrated to be an anti-oncogene and shows markedly declined levels in ESCC (89,90). The levels of circ2646 are elevated and inversely correlated with miR-124 expression in ESCC (91). Increased circ2646 reduces miR-124 levels and promotes tumor cell proliferation (91). Yao *et al* (92) report elevated circHIPK3 levels in ESCC tissues when compared with normal tissues, which correlates with lymph node metastasis (LNM) and poor tumor differentiation. Knockdown of circHIPK3 inhibits ESCC cell proliferation by acting as a sponge for miR-124 (92). These findings suggest that circRNAs can boost ESCC cell proliferation and tumor formation. Moreover, some circRNAs have been shown to increase apoptosis of ESCC cells (93,94). Jiang *et al* (95) found that low circ0086414 expression correlates with poor prognosis in patients with ESCC. They observed that circ0086414 inhibits tumor cell proliferation, suppresses glycolysis and increases apoptosis in ESCC cells. These findings highlight the importance of circRNAs in ESCC development and suggest potential therapeutic strategies that target circRNAs.

The aforementioned studies highlight the involvement of ncRNAs in the regulation of tumor cell proliferation via intricate mechanisms. Future research should aim for a deeper understanding of these mechanisms, to distinguish between ncRNAs that promote or inhibit cancer progression. Such insights can guide clinical approaches to treating ESCC.

NcRNAs regulate invasion and migration of ESCC cells. The two main factors that contribute to therapy failure in individuals with advanced-stage ESCC are local invasion and distant metastases (96). It is crucial to understand the molecular processes behind the spread of ESCC and to investigate prospective treatment targets. The present review provides a summary of current research on the connection between ncRNAs and ESCC metastasis.

The levels of miR-17-5p and miR-4443 are elevated in ESCC cells and correlate with the tumor node metastasis (TNM) stage. Both miR-17-5p and miR-4443 promote ESCC cell invasion and migration by targeting metallopeptidase-2 (97). Exosomes, which transport proteins, lipids and nucleic acids, are vital mediators of intercellular communication (98). Exosomes secreted by tumor cells are crucial for the development and spread of malignancies (99). Liu *et al* (100) revealed a positive correlation between the LNM of patients with ESCC and miR-320b levels in ESCC cell-derived exosomes. MiR-320b is transferred to human lymphatic endothelial cells via exosomes, inhibiting programmed cell death 4, activating protein kinase B (AKT) phosphorylation and promoting peritumoral lymphangiogenesis (100). It also enhances ESCC cell invasion and migration through these pathways (100). In addition, certain miRNAs have been shown to prevent ESCC cell invasion and migration. For instance, miR-338-5p targets epidermal growth factor receptor (EGFR) and the hepatocyte growth factor receptor (cMET) (101). Increasing miR-338-5p levels reduces cMET and EGFR expression and blocks their signaling pathways (101). Consequently, activation of growth factor receptor-bound protein 2-associated binding protein 1, AKT and extracellular signal-regulated kinase are inhibited (101). This prevents the extracellular matrix from remodeling and impedes ESCC cell invasion and migration (101). Moreover, it has been discovered that miR-485-5p significantly inhibits the mRNA and protein expression levels of Flotillin-1 by binding to its 3'-UTR, resulting in increased E-cadherin expression in ESCC cells, whereas the expression levels of Vimentin, N-cadherin, and zinc finger E-box-binding homeobox 1 were decreased (102). This impedes the invasion and migration of ESCC cells by inhibiting the epithelial-mesenchymal transition (EMT) (102). These results underline the critical role that miRNAs play in controlling ESCC cell invasion and migration.

Recently, several lncRNAs have been revealed to act as oncogenic genes and promote ESCC invasion and migration (103,104). The lncRNA LINC02820 correlates with poor prognosis in patients with ESCC. While its overexpression does not impact ESCC cell proliferation, it enhances cell invasion and migration (105). It also causes an increase in levels of the cortactin and phosphorylated Neural Wiskott-Aldrich syndrome protein invadopodia markers (105). A number of malignancies show high levels of expression of the GTPase-activating protein (SH3 domain)-binding protein 2 (G3BP2) oncogene (106,107). Zheng *et al* (108) found that G3BP2 can promote ESCC invasion and migration by upregulating the levels of hepatoma-derived growth factor mRNA, and the poor prognosis of patients with ESCC has a positive relationship with G3BP2 expression. The lncRNA LINC01554 binds to the RNA recognition motif of G3BP2 and prolongs its half-life by reducing the ubiquitination level of G3BP2. This indicates that LINC01554 is essential for the oncogenic effect of G3BP2 (108). The lncRNA BAALC-AS1 can also directly interact with G3BP2 to block G3BP2-mediated c-Myc degradation, and to enable ESCC invasion and migration (109). A study has revealed a correlation between the lncRNA PTPRG-AS1 and pyruvate dehydrogenase kinase 1 (PDK1) expression in tumor cells (110). Notably, PTPRG-AS1 has been revealed to regulate PDK1 expression by acting as a sponge for miR-599. Silencing PTPRG-AS1 has been shown to inhibit ESCC glycolysis, invasion and migration (110).

CircRNAs have been shown to regulate ESCC invasion and migration through their ability to act as a sponge for various types of miRNAs. For example, Shi *et al* (111) revealed that circLPAR3 upregulates MET gene expression and activates the RAS protein/MAPK and phosphoinositide 3-kinase/AKT pathways by acting as a sponge for miR-198. This promotes ESCC cell migration, invasion and metastasis. Meanwhile, Xu *et al* (112) demonstrated that circ0000654 promotes interleukin-6 secretion by acting as a sponge for miR-149-5p, which enhances ESCC cell migration by activating signal transducer and activator of transcription 3 (STAT3) signaling. This leads to malignant progression of the disease. Wang *et al* (113) demonstrated that circ0087378 correlates with poor overall survival (OS) in patients with ESCC and is highly expressed

in ESCC cells. The authors observed a negative correlation between circ0087378 expression and miR-140-3p levels. Through binding to miR-140-3p, circ0087378 alleviates the suppressive effect of miR-140-3p on its target gene, E2F transcription factor 3 (E2F3). This circ0087378/miR-140-3p/E2F3 axis is crucial for promoting ESCC cell invasion and migration (114). The EMT facilitates tumor progression by altering cell-cell adhesion, polarity and morphology, which enhances tumor cell invasion and metastasis (114,115).

Numerous studies have demonstrated that, through affecting the EMT process, circRNAs may regulate the capacity of ESCC to invade and migrate. For instance, circLONP2 can promote EMT and lead to ESCC metastasis by regulating the miR-27b-3p/zinc finger E-box binding homeobox 1 axis (116). Chen *et al* (117) revealed that by reducing circ0004370, EMT-related protein expression can be decreased and ESCC cell invasion and migration can be prevented. Mechanically, collagen type I α 1 expression is upregulated by circ0004370 acting as a sponge for miR-1301-3p (117). Moreover, circARAP2 knockdown elevates E-Cadherin expression, while suppressing N-Cadherin expression. However, these effects are reversed when miR-761 is reduced or Forkhead Box M1 is upregulated (118). The downregulation of circARAP2 results in decreased expression of ESCC tumor stem cell-related genes and inhibits ESCC progression (118). Thus, targeting circRNAs in ESCC may represent a novel strategy to inhibit metastasis (118).

In summary, ncRNAs are pivotal regulators of ESCC metastasis, offering potential as therapeutic targets to curb tumor migration and recurrence. Further research is warranted to elucidate their precise mechanisms and optimize their utilization in controlling metastasis.

NcRNAs are associated with ESCC drug resistance. While chemotherapy and radiotherapy remain the primary treatment modalities for ESCC, frequent drug resistance is a major contributing factor to poor treatment outcomes. In recent years, several reports have indicated a significant association between ncRNAs and resistance to chemotherapy and radiotherapy in ESCC (119-121).

Recent studies have shown that miRNAs are involved in regulating drug resistance in ESCC. For example, Zuo *et al* (122) demonstrated that overexpression of miR-153-3p inhibits the growth of ESCC cells and increases the level of cleaved caspase-3 after treatment with cisplatin. This indicates that upregulation of miR-153-3p may improve cisplatin resistance in ESCC cells. Previous studies have demonstrated that cancer-associated fibroblasts (CAFs) contribute to cisplatin resistance in ESCC (123,124). Another recent study further revealed the critical role of miRNAs in CAFs-induced cisplatin resistance (125,126). Exosomes secreted by CAFs, enriched with miR-21, inhibit phosphatase and tensin homolog (PTEN) activation in monocytes, which leads to STAT3 activation. This promotes monocyte differentiation into myeloid-derived suppressor cells, ultimately inducing cisplatin resistance (127). Gou *et al* (128) revealed that patients with ESCC with low miR-29b expression demonstrate increased resistance to radiotherapy. The authors identified a miR-29b binding site in the 3'-UTR of BTG anti-proliferation factor 2 (BTG2) mRNA. Downregulation of miR-29b increases BTG2 expression, decreases cyclin D1 expression and leads to cell cycle arrest in the G_0/G_1 phase of radiotherapy resistant ESCC cells (128). These findings suggest that targeting miRNAs could be a viable strategy to mitigate resistance to therapy in ESCC (128).

LncRNAs play a crucial role in drug resistance in ESCC. The ALKBH5-mediated m6A demethylation process upregulates lnc-cancer susceptibility 8 (lncCASC8) expression, which induces drug resistance in ESCC cells. LncCASC8 targets heterogeneous nuclear ribonucleoprotein L, preventing its ubiquitination and stabilizing its expression. This leads to increased Bcl2 production and decreased cleaved caspase-3 levels, ultimately resulting in ESCC drug resistance (129). The lnc-non-coding RNA activated by DNA damage (NORAD) is associated with cisplatin resistance and poor prognosis in patients with ESCC (130). Upregulation of lncNORAD increases the IC_{50} value of cisplatin and reduces apoptosis in ESCC cells treated with cisplatin. Mechanistically, lncNORAD acts as a sponge for miR-224-3p and represses miR-224-3p expression (130). Downregulation of miR-224-3p decreases the expression of its target gene, metadherin, and inhibits nuclear accumulation of β-catenin, which results in cisplatin resistance in ESCC (130). The lncPOU3F3 from tumor cell exosomes induces cisplatin resistance in ESCC by promoting the conversion of normal fibroblasts to CAFs (131). In addition, Wang *et al* (132) demonstrated that lnc-Taurine upregulated 1 (lncTUG1) knockdown, combined with radiotherapy, significantly inhibits ESCC cell growth, when compared to radiotherapy alone. Further investigation revealed that lncTUG1 acts as a sponge for miR-144-3p, promoting MET expression. Decreased lncTUG1 levels are associated with reduced MET and AKT phosphorylation, enhancing the efficacy of radiotherapy (132). These findings highlight the regulatory role of the lncTUG1/miR-144-3p/MET axis in ESCC radiotherapy resistance (132).

CircRNAs are also closely associated with ESCC drug resistance. The circ0014879 increases in radiotherapy resistant ESCC cells and controls the miR-519-3p/cell division cycle 25A axis to cause drug resistance (133). The upregulation of circ0000277 in cisplatin-resistant ESCC enhances drug resistance by modulating miR-873-5p and activating the SRY-box transcription factor 4/Wnt/β-catenin axis (134). Knockdown of circ0000277 promotes ESCC cell apoptosis and reduces cisplatin resistance, as evidenced by increased proapoptotic protein levels (PARP and caspase-3) and decreased IC_{50} values, following cisplatin treatment (134). Zhou *et al* (135) revealed that circ-glutamic-oxaloacetic transaminase 1 (circGOT1) is highly expressed in cisplatin-resistant ESCC cells, while miR-606 expression is reduced. This circRNA upregulates the expression of its host gene, GOT1, by acting as a sponge for miR-606. Inhibition of circGOT1 decreases ESCC cell glycolysis and enhances cisplatin sensitivity (135). These effects are reversed by miR-606 knockdown or GOT1 overexpression. It is hypothesized that circGOT1 promotes ESCC resistance via the circGOT1/miR-606/GOT1 axis (135).

Certain circRNAs, such as circDOPEY2, inhibit ESCC resistance and circDOPEY2 is expressed at low levels in cisplatin-resistant ESCC cells (136). It acts as a protein scaffold to enhance the binding between cytoplasmic polyadenylation element binding protein (CPEB4) and TRIM25 E3 ligase. This promotes the formation of the CPEB4/circDOPEY2/TRIM25

complex, accelerating CPEB4 degradation by promoting its ubiquitination and blocking CPEB4-mediated Mcl-1 translation (136). An *in vivo* study demonstrated that combining circDOPEY2 with cisplatin significantly suppresses cisplatin resistance (136). Zhu *et al* (137) indicated that circPSMC3 is downregulated in gefitinib-resistant ESCC cells. Increasing circPSMC3 expression significantly reduces ESCC resistance to gefitinib, inhibits cell proliferation and promotes apoptosis (137). A negative correlation has been found between circPSMC3 and miR-10a-5p expression, but circPSMC3 is positively correlated with PTEN expression, downstream of miR-10a-5p (137). Modulating miR-10a-5p or PTEN expression alters the effect of circPSMC3 on gefitinib resistance in ESCC. These findings suggest that circPSMC3 inhibits gefitinib resistance in ESCC by modulating the miR-10a-5p/PTEN axis (137). Programmed cell death receptor 1 (PD-1)/programmed cell death-ligand (PD-L1) inhibitors can act to slow tumor development, according to recent research (138). However, due to the emergence of resistance, only a small percentage of individuals benefit from this medication (139).

It has been demonstrated that circRNAs regulate drug resistance in PD-1/PD-L1 therapy (140,141). A study has reported elevated levels of circ-vimentin (circVIM) in ESCC cells and showed its ability to suppress miR-124 expression (142). Knockdown of circVIM in ESCC cells results in upregulation of miR-124 expression, a reduction in PD-L1 expression and a mitigation of tumor escape (142). Furthermore, silencing circVIM can be synergized with sevoflurane to inhibit multiple oncogenic activities and counter immune escape in ESCC by targeting the miR-124/PD-L1 axis (142). These findings suggest that circRNAs are an important regulator of drug resistance in ESCC therapy. If the efficacy and application plan can be further clarified, circRNA could have a high impact on the treatment of numerous patients and could reduce the recurrence rate of ESCC.

The aforementioned studies reveal a strong link between ncRNAs and tumor drug resistance, which highlights their potential in overcoming this challenge and guiding future therapeutic strategies.

NcRNAs as biomarkers in ESCC. Due to the subtle onset and rapid progression of ESCC, early detection and diagnosis are crucial for the treatment of this disease. Several studies have validated the use of ncRNAs as reliable biomarkers for the diagnosis of ESCC.

Researchers have shown that patients with ESCC with low miR-378 expression have a short OS and a poor prognosis. Low expression of miR-378 is correlated with TNM stage and LNM of patients (143). These findings indicate that miR-378 serves as an independent prognostic factor for the prediction of OS in patients diagnosed with ESCC (143). MiR-205-5-5p and miR-429 show substantial increases in plasma exosomes among patients with ESCC, while miR-375-3p exhibits a marked decrease (144).

Researchers have evaluated whether these miRNAs in plasma exosomes can be potential biomarkers for ESCC diagnosis using receiver operating characteristic (ROC) curves (144). It has been revealed that the area under the curve (AUC) of miR-205-5p, miR-429 and miR-375-3p are 0.770, 0.699 and 0.741, respectively (144). The sensitivities of miR-205-5-5p, miR-429 and miR-375-3p in diagnosing ESCC were 72.5, 60.0 and 65.0%, respectively, while the diagnostic specificities were 70.0, 60.0 and 65.0%, respectively (144). Wen *et al* (145) has identified miR-135b-5p, miR-139-5p, miR-29c-5p and miR-338-3p as potential predictors of OS in patients with ESCC with local metastasis, post surgical resection. These four miRNAs exhibit predictive capabilities that are comparable to established clinical prognostic indicators, such as pathological tumor-stage, pathological node-stage and lymph node examination count. Notably, the four-miRNA-based classifier has achieved an AUC of 0.597, underscoring its significance as a highly valuable diagnostic tool.

In addition, miRNAs in urine can be used for the diagnosis of ESCC. A study has revealed that the urine of patients contains elevated levels of certain miRNAs, such as miR-1273f, miR-619-5p, miR-150-3p, miR-4327 and miR-3135b. Urinary miR-1273f and miR-619-5p sensitivity and specificity for diagnosing all stages of ESCC were 82.5 and 59.0%, and 80.0 and 65.3%, respectively. These findings suggest that miRNAs have potential as biomarkers for ESCC (146).

LncRNAs have been shown to play a critical role in the diagnosis and prognosis of ESCC. Research suggests that the prognosis of patients with ESCC is inversely related to the risk score associated with an 8-lncRNA signature. This comprises ADAMTS9-AS1, DLX6-AS1, LINC00470, LINC00520, LINC01497, LINC01749, MAMDC2-AS1 and SSTR5-AS1 (147). In addition, six differentially expressed lncRNAs (6-DElncRNAs), namely AP000696.2, LINC01711, RP11-70C1.3, AP000487.5, AC011997.1 and RP11-225N10.1, have been identified as potential prognostic indicators for patients with ESCC. A 6-DElncRNA model has also been developed to classify patients with ESCC into high-risk and low-risk groups, with the former exhibiting lower OS rates. A ROC curve analysis showed that the AUCs for 6-DElncRNAs for predicting 1-, 3- and 5-year survival rates of patients with ESCC are 0.768, 0.825 and 0.822, respectively. As the high-risk group has higher gefitinib and lapatinib IC_{50} values, 6-DElncRNAs may also be able to predict drug susceptibility (148). Liu *et al* (149) demonstrated that a 6-lncRNA signature (AC005091.1, SNHG6, AC091544.4, DNAJB5-DT, HTT-AS and ANKRD10-IT1) has a high predictive value for ESCC. The ROC curve analysis gave AUCs of 0.785 and 0.786 for the 6-lncRNA signature for predicting 3- and 5-year survival rates, respectively. The AUCs of the 6-lncRNA signature for predicting 3- and 5-year recurrence-free survival are 0.795 and 0.783, respectively. These findings provide additional perspectives for the development and research of ESCC biomarkers.

Moreover, exosomal lncRNAs may also be used as ESCC biomarkers. Xie *et al* (150) demonstrated high expression of AC098818.2, LINC00958 and RASSF8-AS1 in ESCC cells, patient serum and exosomes. The diagnostic ability of these three lncRNAs for ESCC is 0.69, 0.72 and 0.78, respectively, in accordance with the ROC curve analysis. However, the diagnostic value ranges from 0.51 to 0.53 for common tumor biomarkers (CEA125, CA199, CA153, SCC, NSE and CYFRA21-1), which indicates that AC098818.2, LINC00958 and RASSF8-AS1 have certain advantages for the diagnosis of ESCC. The levels of these three lncRNAs also decrease in

postoperative patients, which suggests that they have potential as dynamic monitoring indicators for tumor development.

There is growing evidence to suggest that circRNAs can serve as biomarkers for ESCC. Huang *et al* (151) revealed a substantial correlation between the level of circ0004771, vascular invasion and a worse OS in patients with ESCC. Furthermore, the authors observed that circ0004771 levels increase in an extracellular medium in a time-dependent manner and can be downregulated by the GW4869 exosome blocker, without affecting its expression within the cells. A ROC curve analysis provided an AUC for circ0004771 of 0.816, which indicates that circ0004771 has potential as a diagnostic biomarker for ESCC (151). Wang *et al* (152) identified 1,202 circRNAs related to ESCC prognosis through bioinformatics. The authors also revealed four circRNAs (circ0000005, circ0007541, circ0008199 and circ0077536) that are primarily found in the nucleus and can be used to divide patients with ESCC into two groups with noticeably different survival rates. This four-circRNA signature (AUC=0.839) performs better for ESCC prediction compared with using the TNM stage (AUC=0.657). When the four-circRNA signature and TNM are combined, the predictive value is higher (AUC=0.874).

Hu *et al* (153) showed that in individuals with ESCC, circGSK3β in plasma is positively linked with higher LNM and a poorer prognosis. The authors also demonstrated that the level of circGSK3β in the plasma may be a potential biomarker to detect ESCC and early stage ESCC, as indicated by the AUC values of 0.782 and 0.793, respectively. Moreover, diagnostic sensitivity is markedly increased by combining circGSK3β and carcinoembryonic antigen, which indicates that circGSK3β has potential as an early diagnostic marker for ESCC (153). Another study discovered that circADAMTS6 is positively associated with poor pathology grade, large tumors and LNM in patients (154). Patients who express higher levels of circADAMTS6 have a shorter OS compared with patients who express lower levels, which indicates that circADAMTS6 may be a potential prognostic factor for ESCC (154). Meanwhile, circSLC7A5 (155), circBMII (156) and circ0071106 (157) have also been shown to be potential biomarkers for ESCC. These results indicate that circRNAs may be employed as biomarkers for the early identification and prognosis of ESCC. CircRNAs are found in a range of tissues and cells and can withstand RNase R destruction, which makes them easy and cost-effective to detect. Thus, the use of circRNAs as biomarkers for ESCC could have significant clinical and economic benefits.

The aforementioned studies show the significant dysregulation of specific ncRNAs in ESCC, which facilitates early diagnosis. Given their widespread expression and easy detection, ncRNAs serve as promising and cost-effective biomarkers for ESCC.

4. Conclusions and future directions

Since the late 1990s to the present day, an increasing number of ncRNAs have been discovered. Initially, these non-coding fragments of RNA were considered to be useless byproducts (158). However, with the advent of RNA-sequencing technology, ncRNAs have gained growing attention and have emerged as a novel research paradigm within RNA biology (159). Furthermore, an expanding body of research has indicated that ncRNAs play pivotal roles in the onset and progression of various diseases, such as cancer, cardiovascular diseases and neurological disorders. This field of study has evolved into a crucial component of life sciences (160,161).

The present review provides an overview of the biogenesis, characteristics and functions of ncRNA family members, which include miRNAs, lncRNAs and circRNAs, along with the latest developments in the treatment of ESCC. The present study also summarizes, in Table I, studies on the regulation of ESCC progression by ncRNAs that are not detailed in this article. Aberrant expression of ncRNAs has been observed in ESCC cells, tissues and peripheral blood of patients with ESCC, which suggests their potential involvement in the disease and their utility as biomarkers (162). Furthermore, ncRNAs have been found to impact the progression of ESCC through multiple pathways, such as acting as molecular sponges for miRNA, participating in transcriptional regulation and influencing protein coding (163-165). These findings underscore the potential of ncRNAs as biomarkers and therapeutic targets for ESCC, with implications for early diagnosis, treatment and prognosis assessment (162,166).

Although the critical regulatory role of ncRNAs in the occurrence and progression of ESCC has received increasing attention, further in-depth research is still required. It is well known that ncRNAs exhibit rich diversity in terms of quantity and types. Future investigations should focus more on the interactions among ncRNAs, to elucidate their regulatory roles in ESCC progression by constructing and depicting ncRNA regulatory networks. In addition, the subcellular localization of ncRNAs is closely associated with their specific functions (167). Therefore, future studies should explore whether changes in the localization of ncRNAs during disease progression result in alterations to their structure, function and downstream target molecules. Most current studies focus primarily on the functional aspects of aberrantly expressed ncRNAs, *in vivo,* but lack investigation into the causes of their aberrant expression (168,169). Consequently, future research should further elucidate the specific mechanisms that underlie the aberrant expression of ncRNAs in cells or peripheral blood. Moreover, the occurrence and progression of various malignant tumors, such as ESCC, are closely related to the status of the tumor microenvironment. Therefore, subsequent research should not only focus on the role of ncRNAs in tumor cells but should also clarify their effects on the tumor microenvironment. For instance, it is crucial to elucidate the specific mechanisms by which ncRNAs, mediated by exosomes, enter other cells, as this leads to cellular dysfunction and disruption of the tumor microenvironment homeostasis.

Targeted therapies for ESCC have shown promising efficacy, with targeted drugs against key genes and signaling pathways implicated in ESCC now available. Given that ncRNAs can regulate the expression of downstream target genes through multiple mechanisms, future considerations may involve combining ncRNA-targeted therapy with existing targeted drugs for ESCC. This approach could involve the synergistic regulation of key genes in ESCC progression, such as Notch1, EGFR and human epidermal

Table I. Role of ncRNAs in esophageal squamous cell carcinomas.

ncRNAs	Location	Expression	Target	Function	(Refs.)
miR-3656	-	-	ACAP2	Oncogene	(181)
miR-154-5p	-	↓	KIF14	Anti-oncogene	(182)
miR-149	-	↓	RNF2	Anti-oncogene	(183)
miR-624	-	↑	ARRDC3	Oncogene	(184)
miR-335-5p	-	↓	TTK	Anti-oncogene	(185)
miR-942-5p	-	-	CST1	Anti-oncogene	(186)
miR-132-3p	-	↑	KCNK2	Oncogene	(187)
miR-196b	-	↑	SOCS2	Oncogene	(188)
miR-193a-3p	-	↑	ALKBH5	Oncogene	(189)
miR-200a	-	↑	KEAP1	Oncogene	(190)
TMPO-AS1	-	↑	FUS	Oncogene	(191)
PART1	-	↓	miR-18a-5p	Anti-oncogene	(192)
LOC146880	-	↑	miR-328-5p	Oncogene	(193)
GATA2-AS1	-	↓	miR-940	Anti-oncogene	(194)
KTN1-AS1	Cytoplasm and nucleus	↑	RBBP4	Oncogene	(195)
LINC00886	-	↓	ELF3	Anti-oncogene	(196)
BBOX1-AS1	-	↑	miR-513a-3p	Oncogene	(197)
RPL34-AS1	Cytoplasm	↓	miR-575	Anti-oncogene	(198)
LINC00941	-	↑	ILF2 and YBX1	Oncogene	(199)
NCK1-AS1	-	↑	TGF-β1	Oncogene	(200)
CircRUNX1	Cytoplasm	↑	miR-449b-5p	Oncogene	(201)
CircFAM120B	Cytoplasm	↓	miR-661	Anti-oncogene	(202)
Circ0003340	Cytoplasm	↑	miR-940	Oncogene	(203)
Circ0023984	Cytoplasm	↑	miR-1294	Oncogene	(204)
Circ0001093	-	↑	miR-579-3p	Oncogene	(205)
Circ0006948	-	↑	miR-3612	Oncogene	(206)
CircFNDC3B	-	↑	miR-214-3p	Oncogene	(207)
Circ0005231	Cytoplasm	↑	miR-383-5p	Oncogene	(208)
Circ0003823	Cytoplasm	↑	miR-607	Oncogene	(209)
Circ0021727	Cytoplasm	↑	miR-23b-5p	Oncogene	(210)

ACAP2, arfGAP with coiled-coil, ankyrin repeat and PH domains 2; KIF14, kinesin family member 14; RNF2, ring finger protein 2; ARRDC3, arrestin domain-containing 3; TTK, Tyrosine threonine kinase; CST1, cysteine protease inhibitor 1; KCNK2, potassium channel subfamily K member 2; SOCS2, cytokine-signaling 2; ALKBH5, alkB Homolog 5, RNA demethylase; KEAP1, kelch-like ECH associated protein 1 FUS, fused in sarcoma; RBBP4, retinoblastoma-binding protein 4; ELF3, E74-like ETS transcription factor 3; ILF2, interleukin enhancer-binding factor 2; YBX1, Y-box-binding protein 1; TGF-β1, transforming growth factor beta 1; ↑, indicates upregulation; ↓, indicates downregulation; ncRNA, non-coding RNA; miR, microRNA.

growth factor receptor 2 (170-172). In addition, the regulatory effects of ncRNAs on multiple immune checkpoints have been confirmed and a potential combination of ncRNA-targeted therapy with immunotherapy could be trialed for ESCC in future studies (173,174). Increasing attention has been paid to the protein-coding ability of circRNAs. Peptide or protein-based drugs exhibit high specificity and efficiency in the clinical treatment of ESCC, which suggests that proteins encoded by circRNAs may serve as potential sources for screening therapeutic drugs for ESCC (175-177). Indeed, studies have examined the potential of ncRNAs as target in the treatment of ESCC, such as miR-877-3p, miRNA-20b-5p and circFoxo3 (178-180). However, the therapeutic efficacy of these ncRNA for ESCC in the clinic still requires in-depth study.

In summary, ncRNAs have potential as non-invasive diagnostic markers and specific therapeutic targets in clinical diagnosis and treatment. However, there is still a long way to go from basic research to clinical application. Extensive clinical studies are needed to demonstrate the safety of ncRNAs and gradually reduce the risks associated with their use as therapeutic targets, as well as to minimize treatment-related side effects. Moreover, continuous improvement and refinement of high-throughput sequencing technologies are necessary to ensure the specificity and integrity of ncRNA detection.

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Availability of data and materials

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Authors' contributions

LZ, XW and ZH designed and organized this manuscript. LZ, YW and XZ contributed to the first draft of the manuscript. LZ, YW and MH designed the tables and figures. XW, JG and ZH reviewed the manuscript critically for important intellectual content. JG, MH and XZ revised the manuscript. YW, XZ and MH investigated and resolved any parts of the work appropriately. XW and ZH approved the final version to be published. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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