Cancer Cell International

REVIEW

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Competing endogenous RNAs network dysregulation in oral cancer: a multifaceted perspective on crosstalk and competition

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Abstract

Oral cancer progresses from asymptomatic to advanced stages, often involving cervical lymph node metastasis, resistance to chemotherapy, and an unfavorable prognosis. Clarifying its potential mechanisms is vital for developing effective theraputic strategies. Recent research suggests a substantial involvement of non-coding RNA (ncRNA) in the initiation and advancement of oral cancer. However, the underlying roles and functions of various ncRNA types in the growth of this malignant tumor remain unclear. Competing endogenous RNAs (ceRNAs) refer to transcripts that can mutually regulate each other at the post-transcriptional level by vying for shared miRNAs. Networks of ceRNAs establish connections between the functions of protein-coding mRNAs and non-coding RNAs, including microRNA, long non-coding RNA, pseudogenic RNA, and circular RNA, piwi-RNA, snoRNA. A growing body of research has indicated that imbalances in ceRNAs networks play a crucial role in various facets of oral cancer, including development, metastasis, migration, invasion, and inflammatory responses. Hence, delving into the regulatory pathways of ceRNAs in oral cancer holds the potential to advance our understanding of the pathological mechanisms, facilitate early diagnosis, and foster targeted drug development for this malignancy. The present review summarized the fundamental role of ceRNA network, discussed the limitations of current ceRNA applications, which have been improved through chemical modification and carrier delivery as new biomarkers for diagnosis and prognosis is expected to offer a groundbreaking therapeutic approach for individuals with oral cancer.

Keywords Oral cancer, CeRNAs, Long non-coding RNA, MicroRNA, Circular RNA, Pseudogene

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Introduction

Oral cancer (OC) is the sixth most common cancer worldwide [1]. It includes tumors that arise in different areas such as the lips, hard palate, upper and lower alveolar ridges, anterior two-thirds of the tongue, sublingual area, buccal mucosa, retromolar trigone, and the bottom of the oral cavity [2]. From a histological standpoint, oral squamous cell carcinomas (OSCC) account for over 90% of malignant neoplasms in the oral cavity [3]. The absence of distinct diagnostic indicators and clinical features makes early detection challenging for OC, resulting in a lower overall survival rate for patients [4]. Currently, there are about 370,000 new cases of OC worldwide each year, with approximately 170,000 deaths, two-thirds of which come from the Asian region [5]. Simultaneously, diverse non-invasive detection technologies have emerged for identifying precancerous lesions and diagnosing OC [6], such as oral cytology detection [7], oral spectroscopy [8], and the use of biomarkers in saliva to reflect the metabolic status of patients under pathological conditions [9]. These technologies exhibit specific levels of sensitivity and specificity, proving beneficial in the diagnosis of OC. In the treatment of OC, comprehensive treatment regimens have been developed, including expanded primary tumor resection and neck lymph node dissection, as well as preoperative and postoperative adjuvant radiotherapy or chemotherapy [10]. Despite advancements in diagnostic and therapeutic methodologies, the survival rates for individuals with OSCC have shown limited improvement over the preceding decades. Even after surgical resection, 16-20% of patients may experience local recurrence with poor prognosis [11]. The latest progress in genome sequencing has revealed the molecular mechanisms of OSCC pathogenicity, which is mainly caused by abnormal molecular expression. These factors encompass the gathering of genetic and epigenetic alterations, along with abnormalities in signaling pathways associated with cancer [12]. These discoveries have prompted a reconsideration of how OSCC is diagnosed and treated. Although most studies on OSCC have focused on the mechanism of RNA involved in gene expression regulation and post-transcriptional regulation, the network regulatory interactions and crosstalk of overall RNA (especially ncRNA) have not been fully explored at different stages of OSCC development.

A small fraction, less than 2%, of the genes within the human genome is responsible for encoding proteins. Those genes that don't encode proteins are termed non-coding RNAs, and they actively contribute to the intricate regulation of gene expression [13]. While microRNAs (miRNAs) and messenger RNAs (mRNAs) have been extensively investigated, a more in-depth analysis is needed to comprehend the functions of additional non-coding RNAs. The progress in next-generation sequencing technology undeniably has facilitated the identification of a vast array of non-coding RNAs (ncRNAs), gradually unveiling their biological functions [14]. In 2011, Pandolfi and colleagues proposed the competing endogenous RNA (ceRNA) hypothesis based on a comprehensive review of existing microRNA research [15]. The ceRNA hypothesis suggests that as long as ceRNAs contain identical microRNA response elements (MREs) in their 3'-UTRs, it can absorb miRNA, like a sponge, via base complementation, thereby reducing or enhancing the stability of target RNA, and limit or promote the efficiency and degree of target RNA expression, thus mediating physiological and pathological processes within the organism. With the deepening of ceRNAs research, it is found that lncRNA, circRNA, and pseudogene transcripts can also act as ceRNAs and bind to miRNAs [16], modulating the expression of related genes (Fig. 1).

Studies have shown that in OC, ceRNAs can competitively bind miRNAs with the mRNA 3'UTR of oncogenes, tumor suppressor genes, and other cancer-related signaling pathway factor. This competitive binding promotes or inhibits the functions of microRNA [17–19], and plays a crucial role in the occurrence, progression, invasion, metastasis, and drug treatment of tumors. Hence, the exploration of RNA associated with the ceRNA network throughout the progression of OC can offer fresh perspectives on the biological mechanisms underlying the pathogenicity of OC. Furthermore, it may help to explore potential targeted therapy and predict molecular markers. This review aims to demonstrate the various components of ceRNAs network regulation, and highlight the biological functions of miRNAs, lncRNAs, circRNAs and transcriptional pseudogene. More importantly, the discussion focuses on the significant function of recent ceRNAs networks at different stages of OC.

MicroRNAs (miRNAs), small non-coding RNAs present within cells, undergo a complex biogenesis process. The gene encoding miRNA production is transcribed into pri-miRNAs by polymerase II. Subsequently, the enzyme Drosha in the nucleus processes pri-miRNAs, generating pre-miRNAs. These pre-miRNAs are then transported from the nucleus to the cytoplasm through Exportin-5. In the cytoplasm, Dicer, an enzyme, cleaves pre-miRNAs, resulting in the formation of miRNA duplexes. Finally, the miRNA duplexes are unwound and loaded onto Argonauts (Ago) to create miRNA-induced silencing complexes (miRISCs). These complexes have the ability to bind to MRE within the target mRNA molecules, leading to mRNA degradation or inhibition of translation. Additionally, besides mRNA, there are various other RNA molecules exist in cells, including lncRNAs,

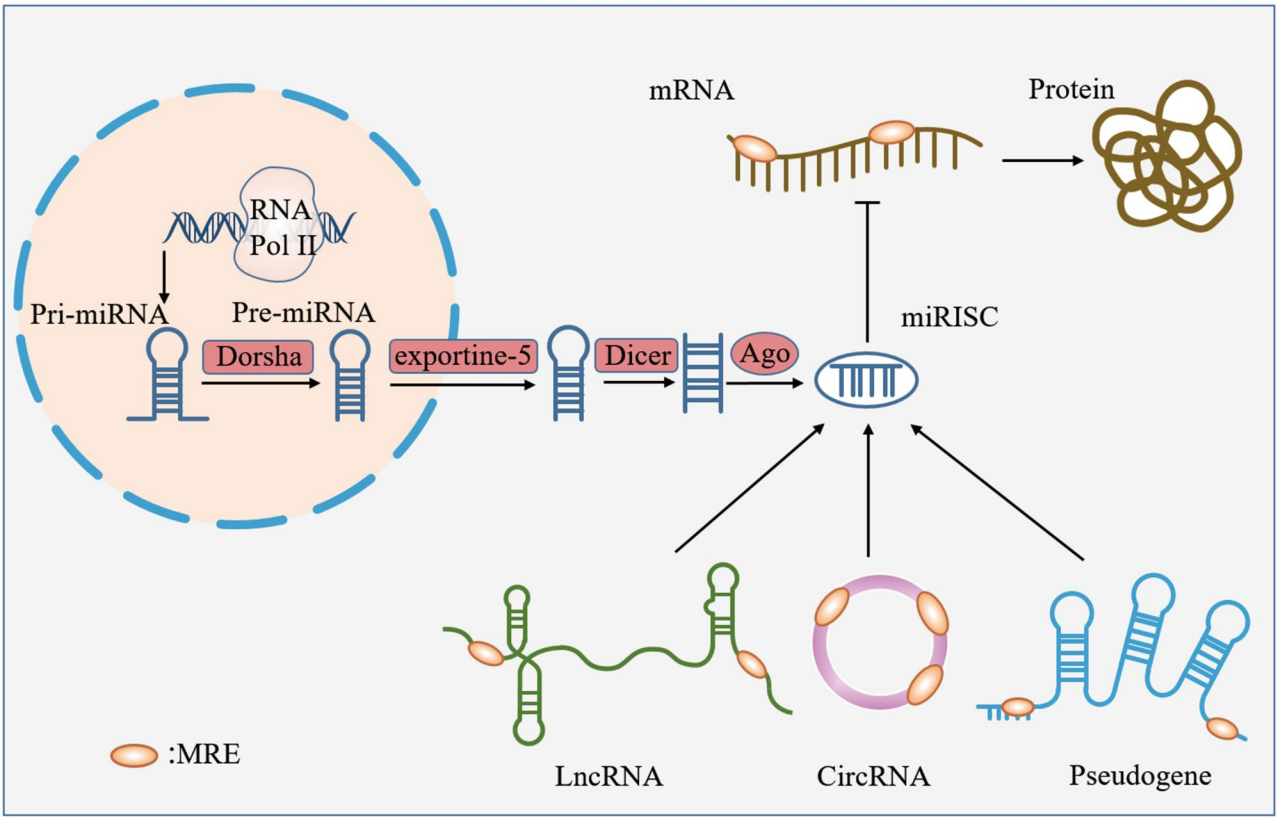

Fig. 1 Interaction of different ceRNAs with microRNAs and mRNA

circRNAs, and transcriptional pseudogenes, which also possess MREs and can function as ceRNAs.

Structural components of ceRNA

MiRNAs as the central node of ceRNA network

miRNAs are endogenously encoded non-coding RNA molecules, typically around 23 nucleotides in length [20]. Throughout the biogenesis of miRNAs, various cleavage events, catalyzed by RNases like Drosha and Dicer, occur to transform primary miRNAs (pri-miRNAs) into mature miRNA duplexes [21]. Subsequently, the miRNA duplex is unwound and loaded onto Ago, forming the core effector complexes called miRISCs [21]. These complexes have the capability to form complementary sequences with the 3'-untranslated region (UTR) of the target mRNA, leading to the inhibition of either its translation or splicing function [22, 23]. Therefore, miRNAs mainly regulate target mRNA at the transcriptional level, impacting diverse biological processes, including organism growth and development, cell apoptosis, proliferation, defense against viruses, and lipid metabolism [24]. Nonetheless, the regulatory influence of miRNAs can undergo additional altered based on the abundance of both coding and non-coding endogenous transcripts. These transcripts can interact with the same miRNAs through shared MERs and are suggested to function as ceRNAs, facilitating indirect crosstalk. Moreover, recent investigations indicate that the efficacy of ceRNAs is subject to variable factors including the relative abundance of ceRNAs and target miRNAs, subcellular localization, and the presence of RNA binding proteins [25]. Changes in any of these elements may contribute to diverse cancers arising from an imbalance in ceRNAs networks. Bioinformatics technology has recently unveiled a burgeoning involvement of numerous ceRNAs in the context of OC. Consequently, delving into ceRNA networks holds the potential to offer innovative perspectives on the pathogenesis and therapeutic approaches for OC.

LncRNA inhibits miRNA interference with target gene mRNA

LncRNA is an RNA molecule exceeding 200 nucleotides in length. It functions as a regulatory element, interacting with various biological components, including proteins, RNA, and DNA [26]. As lncRNA lacks a clear open reading frame, it refrains from engaging in the process of protein synthesis [27]. Owing to this attribute, lncRNA was previously considered mere transcriptional noise associated with genes, lacking any discernible biological significance. However, recent research has illuminated the multifaceted roles of lncRNA, demonstrating its capacity to function as a signaling mediator, decoy molecule,

guide, and scaffold for proteins (Fig. 2A). It is implicated in the regulation of gene expression across various levels, including epigenetics, transcription, and post-transcription. Moreover, lncRNA is implicated in a diverse array of physiological and pathological processes, such as differentiation, development, malignant transformation, and beyond [28, 29]. In particular, lncRNAs exhibit differential expression during the occurrence and development of OC. Researchers have observed that certain lncRNAs compete for miRNAs binding domains in cells through cross-talk in tumors, subsequently inhibiting their ability to interfere with target mRNA encoded proteins [30], becoming factors leading to carcinogenesis or cancer inhibition.

CircRNA are biomarkers with stable structure and specificity in the ceRNAs network

CircRNA is a non-coding RNA molecule produced by irregular splicing of precursor mRNA. Most circRNAs originate from exons through reverse splicing or lasso formation, while a few are derived from intronic and untranslated regions [31]. CircRNA molecule shows a closed circular structure, lacking 5′ terminal cap and 3′ terminal poly(A) tail [32], which makes it resistant to nucleic acid exonuclease and impervious to degradation by enzymes, thus producing more stable expression (Fig. 2B) [33, 34]. Given its remarkably stable structure, disease specificity, and extensive presence in bodily fluids like blood, cerebrospinal fluid, saliva, and urine, circRNA

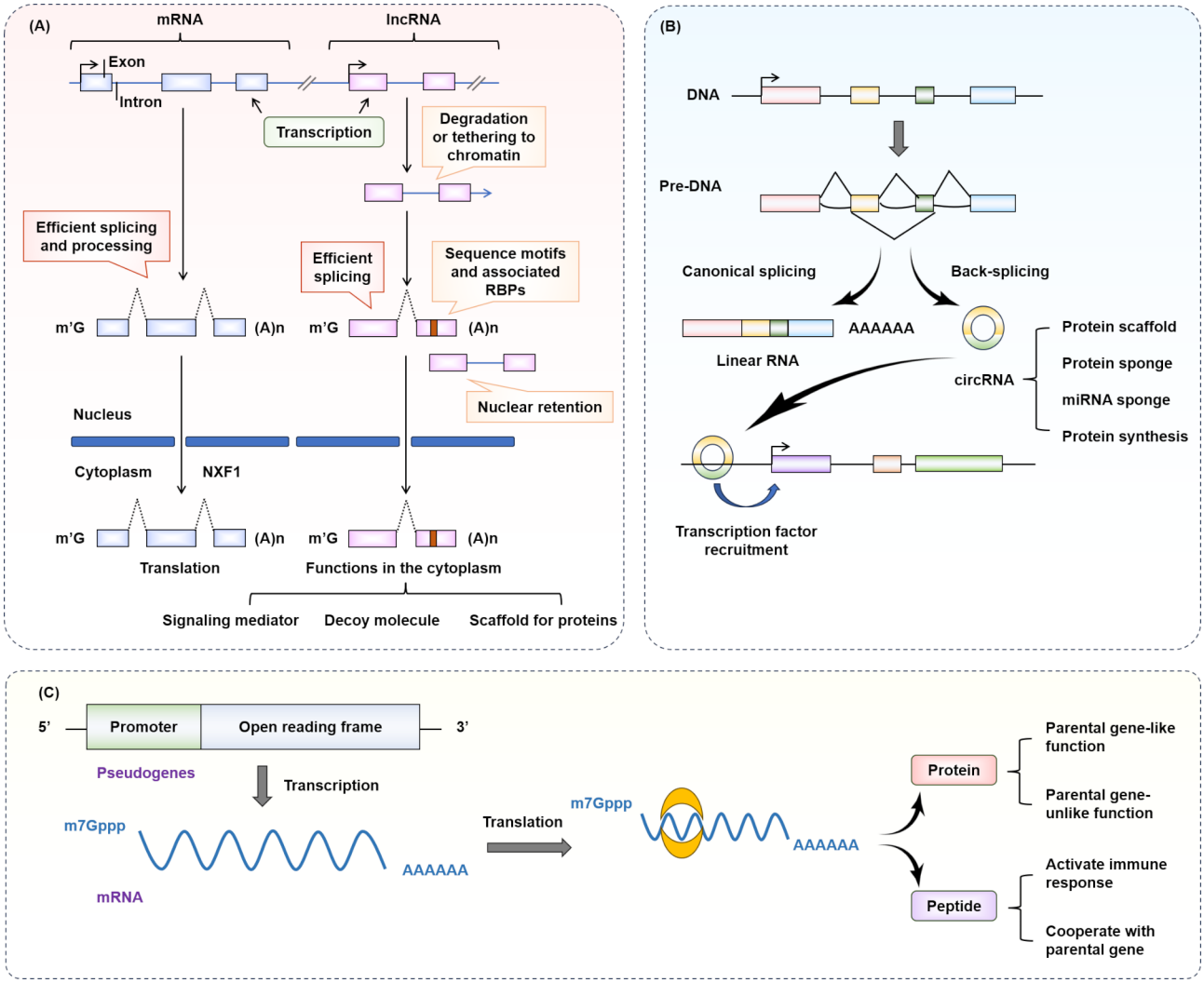

Fig. 2 The biogenesis and functions of lncRNAs, circRNAs, and pseudogenes. (**A**) Biogenesis and cellular function of lncRNAs. lncRNAs are spliced and exported to the cytoplasm. The lncRNAs that contain one or only few exons are exported to the cytoplasm by nuclear RNA export factor 1 (NXF1). (**B**) A schematic showing the biogenesis of circRNAs through the noncanonical back-splicing process, and their reported functional mechanisms. (**C**) Pseudogenes harbor a complete open reading frame to produce mRNAs. These pseudogenes can produce proteins that exert parental gene-like or parental gene-unlike functions. In addition, a small number of pseudogenes can be transcribed as fragments of entire mRNAs, generating different peptides that can induce immune responses or cooperate with parental genes

exhibits significant promise as a biomarker for disease prognosis, diagnosis, and treatment [35]. Research across various cancer types indicates that cellular circRNA expression profiles possess notable tumor and tissue specificity, playing a pivotal role in cancer initiation, metastasis, and resistance to treatment [36, 37]. circRNA harbors numerous binding sites and responsive elements for miRNAs, allowing it to competitively modulate the expression of downstream target genes through the inhibition of miRNAs [38], which is a mechanism of their influence on cancer pathogenesis. Recently data have proved that frequently disordered circRNAs contribute to the pathological development of OC and the malignant phenotype in clinical outcomes [39, 40], making it an effective diagnostic and therapeutic biomarker.

Pseudogenes have the potential to act as ceRNA sponging miRNAs

The preliminary definition of pseudogenes refers to the non-functional DNA sequences in the genome. These sequences are believed to originate from reverse transcription or genomic replication of functional genes [41]. Despite sharing highly similar sequences with normal genes, pseudogenes have undergone functional losses concerning cellular gene expression or protein coding. These losses result from varying levels of deletion/insertion in different regions and defects in the 5' terminal promoter region compared to intact genes [42, 43]. These defective changes prevent pseudogenes from being transcribed or translated, or produce defective proteins, thereby losing their original biological functions (Fig. 2C). However, the progress of sequencing technology shows that pseudogenes can be regulated by their transcripts, leading to the generation of pseudogene antisense chains [44], endogenous small interfering RNAs [45], miRNA sponges [46], to regulate genes. It is worth noting that the ENCyclopedia of DNA Elements project indicates that pseudogene transcription typically occurs at low levels and exhibits tissue or cell line specific patterns [47]. Due to the high homology between pseudogenes and the parental genes, along with the presence of a large number of MREs in both gene types [48], the transcribed pseudogene has the function of serving as a guide, tethering molecule or ceRNAs, thus connecting to sponge miRNAs [49]. While previous studies have demonstrated that pseudogenes and their transcripts play an important regulatory role in tumor development such as breast cancer, hepatocellular carcinoma, among others [50], the role of pseudogenes as ceRNAs in OC has not been well-understood, and detailed data from clinical studies are lacking. Further exploration is required in subsequent experiments.

LncRNA/miRNA/mRNA networks

LncRNA MALAT1 as ceRNAs promotes OC progression

Situated on human chromosome 11q13, the Long non-coding RNA Metastasis Associated Lung Adenocarcinoma Transcript-1 (MALAT1) is a remarkably conserved lncRNA implicated in the carcinogenesis of various cancers, including lung cancer, osteosarcoma, and gastric cancer [51, 52]. OSCC yielded a statistically significant higher expression of MALAT1 than healthy controls [53]. Signal Transducer and Activator of Transcription 3 (STAT3) serves as a pivotal transcription factor, crucial in regulating tumor growth, cell survival, and immune responses [54]. According to bioinformatics findings, it has been identified as the target gene of miR-125b in OSCC. In a groundbreaking discovery, Chang et al. established that MALAT1, for the first time, operates as a ceRNA, influencing STAT3 expression by absorbing miR-125b in OSCC [55]. In addition, MALAT1 can also combines with miR-224-5p to promote the transcription of histone lysine demethylases 2 A, thereby leading to OSCC cell proliferation. During this process, the MRE of MALAT1 competitively binds to miR-224-5p, exerting ceRNAs effects, enhancing the viability and colony formation capacity of OSCC cell [56]. These new findings help to elucidate the key function of the ceRNAs network regulated by MALAT1 in the development of OC, thus providing a potential target for the treatment of OSCC, and representing a promising avenue to slow down tumor progression.

LncRNA CYTOR mediates OC chemotherapy resistance and EMT

Encoded on the human chromosome locus 2p11.2, the long non-coding RNA CYTOR has been demonstrated to enhance the invasion, migration, and drug resistance of tumors [57, 58]. Research has indicated that Forkhead box D1 (FOXD1) experiences upregulation in OSCC and is associated with a predicted poor prognosis [59]. Additionally, the ectopic expression of FOXD1 has been observed to promote the epithelial-mesenchymal transition (EMT) and chemoresistance in OSCC, both *in vitro and in vivo*. Further mechanistic investigations have uncovered that FOXD1 binds to the promoter of CYTOR, activating its transcription. Acting as a ceRNA, FOXD1 suppresses miR-1252-5p and miR-3148, resulting in the upregulation of the lipoma preferred partner (LPP) expression [60]. Notably, the expression of LPP has been found to be positively correlated with patient survival and chemotherapy resistance by regulating endothelial cell motility and permeability [61]. These findings underscore the essential role of the CYTOR/LPP pathway in FOXD1-induced EMT and chemoresistance in OSCC, highlighting the clinical prognostic significance of FOXD1.

LncRNA JPX enhances OSCC carcinogenicity through ceRNA network

LncRNA JPX is a molecular switch of X chromosome activation, which can precisely regulate alleles or loci [62]. Studies have shown that lncRNA JPX is upregulated expression in various cancers such as non-small cell lung cancer [63], ovarian cancer, and lung cancer [64]. Cadherin 2 (CDH2) protein, known as N-cadherin, is a Ca^{2+}-dependent cell-surface protein that mainly facilitates intercellular adhesion and migration [65]. Recent research has found that lncRNA JPX is primarily located within the cytoplasm of OSCC cells, where it binds to miR-944 through the ceRNAs mechanism and promotes the expression of CDH2, consequently enhancing the oncogenic potency of OSCC cells [66]. Notably, the heightened expression of CDH2 reinstated the attenuation of oncogenic behaviors in OSCC cells induced by the silenced long non-coding RNA JPX. In rescue experiments, the absence of lncRNA JPX resulted in the inhibition of proliferation, migration, and invasion of OSCC cells. Conversely, reduced levels of lncRNA JPX expedited apoptosis in OSCC cells [66]. Furthermore, the analysis of Cancer Genome Atlas data has unveiled a correlation between long non-coding RNA JPX and pyroptosis, influencing the presence of immune cells within the microenvironment of OSCC [67].

LncRNA NORAD as ceRNA facilitates OSCC progression

Qi et al. have demonstrated that lncRNA activated by DNA damage (NORAD) acts as a tumour promoter by binding to miR-577, leading to increased expression of tropomyosin 4 (TPM4), thereby contributing to accelerate the progression of OSCC [68]. Additionally, the investigation observed elevated NORAD expression in both OSCC tissues and cells, aligning with the identification of NORAD exhibiting high expression levels in cervical cancer [69]. Notably, lncRNA NORAD is also reported to be up-regulated in in pancreatic cancer [70] and breast cancer [71]. Furthermore, TPM4, belonging to the tropomyosin family of actin-binding proteins, exhibits heightened expression across diverse cancers, encompassing OSCC [72, 73]. The mechanistic investigation unveiled a positive correlation between the expression of TPM4 and lncRNA NORAD. Furthermore, the diminished migratory ability due to NORAD silencing could be partially restored through co-transfection with TPM4 [68]. MiR-577 acts as a mediator between NORAD and TPM4, thereby contributing to the effectiveness of the NORAD/miR-577/TPM4 axis in regulating the behavior of OSCC cells [68].

LncRNA AC007271.3 and lncRNA PVT1 as ceRNAs promotes cell proliferation, invasion, migration and inhibits cell apoptosis of OSCC

Situated on chromosome 2, long non-coding RNA AC007271.3 exhibits elevated expression in serum, showcasing an association with clinical stage and an unfavorable prognosis [74]. Recent research indicates that long non-coding RNA AC007271.3 predominantly resides in the cytoplasm, with a partial presence in the nucleus [75]. Given the close connection between lncRNA function and subcellular localization, it is plausible that lncRNA AC007271.3 primarily operates as an endogenous miRNA sponge, influencing the expression of target genes. A recent investigation has unveiled a potential carcinogenic mechanism, wherein lncRNA AC007271.3 acts as a ceRNA [76]. This leads to the upregulation of Slug expression by binding to miR-125b-2-3p, disrupting the stability of primary miR-125b-2, and subsequently expediting the growth of OSCC [76]. Suppression of lncRNA AC007271.3 results in elevated E-cadherin expression and diminished Slug expression. This suggests that Slug, by inhibiting E-cadherin expression, has the potential to modulate the EMT phenotype, consequently fostering the migration and invasion of OSCC cells [76]. Conversely, the E-cadherin/β-catenin complex, in conjunction with cytoskeletal components, plays a pivotal role in governing the establishment of a mature adherent junction. Recent investigations have also suggested that long non-coding RNA AC007271.3 has the potential to modulate the translocation of β-catenin. This, in turn, activates the Wnt/β-catenin signaling pathway, fostering cell proliferation, migration, and invasion, while concurrently suppressing cell apoptosis in OSCC [77]. This phenomenon may arise due to Slug's role in diminishing E-cadherin expression and enhancing the dissociation of β-catenin. Consequently, β-catenin translocate from the cytoplasm to the nucleus, thereby activating the Wnt/β-catenin signaling pathway.

PVT1 downregulation reversed the effects of PVT1 overexpression, which enhanced cell invasion, motility, and proliferation. In OSCC cell lines and in vivo, the PVT1/miR 150 5p/GLUT 1 signaling axis promoted cell invasion, migration, proliferation, and suppressed apoptosis. PVT1 is elevated in human OSCC tumor tissues and is linked to patients' poor prognoses [78].

LncRNA-p23154 regulates glucose metabolism through ceRNAs networks

The Warburg effect, commonly referred to as glycolysis, is widely acknowledged as a central hallmark present in nearly all types of human cancers [79]. In their earlier research, Wang et al. identified an lncRNA called lnc-p23154, whose expression shows correlation with parameters such as tumor size, clinical stage, and lymph node

metastasis in individuals with OSCC [80]. Furthermore, the increased expression of lnc-p23154 led to elevated glucose consumption and lactate production. Additionally, the glycolysis stress assay indicated that the modulation of lncRNA-p23154 could impact the extracellular acidification (ECAR) level in OSCC cells, influencing glycolysis under basal conditions, as well as glycolytic capacity and the glycolytic reserve [80]. Mechanistically, lnc-p23154 enhances Glut1 expression by inhibiting the transcription of miR-378a-3p, which directly targets the 3 ′UTR of Glut1 [80]. Glut1 stands out as the extensively expressed glucose transporter, regulating basal glucose uptake across various tissues [81]. The excessive expression of GLUT1 usually observed in various types of tumors is considered necessary to meet the enormous energy requirements for cancer growth, suggesting that GLUT1 is an indicator of carcinogenesis [82]. In addition, knockout of Glut1 can significantly inhibit the expression of genes involved in cancer invasion and migration, including MMP1 and CTGF, while lnc-p23154 can reverse this effect [80]. As a result, interfering with lnc-p23154 to switch the metabolic mode of tumors may be a potential target for OC therapy.

LncRNA LTSCCAT mediates TSCC development and EMT

The imbalance in the microbiota and chronic inflammation, particularly in cases of periodontitis, has been established as having a connection to the onset and advancement of tumors, thereby elevating the susceptibility to OC [83]. It is known that Porphyromonas gingivalis (P.g) is the main pathogen of periodontitis. Research findings indicate that the colonization level of P.g in OSCC is notably elevated compared to adjacent tissues, contributing to heightened invasion and migration of gingival epithelial cells [84]. Research conducted by Liu et al. demonstrated that exposing the tongue squamous cell carcinoma (TSCC) cell line to low-concentration lipopolysaccharide (LPS) derived from P.g (P.g-LPS) induces elevated levels of lncRNA LTSCCAT and SMYD3, consequently leading to an increase in the EMT-related transcription factor, Twist1 [85], which induces the transformation of epithelial cells into mesenchymal cells both in vivo and in vitro, ultimately facilitating the invasion and metastasis of TSCC. Mechanistic investigations have revealed that LTSCCAT directly impedes the expression of miR-103a-2-5p, which has binding sites on the 3'UTR of SMYD3, thereby inhibiting its translation [85]. Furthermore, the reduction of LTSCCAT in P.g-LPS-treated TSCC cells led to mesenchymal-epithelial transition (MET), restoring the epithelial phenotype and regaining adhesion ability. In contrast, untreated TSCC cells exhibited an upregulation of LTSCCAT during EMT. Consequently, the expression level of LTSCCAT may regulate EMT/MET in TSCC, and reducing LTSCCAT expression could potentially promote MET, leading to a more favorable prognosis.

LncRNA MPRL participates in the regulation of chemotherapy sensitivity

Cisplatin has been used to treat a wide variety of solid tumors, but it often leads to the development of chemotherapy resistance and therapeutic failure [86]. The initial response rate of patients with OSCC to platinum-based therapies is 80.6% [87]; Nevertheless, more than 70% of patients ultimately experience a recurrence as a result of acquired drug resistance in the tumor [88]. Research has indicated that dysregulated mitochondrial dynamics play a role in apoptosis regulation and are associated with various diseases, encompassing cancer [89]. In their study, Song et al. observed an upregulation of the mitochondrial fission protein FIS1 following cisplatin exposure in TSCC cells. Suppressing FIS1 through knockdown mitigated both mitochondrial fission and cisplatin sensitivity, with FIS1 being a direct target of miR-483-5p. MiR-483-5p demonstrated the ability to impede mitochondrial fission and reduce cisplatin sensitivity in both in vitro and in vivo settings [90]. Moreover, in TSCC cell lines subjected to cisplatin treatment and activated by E2F1, a noteworthy upregulation of lncRNA NR_034085, referred to as miRNAs processing-related lncRNA (MPRL), was observed. Neoadjuvant chemosensitivity and improved prognosis for TSCC patients were substantially correlated with high expression of MPRL and pre-miR-483 and low expression of miR-483-5p [91]. In terms of mechanisms, the cytoplasmic MPRL intricately modulates the miR-483-5p-FIS1 axis by directly interacting with the pre-miR-483. This interaction impedes the recognition and cleavage process facilitated by the TRBP-DICER complex on the pre-miR-483, consequently fostering mitochondrial fission and enhancing the chemical sensitivity to cisplatin [91]. Moreover, the manipulation of MPRL expression, either through overexpression or knockdown, in mouse xenografts resulted in notable changes in tumor cell apoptosis and growth. Conversely, individuals exhibiting low MPRL expression were observed to lack sensitivity to cisplatin-based chemotherapy, thereby precluding any potential benefits from neoadjuvant chemosensitivity [91]. These findings have elucidated a model for the regulation of mitochondrial fission influencing the chemical sensitivity of cisplatin through RNA biosynthesis in cancer cells. This model provides an explanation for the tumor inhibitory effect of MPRL.

Impact of lncRNA HOTAIR polymorphisms linked to the predisposition to OC

Recent research has connected the susceptibility to oral cancers to polymorphisms in HOTAIR. Compared to human oral keratinocytes and normal oral mucosa

tissues, HOTAIR was strongly expressed in both OSCC tissue samples and cell lines [92]. The migration, invasion, and EMT of OSCC cells were markedly reduced by silence of HOTAIR. By efficiently sponging miR-326, HOTAIR functioned as a ceRNA and modulated the suppression of metastasis-associated gene 2 (MTA2) [93].

LncRNA H19 is contribute to glucose metabolism in OC

LncRNA H19 was found to be a crucial lncRNA in OC-associated fibroblasts (CAFs) and was increased in both CAFs and OC cell lines at the same time. Glycolysis, migration, and proliferation in oral CAFs were impacted by lncRNA H19 knockdown. LncRNA H19 was found to be a crucial lncRNA in oral CAFs and was increased in both CAFs and OC cell lines at the same time. Additionally, the glycolysis pathway in oral CAFs was promoted via the lncRNA H19/miR-675-5p/PFKFB3 axis [94]. The majority of tumor tissues from OSCC patients (97%) displayed hypomethylation of lncRNA H19 compared to normal oral mucosa tissues. Hypomethylation of lncRNA H19 was associated with a significantly lower 5-year survival rate in OSCC patients [95].

LncRNA MEG3 and UCA1 inhibits self-renewal and invasion abilities of OC stem cells

The MEG3 gene locus is modified by H3K27me3, which results in low expression of the lncRNA MEG3 [96]. Overexpression of lncRNA MEG3 suppresses the ability to proliferate, invade, and self-renew. LncRNA MEG3-inhibited properties are reversed by elevation of miR-421 in OC stem cells. Additionally, the interaction with GATA3 is necessary for the anticancer activity of lncRNA MEG3 in OSCC cells. In OC tissues, MEG3 is downregulated and associates with a poor bad prognosis [97].

LncRNA UCA1-rich CSC-secreted sEVs were transferred to unpolarized macrophages and induced macrophage polarization toward protumor-related M2 macrophages by targeting LAMC2 via the PI3K/AKT pathway. LncRNA UCA1 was elevated in OSCC-CSC-derived sEVs. By altering the immunosuppressive milieu, OSCC-CSCs employ sEV-transferring UCA1 to promote tumorigenicity and facilitate OSCC cell migration and invasion [98]. UCA1 targets miR-184 and miR-124, which contributes to the malignant progression of OSCC [99, 100]. In tongue squamous cell carcinoma tissues, UCA1 expression levels are abnormally elevated and related to TNM stage and lymph node metastases. Silencing UCA1 causes OSCC to undergo apoptosis and inhibits growth and metastasis [101]. Therefore, more efforts are required to better identify the role and crucial mechanisms of OSCC-specific lncRNAs in the progression of OSCC, which effectively improve our understanding of the occurrence and progression of OSCC and eventually facilitate the development of LncRNA-mediated diagnosis and therapy.

The ceRNA crosstalk mediated by lncRNA in the progression of OC has been compiled in Table 1.

CircRNA/miRNA/mRNA networks

Hsa_circRNA_100290 serves as a ceRNAs to regulate OSCC growth

Chen et al. have expounded upon the role of circRNA_100290 as a ceRNA, opposing the suppression of GLUT1 by miR-378a. This interplay ultimately fosters glycolysis and contributes to increased cell proliferation in OSCC [102]. Regarded as the initial phase of glucose metabolism, the transport of glucose through the cell membrane is identified as a pivotal stage in regulating the rate of glycolysis, with GLUT1 playing a crucial role [103]. Within oral tumor tissue samples and cells, there is a notable increase in the expression of circRNA_100290 and GLUT1. Silencing circRNA_100290 leads to a significant reduction in cell proliferation and glycolysis, a effect that can be restored by the overexpression of GLUT1 [102]. Throughout this sequence, miR-378a establishes direct binding with both circRNA_100290

Table 1 The role of lncRNA as ceRNAs in OC

CeRNA network type	CeRNA member	Shared miRNA	mRNA	Biological functions	Ref
LncRNA/miRNA/mRNA	MALAT1	miR-125	STAT3	Promote proliferation and metastasis	[55]
	MALAT1	miR-224-5p	KDM2A	Promote proliferation	[56]
	CYTOR	miR-1252-5p/ miR-3148	LPP	Promote chemoresistance and EMT	[60]
	JPX	miR-94	CDH2	Promote proliferation and metastasis	[66]
	NORAD	miR-577	TPM4	Promote metastasis	[68]
	AC007271.3	miR-125b-23p	Slug	Promote migration and invasion	[75]
	p23154	miR-378a-3p	Glut1	Promote invasion and metastasis	[80]
	LTSCCAT	miR-103a-25p	SMYD3	Promote invasion and metastasis	[85]
	MPRL	miR-483-5p	FIS1	Inhibit chemoresistance	[91]
	HOTAIR	miR-326	MTA2	Reduce migration, invasion, and EMT	[93]
	H19	miR-675-5p	PFKFB3	Facilitate glycolysis, proliferation and migration	[94]
	MEG3	miR-421	GATA3	Inhibit self-renewal and invasion abilities	[97]
	UCA1	miR-184 and miR-124	LAMC2	promote tumorigenicity, migration and invasion	[98–100]

and the 3'-untranslated region of GLUT1, thereby serving as a connecting bridge in the crosstalk within the ceRNA network [102]. Furthermore, existing data suggest a positive correlation between the expression of circRNA_100290 and advanced TNM staging, as well as lymph node metastasis in patients with LSCC. Elevated levels of circRNA_100290 have been shown to enhance the proliferation, migration, and invasion of LSCC cells while concurrently suppressing cell apoptosis [104].

CircZDBF2 accelerate OSCC progression by ceRNAs network

Derived from the zinc finger DBF-type containing 2, specifically circZDBF2, hsa_circ_0002141 is a circRNA that exhibits elevated expression in OSCC tissues, as indicated by the Gene Expression Omnibus database. Subsequent experiments have validated the heightened expression of circZDBF2 in OSCC cells, thereby fostering accelerated proliferation, migration, invasion, and promotion of the EMT process in OSCC cells [17]. In vivo investigations have demonstrated that suppressing circZDBF2 hampers tumor growth. Mechanistically, circZDBF2 acts as a sponge for miR-362-5p and miR-500b-5p in OSCC cells, liberating its target, ring finger protein 145 (RNF145). This liberation, in turn, activates OSCC progression through the NFκB signaling pathway [17]. RNF145, functioning as an E3 ubiquitin ligase, shares homology with the RNF183 family. RNF183 has the capacity to induce NFκB signaling pathway activation, thereby regulating the transcription of IL-8. This process has been demonstrated to contribute to the tumorigenesis of OSCC [105].

CircDOCK1 suppresses OSCC apoptosis

The dedicator of cytokinesis (DOCK) family consists of atypical guanine nucleotide exchange factors (GEFs) that exhibit evolutionary conservation within the Rho family. In a prior investigation, it was revealed that DOCK1 circRNA represents one of the most abundant circRNAs in epithelial cells. However, its expression was significantly downregulated by 30-fold in response to TGF-β, in contrast to a 2-fold increase observed in DOCK1 mRNA [106]. Given that TGF-β treatment is known to induce EMT, it suggests that one of the potential roles of circRNAs derived from DOCK1 is to instigate the downregulation of mRNAs in epithelial cells, thereby contributing to cellular stability. Conversely, in a separate investigation, Wang et al. established a cellular apoptosis model utilizing TNF-α and acquired differentially expressed circRNA profiles from both the apoptotic cell model and normal cells through high-throughput microarrays. Notably, circDock1 is significantly diminished in the apoptotic cell model [107]. Moreover, the suppression of circDOCK1 and elevation of miR-196a-5p levels through mimetics resulted in heightened apoptosis and diminished formation of baculoviral IAP repeat-containing 3 (BIRC3) in OSCC cells. These findings align with previous data, suggesting that the augmentation of BIRC3, both *in vivo and in vitro*, contributes to evading apoptosis [108]. CircDOCK1 is significantly expressed in OSCC cell lines and tissue, suggesting circDOCK1could be a useful therapeutic target and diagnostic biomarker for OSCC.

CircRNA_0000140 suppresses OSCC growth and metastasis

CircRNA_0000140, originating from exons 7–10 of the KIAA0907 gene, exhibits a compelling link to advanced TMN stage and lymph node metastasis in individuals diagnosed with OSCC [109]. Moreover, survival analysis revealed a notable reduction in the 5-year survival rate among OSCC patients exhibiting low expression of circ_0000140. Peng et al. discovered that circ_0000140 directly interacted with miR-31, suppressing the proliferative, migratory, and invasive capabilities of OSCC cells [109]. Crucially, miR-31 stands out as one of the frequently dysregulated microRNAs across various cancer types, exhibiting aberrant expression in multiple malignancies [110]. LATS2, a pivotal element within the Hippo pathway and a direct miR-31 target, plays a crucial role as the mediator of circ_0000140 function, exerting its influence by repressing the epithelial-mesenchymal transition (EMT) process in OSCC [111]. Additionally, a separate investigation indicated that the upregulation of LATS2 inhibited in vitro cell proliferation, colony formation, and invasion, while also preventing xenograft formation in vivo [112]. Hence, targeting the circ_0000140-mediated Hippo signaling pathway could be a potential candidate for molecular intervention in therapeutic strategies.

CircATRNL1 sensitize OSCC to irradiation

Radiotherapy is a major modality for OSCC at advanced stages, but radioresistance can still lead to recurrence and treatment failure in OSCC patients [113]. Chen's study demonstrated that elevated levels of circATRNL1 effectively suppressed cellular proliferation, colony formation, and prompted apoptosis and cell-cycle arrest in OSCC cells subjected to irradiation [114]. Following this, the research team constructed a putative circATRNL1 miRNA interaction network, utilizing complementary matching sequences. Subsequent screening revealed circATRNL1's role as an endogenous sponge for miR-23a-3p in the context of OSCC [114]. The reduction of PTEN mediated by miRNAs may compromise the radiosensitivity of various human cancers [115]. A noteworthy discovery is that circATRNL1 and PTEN share common MREs for miR-23a-3p. Functionally, circATRNL1 can interact directly with miR-23a-3p, alleviating its inhibitory effect on the target gene PTEN, thereby contributing

to the improved radiosensitivity of OSCC [114]. Moreover, investigations into OSCC have revealed diminished levels of miR-23a-3p in OSCC tissues. Its role as a tumor suppressor has been substantiated, restraining growth and enhancing apoptosis in OSCC cells [116].

Pseudogene/miRNA/mRNA networks

Adam3A and adam5 pseudogenes increase the risk of OPSCC

Copy number variations (CNVs) encompass substantial deletions and duplications of chromosomal fragments. They are extensively observed in tumors, known as somatic CNVs, as well as in germline cells, referred to as inherited CNVs. These variations constitute a pivotal factor influencing the onset and progression of oropharyngeal squamous cell carcinoma (OPSCC) [117]. A family of transmembrane metalloproteinases, A Disintegrin and Metalloproteinases (ADAMs) play a crucial role in various cellular processes [118]. Recent investigations have noted an association between an elevated copy number of ADAM3A and ADAM5 pseudogenes exceeding three copies and an increased risk of OPSCC [119]. The ADAM5 pseudogene exhibits a remarkably homologous sequence at the 3'-UTR of the ADAM9 gene. This sequence is anticipated to serve as the binding site for miR-122b-5p [119]. Particularly, the amplification of ADAM3A and ADAM5 copies can result in elevated transcripts derived from pseudogenes, creating competition for miR-122b-5p. This competition enhances the expression of ADAM9, influencing the onset and prognosis of OPSCC. Additionally, the diminished expression of miR-122b-5p and the heightened expression of ADAM9 serve as valuable biomarkers for the screening and diagnosis of oropharyngeal and oral SCC, respectively [120].

PTENp1 pseudogenes inhibit the proliferation of OSCC

PTENP1, identified as a pseudogene derived from the tumor-suppressor gene PTEN, stands out as one of the initial examples of miRNA sponges that exert a tumor-suppressor function [121]. Among OSCC patients, the expression levels of PTENp1 and PTEN in tumor specimens are notably diminished compared to those in normal tissues [122]. On the contrary, miR-21, a widely recognized oncogenic miRNA, is frequently elevated in diverse malignancies, encompassing OSCC [123, 124]. Gao et al. discovered that PTENp1 serves as a direct and specific target for miR-21. Through its interaction with miR-21, PTENp1 shields PTEN transcripts from the inhibitory effects of miR-21, thereby suppressing proliferation and colony formation [122]. Therefore, the ceRNAs activity of PTENP1 contributes to the posttranscriptional regulation of PTEN, and alterations in PTENP1 expression levels or miRNAs decoy activity may lead to moderate variation in PTEN levels to accelerate cancer development. Furthermore, PTENp1 plays a role in inhibiting cell transformation and proliferation through modulation of the PI3K/AKT pathway [122]. The ceRNA crosstalk in OC progression involving circRNAs and pseudogenes is comprehensively summarized in Table 2.

The emerging roles of piRNA in OC

The non-coding RNAs family includes P-Element induced wimpy testis (PIWI)-interacting RNA (piRNA). They lack appropriate secondary structural characteristics, have a 5'-end uridine or 10th position adenosine bias, and are 24–31 nucleotides long [125]. The single-stranded ncRNAs known as piRNAs interact with PIWI proteins and are composed of a variety of distinct nucleotide sequences [126]. It has been noted that the suppression of OC progression is caused by genes such as GALNT6, SPEDF, and MYBL2 that are coupled with piRNAs [127]. It was identified that 22 differentially expressed genes in human OSCC and mouse OSCC induced by 4NQO. There are 11 genes and piRNAs in the regulatory network. Among the 11 genes, Six31 was downregulated, whereas Galnt6, Spedf, Mybl2, Muc5b, and Tmc5 were elevated in OSCC [127]. Subsequent investigation reveals that a down-regulated piRNA, piR-33,422 is associated with the mevalonate/cholesterol-pathway-related gene FDFT1 in tongue cancer. Further studies are required to understand the regulation of their expression and functional mechanism of piRNAs in OC. piRNAs may serve as a therapeutic target or biomarker for OC.

Differential expression of snoRNAs in OC

SnoRNAs are one of wide variety of non-coding RNA molecules present in the body. The human genome has about 300 different snoRNA sequences. The snoRNAs

Table 2 The role of CircRNAs and Pseudogene as ceRNA in OC

CeRNA network type	CeRNA member	Shared miRNA	mRNA	Biological functions	Ref
CircRNA/miRNA/mRNA	100,290	miR-378a	GLUT1	Promote proliferation and invasion	[102]
	ZDBF2	miR-362-5p/miR-500b-5p	RNF145	Promote proliferation, migration and invasion	[17]
	DOCK1	miR196a5p	BIRC3	Inhibit apoptosis	[107]
	0000140	miR-31	LATS2	Inhibit proliferation, migration, and invasion	[109]
	ATRNL1	miR-23a-3p	PTEN	Cell-cycle arrest	[114]
Pseudogene/miRNA/mRNA	ADAM3A/ADAM5	miR-122b-5p	ADAM9	Promote tumor growth	[119]
	PTENp1	miR-21	PTEN	Inhibit proliferation	[122]

generate small nucleolar ribonucleoprotein complexes (snoRNP complexes) by binding to protein molecules, which then leads to the modification of rRNA bases [128]. SnoRNAs are involved in the government of messenger RNA posttranscriptional modifications and alternative splicing. Different snoRNAs may manifest themselves differently in OC due to changes in snoRNA synthesis and post-transcriptional regulation. 8 OC samples were subjected to a microarray study, which revealed 16 significantly altered snoRNAs in comparison to control samples. Of these, 15 were considerably down-regulated and linked to patient survival [129]. Oral squamous cell migration and proliferation are induced by the SNHG3, a snoRNA that is up-regulated in OC patients. It acts as a biomarker and targets the nuclear transcription factor-Y subunit gamma (NFYC) through the SNHG3/miR-2682-5p axis [130]. Additionally, snoRNA SNHG15 is overexpressed in OC cell lines, which acts as a target for miR-188-5p/DAAM1 to promote OC's malignant tendencies [131]. Therefore, snoRNAs contribute to the formation of tumors in OC. Their importance in cancer treatment may grow with more research.

Limitations and Application of ceRNAs

As high-throughput sequencing and bioinformatics technology advance, the identification of lncRNAs, circRNAs, and pseudogenes acting as ceRNAs in gene expression regulation has become apparent. Notably, certain regulators, such as MALAT1 [132] and TUG1 [133] exhibit a pivotal role in the development of various tumor types. Studies have shown that the expression of lncRNAs exhibits spatiotemporal and tissue-specificity [134], and the sequence conservation observed among lncRNA genes is relatively poor [135, 136]. Therefore, determining the mechanism of lncRNA interactions between different species for mutual reference is of little significant. On the other hand, although circRNAs are insensitive to exonucleases, and its duration in cells may be much longer than their linear isomers, many circRNAs are inconsequential by-products of pre-mRNA splicing [137]. Consequently, realizing the expected miRNA sponge properties remains challenging. Moreover, the stable expression level of pseudogenes rarely reaches the level of its parental gene [138], which limits its effectiveness. It is important to investigate the expression levels of ceRNA at specific developmental stages and different subcellular locations, while also continuing to enrich our understanding of its conservation, including sequences, structures, processing, and spatial distribution. Additionally, it is necessary to establish a comprehensive and accurate database to identify effective biomarkers that can be used in the study and further application of ceRNAs regulatory mechanisms.

The most common post-transcriptional modification pathway is N6-Methyladenosine (m6A) RNA methylation, which is crucial to the pathophysiology of OC. A ceRNA network based on the m6A-related lncRNA growth arrest specific 5 (GAS5) specific transcript (NR_152533) was established in a previous study. GAS5 may have regulated RALYL expression by binding to miR-3912-5p, and RALYL may be a target gene for miR-3912-5p [139]. MALAT1 was upregulated by METTL14-induced m6A alteration of MALAT1. MALAT1 is comparatively bound to miR-224-5p to promote KDM2A transcription, thereby promoting OSCC cell proliferation [56]. Regardless of m6A-mRNA, specific modification styles were displayed by m6A-circRNAs in OSCC. Furthermore, m6A modification on circRNAs usually happened on the lengthy exons in the front portion of the coding sequence (CDS), which was distinct from m6A-mRNA that in 3'-UTR or stop codon (Fig. 3A) [140]. circFOXK2 increased the mRNA stability of GLUT1 through cooperating with insulin-like growth factor 2 mRNA binding protein 3 (IGF2BP3) in a m6A-dependent manner [141]. CircGDI2 functions as a tumour suppressor by binding to the FTO protein to reduce RNA m6A modification levels and ultimately inhibit proliferation and migration in OSCC cells [142].

Existing studies indicate that the RNA-miRNA-mRNA triple network is the main regulatory pathway of ceRNAs. Within this framework, the modulation of crucial miRNAs and ceRNAs to mitigate the excessive repression of target mRNA and reinstate a normal cellular phenotype is anticipated to emerge as a novel strategy for treating OSCC. This can be accomplished by introducing antisense oligonucleotides (ASOs) into host cells through either transfection or viral transduction. These ASOs bind to and redirect natural miRNAs away from their conventional mRNA targets, thereby bolstering mRNA stability and facilitating enhanced translation [143]. At present, ASO is widely used in miRNA loss-of-function study [144], gene therapy and prevention of breast cancer [145], Alport nephropathy [146] and other diseases. Moreover, several clinical trials have verified the efficacy of OGX-011, Tofersen and other ASOs at different stages [147, 148]. However, ASO is easily broken down by enzymes in the body, resulting in low cell uptake efficiency and poor stability [149], which limits its therapeutic potential. In this regard, chemical modification and carrier delivery seem to be potential strategies for improving ASO performance and inhibiting cancer progression. For instance, the stability of ASO to nuclease-induced degradation can be improved by thiophosphoric acid modification and peptide nucleic acid modification [150, 151]. Also, various delivery methods including cell-penetrating peptides [152], exosomes [153] and lipid nanoparticles [154] have been reported as promising

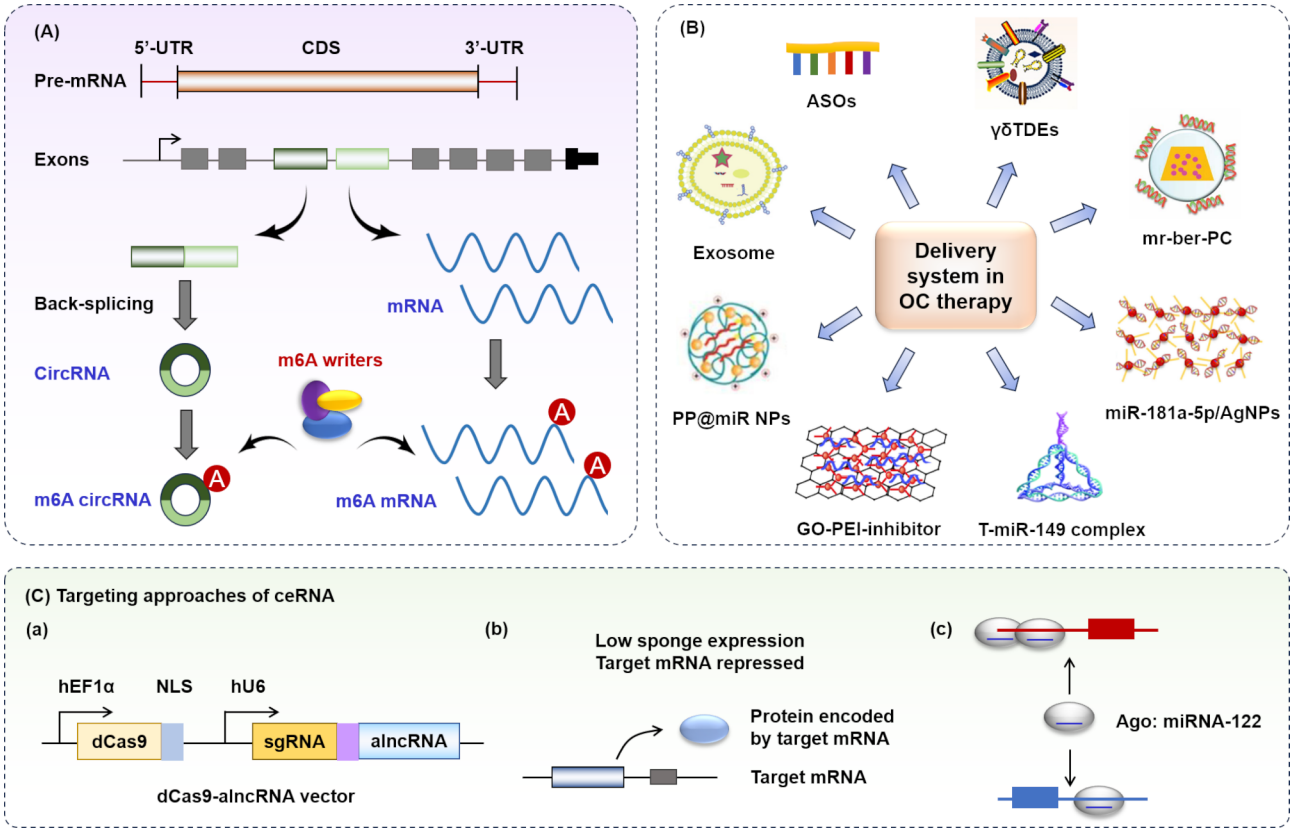

Fig. 3 Schematic representations of chemical modifications, delivery methods, and targeting approaches of ceRNA.**(A)** Schematic diagram illustrated the biogenesis of m6A-circRNAs and m6A-mRNA in OSCC cells. The m6A modification was installed by identical m6A methyltransferase complex (m6A writers). Red A indicated the m6A modification site. **(B)** ASOs, Exosome, PP@miR NPs, GO-PEI complex, T-miR-149, miR-181a-5p/AgNPs, mr-ber-PC, γδTDEs were applied for drug delivery system formation in OC therapy. **(C)** Targeting approaches of ceRNA. **(a)** A CRISPR-based transcription activation system to verify the formation and functionality of the artificial lncRNA. **(b)** In the presence of low sponge expression, target mRNAs are post transcriptionally repressed by the miRNA. **(C)** During infection, viral RNA specifically sequesters miR-122 to de-repress its normal host targets

tools for delivering ASOs to target cells. However, ASOs also directly employed to inhibit lncRNAs and circRNAs, potentially offering a more direct inhibitory effect. LncARSR increases sunitinib resistance by competitively binding miR-34/miR-449 to boost AXL and c-MET expression in RCC cells. Furthermore, sunitinib resistance may spread through the incorporation of bioactive lncARSR into exosomes and transmission to susceptible cells [155]. The role of naturally occurring EGFR isoforms has been poorly studied, with a few studies suggesting that alternate isoforms are secreted in plasma (as secreted EGFR, or sEGFR) and may be prognostic in cancers. Reduced EGFR-AS1 levels shifted splicing toward EGFR isoform D, leading to ligand-mediated pathway activation [156].

Exosome-transmitted lncRNAs and circRNAs have been shown in recent years to facilitate tumor growth and metastasis. Therefore, using liquid biopsy detection technologies, exosomal lncRNAs could be used as predictive biomarkers for cancer diagnosis. Lnc-MLETA1 is important exosomal lncRNA that facilitates interaction in lung cancer cells to encourage cancer spread [157]. Exosomes are essential mediators that facilitate communication between cancer cells and the tumor microenvironment. exosome-derived circATP8A1 from gastric cancer cells causes tumor growth and macrophage M2 polarization via the circATP8A1/miR-1-3p/STAT6 axis [158]. Exosome-mediated lncRNA PART1 overexpression promoted OSCC cell death while suppressing migration, invasiveness, and viability. PART1 upregulated SOCS6 through sponging miR-17-5p. Furthermore, lncRNA PART1 mediated by exosomes inhibited STAT3 phosphorylation. Exosome-derived lncRNA PART1 hampers OSCC progression via miR-17-5p/SOCS6/STAT3 signaling, suggesting that lncRNA PART1 may be potential therapeutic target for OSCC [159].

PP@miR nanoparticles (NPs) were designed using cationic polylysine-cisplatin prodrugs to transport antagomiR-330-3p, a miRNA inhibitory analog, through electrostatic interactions. The crucial involvement of miR-330-3p in OSCC development was validated by the efficient inhibition of subcutaneous tumor progression and partial tumor eradication (2/5) accomplished by PP@miR NPs [160]. A GO-PEI complex regulates the

intracellular release of a miR-214 inhibitor and effectively transports miR-214 inhibitor into OSCC cells. GO-PEI-miR-214 inhibitor complex effectively reduced miR-214 by specifically targeting PTEN and p53, resulting in a decrease in OSCC cell invasion and migration and an increase in cell death [161].

A new nanocomplex (T-miR-149) is successfully constructed and introduced tFNAs as a favorable nucleic acid carrier of miR-149 to delay the progression of OSCC. T-miR-149 markedly increased the capacity of free miR-149 to promote apoptosis in OSCC cells [162]. The biocompatible AgNPs successfully protected miRNA from degradation by serum and RNase. The miR-181a-5p/AgNPs combination dramatically inhibits the growth and progression of OC [163]. For the co-delivery of ber and miR-122, berberine-polyethyleneimine-cholesterol (ber-PC) and miR-122 electrostatically complex to form mr-ber-PC. mr-ber-PC significantly reduced the invasion and migration of OSCC cells [164].

Cas9 mRNA and sgRNAs are encapsulated in lipid nanoparticles as a delivery system. By employing CRISPR systems to identify important factors that contribute to OSCC resistance and then integrating them with other technologies (such as nanotechnology) to create tailored drug delivery platforms, these approaches offered a hint at how to treat OSCC resistance (Fig. 3B). The inhibitory effects of the miR-144/451a cluster on OSCC were effectively improved by biomimetic nanoparticles coloaded with the miR-144/451a cluster, which drastically reduced CAB39 and MIF expression [165]. Since both γδTDEs and miR-138 have direct anti-tumoral effects on OSCC and immunostimulatory effects on T cells, γδTDEs delivering miR-138 may have synergistic therapeutic effects on OSCC. Moreover, γδTDEs may be an effective drug delivery system for miRNAs in cancer treatment [166].

Although targeted protein degradation has emerged as a prominent drug research approach, its use has been constrained by its reliance on protein-based chimeras with limited genetic modification potential. Since lncRNAs can interact with cellular proteins to modify pathways and improve degrading capacities, they have become a promising substitute. Artificial lncRNAs are employed as part of a technique to precisely target protein degradation (Fig. 3C). Artificial lncRNAs preferentially target and facilitate the ubiquitination and degradation of oncogenic transcription factors and tumor-related proteins, such as c-MYC, NF-κB, ETS-1, KRAS and EGFR [167].

A novel miRNA inhibitor based on the ceRNA theory is an artificial miRNA sponge [168], constructed as a vector for expressing 3' UTRs with multiple miRNA binding sites. Compared to traditional miRNA inhibitors and gene knockout techniques, it is likely to achieve regulation and stable expression through the most powerful mammalian promoter systems such as U6 or cytomegalovirus (Fig. 3C) [169]. Besides, other genomic RNAs of retroviruses such as hepatitis C virus can serve as miRNA sponges, binding to miRNAs in the body during host infection, and regulating the expression of target genes (Fig. 3C) [170]. It is essential to highlight that synthetic circular miRNA sponges exhibit promising potential for the prolonged suppression of miRNAs. There have been reports on the utilization of artificial circular miRNA sponges designed to target miR-21, showcasing their application in this context [171, 172].

Conclusions and perspectives

For OC, early malignant lesions are not easy to make non-invasive and accurate diagnosis, while radical surgery for advanced OC usually causes severe oral dysfunction, including speech and dysphagia [173]. Despite significant progress in understanding the carcinogenic process over the past few decades, OSCC treatment strategies have developed slowly. It is necessary to identify novel characteristic diagnostic biomarkers of OC. Recent investigations have indicated that diverse RNA categories, including long non-coding RNA (lncRNA), circular RNA (circRNA), and pseudogenes, can modulate the expression of genes associated with tumors by functioning as competitive endogenous RNAs. The development of targeted miRNA inhibitors based on these mechanisms represents a significant field and hope for the future treatment of OSCC. Moreover, ceRNAs not only pose as a prospective therapeutic target for OSCC but also for other prevalent cancers, including breast cancer [174], thyroid cancer [175] and ovarian cancer [176]. Despite substantial advancements in identifying ceRNAs, numerous phenotypic effects observed in existing studies result from overexpression or gene knockout experiments. Such approaches may not authentically reflect the role of ceRNAs in tumor progression. In the future, it is necesssary to construct endogenous ceRNAs network models and explore their regulatory mechanism. In addition, ceRNAs networks are interconnected and influence each other. The non-specific operation of ceRNAs networks may alter the original normal gene expression, which requires cautious experimental verification before clinical application.

Abbreviations

ADAMs	A disintegrin and metalloproteinases
Ago	Argonauts
ASOs	Antisense oligonucleotides
BIRC3	Baculoviral IAP repeat-containing 3
CDH2	Cadherin 2
ceRNAs	Competing endogenous RNAs
CNVs	Copy number variations
DOCK	Dedicator of cytokinesis
ECAR	Extracellular acidification
EMT	Epithelial-mesenchymal transition
FOXD1	Forkhead box D1

GEFs	Guanine nucleotide exchange factors
LPP	Lipoma preferred partner
LPS	Lipopolysaccharide
MALAT1	Metastasis associated lung adenocarcinoma transcript-1
MET	Mesenchymal-epithelial transition
miRISCs	miRNA-induced silencing complexes
MREs	microRNA response elements
mRNAs	Messenger RNAs
ncRNA	Non-coding RNA
NORAD	Noncoding RNA activated by DNA damage
OPSCC	Oropharynx squamous cell carcinoma
OSCC	Oral squamous cell carcinomas
OC	Oral cancer
P.g	Porphyromonas gingivalis
pri-miRNAs	Primary miRNAs
RNF145	Ring finger protein 145
STAT3	Signal transmitter and activator of transcription 3
TPM4	Tropomyosin 4
TSCC	Tongue squamous cell carcinoma
UTR	Untranslated region

Acknowledgements
Not applicable.

Author contributions
All authors contributed to the development of this review article. Critical analysis and review of the literature were performed by Jiajun Wu and Chanjuan Zhang. The manuscript was written by Jiajun Wu with revisions provided by Hongfang Li, Shuo Zhang, Jingxin Chen. The manuscript was guided by Li Qin.

Funding
This work was supported by the National Natural Sciences Foundation of China (82474133, 82274159), the National Science Fund of Hunan Province (2022JJ80088), Key Project of Hunan Provincial Health Commission (202213055529), Scientific Research Project of Hunan Provincial Health Commission (R2023007), the Outstanding Youth Project of Educational Department of Hunan Province (23B0387), the Social development project of Hainan science and technology department (ZDYF2022SHFZ284), the Outstanding Youth Project of Hunan University of Chinese Medicine (2024XJZB002), National Natural Science Foundation Pre research Project of Hunan University of Traditional Chinese Medicine (2024XJYY08), Academician Liu Liang Workstation Guidance Project (24YS002), Hunan Province College Students Innovation Training Program Project (S202410541062), and the First-Class Discipline of Pharmaceutical Science of Hunan.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 26 April 2024 / Accepted: 19 November 2024
Published online: 26 December 2024

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