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REVIEW ARTICLE

Oral squamous cell carcinoma pharmacological treatment; A long non-coding RNAs (long ncRNAs) story

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ABSTRACT

Oral squamous cell cancer (OSCC) is a major global health issue, ranking sixth in prevalence, particularly in Asia. The diagnosis often occurs late due to inadequate early screening, resulting in a dismal five-year survival rate of around 50%. This document provides a comprehensive analysis of drug-based treatments for oral cavity carcinoma, focusing on chemotherapy, immune modulation, and novel approaches like nanoparticle therapies. Despite advancements in these methods, drug resistance remains a significant obstacle that adversely affects patient outcomes. The research highlights the critical role of long ncRNAs in the progression and treatment of OSCC. These long ncRNAs, which are over 200 nucleotides long, play essential roles in gene regulation and tumor growth, including mechanisms of drug resistance. Some long ncRNAs may promote or inhibit tumor development and influence the effectiveness of anti-cancer drugs like cisplatin. Additionally, the review explores how the tumor microenvironment and immune responses interact, suggesting that inflammation may accelerate the progression of oral cancer. By synthesizing insights from extensive literature, this review clarifies the complex relationship between long ncRNAs and OSCC treatment. The study aimed to improve treatment efficacy and increase survival rates for patients with oral squamous cell carcinoma by identifying potential therapeutic targets. The findings underscore the importance of integrating molecular insights into treatment strategies to combat drug resistance and enhance patient outcomes in oral cancer therapy.

Keywords: Oral squamous cell cancer, Metastasis, long ncRNAs, pathways, treatment

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Introduction

Oral cavity carcinoma represents a complex neoplasm and is among the most commonly occurring types of head and neck malignancies. OSCC constitutes nearly 90% of all cancers found in the oral cavity, originating from the mucosal surfaces of the mouth (1). Regrettably, many OSCC cases are identified at advanced stages, primarily due to the absence of efficient early diagnostic modalities. Ongoing exposure to risk factors such as alcohol consumption, tobacco use, and human papillomavirus (HPV) infection plays a critical role in the development of oral potentially malignant disorders. Oral mucosa lesions typify these disorders with an elevated likelihood of progressing to OSCC.

The oncogenesis process is intricate and multifaceted, encompassing epigenetic alterations, genetic mutations, and modifications within the tumor microenvironment (2,3). Conventional treatment modalities for advanced OSCC encompass surgical intervention, chemotherapy, immunotherapy, derivatives of natural compounds, hormone-based therapies, radiotherapy, nanoparticle-based treatments, and their combinations. Despite notable advancements in these therapeutic approaches in recent years, the five-year survival rate for OSCC hovers around 50% (4). Among the chemotherapeutic agents most frequently administered for the treatment of OSCC are cisplatin, doxorubicin (Dox), 5-fluorouracil (5-FU), and paclitaxel (PTX).

A significant challenge in enhancing patient outcomes is the development of drug resistance, which remains a substantial barrier in cancer therapies (5,6). Drug resistance compromises the effectiveness of both chemotherapy and radiotherapy, resulting in unfavorable prognoses. Fundamental mechanisms contributing to drug resistance include increased cellular detoxification, inhibition of apoptotic pathways, dysregulation of DNA repair mechanisms, and the participation of long ncRNAs. The imperative to tackle drug resistance in OSCC is paramount, as it not only hinders treatment efficacy but also exacerbates the elevated mortality rates associated with advanced disease stages.

Consequently, contemporary cancer research is intensely directed towards identifying novel therapeutic agents that not only counteract drug resistance by enhancing the effectiveness of existing treatments but also demonstrate minimal adverse effects attributable to their low toxicity towards healthy cellular structures (7). Even though approximately 80% of the human genome is transcribed into RNA, only about 2% of this RNA is translated into functional proteins. As a result, ncRNAs, the predominant portion of cellular RNA, are pivotal in regulating physiological, biological, and pathological processes (7). In recent decades, there has been an escalating interest in the significance of ncRNAs, particularly microRNAs (miRNAs) and long ncRNAs, in the initiation and advancement of various human malignancies.

Long ncRNAs are conserved ncRNA molecules that exceed 200 nucleotides in length and do not encode proteins. Initially, long ncRNAs were perceived merely as ‘transcriptional noise’ linked to transient RNA polymerase activity. However, long ncRNAs are increasingly acknowledged for their essential roles across a spectrum of human cancers, although their involvement in cancer drug resistance has yet to attract considerable scrutiny (8).

For example, upregulation of long ncRNAs homeobox A11 antisense RNA (HOXA11-AS) has been documented in OSCC tissues and cells compared to adjacent normal tissues and human oral keratinocytes. Mechanistically, long ncRNA HOXA11-AS functions as a sponge for miR-98–5p, thereby inhibiting the progression of OSCC (9). The significance of long ncRNAs, especially long ncRNAs, in the context of oncological diseases, is progressively gaining prominence, yet the intricate mechanisms linking these molecules to OSCC require further investigation.

Consequently, this review aimed to clarify the regulatory mechanisms of long ncRNAs within OSCC patients, while also seeking innovative strategies for enhancing clinical interventions for these conditions. This study aimed to collaboratively investigate the roles of long ncRNAs in OSCC pathogenesis and therapy, facilitating the design of personalized treatment options.

Literature Search and Selection

A narrative review of the literature on the relationship between OSCC and long ncRNAs in the pathogenesis, metastasis, and treatment ways was carried out. Inclusion criteria encompassed articles written in English, available in full-text format, comprehensive, and directly relevant to the subject matter under investigation. A thorough search was

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conducted in PubMed and Scopus databases in July 2024, utilizing keywords associated with Oral squamous cell carcinoma, OSCC, long ncRNAs, pathogenesis, treatment, and pathways. From the initial search, 157 articles were retrieved based on their titles, abstracts, and publication dates. After eliminating duplicate entries, a total of 66 distinct articles remained. The complete texts of these articles were carefully read, and a subset of 3 articles that was pertinent to the research question was selected. Subsequently, in October 2024, a supplementary search was conducted using Google Scholar, PubMed, and Scopus, which resulted in the identification and inclusion of three additional articles that were directly relevant to the topic of interest. To enhance the clarity and coherence of our arguments, nine additional references were integrated throughout the writing process (Figure 1).

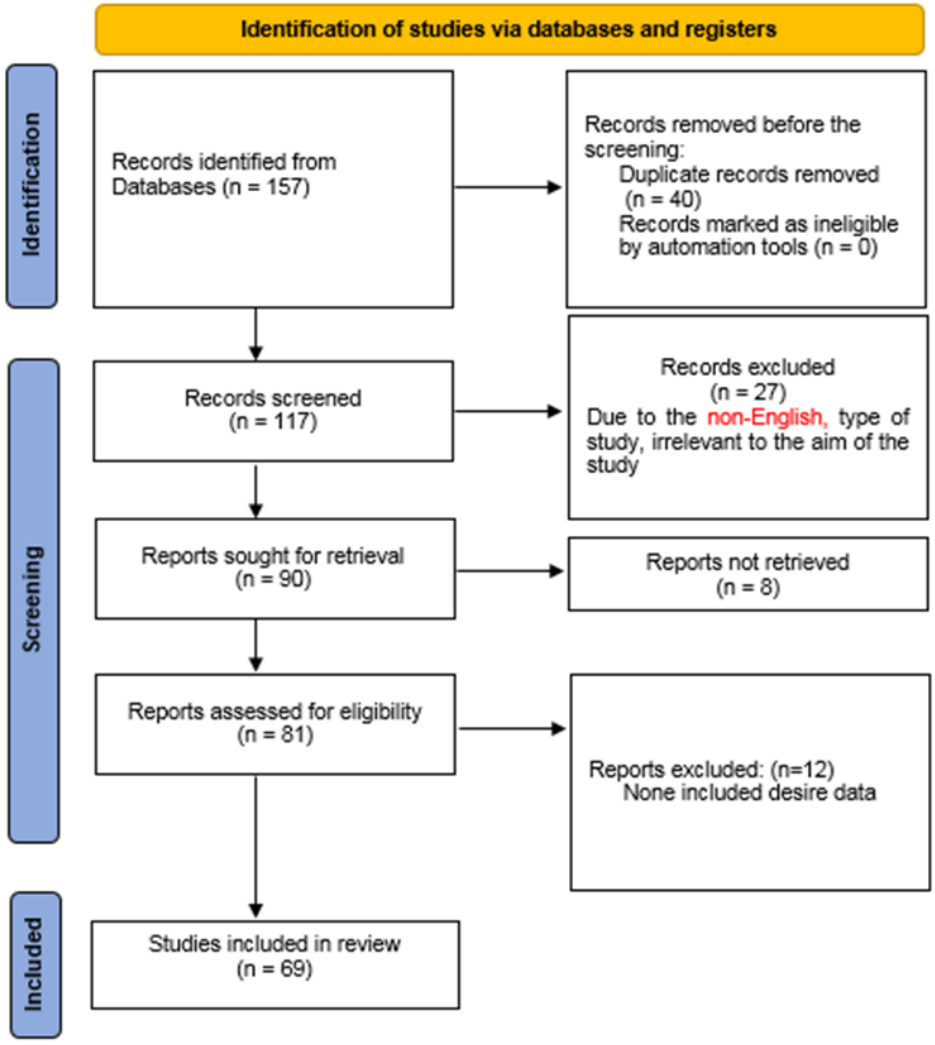

Figure1. Flow diagram of the steps for including studies in the review study.

Oral squamous cell carcinoma (OSCC)

OSCC arises from the epithelial surface of the oral mucosa. It ranks among the most frequently diagnosed fatal malignancies globally, characterized by a dismal prognosis. As per the most recent GLOBOCAN estimates from 2020, OSCC ranks as the seventh most common cancer globally, accounting for roughly 4.5% of all cancer cases worldwide. Additionally, it results in approximately 450,000 fatalities each year, which corresponds to about 4.6% of deaths attributed to cancer on a global scale. OSCC is observed to be more frequent in men compared to women and is particularly prevalent among individuals over the age of 50. As reported in the Global Cancer Statistics 2020, approximately 53,260 new instances and 10,750 fatalities due to oral cancer were recorded in the United

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States, representing nearly 4% of all cancer cases in males (10,11).

OSCC represents a significant global health challenge, ranking as the sixth most prevalent cancer worldwide, with an incidence of 389,846 cases reported in 2022. A substantial portion of these cases, totaling 258,440, was identified in the Asian subcontinent. As per the Globocan 2022 data, OSCC is responsible for 188,438 fatalities, with approximately 75% of these deaths occurring in Asia. The disease disproportionately affects low- and middle-income countries (LMICs), where it constitutes over 25% of all cancer cases in certain areas (12).

Currently, the predominant strategy for managing OSCC consists of surgical intervention in conjunction with radiotherapy and chemotherapy. Innovations in treatment methodologies, including pharmacological advancements and computer-assisted surgical techniques, are anticipated to enhance survival rates among OSCC patients. Nevertheless, OSCC continues to be an untreatable cancer, with treatment outcomes remaining largely unchanged. Additionally, a significant proportion of OSCC patients receive diagnoses at advanced disease stages, with no effective early detection strategies established. Consequently, to augment diagnostic efficacy and achieve improved prognostic outcomes, there is an urgent necessity for extensive research focused on elucidating the molecular underpinnings of OSCC and identifying novel diagnostic instruments and precision therapeutic modalities (13).

Oral carcinoma represents a specialized classification of head and neck malignancies that originates within the oral cavity, encompassing the anterior two-thirds of the tongue, the gingival tissues, the mucosal surfaces of the lips and cheeks, the sublingual region, the hard palate, and the minor retromolar zone. Clinical manifestations associated with oral carcinoma include a mass or non-resolving lesion/ulcer persisting beyond 14 days, the emergence of soft red, white, or mixed (red and white) lesions within the oral cavity, challenges in deglutition, mastication, phonation, movement of the jaw or tongue, malocclusion or poorly fitting prostheses, and unanticipated weight reduction (4). Oral malignancies rank as the sixth most common cancer globally, with 90% classified histologically as squamous cell carcinoma. The five-year survival probability is less than 50% in advanced instances, with female patients exhibiting a more favorable prognosis. The clinical outlook for these individuals is consistently dependent on variables such as age, lymph node involvement, and the size and location of the primary tumor. Predominant risk factors encompass premalignant conditions, the use of tobacco, betel quid, alcohol, substandard oral hygiene, ultraviolet radiation, Epstein-Barr virus (EBV), and HPV, particularly types 16 and 18 (14–16).

A growing body of evidence substantiates the notion that the human microbiome is significantly linked to various cancer types. OSCC represents the most extensively investigated oral malignancy and is also the most commonly occurring head and neck cancer overall. Nevertheless, there exists contention regarding the influential role of the oral microbiome in the pathogenesis of OSCC. A unique oral microbiome composition associated with OSCC has not been established in prior investigations. Individual variations in the oral microbiome possess the potential to amplify distinct tumor-promoting mutations in the development of OSCC; however, a definitive causal relationship has yet to be confirmed. The primary oral microorganisms, *Fusobacterium nucleatum*, and *Porphyromonas gingivalis*, have been demonstrated to promote tumorigenesis in murine models. Infection with *P. gingivalis* has been correlated with tumors in the oro-digestive tract, increased invasiveness of oral carcinoma, and enhanced proliferation of associated stem cells (17).

Prior research has indicated that periodontal inflammation may exacerbate gastrointestinal inflammation in vivo by transferring oral pathobionts to the gut, thereby activating colonic mononuclear phagocyte inflammasomes and fostering inflammatory responses. Furthermore, periodontitis facilitates the generation of reactive Th17 cells against oral pathogens. These reactive Th17 cells subsequently migrate to the gastrointestinal tract, where they are activated by oral pathobionts translocated from the oral cavity, instigating colitis; conversely, the gut microbiota does not activate these cells. The extent to which gastrointestinal inflammation may similarly influence the oral cavity environment, potentially heightening the severity of inflammatory responses and head and neck malignancies, remains to be elucidated. Limited studies have explored the effect of the gut microbiome on the immune response to oral cavity cancer, yet they may merit further investigation (18).

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Long ncRNAs

Long ncRNAs are extended RNA molecules, typically exceeding 200 nucleotides in length, which constitute a significant and distinct subset of ncRNAs, essential for the regulation of gene expression. Research indicates that the human genome harbors over 18,000 long ncRNAs, which are defined by their incapacity to be translated into proteins or yield functional protein products(19). The predominant synthesis of these entities is conducted by the enzyme RNA polymerase II. Notably, around 60% of these molecules exhibit key features such as a methylguanine cap at the 5′ terminus and a polyadenylated tail at the 3′ terminus. Complex mechanisms underpin the biogenesis of long ncRNAs, including cleavage reactions mediated by ribonuclease P to produce mature ends, capping of the ends facilitated by small nuclear RNA-protein complexes, and circularization. Long ncRNAs can be classified based on their chromosomal localization into various categories: long intergenic RNAs, enhancer RNAs, antisense RNAs, bidirectional long ncRNAs, long intronic RNAs, and promoter-associated long ncRNAs (19,20).

Long ncRNAs represent transcripts that arise from intergenic regions or overlapping existing genes, occurring in either a sense or antisense orientation. Their structural characteristics often resemble those of mRNA, featuring a 5' cap, a 3' polyA tail, and internal splicing. Notably, long ncRNAs can be located within the nucleus, cytoplasm, or both compartments of a single cell. The specific localization of long ncRNA is instrumental in delineating its functional responsibilities within the cellular context. Nuclear long ncRNAs, which are the predominant subtype, serve a regulatory function concerning nuclear architecture, chromatin arrangement, and epigenetic modifications. Furthermore, they may engage with DNA to create R-loops, thereby modulating gene transcription and upholding genomic integrity (19).

On the other hand, cytoplasmic long ncRNAs are pivotal in the regulation of protein synthesis by modulating mRNA stability and translational efficiency. They also interact with proteins and miRNAs, thereby adding additional layers of complexity to cellular regulatory mechanisms. Long ncRNAs exert their influence on gene regulation via chromatin remodeling, transcriptional activation, RNA interference, and splicing processes (21). Intriguingly, a majority of long ncRNAs are found to be upregulated in ovarian cancer (OC) tissues, while a select few, such as C5orf66-AS1, CASC2, ENST00000470447.1, FALEC, LINC01315, and MORT, exhibit down-regulation. Despite the intricate nature of chromatin remodeling, in which histone modifications are paramount for gene regulation, certain long ncRNAs like HOTAIR and FALEC have been recognized for their roles in modulating histone alterations and gene expression in OSCC. Recent investigations indicate that long ncRNAs might affect gene expression by modifying chromatin architecture or by displacing architectural proteins such as CTCF, which is vital for chromatin architecture, possibly disrupting loops and regulatory processes of genes (22,23).

Long ncRNAs contribute to the progression of OSCC by engaging with either DNA or proteins within the nucleus. For example, the long ncRNA p23154 inhibits miR-378a-3p, leading to an upsurge in Glut1 expression that promotes glycolysis, while long ncRNAs HAS2-AS1 activates HAS2, thereby advancing hypoxia-induced cancer progression in OSCC cells. Researchers posit that long ncRNAs may also be implicated in the metastasis of OSCC. These long ncRNAs could modulate migration, invasion, and the development of new lymphatic vessels (lymphangiogenesis) through diverse signaling pathways, potentially affecting the metastatic spread of OSCC (22,24).

Noteworthy is the role of epithelial-to-mesenchymal transition (EMT) in OSCC metastasis, with evidence suggesting that long ncRNAs are involved in modulating EMT within these cancerous cells. Furthermore, research has identified hypoxia-associated long ncRNAs, such as long ncRNA HIFCAR, that directly interact with the protein HIF-1α, facilitating the activation of genes associated with metastasis and thereby promoting OSCC progression. Investigations into OC have unveiled genetically altered pathways, including the Wnt/β-catenin and the PI3K/AKT/mTOR pathways, which are essential for cellular development and regeneration, frequently exhibiting hyperactivation (25,26).

Long ncRNAs play a significant role in the regulation of these pathways within the context of OC. They may exert epigenetic effects on genes (e.g., FALEC recruiting EZH2 for the methylation of specific sites leading to chromatin condensation) or directly influence transcription (e.g., via inhibition of NF-κB transcription factors that suppress Twist

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expression). Long ncRNAs can also modulate signaling cascades, such as inhibiting the Hippo pathway through interactions with the LATS1 protein, thereby reducing YAP1 phosphorylation (27,28). Moreover, ncRNAs can function as miRNA sponges, exemplified by H19, which sequesters miR-138, thereby augmenting the expression of its associated target genes(28,29). The general long ncRNAs involved in OSCC metastasis and related biological processes are mentioned in Figure 2.

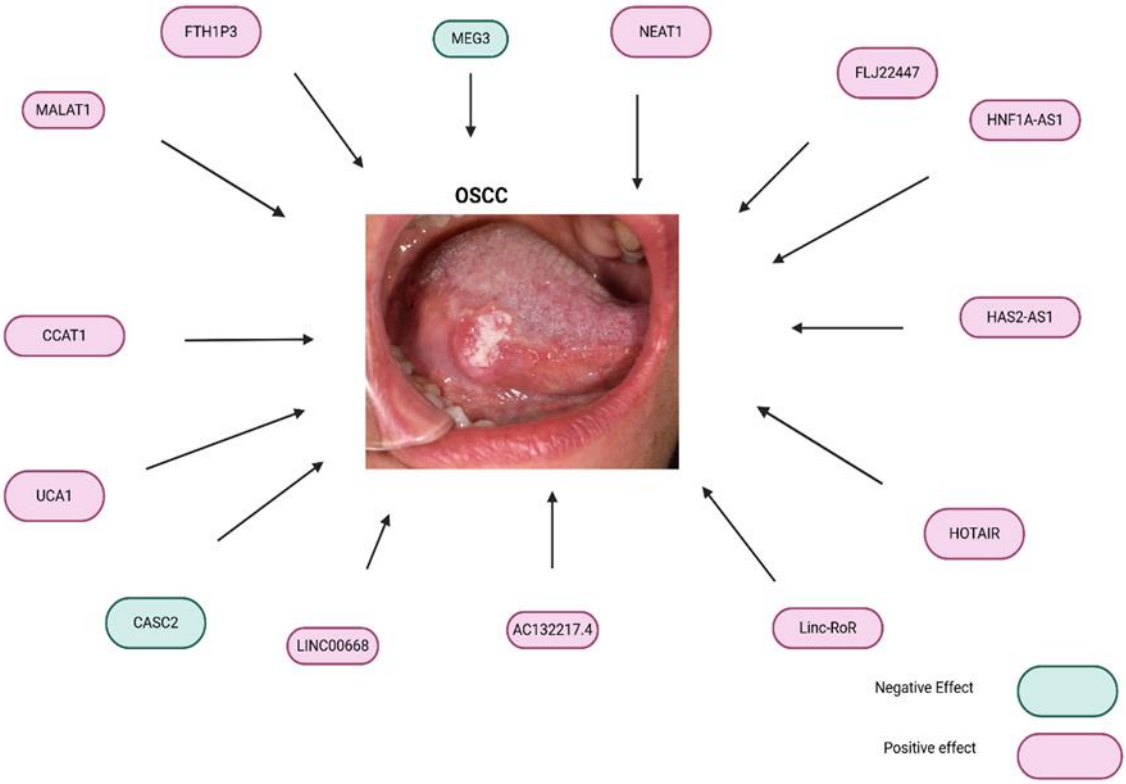

Figure2. long ncRNAs involved in OSCC metastasis and related biological processes.

Certain long ncRNAs have been identified as influential in cancer prognosis through their regulation of ferroptosis. The involvement of ferroptosis-related long ncRNAs (fr long ncRNAs) in OSCC has been discussed in various studies. Specifically, cancer susceptibility candidate 2 (CASC2) and maternally expressed 3 (MEG3) have been reported to negatively affect OSCC. Research indicates that MEG3 is downregulated in OSCC due to the trimethylation of H3K27 at its gene locus (30). The ability of MEG3 to inhibit the proliferation and invasion of OSCC cells is contingent upon its interaction with GATA Binding Protein 3 (GATA3). Furthermore, CASC2 has been shown to hinder the migration, invasion, and proliferation of OSCC cells by downregulating Cyclin-dependent kinase 1 (CDK1), suggesting a potential avenue for therapeutic intervention in OSCC patients (30). Conversely, long ncRNAs such as Urothelial carcinoma associated 1 (UCA1), HOX transcript antisense RNA (HOTAIR), and Nuclear Enriched Abundant Transcript 1 (NEAT1) positively influence OSCC. Existing literature indicates that UCA1 promotes apoptosis in OSCC cell lines both in vitro and in vivo, potentially linked to the activation of the WNT/β-catenin signaling pathway (31,32).

Additionally, metastasis associated in lung adenocarcinoma transcript 1 (MALAT1) acts as a competing endogenous RNA (ceRNA), modulating Signal transducer and activator of transcription 3 (STAT3) expression by sequestering miR-125b in OSCC, thereby presenting a novel therapeutic target for diagnosing and treating this malignancy (33). The role of long ncRNAs is pivotal in the management and prognosis of OSCC, as they influence a multitude of biological processes, encompassing tumor advancement, immune responses, and sensitivity to pharmacological agents. Recent investigations have pinpointed particular long ncRNAs that may serve as biomarkers

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and potential therapeutic targets, underscoring their significance in enhancing patient prognoses. Lastly, long ncRNAs can stabilize mRNAs, as evidenced by their interaction with mRNA, thereby promoting their stability and amplifying the expression of their target transcripts. Continued research into long ncRNAs is promising for formulating innovative diagnostic and therapeutic approaches for OC (8). By elucidating the mechanisms through which these molecules modulate gene expression and cellular functions, scientists may discern novel targets for therapeutic intervention, ultimately leading to improved patient outcomes.

Role of long ncRNAs in oral cancer pathogenesis

A substantial body of prior research has validated the significance of long ncRNAs in the diagnosis, prognosis, and treatment of oral cancer. Two categories of long ncRNAs exhibit dysregulation in oral cancer: upregulated long ncRNAs also referred to as oncogenic long ncRNAs, and downregulated long ncRNAs, known as tumor suppressor long ncRNAs. Yang et al. have identified long ncRNA-UCA1 as a notable long ncRNAs with crucial roles in the advancement of OSCC, which may also serve as a diagnostic biomarker (34). Another long ncRNA demonstrating diagnostic potential in oral cancer is long ncRNA-LOC284454. In an investigation led by Fan et al., elevated serum concentrations of this long ncRNA were observed in individuals diagnosed with oral cancer. The area under the curve (AUC) for the diagnostic efficacy of long ncRNA-LOC284454 was determined to be 0.698 (35).

In additional research conducted by Lie et al., the authors documented the upregulation of long ncRNA-RBM5-AS1 in oral cancer cells. This long ncRNA has also been reported to regulate miR-1285–3p and influence YAP1 gene expression levels. The indirect mediation of YAP1 gene expression by long ncRNA-RBM5-AS1 is proposed as a potential mechanism underlying oral carcinogenesis, thereby increasing the prospects for employing this long ncRNAs as a diagnostic and therapeutic marker (36). Prior investigations have illustrated a substantial correlation between the expression profiles of diverse long ncRNAs and tumor node status, lymph node metastasis, as well as reduced overall survival rates among patients. The involvement of long ncRNAs in the invasion and migration of oral cancer cells has been documented in a growing number of studies. These long ncRNAs-mediated effects are frequently reported to occur through the targeting of epithelial-mesenchymal transition (EMT), a critical process in normal embryogenesis and organogenesis, as well as in cancer cell metastasis. By augmenting the capacity of cancer cells to invade and migrate, EMT contributes to increased metastasis, recurrence risk, and poor overall survival outcomes. A principal characteristic of EMT is the overexpression of mesenchymal marker N-cadherin and the downregulation of epithelial marker E-cadherin. Noteworthy, long ncRNAs such as MIAT, SNHG12, PRKG1-AS1, HOXA11-AS, KRT16P3, HNF1A-AS1, CILA1, NEAT1, LINC00958, and H19, are recognized as pivotal long ncRNAs that significantly facilitate EMT in oral cancer (19,24).

It is not surprising that long ncRNAs have also been extensively shown to target and regulate signaling pathways that exhibit aberrant functional patterns in oral cancer. For instance, long ncRNA-LEFT1 promotes the proliferation of OSCC cells while simultaneously diminishing their apoptotic rates by targeting the YAP1 tumor suppressor gene, which is a component of the Hippo signaling pathway (37). The PI3K/AKT/mTOR signaling pathway, known for its significant role in proliferative signal transduction, is influenced by long ncRNA MALAT1, which promotes the EMT process in OSCC. Additionally, NEAT1 is critical for the progression of oral cancer through the modulation of Notch signaling pathways. Additionally, long ncRNA AC007271.3 enhances the proliferation and invasive characteristics of OSCC by targeting the Wnt/β-catenin pathway (37,38).

Besides their cancer-inducing attributes, specific long ncRNAs have been discovered as tumor suppressors, seen as negative controllers of oral tumor development. An investigation by Huang et al. indicated a notable decline in NKILA expression in cases of tongue squamous cell carcinoma. Raising NKILA levels stopped epithelial to mesenchymal transition and cell movement in Tongue Squamous Cell Carcinoma-1 (TSCC) and CAL27 cells by turning on the NF-κB/Twist pathway, impacting TSCC behavior (39,40). Concurrently, MEG3, an established tumor inhibitor, has been the subject of extensive studies across various cancers, especially oral squamous cell carcinoma. Overexpression of MEG3 diminishes cell movement and multiplication in SCC15 cells, with increased cell death observed in CAL27 cells. The cancer-preventing activities of MYC protein involve blocking the WNT/β-catenin

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route and acting like a sponge for miR-548d-3p, which adjusts the JAK-STAT signaling system (41,42). Zeng et al. elucidated that GAS5 is integral in inhibiting tumor cell growth, migration, invasion, and the process of EMT in OSCC by modulating the miR-21/Phosphatase and TENsin homolog deleted on chromosome 10 (PTEN) signaling pathway. Moreover, MEG3 has emerged as a significant tumor suppressor that has been thoroughly investigated across various cancers, including OSCC.

The heightened expression of MEG3 correlates with reduced proliferation and migration of SCC15 cells, while it enhances apoptosis in CAL27 cells. Mechanistically, MEG3 demonstrates its tumor-suppressive effects by downregulating the WNT/β-catenin signaling cascade and functioning as a miRNA sponge for miR-548d-3p, which subsequently affects the JAK-STAT signaling pathway. Additionally, the long ncRNA FALEC has been identified as another tumor suppressor with reduced expression in OSCC, where its increased expression markedly hinders OSCC cell proliferation and migration in both in vitro and in vivo experiments, corresponding with better prognostic outcomes for patients with OSCC (43). In a similar vein, GAS5, a notable long ncRNA, has been recognized as an important tumor suppressor across various cancers (43).

Zeng et al. demonstrated that GAS5 functions as a tumor suppressor in OSCC through the miR-21/PTEN signaling pathway, which leads to the inhibition of tumor cell proliferation, EMT, invasion, and migration. Notwithstanding the recognized oncogenic functions of long ncRNAs, investigations into their tumor-suppressive capacities in OSCC remain scarce. Therefore, there is a pressing need for more extensive studies to elucidate these molecular mechanisms in OSCC (43).

Chemotherapeutic agents kill tumor cells by the induction of apoptosis; hence, disturbances in apoptosis and related signal transduction pathways lead to the failure of apoptosis and loss of chemosensitivity, contributing to drug resistance. It has been reported that various resistant oral cancer cells express high levels of anti-apoptotic proteins while expressing low levels of pro-apoptotic proteins. Thus, evasion from apoptosis is a hallmark of resistant oral cancer cells. In this regard, numerous long ncRNAs have been reported to play critical roles in the chemoresistance of oral cancer cells through regulating apoptosis (44,45). For instance, Wang et al. demonstrated that long ncRNA HOXA11-AS, a type of oncogenic long ncRNA, was significantly overexpressed in the cisplatin-resistant OSCC cells and played a critical role in the promotion of proliferation, growth, migration, and invasion of cancerous cells. This long ncRNA enhanced the ability of cell proliferation and inhibited the cytotoxic effects of cisplatin on resistant cells by suppressing any apoptosis. Silencing of HOXA11-AS in resistant cells significantly induced apoptosis, along with upregulation of caspase-3 expression, which enhanced cisplatin cytotoxicity in those cells. Moreover, during the development of resistance to cisplatin in oral cancer cells, the authors found that HOXA11-AS interacts with and negatively regulates miR-214–3p (46). Another long ncRNA showing upregulation in cisplatin-resistant oral OSCC cells is UCA1.

It has been demonstrated in a study by Fang et al. that this long ncRNA promotes the proliferation of cisplatin-resistant OSCC cells and suppresses apoptosis, a process occurring via its interaction with and suppression of miR-184 (32). Conversely, KCNQ1OT1 has been associated with the promotion of cellular proliferation and the development of resistance to cisplatin-induced apoptosis, both in vitro and in vivo. This long ncRNAs, akin to the previously mentioned examples, exerts its influence by targeting the microRNA, miR-211–5p; thus, its overexpression in resistant oral cancer cells markedly diminished cellular proliferation and reinstated sensitivity to cisplatin (47).

Researchers led by Wang et al. have shed light on the function of another cancer-promoting coding RNA called PVT in the resistance of OSCC cells, to cisplatin treatment. This specific long ncRNA shows an increase in expression levels, in cisplatin OSCC cells and is linked to poorer overall survival rates. The mechanism through which this long ncRNA contributes to cisplatin resistance involves boosting cancer cell growth and preventing cell death by influencing HIFla and miR l94–Sp. Furthermore long ncRNAs have also been identified as playing a role, in the development of cisplatin resistance in TSCC.MPRL long ncRNA is particularly significant in influencing cisplatin sensitivity through its impact, on pathways and miRNA miRNA receptor 483–five pence (48). A prior investigation concerning CASC2 revealed that this long ncRNA modulates the miR-31–5p/KANK1

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pathway, thereby influencing the chemosensitivity of OSCC cells. KANK1, a key constituent of the Kank gene family, plays a critical role in the advancement of various malignant neoplasms. Its principal function is to polymerize with cytoplasmic actin, thereby governing the cytoskeletal structure and promoting cellular motility (49).

Considering the significance of long ncRNAs in chemoresistance, the strategic targeting of these molecules may provide innovative methods to counteract pharmacological resistance in oral malignancies. For example, the modulation of long ncRNAs such as CASC2, which facilitate apoptosis, could enhance the therapeutic effectiveness of cisplatin. The characterization of distinct long ncRNA profiles in patients with oral cancer may pave the way for personalized therapeutic interventions. Customizing treatment modalities according to an individual's long ncRNA expression profiles has the potential to optimize therapeutic outcomes and mitigate resistance by elucidating the precise role of long ncRNAs in the apoptosis of cancer cells (49).

One of the key long ncRNAs, LINC00473, has garnered attention for its role in radioresistance in OSCC. Studies have shown that LINC00473 is notably upregulated in OSCC tissues and cell lines. Functional assays revealed that LINC00473 acts as an oncogene, promoting cell growth and inhibiting apoptosis. Significantly, reducing LINC00473 expression has been shown to increase the sensitivity of OSCC cells to radiotherapy, thereby demonstrating its potential as a therapeutic target (50). Moreover, the long ncRNA BLACAT1 has been implicated in modulating radiosensitivity through its interaction with Presenilin 1 (PSEN1). PSEN1 is known to influence the processing of amyloid precursor protein (APP) via its effects on γ-secretase, an enzyme involved in APP cleavage. Elevated PSEN1 expression has been associated with poor prognosis and reduced radiosensitivity in various cancers, including liver and oral cancers (51). Additionally, long ncRNAs play a role in cell cycle regulation and apoptosis inhibition in OSCC. For instance, silencing the long ncRNA LEF1-AS1 results in G0/G1 cell cycle arrest and reduced cell proliferation and growth in vitro, attributed to the inactivation of the Hippo signaling pathway. Certain long ncRNAs have also been shown to enhance OSCC invasion, metastasis, and angiogenesis. MALAT-1, for example, is significantly associated with the growth and metastasis of OSCC cells, promoting distant metastasis through the regulation of the small proline-rich protein (SPRR) (52). LINC00319, which is downstream of Chemokine ligand 18 (CCL18), when overexpressed, influences the expression of VEGFA and MMP-9, thereby enhancing the angiogenic potential of OSCC cells (53).

Long ncRNAs serve dual roles in cancer biology, acting both as oncogenes that facilitate tumor initiation and progression, and as tumor suppressors that inhibit growth and metastasis. For instance, long ncRNA NKILA has been identified as a tumor suppressor, showing a negative correlation with metastasis and prognosis in breast cancer. Supporting these findings, Huang et al. demonstrated that NKILA expression is significantly reduced in tongue squamous cell carcinoma (TSCC). Elevated levels of NKILA were found to inhibit EMT and migration in TSCC and CAL27 cells by activating the NF-κB/Twist signaling pathway, thereby influencing the biological behavior of TSCC. Another notable long ncRNA, growth-arrest-specific transcript 5 (GAS5), has been extensively recognized as a tumor suppressor across various cancers (39).

In contrast to the extensively characterized oncogenic roles of long ncRNAs, investigations into their tumor-suppressive roles in OSCC remain sparse, underscoring the necessity for more thorough research in this domain. Long ncRNAs HOXA11-AS (homeobox A11 antisense RNA) is significantly elevated in tissues and cellular models of oral squamous cell carcinoma. Moreover, it has been established that HOXA11-AS promotes the expression of YBX2 (Y box binding protein 2) through the inhibition of miR-98-5p, thereby enhancing the migratory, invasive, and EMT capacities of OSCC cells (9). Conversely, long ncRNAs GAS5 (growth-arrest-specific transcript 5) is characterized by low expression levels in OSCC. Notably, the upregulation of GAS5 expression has been demonstrated to obstruct the migratory, invasive, and EMT processes in OSCC cells, operating through a competing endogenous RNA (ceRNA) mechanism. Specifically, GAS5 increases the expression of PTEN (phosphatase and tensin homolog) by binding to miR-21, subsequently inhibiting the activation of the PI3K/AKT signaling pathway (54).

Additionally, the suppression of miR-21 by GAS5 results in an increased expression of E-cadherin while concurrently reducing the levels of N-cadherin,

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Vimentin, and Snail, indicating that the EMT of OSCC cells was also hindered. Findings from another study revealed that HOTAIR can enhance the expression of MTA2 (metastasis-associated gene 2) via the miR-326/MTA2 regulatory axis, thereby facilitating the migration, invasion, and EMT of OSCC cells. Similarly, long ncRNA CASC15 (cancer susceptibility candidate 15) has been implicated in advancing metastasis during OSCC progression. The underlying mechanism may involve the interaction between CASC15 and miR-33a-5p, which elevates the expression of the downstream target ZEB1 of miR-33a-5p (38). Mechanistic studies confirmed that by directly interacting with miR-378a-3p, long ncRNA-p23154 is capable of enhancing Glut1 (glucose transporter 1) expression, thus strengthening the glycolytic processes of OSCC cells, ultimately resulting in increased migration, invasion, EMT, and metastasis of these cells.

Furthermore, long ncRNAs CCAT1, LINC01116 (long ncRNA 1162), SNHG17 (small nucleolar RNA host gene 17), and RC3H2 have been shown to promote metastasis-associated biological activities in OSCC cells through the modulation of the miR-181a/Wnt/b-catenin, miR-136/FN1 (fibronectin 1), miR-876/SP1 (specificity protein 1), and miR-101-3p/EZH2 signaling pathways, respectively. In conclusion, long ncRNAs are integral to the metastatic processes of OSCC, functioning as ceRNAs (55). The summary of long ncRNAs involved in OSCC metastasis is manifested in Figure 3.

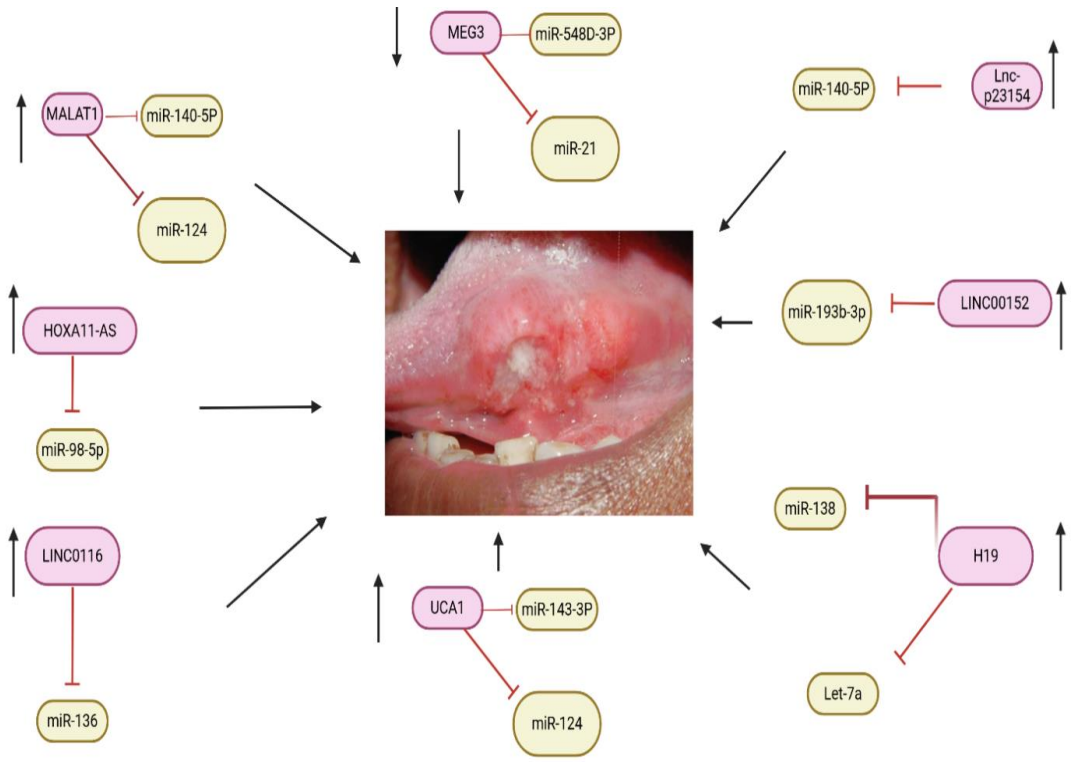

Figure 3. Long noncoding RNAs (Long ncRNAs) involved in oral squamous cell carcinoma (OSCC) metastasis by functioning as miRNAs.

The role of coding RNA in the field of immunotherapy

Many long ncRNAs that are linked to the system play roles in regulating immune processes at the epigenetic level according to scientific studies. These long ncRNAs are actively involved in triggering and shaping T and B lymphocytes responses, in the system besides impacting the behaviors of innate immune cells and the release of inflammatory cytokines. Through their influence over maintaining a balance, within cells' functions and activities and controlling the secretion of inflammatory substances long ncRNAs can adjust immune reactions. Therefore known as immune-related coding RNAs these molecules could potentially play a significant role in the development of resistance to immunotherapy due, to their ability to change different immune responses mediated by T

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cells and create an immunosuppressive environment (56,57). In general cancer cells often use glycolysis to generate energy, which can result in a buildup of lactate due, to issues with mitochondria functioning and the presence of oxygen in the environment around the tumor cells. This build-up of lactate causes the nature of the tumor microenvironment (known as TME) which can impair the effectiveness of cells and prevent the release of certain substances that fight against cancer. Glucose transportation within cells is made possible by proteins, in cell membranes called glucose transporters (GLUTs). When these transport proteins are excessively expressed on the surface of tumor cells it boosts both glycolysis and glucose absorption. Studies have indicated that ncRNAs play a role, in controlling GLUT in types of cancers. For instance, in cell carcinoma mir 340 decreases GLUT expression long ncRNA p23154 enhances GLUT expression and mir 375 reduces LDHA activity resulting in inhibiting aerobic glycolysis (58).

Natural killer cells represent a crucial component of the innate immune system, serving as a fundamental barrier against infections and playing a significant role in orchestrating antitumor immune responses. Emerging evidence underscores the involvement of long ncRNAs in the maturation of NK cells and their ability to evade tumor recognition. A recent investigation highlighted that long ncRNA GAS5 is essential for the secretion of IFNγ, which is notably downregulated in NK cells derived from patients with liver cancer (54).

Furthermore, the research suggested that silencing GAS5 may result in a reduction in the proportion of CD107a+ NK cells, subsequently leading to diminished apoptosis in HepG2 and Huh7 cell lines. Conversely, the enhanced expression of long ncRNA GAS5 was found to lower the levels of miR-544 by up-regulating runt-related transcription factor 3 (RUNX3), thereby promoting increased cytotoxicity mediated by activated NK cells, indicating a promising candidate for targeted cancer therapy (59). Ben Ma et al. established computational frameworks aimed at identifying tumor-infiltrating immune-related long ncRNA in head and neck squamous cell carcinoma and scrutinized their associations with clinicopathological characteristics, molecular alterations, and responses to immunotherapy. The expression of PD-1 is linked to methylation patterns in HNSCC (60). Methylation analyses of CpG sites within the TCGA database revealed that PD-1 and the adjacent long ncRNA AC131097.3 exhibited co-expression in 528 HNSCC specimens alongside 50 adjacent non-malignant tissues. Specifically, the levels of PD-1 mRNA and AC131097.3 demonstrated a negative correlation with promoter methylation and a positive correlation with gene body CpG methylation (61).

It is posited that AC131097.3 may have a significant role in modulating immune responses in HNSCC. The endogenous induction of PD-1 and PD-L1 via IFN-α represents a novel hypothesis regarding immunosuppression in HNSCC. Recently, it was observed that long ncRNA MX1-215, a newly identified IFN-α-induced long ncRNA, exhibited reduced expression in HNSCC. The expression levels of long ncRNA MX1-215 were positively correlated with the pathological grade of HNSCC. Mechanistically, long ncRNA MX1-215 directly interacts with the acetyltransferase GCN5, disrupting its association with H3K27 acetylation binding sites on the promoters of PD-L1 and galectin-9. These findings yield novel perspectives on immunotherapeutic strategies in HNSCC (62).

Clinical trials involving long ncRNAs in oral cancer

Long ncRNAs are promising candidates for cancer biomarkers and therapeutic targets due to their ability to regulate a broad spectrum of druggable and non-druggable proteins and signaling pathways. This renders them especially appealing for the advancement of tailored therapies in cancer care. Unlike conventional metabolites and protein indicators, long ncRNAs can affect various elements of tumor development, providing novel methods for the diagnosis and treatment of oral cancer. A multitude of long ncRNAs are undergoing clinical tests for their health treatment and disease-detecting capabilities in various human cancers, such as oral cancer (63,64). Despite the fairly scant number of long ncRNA investigated in clinical studies, early outcomes have been encouraging, hinting at wider uses in oncology therapies. Consider the continuous medical study targeting the long ncRNA MALAT1, recognized for its involvement in tumor spread and resistance to medication. This experiment investigates the diagnostic and treatment importance of MALAT1 and its target, miR-124, in saliva from individuals with oral malignancies. It could be useful for early tumor detection and new therapies. Another long ncRNA

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under clinical scrutiny is ESCCR-1, frequently suppressed in oral carcinoma tissues (65).

While these investigations underscore the perspective of long ncRNAs in medical applications, however, numerous obstacles remain to surmount. The stability and delivery of long Upcoming studies should concentrate on refining RNA molecule delivery mechanisms, advancing their precision, and investigating therapies that exploit the distinct characteristics of long ncRNAs to boost therapeutic outcomes. The assimilation of long ncRNAs into medical applications offers substantial potential for improving the identification and management of oral malignancies, especially in surmounting pharmacological resistance. Nonetheless, ongoing investigation and clinical verification are crucial to maximize the benefits of these innovative therapeutic compounds (66).

Resistance to chemotherapeutic agents constitutes a significant obstacle in the management of cancer (32). A principal area of inquiry within oncology research is the elucidation of the mechanisms through which cancer cells develop resistance to chemotherapeutic agents. Empirical studies have demonstrated that long ncRNA UCA1 is markedly overexpressed in cisplatin-resistant OSCC. Furthermore, there is an increasing corpus of evidence indicating that long ncRNA UCA1 can facilitate the proliferation of OSCC cells while concurrently diminishing their sensitivity to cisplatin. Additionally, the previously mentioned findings imply that long ncRNA UCA1 may also exert regulatory effects on the growth of OSCC through the modulation of miR-184. This observation intimates that an interaction between long ncRNA and microRNA could play a pivotal role in the pathogenesis of oral cancer (32).

Jie Deng's 2023 study simplifies the role of long ncRNA, named long ncRNA AC103563.8, in the advancement of oral squamous cell carcinoma and explores its mechanisms. A Cal-27 cell line was engineered to lack the long ncRNA AC103563.8 gene. Several of the identified proteins were validated through parallel reaction monitoring (PRM) to confirm their interaction with long ncRNA AC103563.8. The expression of long ncRNA-AC103563.8 is elevated in OSCC tissue, and the long ncRNA is detectable in both nuclear and cytoplasmic locations (67). Long ncRNA AC103563.8 facilitates the invasion and metastasis of OSCC cells. Methylation is observed within the promoter of the MAL gene. ChIRP-MS identified a total of 330 proteins that bind to long ncRNA AC103563.8, and bioinformatics analysis revealed their involvement in diverse biological processes. PRM experiments substantiated the binding of certain proteins to long ncRNA AC103563.8. This long ncRNA is characterized as a functional entity that promotes OSCC progression through its interaction with MAL or other tumor-associated proteins. Furthermore, this study suggests that long ncRNA AC103563.8 may have regulatory roles in OSCC and represents a potential therapeutic target for treating OSCC (67).

In an experimental study by Weiyu Li et al. in 2023, long ncRNAs microarray assays, in situ hybridization staining, and clinicopathological data analyses were conducted to elucidate the expression profile of BRAF-activated non-protein coding RNA in tissue samples of oral squamous cell carcinoma. The overexpression of BRAF-activated non-protein coding RNA resulted in an increased proportion of 5-ethynyl-2'-deoxyuridine-positive cells, enhanced viability, and elevated migration and invasion rates of oral squamous cell carcinoma cells, whereas the silencing of BRAF-activated non-protein coding RNA led to diminished effects in vitro. Moreover, BRAF-activated non-protein coding RNA was predominantly localized within the nucleus of oral squamous cell carcinoma cells and demonstrated binding with Ras-associated binding 1A. The silencing of Ras-associated binding 1A adversely affected the motility and phosphorylation levels of nuclear factor-κB in oral squamous cell carcinoma cells induced by the overexpression of BRAF-activated non-protein coding RNA. An inverse trend was also documented. Serving as a promoter in the metastasis of oral squamous cell carcinoma, BRAF-activated non-protein coding RNA facilitates the proliferation and motility of oral squamous cell carcinoma cells through the regulation of the BRAF-activated non-protein coding RNA/Ras-associated binding 1A complex, thus activating the nuclear factor-κB signaling pathway (68).

The objective of this research is to investigate the prognostic relevance of ferroptosis-related long ncRNAs in the context of OSCC and to construct a prognostic risk and immune activity framework. The study utilized clinical and RNA-seq datasets about OSCC patients, acquired from The Cancer Genome Atlas (TCGA) Genome Data Sharing (GDC) portal.

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Through the integration of differential expression analysis, Pearson correlation evaluations, and Cox regression modeling, ferroptosis-related long ncRNAs were identified, culminating in the creation of a prognostic model based on these long ncRNAs. The model's predictive precision was evaluated through survival curve analyses, receiver operating characteristic (ROC) curve evaluations, and clinical decision curve analysis (DCA). Both univariate and multivariate Cox regression analyses were performed to identify independent prognostic factors. Subsequently, the infiltration and functional enrichment of immune cell populations were compared across high- and low-risk categories (69).

Ultimately, several small-molecule compounds with potential efficacy against OSCC were identified through the L1000FWD database. The prognostic model comprised eight ferroptosis-associated long ncRNAs (FIRRE, LINC01305, AC099850.3, AL512274.1, AC090246.1, MIAT, AC079921.2, and LINC00524). The area under the ROC curve (AUC) was determined to be 0.726. The DCA indicated that the risk score derived from the prognostic model served as a superior prognostic marker compared to other clinical indicators. Multivariate Cox regression analysis indicated that the risk score functioned as an independent prognostic factor for OSCC. Notable discrepancies between high- and low-risk groups were observed in immune cell infiltration, immune functionality, m6A-related gene expression levels, and signaling pathway enrichment. Following this, several small-molecule drugs were forecasted to target differentially expressed ferroptosis-related genes in OSCC. This model holds significant potential for prognostic forecasting and immune assessment, providing a foundation for further research on ferroptosis-associated long ncRNAs in OSCC (69).

Some long ncRNAs influence cancer prognosis by regulating ferroptosis, although their role in OSCC has only been briefly addressed in related literature. Figures 1 and 2 show that CASC2 and MEG3 negatively impact OSCC. Research indicates that MEG3 is downregulated in OSCC due to H3K27 trimethylation at its gene locus, and its inhibition of OSCC cell proliferation and invasion relies on GATA3 binding (30). CASC2 also suppresses OSCC cell migration, invasion, and proliferation by downregulating CDK1, suggesting new therapeutic interventions for OSCC patients. Conversely, long ncRNAs like UCA1, HOTAIR, and NEAT1 positively affect OSCC. UCA1 has been shown to induce apoptosis in OSCC cell lines both in vitro and in vivo, potentially linked to the WNT/β- catenin signaling pathway's activation (31). Additionally, MALAT1 is a competing endogenous RNA (ceRNA) that modulates STAT3 expression by sequestering miR-125b, positioning it as a novel therapeutic target for OSCC diagnosis and treatment (33).

Long ncRNAs have emerged as key regulators in developing drug resistance through multiple mechanisms. Their involvement spans the regulation of apoptosis, autophagy, EMT, DDR, and CSC properties. According to long ncRNAs, such as HOXA11-AS, UCA1, and KCNQ1OT1 are implicated in modulating apoptosis pathways, conferring resistance to chemotherapeutic agents (47). In contrast, long ncRNAs like MALAT1 and SNHG26 contribute to resistance through their regulatory effects on EMT processes, which are crucial for tumor progression and metastasis. Additionally, long ncRNAs such as long ncRNA POP1–1 play significant roles in DNA repair mechanisms, further influencing the resistance phenotype by facilitating the repair of chemotherapy-induced DNA damage.

The identification of CASC2 as a unique tumor suppressor long ncRNA that enhances apoptosis in response to cisplatin treatment highlights a critical distinction among long ncRNAs involved in drug resistance. Many long ncRNAs act as oncogenic agents; CASC2’s role as a ceRNA provides a contrasting example of how long ncRNAs can potentially be harnessed for therapeutic advantage. This contrast underscores the importance of distinguishing between different types of long ncRNAs and their functional roles in drug resistance (49).

Therapeutic strategies targeting long ncRNAs such as GAS5 and UCA1, known for their tumor-suppressive and chemoresistance-modulating effects, are gaining traction in cancer research. These strategies concentrate on oligonucleotide therapeutics and advanced delivery systems to improve long ncRNA-targeted treatment efficacy (54). Modifications like 2'-O-methyl and locked nucleic acids enhance the stability and effectiveness of these oligonucleotides. Innovations such as viral vectors and nanoparticles improve pharmacokinetics and cellular uptake for targeted tumor delivery. Combining long ncRNA targeting with traditional chemotherapeutics may help

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overcome resistance mechanisms, exemplified by GAS5's ability to sensitize breast cancer cells to radiation by inhibiting DNA repair. Since long ncRNAs degrade rapidly in biological environments, developing stable formulations is crucial for extending their therapeutic effects. However, the potential of long ncRNAs to trigger immune responses presents a significant challenge for clinical application (58). Several long ncRNAs have been previously identified as potential biomarkers, with some currently undergoing evaluation in clinical trials, for instance, HOTAIR, MEG3, MALAT1, UCA1, NEAT1, and CCAT1 (9).

Compared to the adjacent normal tissues, the expression levels of long ncRNA C5orf66-AS1 were markedly diminished in OSCC tissues. Furthermore, long ncRNA EGFR-AS1 exhibited significant upregulation in neck squamous cell carcinoma, leading to the hypothesis that it may be a biomarker for OSCC (70). The expression of the MEG3 gene is diminished in an increasing array of primary human neoplasms and tumor-derived cell lines. Various mechanisms are implicated in reducing MEG3 expression within tumors, such as gene deletion, promoter hypermethylation, and hypermethylation of the intergenic differentially methylated region. The re-establishment of MEG3 expression suppresses tumor cell proliferation in vitro and inhibits colony formation in soft agar. This growth suppression is partly a consequence of apoptosis triggered by MEG3. MEG3 promotes the accumulation of p53 (TP53) protein, enhances transcription from a p53-dependent promoter, and selectively modulates the expression of p53 target genes (71,72).

Discussion

In sum, the document emphasizes the intricacy of mouth SCC and the crucial function of long ncRNA in its advancement and resistance to therapy. Despite recent medical breakthroughs, the five-year survival rate stays low, highlighting the necessity for inventive treatments. Long ncRNAs are essential in managing drug resistance, implying that focusing on these elements might improve therapeutic outcomes. Persistent study of OSCC's molecular processes and long ncRNAs' roles is crucial for crafting superior diagnostic and treatment methods to enhance survival rates.

Future Directions in the Management of OSCC

Investigating the role of long ncRNAs in the pathogenesis of OSCC is urgent. Understanding how these molecules influence tumor development, drug resistance, and patient outcomes could lead to new intervention strategies. Although evidence linking long ncRNAs to OSCC is increasing, our understanding remains limited, necessitating further research into their effects on OSCC pathways. Future studies should correlate long ncRNAs with clinicopathological features to assess their potential as biomarkers for diagnosis, prognosis, and treatment prediction. Given the challenges of drug resistance in OSCC, new research will also explore long ncRNAs' roles in this context. Insights from studies on treatment response sensitivity may inform the development of effective long ncRNAs -targeted therapies.

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