Review Article

Current advances in the functional role of long non-coding RNAs in the oncogenesis and metastasis of esophageal squamous cell carcinoma: a narrative review

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Background and Objective: Esophageal squamous cell carcinoma (ESCC) is a significant global health challenge characterized by increasing incidence and generally poor prognosis. The search for novel biomarkers and therapeutic targets is crucial for improving patient outcomes. Long non-coding RNAs (lncRNAs) have emerged as key players in cancer research. The objective of this review is to explore the role of lncRNAs in ESCC, identifying their potential as diagnostic indicators and therapeutic targets. This review aims to provide a strategic overview of lncRNAs in ESCC, emphasizing their significance in disease progression and clinical implications for patient management.

Methods: To identify published lncRNAs biomarkers for diagnosing or predicting the course of ESCC, we performed a literature search in the PubMed and PubMed Central databases, utilizing specific search terms.

Key Content and Findings: This paper reviews the critical role of lncRNAs in ESCC and explores their functions in tumourigenesis and metastasis. Differential expression of lncRNAs is closely related to tumour aggressiveness and patient prognosis. Up-regulated lncRNAs usually promote tumour growth and predict poor prognosis, whereas down-regulated lncRNAs exert oncogenic effects and are associated with better clinical outcomes. In addition, lncRNAs play a role in the tumour microenvironment, influencing immune escape and treatment resistance. Despite the promising role of lncRNAs in ESCC therapy, their heterogeneity and complex regulatory mechanisms remain a challenge for clinical application. Future studies should focus on revealing their specific mechanisms and developing precise targeted therapeutic strategies to improve the outcome of ESCC patients. The dysregulation of lncRNAs correlates with tumor aggression and patient prognosis, underscoring a need for targeted therapies. Understanding lncRNAs mechanisms could pave the way for personalized medicine, enhancing early detection, and treatment efficacy in ESCC.

Conclusions: LncRNAs represent a novel frontier in ESCC research, with significant implications for patient management. Future studies should focus on deciphering lncRNAs functions within ESCC's molecular landscape to facilitate the development of effective targeted therapies. The integration of lncRNAs research into clinical practice is poised to transform ESCC treatment strategies, offering hope for improved patient outcomes.

Keywords: Long non-coding RNAs (lncRNAs); esophageal squamous cell carcinoma (ESCC); differential expression; signaling pathways; biomarkers

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Introduction

Background

Esophageal squamous cell carcinoma (ESCC) stands as a formidable adversary in the realm of oncology, characterized by a relentless rise in incidence and a stubbornly poor prognosis. The quest for novel biomarkers and therapeutic targets has never been more critical, as they hold the promise of transforming patient outcomes. In this context, long non-coding RNAs (lncRNAs) have emerged from the shadows of the genomic landscape to take center stage in cancer research. LncRNAs, a class of transcripts exceeding 200 nucleotides in length that do not code for proteins, have emerged as pivotal regulators within the complex networks orchestrating cellular homeostasis. Their roles extend across a spectrum of cellular processes, prominently influencing gene expression, cell cycle regulation, and apoptosis, thereby implicating them in the pathogenesis of various diseases, including cancer (1,2).

LncRNAs have emerged as pivotal regulatory factors in the complex molecular landscape of ESCC, exerting a significant impact on the initiation and progression of aggressive malignant tumors (3). The biological relevance of lncRNAs in ESCC is multifaceted, encompassing their roles in epigenetic regulation, post-transcriptional modifications, and the modulation of signaling pathways that control cellular behaviors such as proliferation, invasion, and apoptosis. LncRNAs can act as oncogenes or tumor suppressors, depending on their specific functions and interactions within cellular networks. Some lncRNAs may promote epithelial-mesenchymal transition (EMT), with studies indicating that downregulation of LINC01094 reduces the expression levels of Snail family proteins *in vitro*, suggesting a strong correlation with the EMT pathway. The lncRNAs MALAT1 participates in transforming growth factor beta 1 (TGF-β1)-mediated EMT by significantly inducing the expression of ZEB1, offering new avenues for disease diagnosis and treatment (4). Conversely, some lncRNAs may inhibit tumor growth by targeting oncogenic pathways or enhancing DNA damage response, thereby promoting cellular senescence or apoptosis. LncRNAs-PR-LncRNAs-1, regulated by p53, interacts with Sam68 to promote the transcription of p21, modulating the cell cycle and potentially involved in the regulation of cellular senescence (5,6). Clinically, lncRNAs play a significant role in various biological processes of tumor development, including cell proliferation, differentiation, apoptosis, and tumor invasion and metastasis. They participate in the biological behavior of tumors by interacting with proteins, affecting gene expression, and regulating signaling pathways. The expression patterns of lncRNAs correlate with clinical outcomes, such as survival and recurrence rates, and these correlations have been studied in various cancer types. LncRNAs DGCR5 exhibits higher expression levels in ESCC tissues compared to normal esophageal tissues, with its high expression closely associated with the tumor node metastasis (TNM) stage, lymph node metastasis, and poor prognosis in ESCC patients. The high expression of DGCR5 may serve as a negative prognostic factor in ESCC patients, correlating with adverse outcomes. LncRNAs GAS5 is expressed at lower levels in esophageal cancer, but its overexpression can exert anti-tumor effects by inhibiting miR-21, increasing cellular radiosensitivity, and potentially acting as a radiosensitizer in radiotherapy. The response to neoadjuvant immunotherapy in ESCC is associated with the heterogeneity of $CD8^+$ T cell exhaustion, with $SPRY1^+PD1^+CD8^+$ T cells serving as an effective biomarker for predicting clinical benefits from immunotherapy (7).

Esophageal cancer (EC) is a complex disease of the esophagus, originating in the middle or upper segments. It is primarily characterized by two histological types: ESCC and esophageal adenocarcinoma (EAC) (8). EC correlates to a variety of gene mutations, epigenetic changes, chromosomal translocation, deletion, and amplification, and is one of the deadliest cancers in the world (9). According to global cancer statistics from 2020, the mortality rate for EC stands at 5.44%, indicating that one in every 18 cancer-related deaths is attributed to EC (10). While the incidence of EAC has been escalating in Western countries, particularly in Europe and the United States, ESCC remains the predominant subtype in China and across other regions in Asia and Africa (11). This geographical variation in the prevalence of ESCC highlights the necessity for region-specific research and therapeutic strategies.

In Western societies, the rising incidence of EAC has been linked to various factors, including shifts in dietary

habits and the increasing prevalence of obesity, which have collectively altered the epidemiological profile of esophageal cancer. Nonetheless, ESCC continues to pose a significant health burden globally, especially in East Asia, where it constitutes the majority of esophageal cancer cases.

The unique genetic, environmental, and lifestyle factors contributing to the development of ESCC in these regions underscore the importance of targeted research endeavors (12). Gaining insights into the molecular mechanisms, risk factors, and therapeutic targets specific to ESCC is essential for advancing our understanding and improving clinical outcomes for patients afflicted with this aggressive form of cancer (13).

This review aims to provide a global overview of ESCC, emphasizing the significance of research advancements in Western countries while also recognizing the unique challenges that the disease presents in China (14). By examining the current state of knowledge and the latest developments in the field, we aim to highlight the importance of ESCC research and its potential to inform personalized treatment strategies that could benefit patients worldwide (15).

Objective

Given the increasing incidence and often poor prognosis of ESCC, the aim of this study was to systematically investigate the functional roles of lncRNAs in the tumourigenesis and metastasis of ESCC. The main goal of this study was to profile the expression of lncRNAs in ESCC and assess their potential as diagnostic biomarkers and therapeutic targets. Through in-depth characterisation of lncRNAs associated with ESCC, we plan to reveal how they regulate key signalling pathways affecting tumour cell behaviour, including proliferation, apoptosis, migration and metabolism. In addition, this study seeks to explore the interactions between lncRNAs and the tumour microenvironment, as well as their involvement in tumour immune escape and treatment resistance. We anticipate that these findings will provide a theoretical basis for individualised medical strategies in ESCC and contribute to improved early diagnosis and treatment outcomes for patients. We present this article in accordance with the Narrative Review reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-1048/rc).

Methods

In order to distinguish lncRNAs biomarkers that have been published for the diagnosis or prognosis of patients with ESCC, we conducted a search in the PubMed and PubMed Central databases using the following keywords till May 2024. From these studies, we identified 83 up-regulated lncRNAs and 19 down-regulated lncRNAs. The search strategy summary for this study is detailed in *Table 1* and the block diagram of differential expression in ESCC in *Figure 1*.

The differential expression of lncRNAs in ESCC

In the research of ESCC, lncRNAs are considered as effectors that mediate metastasis, playing a significant role in the processes of tumor invasion and metastasis (16). LncRNAs can promote the invasion and metastasis of tumor cells by regulating the EMT process. EMT is a key step for tumor cells to acquire an invasive phenotype, involving changes in the expression of cell adhesion molecules, such as the downregulation of E-cadherin and the upregulation of N-cadherin and vimentin (17).

LncRNAs can interact with transcription factors, microRNAs (miRNAs), or proteins, affecting the expression of these molecules and thereby regulating EMT. LncRNAs are capable of modulating the migration and invasion capabilities of tumor cells by affecting cytoskeletal reorganization, extracellular matrix degradation, and the function of cell adhesion molecules. These processes often involve specific signaling pathways, and lncRNAs can interact with key molecules in these pathways, thereby influencing tumor metastasis. On the other hand, lncRNAs also play an important role in the tumor microenvironment, affecting the function of stromal cells such as tumor-associated macrophages and fibroblasts, and thus influencing tumor invasion and metastasis. LncRNAs can regulate processes like inflammatory responses, angiogenesis, and immune evasion, creating favorable conditions for tumor cell metastasis. LncRNAs can interact with various signaling pathways related to tumor metastasis, such as Wnt/β-catenin signaling pathway, TGF-β, and Notch, affecting the metastatic behavior of tumor cells. These pathways involve the regulation of cell proliferation, survival, invasion, and metastasis, and lncRNAs can act as regulatory factors in these pathways, influencing tumor progression. Therefore,

Table 1 The search strategy summary

Items	Specification
Date of search	May 31, 2024
Databases and other sources searched	PubMed and PubMed Central databases
Search terms used	(I) (LncRNAs or long non-coding RNA) AND (esophageal squamous cell carcinoma or ESCC) AND (up-regulated or down-regulated)
	(II) LncRNAs/LNCRNAS differential expression esophageal squamous cell carcinoma
	(III) LncRNAs/LNCRNAS differential expression ESCC
	(IV) LncRNAs/LNCRNAS high expression low expression esophageal squamous cell carcinoma
	(V) LncRNAs/LNCRNAS high expression low expression ESCC
	(VI) LncRNAs differential expression ESCC tissue expression
Timeframe	From May 1, 1990 to May 31, 2024
Inclusion and exclusion criteria	Inclusion criteria: (I) ESCC; (II) lncRNAs; (III) experimental; (IV) differentially expressed
	Exclusion criteria: (I) other cancers and tumors; (II) non-experimental; (III) review; (IV) meta-analysis; (V) case report; (VI) EAC; (VII) non-lncRNAs
Selection process	The entire selection process was jointly completed by H.W. and R.F., with quality control managed by L.L. Finally, they established the inclusion and exclusion criteria and reached a consensus

EAC, esophageal adenocarcinoma; ESCC, esophageal squamous cell carcinoma; lncRNAs, long non-coding RNAs.

lncRNAs have an important role in tumor metastasis and are considered potential therapeutic targets.

High-level expression lncRNAs in EC and clinical significance

This comprehensive review presents a compilation of up-regulated lncRNAs that exhibit heightened expression in ESCC. Identified through rigorous analysis, these molecules are linked to a spectrum of oncogenic processes, including the promotion of cell proliferation, invasion, and migration. The up-regulation of these lncRNAs is portrayed as a potential indicator of tumor aggressiveness and poor patient prognosis, underscoring their importance as diagnostic and therapeutic targets. Please refer to *Table 2* for details.

Low-level expressed lncRNAs in EC and clinical significance

This manuscript delineates a set of lncRNAs that exhibit diminished expression in ESCC. The downregulation of these lncRNAs correlates with attenuated tumor progression, suggesting their potential as tumor suppressors. The inverse relationship between lncRNAs expression levels and the aggressiveness of the tumor indicates a beneficial effect on patient outcomes. These findings lay the groundwork for further exploration of their role in inhibiting oncogenesis and metastasis. Please refer to *Table 3* for details.

The regulation of signaling pathway that lncRNAs participates in ESCC

LncRNAs play a significant role in the pathogenesis of ESCC. They regulate various signaling pathways, including Phosphatidylinositol 3-kinase/Protein kinase B/Mammalian target of rapamycin (PI3K/AKT/mTOR), Wnt/β-catenin, and p53, which influence tumor cell proliferation, apoptosis, migration, and metabolism. For instance, CASC9 promotes tumor cell proliferation and survival by activating the PI3K/AKT/mTOR pathway, while GAS5 suppresses tumor development by inhibiting this pathway. Additionally, lncRNAs are involved in modulating the tumor microenvironment, including tumor immune evasion and therapeutic resistance, making them potential targets for drug development. Therapeutic strategies targeting specific lncRNAs may involve the use of small interfering RNAs

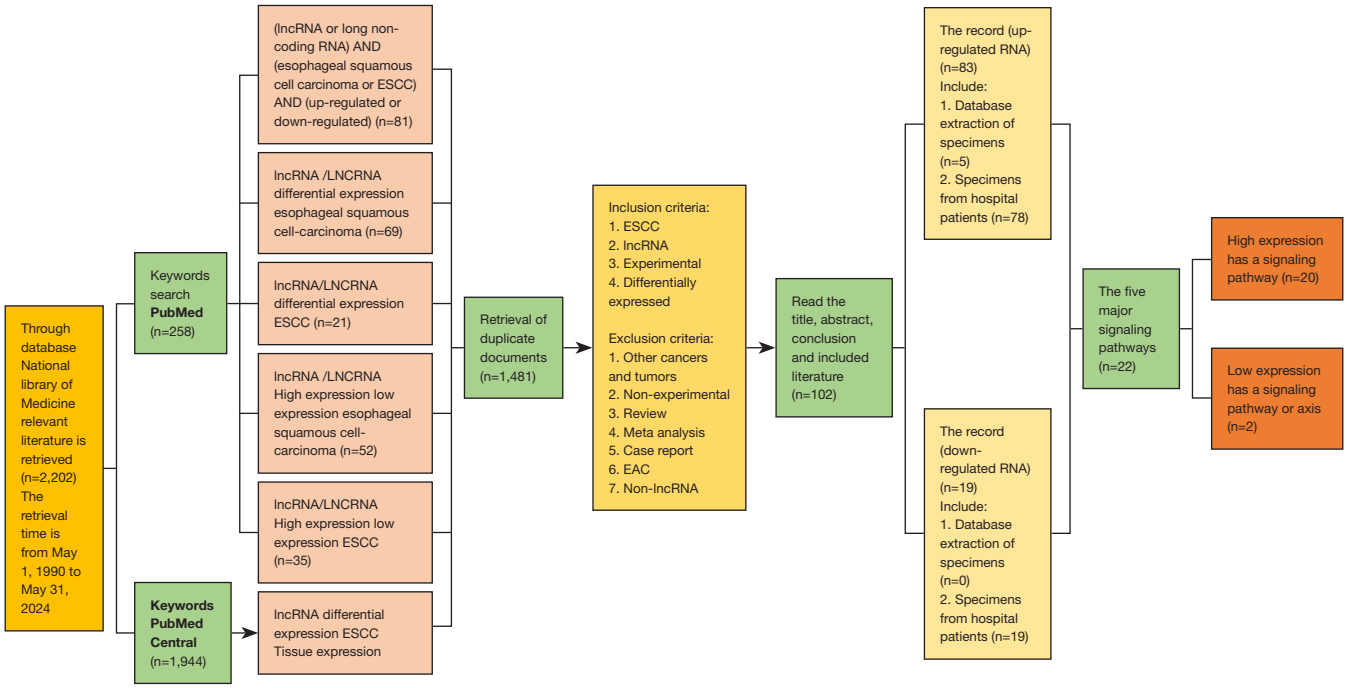

Figure 1 The block diagram of differential expression in esophageal squamous cell carcinoma. EAC, esophageal adenocarcinoma; ESCC, esophageal squamous cell carcinoma; lncRNA, long non-coding RNA.

(siRNAs), antisense oligonucleotides (ASOs), or other gene silencing technologies to reduce the expression of oncogenic lncRNAs or enhance the function of tumor-suppressive lncRNAs. The advantage of lncRNAs as drug development targets lies in their specificity and multifunctionality in tumor progression. Future drug development could focus on designing small molecule drugs or biologics that can specifically target lncRNAs. These drugs may function by inhibiting lncRNAs-protein interactions, blocking their intracellular transport, or modulating their stability. Furthermore, the expression profile of lncRNAs can serve as biomarkers for predicting drug response and monitoring disease progression, thereby enabling more personalized treatment strategies. By gaining a deeper understanding of the functions of lncRNAs in ESCC, we can anticipate the development of new therapeutic drugs to improve the treatment outcomes and prognosis for patients with ESCC (18).

PI3K/AKT/mTOR signaling pathway

The PI3K/AKT/mTOR signaling pathway is a pivotal regulatory network integral to maintaining cellular homeostasis, primarily by orchestrating cell growth, metabolism, and survival. This pathway is often hijacked in cancerous cells, leading to aberrant cell proliferation and resistance to apoptosis. LncRNAs, a class of non-protein-coding transcripts, have emerged as key regulators of this pathway. They exert their influence through diverse mechanisms, such as acting as molecular scaffolds or decoys to modulate the activity of pathway components. Depending on their function, lncRNAs can either promote tumorigenesis by enhancing the activation of the PI3K/AKT/mTOR pathway or impede cancer progression by dampening its signaling, thus representing a double-edged sword in the context of cancer biology. See *Figure 2* for details.

Wnt/β-catenin signaling pathway

The Wnt/β-catenin signaling pathway plays a crucial role in determining cell fate and maintaining tissue homeostasis, with its dysregulation implicated in various cancers. LncRNAs, emerging as pivotal regulators in this context, can modulate the Wnt/β-catenin pathway by influencing the nuclear translocation of β-catenin. This process is critical as it allows β-catenin to act as a transcriptional co-activator, leading to the activation of Wnt target genes. In the

Table 2 Data management for high-expression profiles

Order (high expression)	Pathology type	Sample	Expression	Clinicopathological parameters associated	Cell biological function	Overall survival is low	PMID	DOI
WTAP	ESCC	Tissue/cell	Up	Tumor size pathological stage survival status	Cell proliferation invasion and migration	Poor prognosis	36175708	10.1007/s12032-022-01830-9
MALAT1	ESCC	Tissue	Up	Pathological stage TNM stage lymph node metastasis	Cell proliferation, invasion and migration	Poor prognosis	26406400	10.3233/CBM-150513
HOTAIR	ESCC	Tissue/cell	Up	Histological grade lymph node status	Cell proliferation migration invasion	Poor prognosis	24118380	10.1111/cas.12296
RP 11366 H4.1.1, LINC00460, AC 093850.2	ESCC	Tissue	Up	Clinical stage and lymph node metastasis	Cell apoptosis proliferation migration	Poor prognosis	29409459	10.1186/s12885-018-4058-6
TUG1	ESCC	Tissue/cell	Up	TNM stage lymph node metastasis low survival rate	Cell growth migration, prognosis	Poor prognosis	32305055	10.4149/neo_2020_190805N717
LINC01980	ESCC	Tissue/cell	Up	TNM stage lymph node metastasis depth of infiltration	Cell migration and invasion	Poor prognosis	32325088	10.1016/j.abb.2020.108371.
HLA-P5	ESCC	Tissue/animal	Up	Tumor size TNM stage lymph node metastasis	Cell proliferation	Poor prognosis	35389828	10.1080/21655979.2022.2051854
BC200	ESCC	Tissue	Up	TNM stage lymph node metastasis histological stage	Cell migration and invasion	Poor prognosis	27143917	10.2147/OTT.S99401
LINC00473	ESCC	Tissue/cell	Up	Lymph node metastasis depth of infiltration	Migration and invasion	Poor prognosis	32468021	10.3892/ijmm.2020.4616
XIST	ESCC	Tissue/cell	Up	TNM stage and lymph node metastasis	Cell proliferation migration invasion apoptosis	Poor prognosis	29100288	10.18632/oncotarget.18638
TINCR	ESCC	Tissue/cell	Up	Cell apoptosis and cell cycle	Cell migration and invasion	Poor prognosis	26833746	10.1111/dote.12436
LincRNA-p21	ESCC	Tissue/cell	Up	Lymph node metastasis histological stage	Cell migration and invasion	Poor prognosis	31308755	10.2147/CMAR.S197557
LTBP1	ESCC	Tissue	Up	Tumor stage and lymph node metastasis	Cell migration and invasion	Poor prognosis	32216815	10.1186/s12967-020-02310-2
LINC01419	81372554	Tissue/cell	Up	Tumor stage and lymph node metastasis	Cell grouping and transfection invasion	Poor prognosis	31019568	10.1177/1758835919838958
m6A	ESCC	Tissue/cell	Up	Tumor stage and lymph node metastasis	Cell viability, and invasion	Poor prognosis	34544449	10.1186/s13046-021-02096-1
LINC00640	ESCC	Tissue/cell	Up	lymph node metastasis histological stage	Lymph node metastasis histological stage	Poor prognosis	28939763	10.1042/BSR20171019
DANCR	ESCC	Tissue/cell	Up	Tumor stage and lymph node metastasis	Cell migration and invasion	Poor prognosis	29997918	10.21037/jtd.2018.04.109
CASC2	ESCC	Tissue/cell	Up	Tumor stage and lymph node metastasis	Cell culture and transfection proliferation detection	Pooor prognosis	31728180	10.1186/s13578-019-0353-4
SNHG 6	ESCC	Tissue/cell	Up	Tumor stage and lymph node metastasis	Cell proliferation migration invasion apoptosis	Poor prognosis	33192074	10.2147/OTT.S275135
PCAT6	ESCC	Tissue/cell	Up	Lymph node metastasis histological stage	Cell migration proliferation and migration	Poor prognosis	35069911	10.7150/jca.62671
LINC00680	ESCC	Tissue/cell	Up	Tumor stage and lymph node metastasis	Cell migration proliferation and migration	Poor prognosis	35255921	10.1186/s12943-022-01539-3
LINC00152	ESCC	Tissue/cell	Up	TNM stage and lymph node metastasis	Cell migration and invasion	Poor prognosis	31191025	10.2147/CMAR.S198905
LncRNAs-ECM	ESCC	Tissue	Up	TNM stage tumor diagnosis prognosis	Cell invasion and migration	Poor prognosis	30128011	10.3892/ol.2018.9130
LINC00491	ESCC	Tissue/cell	Up	Tumor stage and lymph node metastasis	Cell migration and invasion	Poor prognosis	33537830	10.3892/ijmm.2021.4866
TRAIL	ESCC	Tissue/cell/animal	Up	Tumor stage and lymph node metastasis	Cell proliferation migration invasion apoptosis	Poor prognosis	34167551	10.1186/s13046-021-01972-0
LINC00941	ESCC	Tissue	Up	Tumor stage and lymph node metastasis	Cell proliferation migration invasion apoptosis	Poor prognosis	34254950	10.18632/aging.203286
GIHCG	ESCC	Tissue/cell	Up	Tumor stage and lymph node metastasis	Cell migration proliferation and migration	Poor prognosis	33408485	10.2147/OTT.S282348
RPS15	ESCC	Tissue/animal	Up	Tumor grade, depth of invasion, and lymph node metastasis	Cell migration and invasion	Poor prognosis	37264021	10.1038/s41392-023-01428-1
ZNF667-AS1	ESCC	Tissue/cell/animal	Up	Tumor stage and lymph node metastasis	Cell proliferation migration invasion apoptosis	Poor prognosis	35504176	10.1016/j.tranon.2022.101371
FAM225A	ESCC	Tissue/cell/animal	Up	Tumor grade, depth of invasion, and lymph node metastasis	Cell migration and invasion	Poor prognosis	33442405	10.7150/jca.51292

Table 2 (*continued*)

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Order (high expression)	Pathology type	Sample	Expression	Clinicopathological parameters associated	Cell biological function	Overall survival is low	PMID	DOI
TMEM44-AS1	ESCC	Tissue	Up	Tumor stage and lymph node metastasis	Cell proliferation, invasion, and migration	Poor prognosis	38040698	10.1038/s41420-023-01727-0
LINC01296	ESCC	Tissue	Up	Tumor stage and lymph node metastasis	Cell proliferation migration invasion apoptosis	Poor prognosis	30058683	10.26355/eurrev_201807_15507
SNHG7	ESCC	Tissue	Up	Tumor stage and lymph node metastasis	Cell migration proliferation and migration	Poor prognosis	34012636	10.21037/jgo-21-147
PCSK9	ESCC	Tissue/cell	Up	Tumor stage and lymph node metastasis	Cell proliferation migration invasion apoptosis	Poor prognosis	37854863	10.3892/ol.2023.14086
PSMA3-AS1	ESCC	Tissue/cell	Up	Tumor grade, depth of invasion, and lymph node metastasis	Cell migration and invasion	Poor prognosis	32005028	10.18632/aging.102716
eIF4A2	ESCC	Tissue/cell	Up	Tumor stage and lymph node metastasis	Cell migration and invasion	Poor prognosis	32934744	10.3892/ol.2020.12038
MARCKSL1	ESCC	Tissue/cell	Up	Tumor stage and lymph node metastasis	Cell migration and invasion	Poor prognosis	35894387	10.1002/cam4.5079
lnc-ATB	ESCC	Tissue/cell	Up	Tumor stage and lymph node metastasis	Cell proliferation migration invasion apoptosis	Poor prognosis	28640252	10.1038/cddis.2017.245
HIF-1α	ESCC	Tissue/cell	Up	Depth of invasion, and lymph node metastasis	Cell proliferation migration invasion apoptosis	Poor prognosis	31892989	10.7150/jca.35537
WNT5A	ESCC	Tissue	Up	Tumor stage and lymph node metastasis	Cell proliferation migration invasion apoptosis	Poor prognosis	35595735	10.1038/s41419-022-04901-x
MELK	ESCC	Tissue	Up	Depth of invasion, and lymph node metastasis	Cell migration and invasion	Poor prognosis	32047721	10.3389/fonc.2020.00010
PEDF	ESCC	Tissue	Up	Depth of invasion, and lymph node metastasis	Cell proliferation migration invasion apoptosis	Poor prognosis	33718190	10.3389/fonc.2021.625612
BANCR	ESCC	Tissue/cell	Up	Depth of invasion, and lymph node metastasis	Cell migration and invasion proliferation	Poor prognosis	31807012	10.2147/OTT.S227220
BCAR4	ESCC	Tissue/cell/animal	Up	Tumor stage and lymph node metastasis	Cell proliferation migration invasion apoptosis	Poor prognosis	33602031	10.1080/21655979.2021.1887645
RMRP	ESCC	Tissue/cell	Up	Depth of invasion, and lymph node metastasis	Cell proliferation migration invasion apoptosis	Poor prognosis	34516335	10.1080/21655979.2021.1974656
PKMYT1	ESCC	Tissue/cell	Up	Depth of invasion, and lymph node metastasis	Cell proliferation migration invasion	Poor prognosis	31695486	10.2147/CMAR.S214243
AK001796	ESCC	Tissue	Up	Tumor stage and lymph node metastasis	Cell proliferation migration invasion apoptosis	Poor prognosis	29568233	10.1186/s12935-018-0537-8
PVT1	ESCC	Tissue/cell/animal	Up	Tumor stage and lymph node metastasis	Cell proliferation migration invasion	Poor prognosis	28404954	10.18632/oncotarget.15878
FOXP4-AS1	ESCC	Tissue	Up	Tumor stage and lymph node metastasis	Cell proliferation migration invasion	Poor prognosis	34970490	10.3389/fonc.2021.773864
TGF-β1	ESCC	Tissue	Up	Depth of invasion, and lymph node metastasis	Cell migration and invasion	Poor prognosis	33123280	10.7150/jca.48426
KCNQ1	ESCC	Tissue	Up	Depth of invasion, and lymph node metastasis	Cell invasion, clinical stage	Poor prognosis	33909822	10.6061/clinics/2021/e2175
GACAT3	ESCC	Tissue/animal	Up	Tumor stage and lymph node metastasis	Cell proliferation migration invasion	Poor prognosis	34496842	10.1186/s12935-021-02192-4
LINC00941	ESCC	Tissue	Up	Lymph node metastasis	Cell proliferation migration invasion apoptosis	Poor prognosis	36717549	10.1038/s41419-023-05605-6
MYU	ESCC	Tissue	Up	Depth of invasion, and lymph node metastasis	Cell migration and invasion	Poor prognosis	33968175	10.3892/etm.2021.10076
AFAP1-AS1	ESCC	Tissue	Up	TNM stage tumor grade, depth of invasion, and lymph node metastasis	Cell migration and invasion	Poor prognosis	26756568	10.1002/mc.22454
LINC02820	ESCC	Tissue	Up	Tumor stage and lymph node metastasis	Cell migration and invasion	Poor prognosis	36357564	10.1038/s41417-022-00554-2
ZFPM2-AS1	ESCC	Tissue	Up	TNM stage tumor grade, depth of invasion, and lymph node metastasis	Cell proliferation migration invasion apoptosis	Poor prognosis	32065218	10.1042/BSR20194352
H3K27	ESCC	Tissue	Up	Tumor stage and lymph node metastasis	Cell viability, migration, and invasion, apoptosis	Poor prognosis	27956498	10.1093/nar/gkw1247
HOXC-AS1	ESCC	Tissue	Up	Depth of invasion, and lymph node metastasis	Cell proliferation migration invasion apoptosis	Poor prognosis	36510377	10.1002/jcla.24801
CCAT2	ESCC	Tissue	Up	TNM stage tumor grade, depth of invasion, and lymph node metastasis	Cell migration and invasion	Poor prognosis	34057837	10.1177/03000605211019938
LIPH-4	ESCC	Tissue	Up	Tumor stage and lymph node metastasis	Cell invasion, clinical stage	Poor prognosis	35971159	10.1186/s40364-022-00408-x
CASC8	ESCC	Tissue	Up	Tumor stage and lymph node metastasis	Cell grouping and transfection invasion	Poor prognosis	35982900	10.7150/ijbs.71234
CCAT1	ESCC	Tissue	Up	Linked to advanced stage	Cell invasion and migration	Poor prognosis	36624401	10.1186/s12885-022-10464-z
TMPO-AS1	ESCC	Tissue/cell/animal	Up	Tumor stage and lymph node metastasis	Cell proliferation, migration, and invasion	Poor prognosis	35760875	10.1038/s12276-022-00791-3

Table 2 (*continued*)

Table 2 (*continued*)

Order (high expression)	Pathology type	Sample	Expression	Clinicopathological parameters associated	Cell biological function	Overall survival is low	PMID	DOI
DDX11-AS1	ESCC	Tissue	Up	TNM stage tumor grade, depth of invasion, and lymph node metastasis	Cell migration and invasion	Poor prognosis	34866524	10.1080/21655979.2021.2008759
NCK1-AS1	ESCC	Tissue	Up	Depth of invasion, and lymph node metastasis	Cell viability, migration, and invasion, apoptosis	Poor prognosis	35311444	10.1080/21655979.2022.2038449
SNHG 17	ESCC	Tissue	Up	Reduce overall survival, and lymph node metastasis	Cell proliferation migration invasion apoptosis	Poor prognosis	34429400	10.1038/s41419-021-04093-w
LINC00514	ESCC	Tissue	Up	TNM stage tumor diagnosis prognosis	Cell migration and invasion	Poor prognosis	34533201	10.3892/ijo.2021.5266
CASC9	ESCC	Tissue/cell/animal	Up	Tumor stage and lymph node metastasis	Cell invasion and migration	Poor prognosis	29511340	10.1038/s41418-018-0084-9
CDKL3	ESCC	Tissue	Up	Depth of invasion, and lymph node metastasis	Cell migration and invasion	Poor prognosis	32974198	10.3389/fonc.2020.01602
RBBP7	ESCC	Tissue	Up	Depth of invasion, and lymph node metastasis	Cell migration and invasion	Poor prognosis	30546458	10.3892/ol.2018.9543
S100A7	ESCC	Tissue/serum	Up	TNM stage tumor diagnosis prognosis	Cell migration and invasion	Poor prognosis	34323409	10.1002/ctm2.459
AP-1	ESCC	Tissue	Up	Depth of invasion, and lymph node metastasis	Cell migration and invasion	Poor prognosis	38136265	10.3390/cancers15245719
APOC1	ESCC	Tissue	Up	TNM stage tumor diagnosis prognosis	Cell proliferation migration invasion apoptosis	Poor prognosis	36969562	10.3389/pore.2023.1610976
TPM3	ESCC	Tissue	Up	Higher rates of advanced stage and lymph node metastasis	Cell proliferation migration invasion apoptosis	Poor prognosis	34532475	10.21037/atm-21-4043
CKAP2L	ESCC	Tissue	Up	Depth of invasion, and lymph node metastasis	Cell migration and invasion	Poor prognosis	36090903	10.1155/2022/2378253
LINC01234	ESCC	Tissue	Up	Higher rates of advanced stage and lymph node metastasis	Cell migration and invasion	Poor prognosis	30519325	10.7150/jca.26095
LOC100133669	ESCC	Tissue	Up	Tumor stage and lymph node metastasis	Cell proliferation migration invasion apoptosis	Poor prognosis	32130753	10.1111/cpr.12750
VRK1	ESCC	Tissue	Up	TNM stage tumor diagnosis prognosis	Cell proliferation migration invasion apoptosis	Poor prognosis	29029460	10.18632/oncotarget.20020
RASSF8-AS1	ESCC	Tissue/serum	Up	Depth of invasion, and lymph node metastasis	Cell migration and invasion	Poor prognosis	36266257	10.1111/1759-7714.14690
ZFAS1	ESCC	Tissue	Up	TNM stage tumor grade, depth of invasion, and lymph node metastasis	Cell proliferation, migration, invasion and apoptosis	Poor prognosis	31775815	10.1186/s13046-019-1473-8
LOC146880	ESCC	Tissue	Up	Tumor stage and lymph node metastasis	Cell proliferation migration invasion apoptosis	Poor prognosis	34016787	10.18632/aging.203037
LINC01535	ESCC	Tissue	Up	Depth of invasion, and lymph node metastasis	Cell migration and invasion	Poor prognosis	32329845	10.26355/eurrev_202004_20832

The literature mentioned in this table can be found at supplementary file (Appendix 1). ESCC, esophageal squamous cell carcinoma; TNM, tumor node metastasis.

Table 3 Data collation for low-expression profiles

Order (low expression)	Pathology type	Sample	Expression	Clinicopathological parameters associated	Cell biological function	Prognosis	PMID	DOI
PGM5-AS1	ESCC	Tissue	Down	TNM stage lymph node metastasis	Cell migration invasion and apoptosis	Poor prognosis	31185143	10.1002/iub.2069
MAGI2-AS3	ESCC	Tissue/cell/animal	Down	Tumor size and tumor distant tumor metastasis	Cell migration invasion	Poor prognosis	33330444	10.3389/fcell.2020.552822
TUSC2P	ESCC	Tissue	Down	Tumor size and tumor distant tumor metastasis	Cell proliferation migration invasion	Poor prognosis	30219035	10.1186/s12885-018-4804-9
BANCR	ESCC	Tissue	Down	Lymph node metastasis	Cell invasion	Poor prognosis	32945416	10.3892/ijmm.2020.4687
TUG1	ESCC	Tissue	Down	Tumor size and tumor distant tumor metastasis EMT stage	Cell proliferation migration invasion	Poor prognosis	32139664	10.12659/MSM.919714
ZEB1-AS1	ESCC	Tissue	Down	TNM stage, lymph node metastasis and poor prognosis	Cell proliferation migration invasion	Poor prognosis	31638344	10.1111/jcmm.14692
TMEM161B-AS1	ESCC	Tissue	Down	TNM stage and lymph node metastasis	Cell proliferation migration invasion	Poor prognosis	34046994	10.1111/jcmm.16652
GAS5	ESCC	Tissue	Down	Tumor size and tumor distant tumor metastasis	Cell migration invasion	Poor prognosis	30368517	10.12659/MSM.910867
HEIH	ESCC	Tissue	Down	Tumor size and tumor distant tumor metastasis	Cell proliferation migration invasion	Poor prognosis	34790377	10.21037/jgo-21-586
AFAP1-AS1	ESCC	Tissue	Down	Tumor size and tumor distant tumor metastasis	Cell migration and invasion and transfection	Poor prognosis	32801880	10.2147/CMAR.S254302
HEIH	ESCC	Tissue	Down	TNM stage and lymph node metastasis	Cell proliferation migration invasion	Poor prognosis	32449803	10.1111/1759-7714.13489
MEG3	ESCC	Tissue	Down	TNM stage tumor size and tumor distant tumor metastasis	Cell migration invasion	Poor prognosis	32901893	10.3892/or.2020.7754
ZNF667-AS1	ESCC	Tissue	Down	Tumor size and tumor distant tumor metastasis	Cell migration and invasion and transfection	Poor prognosis	31804468	10.1038/s41419-019-2171-3
WDFY3-AS2	ESCC	Tissue	Down	Tumor size and tumor distant tumor metastasis	Cell migration and invasion and transfection	Poor prognosis	34194502	10.1155/2021/9951010
IUR	ESCC	Tissue	Down	Not significantly correlated with patients age, gender, BMI, serum albumin as well as clinical stages	Cell proliferation and apoptosis	Poor prognosis	32124090	10.1007/s10388-020-00724-x
RPL34-AS1	ESCC	Tissue	Down	Reduce tumor size and volume	Cell invasion and migration, and tumor volume, cell apoptosis	Poor prognosis	36162992	10.1186/s12885-022-10104-6
PART1	ESCC	Tissue	Down	TNM stage, lymph node metastasis and poor prognosis	Cell proliferation and invasion	Poor prognosis	33432363	10.3892/or.2021.7931
P21	ESCC	Tissue	Down	No significant difference with age and clinical performance; increased risks of developing esophageal cancer are connected with downregulation level of lincrna-p21	Cell proliferation, migration, invasion, and the transition	Poor prognosis	31308755	10.2147/CMAR.S197557
HAGLROS	ESCC	Tissue	Down	Tumor size and tumor distant tumor metastasis	Cell proliferation migration invasion	Poor prognosis	34790377	10.21037/jgo-21-586

The literature mentioned in this table can be found at supplementary file (Appendix 1). EMT, epithelial-mesenchymal transition; ESCC, esophageal squamous cell carcinoma; TNM, tumor node metastasis.

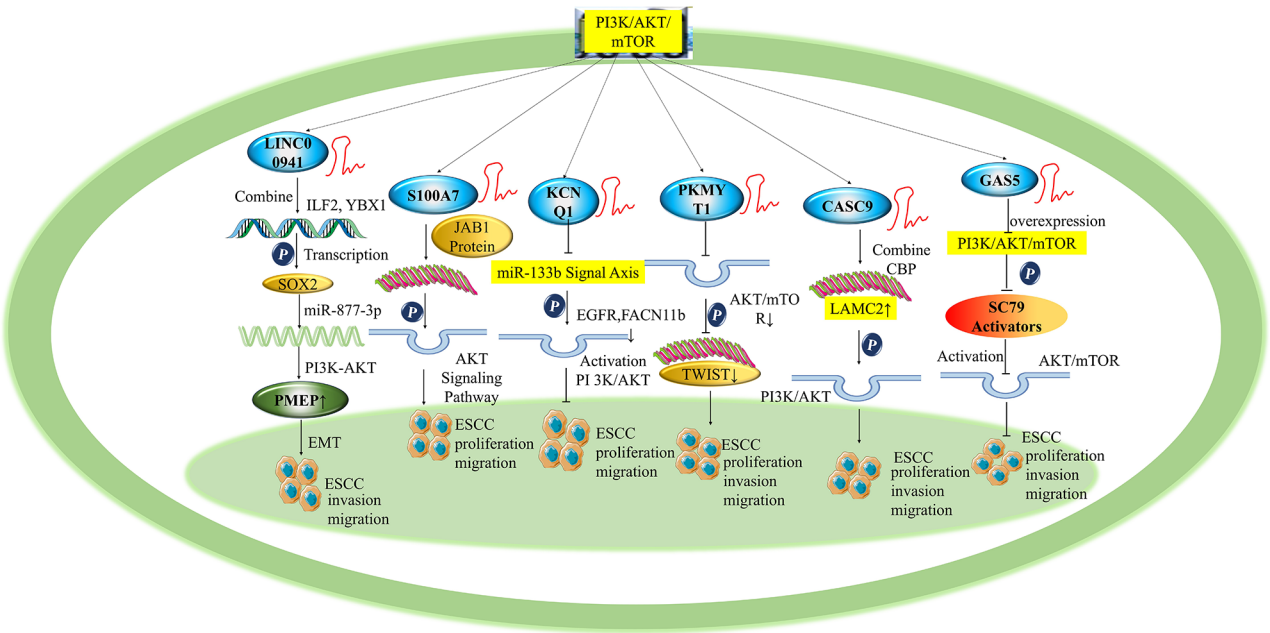

Figure 2 The regulatory function of oncogenic and tumor suppressor long non-coding RNAs in PI3K/AKT/mTOR signaling pathway in the pathogenesis of esophageal cancer. EMT, epithelial-mesenchymal transition; ESCC, esophageal squamous cell carcinoma; JAB1 Protein, c-Jun activation domain-binding protein 1; LAMC2, Laminin γ2 chain; miR-133b, microRNA-133b; miR-877-3p, microRNA-877-3p; P, phosphorylation; PI3K/AKT/mTOR, phosphatidylinositol 3-kinase/protein kinase B/mammalian target of rapamycin; PMEP, pemetrexed; SOX2, Sex-determining region Y box 2; TWIST, Twist-related protein.

context of ESCC, lncRNAs contribute significantly to cell proliferation and the maintenance of stem cell properties, which are essential for tumor growth and resistance to therapy. The intricate interplay between lncRNAs and the Wnt/β-catenin pathway underscores the complexity of molecular mechanisms in cancer progression and offers potential therapeutic targets for intervention. See *Figure 3* for details.

P53 signaling pathway

The p53 pathway, often hailed as the "guardian of the genome", is a linchpin in the preservation of genomic stability, playing a central role in preventing the proliferation of cells with DNA damage. LncRNAs have been identified to possess the capacity to modulate p53 activity, thereby influencing critical cellular processes such as cell cycle arrest, DNA repair, and apoptosis-key mechanisms through which p53 exerts its tumor-suppressive effects. Depending on their specific functions, lncRNAs can act as either positive or negative regulators of the p53 pathway, with some lncRNAs amplifying p53's tumor-suppressive functions, while others may attenuate its activity, leading to a delicate balance in the cellular response to stress and damage. The intricate relationship between lncRNAs and the p53 pathway underscores the multifaceted nature of gene regulation in the context of cancer biology, offering a rich landscape for therapeutic exploration. See *Figure 4* for details.

Mitogen-activated protein kinase (MAPK) signaling pathway

MAPK pathway is an essential signaling cascade that translates extracellular signals into intracellular responses, critically regulating cell proliferation, differentiation, and survival. LncRNAs have been recognized as key modulators of the MAPK pathway, exerting their influence by interacting with components of the signaling network or affecting the expression of genes involved in the pathway. These lncRNAs fine-tune the cellular response to diverse stimuli, such as growth factors and stress signals, thereby impacting the cellular decision-making process. In the context of ESCC, the dysregulation of lncRNAs can lead to

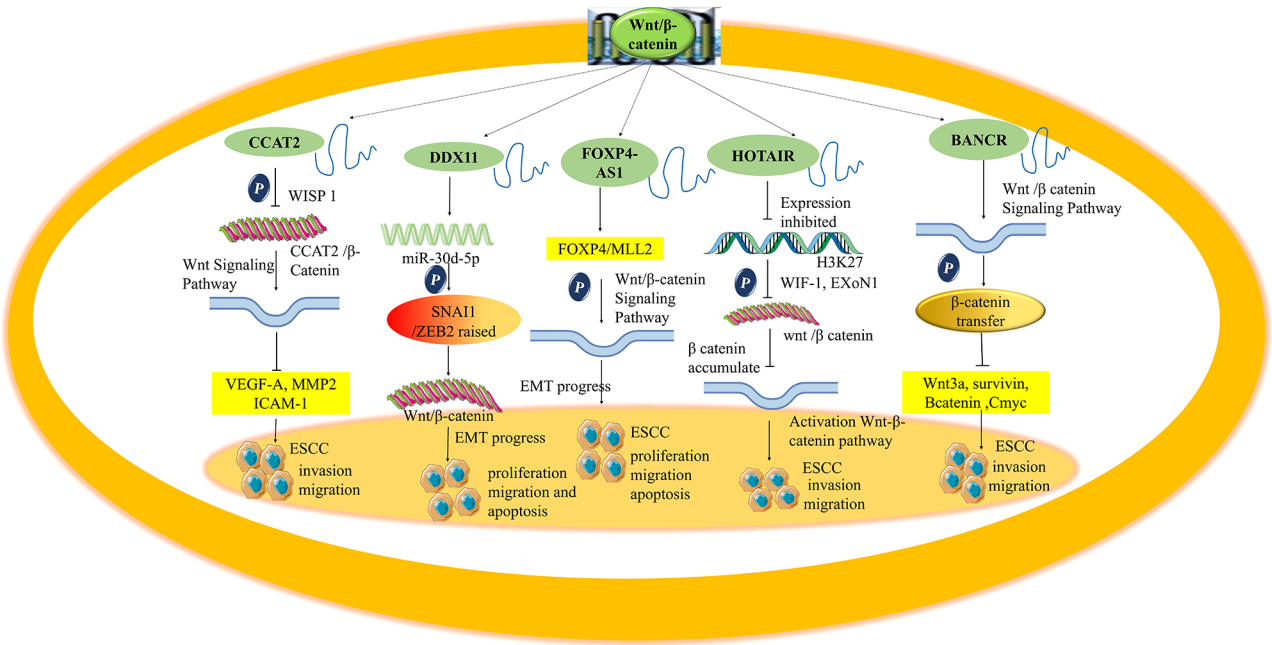

Figure 3 The regulatory function of oncogenic and tumor suppressor long non-coding RNAs in Wnt/β-catenin signaling pathway in the pathogenesis of esophageal cancer. EMT, epithelial-mesenchymal transition; ESCC, esophageal squamous cell carcinoma; EXoN1, exonuclease 1; FOXP4, forkhead box p4; ICAM-1, intercellular adhesion molecule-1; MMP2, matrix metalloproteinase 2; MLL2, mixed lineage leukemia 2; P, phosphorylation; SNAI1, Snail family zinc finger 1; VEGF-A, vascular endothelial growth factor A; WIF-1, WNT inhibitory factor 1; WISP1, WNT1 inducible signaling pathway protein 1; ZEB2, Zinc finger e-box binding homeobox 2.

the aberrant activation of the MAPK pathway, which in turn contributes to the acquisition of a malignant phenotype, including uncontrolled growth and resistance to apoptosis. The precise mechanisms by which lncRNAs intersect with the MAPK pathway to drive ESCC progression highlight the complexity of the interplay between non-coding and coding elements in cancer pathogenesis. See *Figure 5* for details.

Janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling pathway

The JAK/STAT pathway is a central signaling mechanism that controls various cellular functions, including immune responses and cell growth. LncRNAs have been identified as significant regulators within this pathway, affecting the activity of STAT proteins, which are essential for JAK/STAT signaling. LncRNAs can alter the behavior of cancer cells by influencing gene transcription related to cell proliferation, survival, and invasion. Additionally, they play a role in the tumor microenvironment by aiding cancer cells in evading the immune system, which is important for tumor progression and therapy resistance. The regulatory capacity of lncRNAs in the JAK/STAT pathway highlights their potential as biomarkers and therapeutic targets in cancer treatment. See *Figure 6* for details.

MiR-Axis signaling pathway

miRNAs are essential regulators of gene expression that influence key cellular processes, including cell growth, differentiation, and programmed cell death. They are particularly important in the context of cancer, where their normal regulatory functions can be disrupted. LncRNAs interact with miRNAs, modulating their activity and affecting gene regulation. This interaction can either absorb miRNAs to release their targets or enhance miRNA access to specific messenger RNAs (mRNAs). Disruptions in this lncRNAs-miRNA regulatory network can lead to uncontrolled cell cycle progression, cell survival, and tumor formation. Maintaining the balance between lncRNAs and miRNAs is vital for cellular stability, and understanding their interplay is crucial for developing cancer therapies. See *Figure 7* for details.

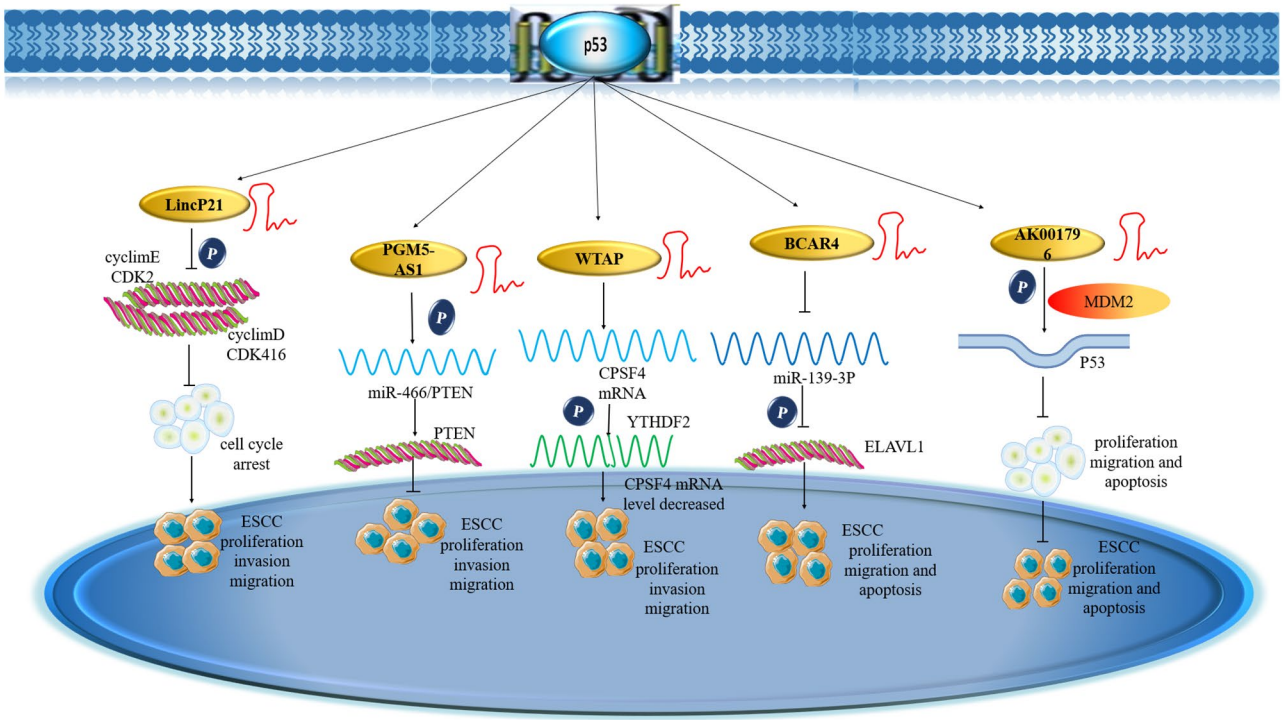

Figure 4 The regulatory function of oncogenic and tumor suppressor long non-coding RNAs in p53 signaling pathway in the pathogenesis of esophageal cancer. CDK2, cyclin dependent kinase 2; CDK416, cyclin dependent kinase 416; CPSF4, cleavage and polyadenylation specific factor 4; ELAVL1, ELAV like RNA binding protein 1; ESCC, esophageal squamous cell carcinoma; MDM2, murine double minute 2; miR-139-3P, microRNA-139-3p; miR-466, microRNA-466; mRNA, messenger ribonucleic acid; P, phosphorylation; P53, tumor protein p53; PTEN, phosphatase and tensin homolog; YTHDF2, YTH N6-methyladenosine RNA binding protein 2.

TGF-β1 signaling pathway

The TGF-β1 pathway is a complex signaling system crucial for controlling cell processes vital to tissue maintenance and repair. It has a dual nature in cancer: it can act as a suppressor in early stages but may promote tumor growth later on. LncRNAs significantly influence this pathway, impacting the tumor microenvironment. They can interact with pathway components and affect mRNA stability, tipping the balance between suppression and promotion of tumors. Misregulation of lncRNAs can result in hallmarks of aggressive cancer such as uncontrolled cell growth, apoptosis resistance, and increased metastasis. Grasping the interaction between lncRNAs and the TGF-β1 pathway is key to understanding cancer progression and discovering new therapeutic targets. See *Figure 8* for details.

Glycogen synthase kinase-3 Beta (GSK-3β)/snail signaling pathway

The GSK-3β/Snail pathway is a critical mediator of EMT, enabling cancer cells to transition from a non-invasive to an invasive phenotype, thereby facilitating invasion and metastasis. LncRNAs, through their diverse regulatory roles, can modulate this pathway, influencing the aggressive behavior of cancers such as ESCC. Targeting the interplay between lncRNAs and the GSK-3β/Snail axis holds promise for developing new therapeutic strategies to combat cancer progression and metastasis. See *Figure 9* for details.

In summary, lncRNAs exert a profound influence over the signaling pathways that drive ESCC progression. Their ability to modulate these pathways underscores their potential as biomarkers for diagnosis and as targets

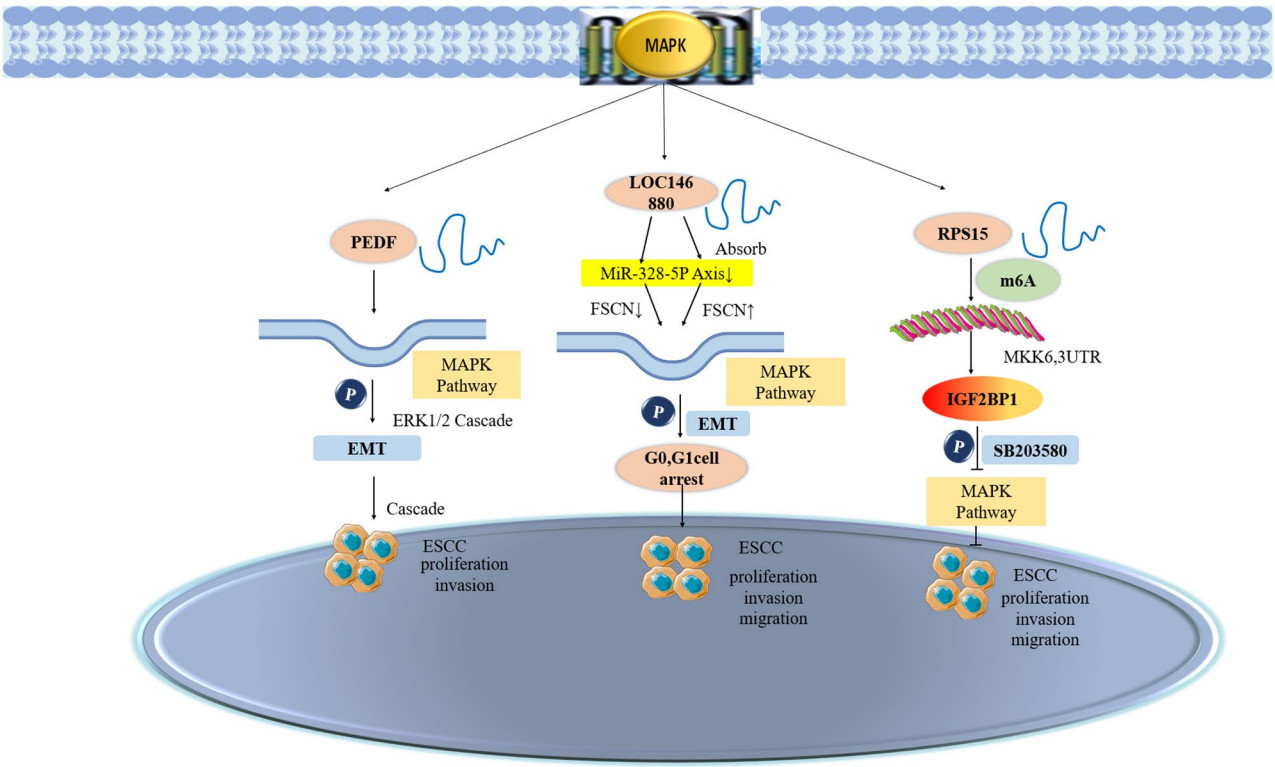

Figure 5 The regulatory function of oncogenic and tumor suppressor long non-coding RNAs in MAPK signaling pathway in the pathogenesis of esophageal cancer. 3UTR, 3' untranslated region; EMT, epithelial-mesenchymal transition; ERK1/2, extracellular-regulated kinase 1/2; ESCC, esophageal squamous cell carcinoma; IGF2BP1, insulin-like growth factor 2 mRNA binding protein 1; MAPK, mitogen-activated protein kinase; MKK6, mitogen-activated protein kinase kinase 6; m6A, N6-methyladenosine; miR-328-5P, microRNA-328-5p; P, phosphorylation.

for therapeutic intervention. Future research should focus on elucidating the precise mechanisms of lncRNAs action within these pathways to facilitate the development of novel, targeted treatments for ESCC.

The application of LncRNAs in clinical ESCC

Reconstructive therapy is an emerging treatment approach, and the exploration of lncRNAs as targets for ESCC treatment is a novel field. By intervening in their expression or function, the progression of tumors can be hindered. siRNA and Antisense oligonucleotides (ASO), which target and degrade oncogenic lncRNAs, are promising directions for future clinical applications. siRNA is a double-stranded RNA molecule that can specifically degrade target mRNA through the RNA interference pathway, thereby inhibiting the expression of specific genes (19). In the treatment of ESCC, designing specific siRNA molecules to target and degrade lncRNAs that promote tumor growth and metastasis can effectively suppress the malignant behavior of tumor cells. The therapeutic potential of siRNA lies in its high specificity and effective gene silencing capability, but it also faces challenges in improving its stability and targeted delivery in the body. ASOs are single-stranded DNA or RNA molecules that inhibit gene expression by binding to target RNA sequences, preventing their translation or promoting their degradation. In ESCC treatment, ASOs can be designed to be complementary to specific lncRNAs sequences, inhibiting tumor progression by blocking their function or promoting their degradation (20). The advantage of ASOs lies in their good chemical stability and cell permeability, but ensuring their specificity and minimizing off-target effects are current research focuses.

In clinical applications, the delivery systems for siRNA and ASOs are key to achieving therapeutic effects. Various

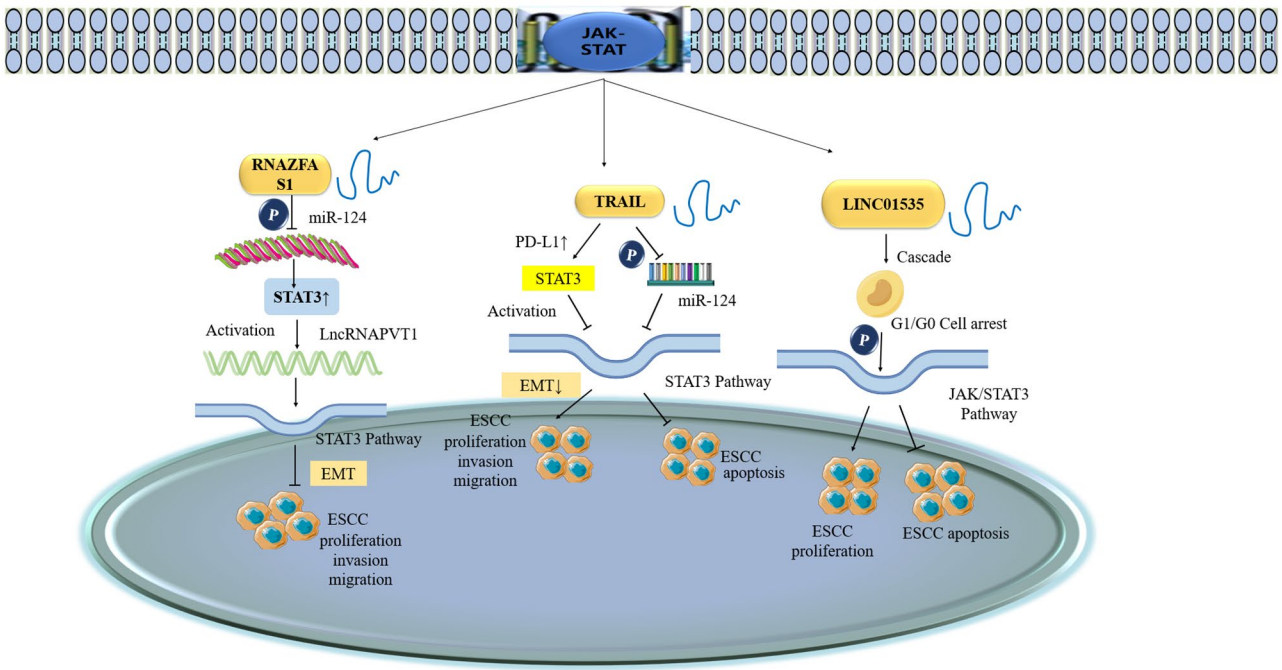

Figure 6 The regulatory function of oncogenic and tumor suppressor long non-coding RNAs in JAK/STAT signaling pathway in the pathogenesis of esophageal cancer. EMT, epithelial-mesenchymal transition; ESCC, esophageal squamous cell carcinoma; JAK/STAT, Janus kinase/signal transducer and activator of transcription; miR-124, microRNA-124; P, phosphorylation; PD-L1, programmed cell death-ligand 1.

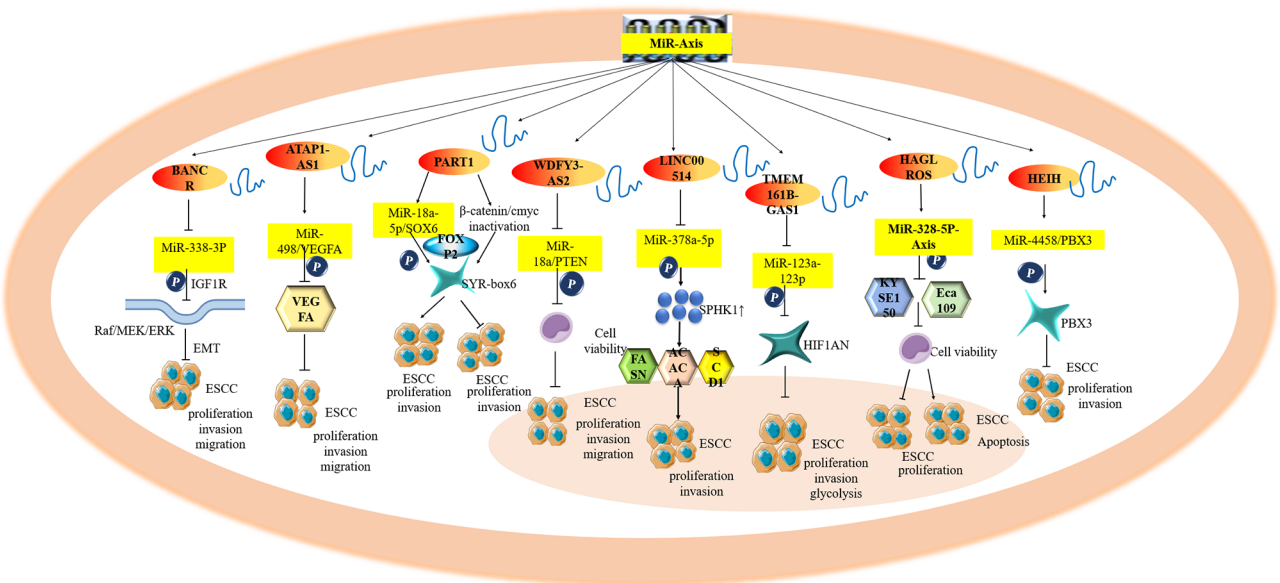

Figure 7 The regulatory function of oncogenic and tumor suppressor long non-coding RNAs in MiR-Axis signaling pathway in the pathogenesis of esophageal cancer. ACACA, acetyl-coenzyme A carboxylase alpha; EMT, epithelial-mesenchymal transition; ESCC, esophageal squamous cell carcinoma; FASN, Fatty acid synthase; FOXP2, forkhead box p2; HIF1AN, Hypoxia inducible factor 1 subunit alpha inhibitor; IGF1R, insulin-like growth factor 1 receptor; P, phosphorylation; PBX3, Pre-B cell leukemia homeobox 3; SCD1, Stearoyl-coA desaturase 1; SPHK1, sphingosine kinase 1; VEGFA, vascular endothelial growth factor A.

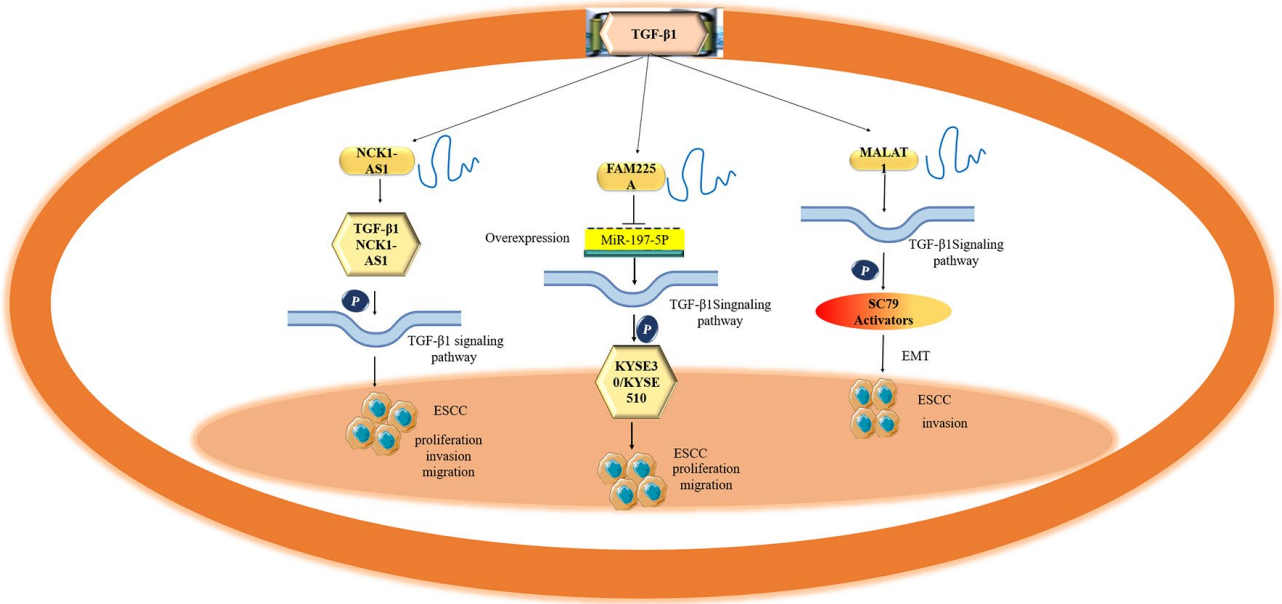

Figure 8 The regulatory function of oncogenic and tumor suppressor long non-coding RNAs in TGF-β1 signaling pathway in the pathogenesis of esophageal cancer. EMT, epithelial-mesenchymal transition; ESCC, esophageal squamous cell carcinoma; NCK1-AS1, NCK 1 antisense RNA 1; P, phosphorylation; TGF-β1, transforming growth factor beta 1.

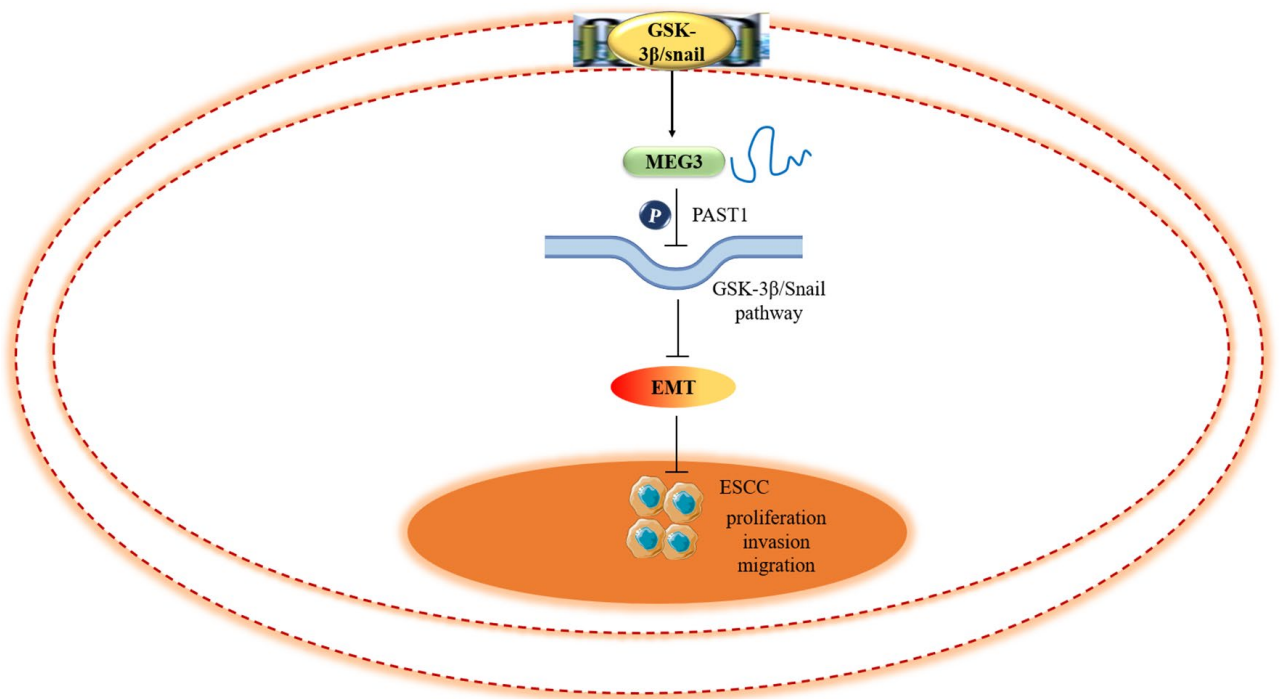

Figure 9 The regulatory function of oncogenic and tumor suppressor long non-coding RNAs in GSK-3β/snail signaling pathway in the pathogenesis of esophageal cancer. EMT, epithelial-mesenchymal transition; ESCC, esophageal squamous cell carcinoma; GSK-3β, glycogen synthase kinase-3 beta; MEG3, maternally expressed gene 3; P, phosphorylation.

delivery routes are being studied, including the use of viral vectors, nanoparticles, liposomes, etc. These delivery systems aim to enhance the stability of siRNA and ASOs, protect them from degradation by nucleases in the body, and ensure their efficient entry into tumor cells. Study indicates (21) that LINC00624, an immunosuppressive lncRNAs in cancer, has significant therapeutic potential when targeted by ASOs in tumors expressing high levels of LINC00624. TGF-β pathway antagonists have shown progress in clinical trials and have demonstrated safety and significant therapeutic efficacy in cancer patients (22). For instance, Vactosertib has been proven to have good tolerability and promising activity against various cancer types when combined with chemotherapy and immunotherapy. AVID200 has been shown to be safe in clinical trials, binding well to peripheral targets throughout the treatment period, leading to TGF-β target modulation and immune activation. The combination of TGF-β pathway antagonists with other treatment modalities is highly relevant as they offer a fast-acting, cost-effective, and feasible method to improve cancer treatment.

In summary, siRNA and ASO as recombinant therapeutics targeting lncRNAs provide new insights for ESCC treatment. Precise regulation of tumor-associated lncRNAs will undoubtedly play a significant role in future cancer therapy.

Discussion

This review highlights the significant role of lncRNAs in ESCC, where their dysregulation affects tumor behavior and survival rates. LncRNAs are considered as diagnostic markers and therapeutic targets, with their expression levels correlating to the aggressiveness of the tumor. However, the heterogeneity and variable expression of lncRNAs across different patients and tumor tissues present challenges for the standardization of lncRNAs as biomarkers. Large-scale, multi-center clinical sample analyses are needed to establish the expression patterns and mechanisms of action of specific lncRNAs in ESCC. Although numerous lncRNAs associated with ESCC have been identified, our understanding of their functions is still limited (23). Further experimental studies, such as gene knockout and overexpression experiments, are required to clarify the specific roles of lncRNAs in the development of ESCC. LncRNAs influence the occurrence and development of tumor cells through interactions with various signaling pathways, but the molecular mechanisms of these interactions are not fully elucidated. Future research should delve into how lncRNAs regulate signaling pathways such as PI3K/AKT/mTOR, Wnt/β-catenin, and p53, and how these regulations impact the progression of ESCC. The stability of lncRNAs *in vivo*, their degradation rates, and the efficiency of their extraction from different biological samples all affect the reliability of lncRNAs as clinical biomarkers. More sensitive and specific detection technologies need to be developed to accurately measure the expression levels of lncRNAs. As potential therapeutic targets, the regulatory mechanisms of lncRNAs are complex and may involve multiple molecules and signaling pathways. Developing intervention strategies targeting lncRNAs, such as small molecule drugs and gene editing technologies, requires overcoming challenges in drug delivery, specificity, and side effects. Despite advances in basic research, translating lncRNAs research findings into clinical practice faces many difficulties (24). More clinical trials are needed to verify the effectiveness and safety of lncRNAs as diagnostic markers, prognostic assessment tools, and therapeutic targets. Given the individual differences in lncRNAs expression, future treatment strategies may need to be tailored based on the lncRNAs expression profiles of patients. This requires the establishment of a precise lncRNAs typing system, combined with other clinical information, to provide personalized treatment plans for patients. In summary, the clinical application of lncRNAs in ESCC is full of opportunities, but to achieve widespread clinical application, a series of challenges from basic research to clinical translation must be overcome. This requires interdisciplinary collaboration, the introduction of innovative technologies, and rigorous clinical study design and execution (25).

Conclusions

In summary, lncRNAs play a pivotal role in ESCC, with their expression levels being closely associated with tumor aggressiveness and prognosis. Despite the significant potential of lncRNAs as biomarkers and therapeutic targets, their heterogeneity and complex regulatory mechanisms pose challenges for clinical application. Future research should concentrate on the functional studies of lncRNAs in ESCC, investigate their interactions with key signaling pathways, and develop more accurate detection technologies. Moreover, additional clinical trials are necessary to validate the utility of lncRNAs in diagnosis, prognosis assessment, and treatment. Ultimately, the clinical translation of lncRNAs requires interdisciplinary

collaboration, technological innovation, and rigorous clinical study design to advance personalized medicine and enhance treatment outcomes for ESCC patients.

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Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-1048/rc

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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