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Expression of lncRNA MALAT1 in Oral Squamous Cell Carcinoma: Correlation with Tumor Invasiveness and Prognosis

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ABSTRACT

This molecular study investigates the expression of the long non-coding RNA (lncRNA) MALAT1 in tissue samples from patients with oral squamous cell carcinoma (OSCC). Quantitative PCR was used to assess MALAT1 levels in 40 OSCC samples and 20 adjacent normal tissues. High MALAT1 expression was significantly correlated with increased tumor size, lymph node metastasis, and poor 3-year survival outcomes. These results highlight MALAT1 as a potential biomarker for OSCC progression and a possible target for therapeutic intervention. Functional studies are warranted to explore its role in epithelial-mesenchymal transition and invasion.

Keywords: Oral cancer, lncRNA, MALAT1, tumor markers, prognosis.

1 Introduction

Oral squamous cell carcinoma (OSCC) is one of the ten most common malignancies worldwide. In the United States, the estimated incidence of OSCC is 39,000, with a mortality rate of 8,300 patients every year. In China, OSCC morbidity, with incidence rates of 64.86 per 100,000 populations, ranks as the sixth most common malignancy, accounting for 34.04% of the total incidence of head and neck cancers. Despite surgical resection and adjuvant chemo/radiotherapy, the overall OSCC diagnosis shows unreassuring results due to local recurrence and/or metastasis. Therefore, it is important to identify novel and effective early diagnostic and therapeutic targets for OSCC [1, 2]. Long non-coding RNAs (lncRNAs) are defined as non-protein-coding transcripts longer than 200 nucleotides. Recent studies have indicated that lncRNAs are

frequently aberrantly expressed in many cancers and are involved in cancer initiation, progression, as well as metastasis [3–5].

Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1), another lncRNA, is located in human chromosome 11q13.1 and is highly conserved across species. This lncRNA is associated with the invasive and metastatic potentials in many cancers, contributing to cancer cell invasion and metastasis [6]. Hirata et al. reported that MALAT1 was involved in the mesenchymal-like phenotype of breast cancer and promoted metastasis [7]. Wang et al. demonstrated that MALAT1 was upregulated in OSCC tissues and cell lines. In Tca8113 and TSCCA cells, MALAT1 knockdown inhibited cell migration and invasion [8].

The goal of this study was to investigate MALAT1 expression in human OSCC tissues and cell lines. The association of MALAT1 expression with the clinicopathological features of OSCC patients was analyzed. The effects of MALAT1 expression on in vitro invasive and migrative abilities were also studied. This study revealed that MALAT1 was upregulated in OSCC tissues, and its higher expression was associated with more advanced tumorous stages and lymph node metastasis. Moreover, higher MALAT1 expression was correlated with poorer overall survival and relapse-free survival rates [6,7]. Functional studies indicated that MALAT1 silencing inhibited the invasive and migrative abilities of OSCC cells. The results suggest that increased expression of lncRNA MALAT1 is correlated with OSCC invasiveness and poor prognosis, which may create new possibilities for developing therapeutic targets of OSCC [9, 10].

2 Background on lncRNA

Long non-coding RNAs (lncRNAs) are broadly defined as transcripts over 200 nucleotides of non-coding transcripts. LncRNAs are now recognized as key players in many essential cellular processes. They are implicated in the regulation of fundamental biological processes such as pluripotency, differentiation, and response to stimuli [11]. Although most lncRNAs have not yet been characterized, they have been shown to act as regulators of transcription or in the processing and stability of other smaller RNAs [12]. The discovery of lncRNA MALAT1/regulator of genome 2 (Rog) provides a new insight into the regulation of gene expression. The lncRNA MALAT1 gene locus is located on human chromosome 11q13, which harbors an exclusive and highly conserved primary transcript that is processed to yield multiple nuclear-enriched MALAT1 isoforms that are retained in the nucleus [13].

LncRNA MALAT1 acts as a transcriptional regulator of androgen receptor target genes by competing with the Androgen receptor for common transcriptional co-activators [14]. Natural killer (NK) cells are important mediators of early immune responses against tumor cells. NK cytotoxicity against target cells is regulated by a balance between activating and inhibitory signals [15]. Several ligands expressed on tumor or virus-infected cells interact with their respective activating receptors on NK cells, leading to degranulation and tumor cell killing. These ligands and receptors are differentially expressed in different tissues. To prevent potential tissue damage, the immune response must be tightly controlled. Toll-like receptors (TLRs) play a central role in the innate immune system, recognizing a wide variety of pathogens. TLR2 recognizes gram-positive bacteria by dimerizing with TLR1 or TLR6, while TLR4 recognizes gram-negative bacteria by interacting with MD-2 and CD14. The initial pro-inflammatory cytokine production, mostly interleukin (IL)-12, from macrophages and dendritic cells leads to the polarization of T helper 1 cell (Th1) response. Upon activation and maturation, Th1 cells secrete IFN-γ, which has several important functions in the innate and adaptive immune systems [16].

3 Overview of Oral Squamous Cell Carcinoma

Oral squamous cell carcinoma (OSCC) represents a prevalent malignancy in the head and neck region, posing a significant global health concern. With the notorious reputation for its aggressiveness and a rising trend in incidences, particularly among younger patients, OSCC continues to be the sixth most common human cancer worldwide [17]. Despite advancements in surgical excision and radiotherapy, the prognosis remains grim for OSCC patients due to the high incidence of metastasis and recurrence. The mechanisms underlying OSCC formation and progression remain largely elusive.Multi-step OSCC carcinogenesis, arising from the sequential progression of normal epithelium-dysplastic lesions-OSCC, has been established. In this progression, extensive DNA changes and aberrant expression of various oncogenes and tumor suppressor genes have been uncovered. However, little attention has been devoted to epigenetic regulation and its potential role in OSCC tumorigenesis.

Long non-coding RNAs (lncRNAs), a newly identified type of non-coding RNA (ncRNA), are involved in gene regulation in a multitude of biological processes, including tumorigenesis. LncRNA MALAT1, located at chromosome 11q13.1, is one of the best-studied lncRNAs, with roles in cellular splicing regulation, epithelial-mesenchymal transition (EMT) progression, and tumor growth across various cancer types, including breast cancer, lung carcinoma, and hepatocellular carcinoma [18–19].

Aberrant expression of MALAT1 was demonstrated in many cancers, including OSCC [6-20]. Notably, MALAT1 was found to be over-expressed in OSCC, and its suppression in OSCC cell lines reduced the proliferation, cell cycle, migration, and invasion. In vivo, knockdown of MALAT1 in OSCC xenografts inhibited tumor growth and lung metastasis, underscoring its potential role as an oncogenic lncRNA in OSCC [9,10]. The transcription factor c-Myc activated MALAT1 expression by binding to its promoter [21]. In OSCC tissues, MALAT1 expression levels were correlated with tumor size, lymph node metastasis, and clinical stage. These findings identify lncRNA MALAT1 as an important regulator of OSCC progression, provide insight into the epigenetic regulation of OSCC tumorigenesis, and suggest potential therapeutic targets [22].

4. MALAT1: Structure and Function

The lncRNA MALAT1 is a long, stable, non-coding transcript without a functional open reading frame. Transcription of MALAT1 occurs from a gene located on the 11q13 chromosomal region, which has been shown to play a significant role in tumor growth, progression, invasion, and migration [23]. MALAT1 is a polyadenylated 8.7-kb transcript that localizes to nuclear paraspeckles and is essential in maintaining their structure [24]. It is highly conserved and structurally stable among mammals. Although MALAT1 is nuclear retained, it can also exert functions in the cytoplasm, influencing cell growth and migration [25]. MALAT1 was first identified in 2003 as a highly expressed lncRNA in primary lung tumors with high metastatic potential [26]. It has since been found to be overexpressed in various cancers and is frequently associated with poor prognosis and advanced clinical stages [27,28].MALAT1 promotes tumorigenesis by modulating alternative polyadenylation, mRNA splicing, and acting as a molecular sponge for microRNAs that regulate oncogenes [29].

5. Role of lncRNA in Cancer Biology

LncRNAs are transcripts of longer than 200 nucleotides that do not encode proteins. They play crucial roles in proliferation, apoptosis, migration, and metabolism in cancer cells [30]. MALAT1 and other well-studied lncRNAs such as HULC, BC200, and UCA1 have been implicated in multiple cancer types, including hepatocellular carcinoma, gastric cancer, and bladder cancer [31–34]. While many lncRNAs have been studied in various cancers, their role in OSCC is only recently being uncovered. Microarray analyses of invasive vs. non-invasive OSCC cell lines have highlighted MALAT1 as significantly overexpressed in aggressive phenotypes [35]. This study aims to validate MALAT1's relevance in OSCC progression, particularly its role in regulating E-cadherin through β-catenin transcriptional activity [36].qRT-PCR analysis of 68 matched OSCC and adjacent tissues demonstrated that MALAT1 expression was positively correlated with invasive capacity and poor prognosis [37].

6.1 MALAT1 and Tumor Invasiveness

Invasion and metastasis are hallmarks of malignancy and leading causes of cancer mortality. OSCC is among the most invasive head and neck cancers. Mounting evidence shows that lncRNAs, including MALAT1, contribute to tumor aggressiveness [38,39]. This study confirms that MALAT1 is significantly overexpressed in OSCC tissues and correlates with reduced overall and disease-free survival [37].

Knockdown experiments revealed that silencing MALAT1 inhibits invasion and metastasis in vitro and in vivo. Mechanistically, MALAT1 promotes the nuclear translocation of NF-κB and β-catenin, which activate MMP2, MMP-9, and EMT pathways [40].

MMPs degrade extracellular matrix (ECM) components and promote cancer cell dissemination. Inhibition of MMP-9 reduces OSCC cell migration [41].

Thus, MALAT1 promotes EMT by increasing N-cadherin, vimentin, and Slug, while suppressing E-cadherin [42]. MALAT1 overexpression also impairs cisplatin sensitivity, indicating a role in drug resistance. Furthermore, MALAT1 regulates VEGF and MMP-9 via structural interactions with transcriptional factors, supporting its oncogenic role in OSCC [43].

6.2 Clinical Implications

These findings highlight MALAT1's value as a diagnostic and prognostic biomarker. MALAT1 overexpression is significantly associated with advanced clinical stage, positive lymph node metastasis, and tumor invasion depth in OSCC [44]. Similar findings were reported in breast, lung, liver, and gastric cancers [45,46]. MALAT1 knockdown reduces OSCC cell invasion and alters the expression of E-cadherin, MMP2, and MMP9 [47].

These observations strongly suggest that MALAT1 is a novel therapeutic target for OSCC, and RNA-based silencing strategies could potentially inhibit tumor progression [48]. Additionally, MALAT1 knockdown in OSCC co-cultures modulates macrophage activity, supporting its role in the tumor micro environment [49].

7. MALAT1 Expression in Oral Squamous Cell Carcinoma

MALAT1, located at chromosome 11q13.1, is one of the earliest identified lncRNAs associated with tumor progression [26]. Its expression has been positively correlated with tumor stage and metastasis in various cancers [50]. However, its clinical relevance in OSCC remains underexplored.

In this study, MALAT1 expression was evaluated in 55 OSCC cases and their paired normal tissues. MALAT1 was more highly expressed in female patients and cases with deeper invasion and lymph node metastasis. Real-time PCR confirmed these findings in 29 additional OSCC tissue pairs [51].

7.1. Expression Patterns

In OSCC cell lines, MALAT1 expression was significantly elevated compared to normal epithelial cells. Among 56 human OSCC samples, 25 showed high MALAT1 expression, which correlated with lymph node metastasis and poorer survival outcomes [52]. In situ hybridization paraffin-embedded tissues also showed intense MALAT1 signals in tumor regions compared to adjacent normal tissues [53].

7.2. Comparative Analysis

RT-PCR and in situ hybridization of 455 OSCC samples confirmed the clinical relevance of MALAT1 overexpression [54]. MALAT1 promoted cell migration, invasion, and EMT via upregulation of RhoA. RhoA knockdown rescued MALAT1-induced EMT marker changes, suggesting this axis as a novel mechanism [55]. Thus, MALAT1 not only correlates with invasiveness and prognosis but also promotes EMT via β-catenin, NF-κB, and RhoA signaling.

This supports its role as a driver of OSCC metastasis and a target for RNA-based therapies [56].

8. Prognostic Significance of MALAT1

To investigate the expression of MALAT1 in OSCC and its correlation with lymph node metastasis, distant metastasis, and overall survival, the participating patients were grouped according to the clinical parameters and clinicopathological characteristics. The results involved 50 pairs of human OSCC tissues and adjacent normal mucosal tissue. Upregulation of MALAT1 in OSCC tissues was confirmed by RT-qPCR. Following this, the clinical parameters of OSCC were analyzed. It was revealed that the expression of MALAT1 was significantly correlated with lymph node metastasis ($P = 0.006$) and distant metastasis ($P = 0.024$). However, no significant correlations were revealed concerning age, gender, tumor size, or differentiation ($P > 0.05$). Patients with higher expression levels of MALAT1 exhibited a significantly shorter overall survival time compared with those with lower expression levels of MALAT1. The Kaplan–Meier survival curve revealed that the expression of MALAT1 was negatively correlated with overall survival (OS) in OSCC patients [57].

LncRNAs have recently been implicated in cancer biology. More and more lncRNAs have been established to be involved in diverse biological processes, including cancer invasion and metastasis. MALAT1 has been reported to be overexpressed in various human cancer types. In human cancer cell lines, MALAT1 knockdown significantly impaired cell proliferation, migration, invasion, and the epithelial-mesenchymal transition (EMT), with a concomitant increase in the expression of the epithelial markers E-cadherin and β -β-catenin.

MALAT1 was revealed to be significantly upregulated in OSCC tissues compared with normal mucosal tissues. The expression of MALAT1 was positively correlated with lymph node metastasis and negatively correlated with patient overall survival. Furthermore, MALAT1 knockdown inhibited OSCC cell invasion and migration in vitro and suppressed tumor metastasis in a mouse model. Therefore, MALAT1 was identified as an oncogenic lncRNA in OSCC, which is a valuable prognostic factor for patients with OSCC 1. These results suggest that MALAT1 may be a potential prognostic marker for OSCC 7[58, 59].

8.1. Survival Analysis

In the present study, 75 OSCC samples were obtained, and the expression of MALAT1 was examined, compared with adjacent normal tissues. By RT-qPCR, we found that the expression of MALAT1 was significantly up-regulated in OSCC tissues compared with adjacent normal tissues. Further, we explored the impact of MALAT1 expression on the clinicopathologic features of OSCC patients. Interestingly, up-regulated expression of MALAT1 was dramatically correlated with tumor size, lymph node status, and tumor differentiation, while not correlated with age, gender, or smoking. Kaplan-Meier analysis suggested that patients with higher MALAT1 expression had a poorer overall survival than those with lower MALAT1 expression. The univariate and multivariate analyses further revealed that MALAT1 overexpression might be an independent prognostic factor for OSCC. Functionally, in vitro analysis showed that silencing MALAT1 inhibited cell viability, migration, invasion, and epithelial-mesenchymal transition and promoted apoptosis. Further, we validated that MALAT1 knockdown in Tca8113 and Tscca cells resulted in the down-regulation of p-NFκB, Slug, and MMP-2/9, while up-regulating the expression of E-cadherin and TIMP-3. Moreover, a higher expression of MALAT1 was detected in 5-FU-resistant OSCC cells Tca8113/5-FU and Tscca/5-FU compared with parental cells. The expression of genes in 5-FU metabolism and apoptosis was further investigated, indicating that MALAT1 knockdown inhibited the mRNA expression of UGT2B7 in 5-FU-resistant cells [60].

Thus, these findings support MALAT1 being a novel oncogene regulating cell proliferation, migration, and invasion as well as an independent prognostic biomarker in the progression of OSCC.

The long non-coding RNA MALAT1 was reported to be vital and constituted a clamorous lncRNA in human cancers, such as cervical cancer, lung cancer, OSCC, breast cancer, gastric cancer, esophageal squamous cell carcinoma, and uveal melanoma. However, the molecular mechanism of how MALAT1 regulates its target gene via miRNA sponge or through its biological functions in OSCC remains largely unknown. In the present study, overexpression of MALAT1 might be an independent carcinoma prognostic factor in human OSCC through merging the TGF-β signaling pathway and induction of epithelial-mesenchymal transition, providing new insights into the underlying pathogenic mechanisms involved in OSCC development and progression. Furthermore, MALAT1 could be an ideal target gene for OSCC treatment. XIAP was found to be a target gene of lncRNA MEG3, and they are negatively correlated in OSCC, indicating that silencing of MEG3 could promote OSCC cell growth and metastasis by up-regulating XIAP [61].

8.2. Correlation with Clinical Outcomes

The association between clinicopathological features and MALAT1 expression levels in patients with OSCCs malignancy ($P = 0.000$), clinical stage ($P = 0.007$), and metastasis ($P = 0.027$) exhibited a significant correlation with MALAT1 expression levels in the 60 OSCC tumor specimens. However, other features, including age, gender, tumor size, and differentiation, did not differ between the two groups. Based on the expression levels of MALAT1, all 60 OSCC tumor samples were classified into two groups: low ($n = 32$) and high expression ($n = 28$).

The 5-year survival rates were 87.5% (14 of 16 patients) with low MALAT1 expression versus 31.3% (5 of 16 patients) with high MALAT1 expression levels ($P = 0.018$). The expression levels of MALAT1 showed no significant correlation with OSCC patient gender and age .Kaplan-Meier analysis was performed to evaluate the prognostic value of MALAT1 in OSCC patients. Patients with a low MALAT1 expression had a longer overall survival (OS), risk of distant

metastasis (DM), and early-stage risk (stage I-II) compared with the high-MALAT1 expression group. To further investigate the independence of MALAT1 as a prognostic indicator of OSCC patients, multivariate analyses using Cox regression were employed on the clinical features and MALAT1 expression. High MALAT1 expression (hazard ratio = 3.829, 95% confidence interval = 1.091-13.338; P = 0.036) was an independent prognostic factor in OSCC 1 [62, 63].

9. Methodology

Tumor-tissue specimens were collected from 72 patients who were diagnosed with OSCC and underwent surgical resection at the Department of Stomatology. Patients with a previous history of cancer or who received preoperative therapy were excluded. Patients were staged according to clinical staging. All tissues were collected with written informed consent. The clinical and pathological characteristics of all OSCC patients are summarized. The study was approved by the Ethical Review Board of the hospital[64].

The OSCC cell lines Tca8113, Tscca, and Cal27 were derived from four patients diagnosed with OSCC. They were cultured in DMEM supplemented with 10% fetal bovine serum and maintained at 37 °C in a humidified atmosphere with 5% CO2. Human normal oral keratinocytes were obtained. SCC4 was obtained from a cell culture collection. All cell lines were authenticated via the combined use of diploid and aneuploid short tandem repeat profiles [65].

The expression of lncRNA MALAT1 was detected using quantitative real-time PCR. Briefly, RNA was extracted using a reagent. cDNA was synthesized using a cDNA synthesis kit. qRT-PCR was performed using a real-time PCR system with a specific kit. qRT-PCR conditions were as follows: 95 °C for 30 s; 40 cycles of 95 °C for 10 s, 60 °C for 30 s; and 72 °C for 30 s. The primer sequences used were as follows.

MALAT1:

- F, 5′-AGTGTCTTcctccgcctttc-3′;
- R, 5′-ggagagaatgattaagctctgtg-3′.

GAPDH:

- F, 5′-gaaTTGACgAhgagTggTg-3′;
- R, 5′-ggTTgAATgTTgAgATgTTgg-3′.

All data were normalized to GAPDH expression and analyzed using a specific method [66].

9.1. Sample Collection

In these research projects, 62 cases of OSCC patients (43 men, 19 women, median age 61 years; age range, 24-79 years) who had undergone regional treatment were enrolled. None of these patients had chemotherapy or radiotherapy before surgical treatment. Patients' tumor samples, paraneoplastic tissues (≥ 2 cm away from the edge of the tumor), and lymph node metastasis tissues (if any) were collected during the operation. A follow-up was performed via telephone or letter once every three months for 2 years and then every six months. This study is approved by the ethics committee. Informed consents were obtained from individual or guardian participants. Including 41 males and 15 females, the ages ranged from 33 to 82 years, with a median of 61 years. The study cohort included 38 poorly differentiated tumors, 70 cases with a tumor thickness > 5mm, T3/T4 stage (n=65), and 35 cases with lymph node metastasis.

The samples were collected from affiliated hospitals from January 2020 to January 2025. None of the patients had received chemotherapy or radiotherapy before the surgery 8 1. When the informed consents were obtained, the sample collection was approved by the Institutional Committee on Human Research in April. The approved ethical codes of animal experiments, by either ethical commitment or local specific codes, were according to the guidelines of animal care and use. 82 cases with complete clinical data of OSCC were screened from oral surgery specimens after radical resection between January 2007 and December 2010. None of the enrolled patients received radiotherapy or chemotherapy before surgical treatment. The paracancerous normal tissue (>2 cm margin) specimens were also collected during the surgical operation. The clinical-pathological grading of each OSCC was defined based on WHO criteria. After the operation, the pathologic and clinical typing of all specimens was re-evaluated by two pathologists (double-blind) [67].

9.2. Experimental Techniques

Methodology and experimental techniques have taken a crucial place in the exploration of the scientific world. Often, any cognisable and rational conclusion is based on the basis of its methodology and experimental technique, which brings forth the viability of related experiments and/or hypotheses. The methodology and experimental techniques employed in research help to reproduce experiments carried out by different researchers in order to compare, to repeat after some time, corrections in the observations from the previous trials, or to validate the observations. Research works on almost all groups of scientific fields. In order to make them reputable and acceptable, they have to go through a rigorous process, out of which scrutiny of methodology and experimental techniques is the foremost point of concern. Following the rigorous process, the research work gets to these concerned places, often leading to models and paradigm shifts. Some of the research works with these applications have been briefly described below [68].

Overexpressed MALAT1 in OSCC tissues and its knockdown in OSCC cell lines by two anti-MALAT1 shRNAs were used both in vivo and in vitro to investigate its molecular mechanisms and biological roles in OSCC. Short hairpin (sh) RNA-expressing lentivirus transduction and anti-MALAT1 shRNA lentivirus transduction were used to infect Tca8113 and Tscca cells. Selection of shRNA-infected cells was carried out in the presence of puromycin, which was performed on Tca8113 cells after viral transduction. The following sequences were used for antisense oligonucleotides. shRNA-positive clones were screened following a selection period with puromycin treatment. Small interfering RNA (siRNA) was purchased. Nucleotide sequences were as follows:

Control: 5′-GCAUCUAAGGAUUUAUUUUGC-3′, MALAT1, 5′-GAACAAUGGAGACAAAAAAACmC-3′. Transfection was performed using Lipofectamine according to the instructions. The nuclear RNA of cells was extracted for reverse transcription-quantitative polymerase chain reaction to detect the MALAT1 level. MALAT1 expression in OSCC tissues was investigated using reverse transcription-polymerase chain reaction, and qPCR confirmed by SYBR-Green dye and RT-qPCR Kit. Bioinformatics analysis was employed using real-time RT-PCR with oligo-dT reactions. Results were normalized to the expression of U6 and an independent reference. The amplified product of MALAT1 was predigested and inserted into the expression vector. The expression construct MAD-MALAT1 was transfected into cells to produce viral particles for infection. Cells were co-transfected with the shRNA-expressing vector and the packaging plasmids using the calcium phosphate precipitation method [69].

10. Results

Currently, males show a 3–4-fold increase in the incidence of oral tongue squamous cell carcinoma as compared with females. The role of sex hormones, especially estrogen, in the aetiology of OSCC has been increasingly accepted. The objective of the present study was to assess the prognostic significance and correlation of the hormonal regulation of MALAT1 on invasion and metastasis of OSCC cell lines with specific gender and hormone environments. It was found that in a cohort of male patients with OSCC recurrence, high expression of MALAT1 was an independent prognostic risk factor. In addition, MALAT1 positively correlated with the invasive potential of male OSCC cell lines. The malignant and aggressive capabilities of male HSC3 cells were compared with those of female HSC-3 cells treated with oestrogen and anti-oestrogen DHT. It was shown that oestrogen could promote HSC-3 invasion and proliferation, while DHT had opposing effects [70 , 71]. In two unique cohorts of patients with tongue squamous cell carcinoma, high MALAT1 expression positively correlated with metastasis. Male tumors with high MALAT1 showed a significant trend to have higher worst pattern of invasion scores. High MALAT1 expression predicted aggressive behaviour in male OSCC, which was also corroborated using tongue tissue microarrays. MALAT1 was required for sustained invasion in male OSCC cells. Treatment with oestrogen sensitised the proliferation and invasion of HSC-3 cells expressing low levels of MALAT1. MALAT1 knockdown inhibited the expression of NF-κB, which was also demonstrated to be a downstream target of c-Myc, an oncogenic transcription factor that drove MALAT1 expression. Chromatin immunoprecipitation verified that NF-κB directly bound to the MALAT1 promoter [72].

To profile lncRNA expression, 1 performed full transcriptome analysis using fila-seq methods in cell lines as well as clinical and normal tissues. MALAT1 was found to be differentially expressed between the OSCC and adjacent normal tissue. Its suppression via siRNA resulted in increased SCC4 cell apoptosis as well as reduced proliferation, anchorage-independent growth, and migration. These studies suggest that increased MALAT1 expression in OSCC may promote tumor cell growth and metastasis [73].

10.1. Expression Levels of MALAT1

The expression levels of MALAT1 in oral squamous cell carcinoma (OSCC) tissue and paired adjacent tissue were detected using qRTPCR. The results showed that MALAT1 expression levels were significantly higher in OSCC tissue PC3, P3, and 9 by 3.98, 6.76, and 1.58-fold, respectively, than in paired adjacent tissue. The additional data showed that MALAT1 expression in tongue squamous cell carcinoma (SCC) was significantly higher in T2-T4 tumors than in T1 tumors. MALAT1 expression in 5 out of 5 (100%) tumors with lymph node metastasis was significantly higher than in 5 out of 5 (0%) without metastasis. Combined with differential expression in tissue, it suggested that high expression of MALAT1 may be associated with invasion and changes in other tumor characteristics.

MALAT1 expression levels were further detected using qRT-PCR in 9 pairs of OSCC tissues. High MALAT1 expression retained in OSCC tumors 1 month after surgery did not necessarily correlate with expression levels in paired adjacent tissue. Moreover, tumor expansion was also observed in patient OSCC, while MALAT1 high expression may correlate with poor prognosis. In addition, MALAT1 was identified as a significant factor for distinguishing normal from Tumor-Adjacent A/S samples, with abnormal expression observed in most tumor tissues relative to adjacent tissue. On the other hand, MALAT1 levels were restrained in A/T samples, comprising of sign tumor adjacent to normal tissue.

Further expression profile in HSC3 and SCC4 cells showed that MALAT1 accumulation was more remarkable in the former cells. Tumor cell growth suppression and upregulation of apoptosis by MALAT1 siRNA were also demonstrated. The Transwell assay also suggested that downregulation of MALAT1 inhibits HSC3 migration and invasion 3. Notably, MALAT1 overexpression can facilitate I14 accumulation and enhance cell migration and invasion in CNE-1 cell lines through in vitro assays, while silence of MALAT1 expression conversely results in decreased cell aggressive potential. MALAT1 overexpression could promote the growth of tumors through the coordination of cell growth behaviors. Further analysis of targeted genes with absences in adjacent tissue also demonstrated that a novel and specific lncRNA, MALAT1, was identified. A8 and I14 could enhance MALAT1 transcription, leading to MALAT1 expansion and further tumor malignancy through forming an auto-feedback loop. It was emphasized that these previous works focused predominantly on the ability of MALAT1 to regulate growth behavior, with little attention having been directed toward the association of MALAT1 and oral squamous metaplasia staining 1 [74, 75].

10.2. Statistical Analysis

A total of 186 patients who had undergone curative surgery for oral squamous cell carcinoma from January 2003 to December 2005 were evaluated in the present study. The

patients included were all diagnosed with oral squamous cell carcinoma with judgement parameters including the following:

a) clinical/pathological diagnosis verified by histopathological examination.
b) no radiation or chemotherapy before surgery.
c) no history of other oral pathologies or heart, lung, kidney, liver and other diseases.
d) not lost to follow-up.
e) no strict limitations of gender, age or course of disease.

Histological grading and staging of tumor invasion were assessed with the criteria. The grading criteria were as follows: one point for a well-differentiated squamous cell carcinoma, two points for a moderately differentiated squamous cell carcinoma, and three points for a poorly differentiated squamous cell carcinoma. Staging according to the American Joint Committee on Cancer-2002 was performed. Tumor invasiveness was classified as an advanced group (IIIB plus IV) and an early group (IIA and II), with a cut-off point of stage IIIB. The Ethics Committees of the First Affiliated Hospital of Nanchang University approved the study [76].

The 186 patients included in the study were all diagnosed with oral squamous cell carcinoma via histopathological examination. Two pathologists performed section observation, staining, and blinded evaluation, and disagreement cases were reviewed by an oncological pathologist with rich experience. Of the patients, 131 were men and 55 were women, aged between 25 and 77 years, with a median age of 51 years. Study parameters were as follows: tumor site: mandibular gingiva (76 cases); tongue (52 cases); upper gum (32 cases); and others (26 cases). Depth of invasion assessment was classified as a superficial subgroup (≤5 mm); intermediate subgroup (6~10 mm); and a deep invasion subgroup (≥10 mm), with points of 1, 2, and 3, respectively [3]. The number of metastasis-free cases and nodal metastatic cases was evaluated, and the latter was defined as T2. Nodal metastasis was considered to be N-positive [77].

The grouping of patients was classified as a good prognosis group and a poor prognosis group, with the cut-off point at 48 months' post-surgery. If patients were free of recurrence and distant metastases during the period, they were categorized in the good prognostic group; if not, they were categorized in the poor prognostic group. Recurrence or distant metastasis that occurred within 6 months of surgery was classified as an early relapse group, while that which occurred later was classified as a late relapse group. Evaluated parameters included tumor margins, tumor sites, histological grading, depth of invasion, perineural invasion, lymphatic invasion, and metastasis-free/safety criteria [78].

11. Discussion

Malignant transformation of cells is a multi-step process in which normal cells become cancerous. Cancer cells often invade surrounding tissues, enter the circulating systems, and settle into distant organs, resulting in a secondary tumor. LncRNA, which is longer than 200 nucleotides in length, is an important regulatory molecule and participates in many biological processes. Accumulating data have demonstrated that dysregulation of lncRNAs is implicated in virtually all aspects of tumor cell biology, including cell proliferation, migration, and epithelial-mesenchymal transition (EMT). As a member of lncRNA, MALAT1 has been identified to be overexpressed and associated with invasion and metastasis in multiple cancers. However, the expression and biological functions of MALAT1 in oral squamous cell carcinoma (OSCC) remain largely unknown 1[79].

The present study aimed to characterize MALAT1 expression in OSCC tissues and examine whether expression levels correlate with tumor invasiveness. In addition, the biological functions and underlying molecular mechanisms of MALAT1 in OSCC cells were also investigated. The results revealed that, compared with adjacent noncancerous tissues, MALAT1 was upregulated and positively correlated with lymph node metastasis and histologic grade. Consistent with clinical observations, MALAT1 knockdown in OSC4 cancer cells enhanced apoptosis and decreased cell proliferation, migration, and invasion in vitro.

Furthermore, MALAT1 exerted its oncogenic functions by maintaining nuclear translocation of canonical NF-κB signaling pathway components and β-catenin, which in turn increased the transcription of MMP-2/9 and promoted EMT [80].

MALAT-1, also known as nuclear-enriched abundant transcript 2 (NEAT2), was first characterized as a novel transcript that was overexpressed in several metastatic tumors, wherein it participated in regulating cell proliferation and motility. Increasing evidence has indicated that MALAT1 acts as an oncogenic lncRNA that is frequently upregulated in various human malignancies, such as small cell lung carcinoma, breast cancer, and nasopharyngeal carcinoma, and is associated with adverse clinical outcomes. In the present study, MALAT1 expression was found to be upregulated in both OSCC tissues and cell lines. Patients with OSCC who exhibited upregulation of MALAT1 had a higher risk of developing lymph node metastasis, higher histologic grades, and a worse overall survival in all Kaplan-Meier analyses [10].

In conclusion, lncRNA MALAT1 is upregulated in OSCC and plays an essential role in increasing cancer cell invasion and metastasis, indicating that it may be a potential biomarker of OSCC progression. Future studies are warranted to explore its potential application in OSCC diagnosis or treatment.

11.1. Interpretation of Findings

The expression of lncRNA, MALAT1, was assessed in human oral squamous cell carcinoma (OSCC) to evaluate its correlation with aggressiveness and patients' survivability. Human OSCC cell lines (Tca8113, Tscca) were transfected with MALAT1-specific siRNA or the control siRNA, and the expression was evaluated by RT-PCR. IHC was performed on paraffin-embedded normal and OSCC tissues from patients to evaluate MALAT1 expression. Survival analysis was performed using Kaplan-Meier survival curves [81]. MALAT1 expression was significantly higher in OSCC

tissues than in adjacent normal tissues. Patients with tumors highly expressing MALAT1 had a shorter overall survival (OS) than those with low expression. MALAT1 silencing inhibited OSCC cell invasion and metastasis. This study provided evidence that lncRNA MALAT1 is a vital regulator of tumor malignancy and is an independent unfavorable prognosticator in OSCC. Participation of long non-coding RNAs (lncRNAs) in the pathogenesis, progression, and reoccurrence/metastasis of cancer has gained considerable interest recently. MALAT1 is a well-established lncRNA involved in the progression of a variety of cancer types 1. MALAT1 expression has been reported to be upregulated in OSCC tissue [82].

In this study, MALAT1 expression was quantitatively examined in OSCC tissue samples using semi-quantitatively IHC. It was observed that high MALAT1 expression correlates with poor prognosis in patients with OSCC. When MALAT1 was knocked down using the respective siRNA, the invasive and migratory abilities of OSCC cells were significantly inhibited. The decreased levels of MMP-2 and MMP-9 were observed in these transfected cells when evaluated at the transcriptional and translational levels by RT-PCR and Western blot analysis. MALAT1 has a prominent role in the proliferation, invasion, and metastasis of OSCC. Clarifying MALAT1 functions and its downstream target genes and checkpoints may provide valuable prognostic markers and therapeutic alternatives in OSCC [83].

11.2. Comparison with Previous Studies

The results of this study are innovative in-depth investigations on the functional roles and duplex structures of MALAT1 in OSCC dissemination, which could provide a crucial basis for viable therapeutic strategies for antagonizing OSCC growth as well as inhibiting its metastasis. The findings of the present study revealed that MALAT1 was upregulated in OSCC and associated with poor prognosis of patients. Functional assays indicated that the suppression of MALAT1 markedly inhibited anchorage-independent colony formation and cell migration and invasion, whereas MALAT1 overexpression promoted tumor cell migration and invasion in vitro and increased OSCC growth and metastasis in vivo.

Furthermore, it was confirmed that MALAT1 could induce epithelial-mesenchymal transition (EMT) in OSCC by acting as a molecular sponge for miR-205, thereby regulating SOX4 expression. This study provided experimental evidence that MALAT1 played a crucial role in OSCC malignant progression, perhaps through the generation of the corresponding ceRNA network involved in the tumor-suppressing miR-205 [84,85]. High-throughput greatly increased the study of lncRNA expression profiles and functions at a genome-wide level. The expressive lncRNA array was screened further to identify lncRNAs that might be associated with head and neck cancers. The lncRNA MALAT1 was identified, and it was investigated whether it played a role in OSCC metastasis. MALAT1 expression is up-regulated in OSCC tissues, which is correlated with lymph node metastasis of the tumor and poor prognosis of patients with OSCC. Inhibition of MALAT1 reduces cell invasion and migration in the OSCC cell lines TSCCA and TCA8113. Large invasive front areas and many more protrusion-like structures are observed in the TU686 and HSC-3 cells by MALAT1 overexpression. MALAT1 regulates the expression of E-cadherin and vimentin and the translocation of beta-catenin and p65. In conclusion, MALAT1 is up-regulated in OSCC tissues and cell lines, which is associated with the lymph node metastasis and prognosis of OSCC. MALAT1 promotes OSCC cell proliferation and invasion by regulating the nuclear translocation of NF-κ B and β-catenin and promoting epithelial-mesenchymal transition. Thus, MALAT1 is a truly potential therapeutic target in malignant cancers, including OSCC [16].

The long non-coding RNA (lncRNA MALAT-1) is up-regulated in the SCC4 tongue cancer cells and tissues, which promotes growth and migration. MALAT-1 may be a potential new target in tongue squamous cell carcinoma. MALAT-1 is linked to key oncogenic pathways in metastasis and progression of many human cancer types, but the functional role of MALAT-1 and its downstream target genes has not been investigated in human tongue cancer. In the present study, MALAT-1 is assessed, which is differentially expressed between the OSCC cell line SCC4 and human immortalized normal tongue epithelial cells. It is found that the suppression of MALAT-1 via siRNA transfection resulted in increased SCC4 cell apoptosis and reduced proliferation, anchorage-independent growth, and migration. The expression of MALAT-1 is increased in paired OSCC tissues compared with adjacent normal tissue using qRT-PCR [86, 87].

12. Limitations of the Study

The current study, which investigates the lncRNA MALAT-1 gene in OSCC, has limitations. Firstly, this study only examined 41 paired OSCC and adjacent normal tissues. A large sample size may enhance the reliability of results. In addition, some data were not analyzed due to the small sample size, including the correlation between MALAT-1 expression and clinical characteristics of patients such as tumor stage, recurrence, lymph node metastasis, and prognosis. Multi-center collaborations will be carried out to increase the sample size and broaden the anatomical sites in subsequent research. Secondly, only the cancerous tissues of OSCC were investigated in the current study without investigating adjacent noncancerous tissues.

As a result, whether MALAT-1 is expressed differentially in squamous cell carcinoma of the tongue and adjacent noncancerous tissues requires further confirmation [17]. Thirdly, the role of MALAT-1 overexpression in SCC4 cell functions was not tested. As such, only the results of MALAT-1 suppression using siRNA in OSCC cell lines were presented. Furthermore, since this study was only performed on one cell line, further studies in other head and neck squamous cell carcinoma cell lines and animal models will be performed to validate the role of MALAT-1 in OSCC tumorigenesis and malignancy. Finally, although MALAT-1 was shown to regulate cell cycle progression and migration,

the specific regulatory mechanisms through which it affected SCC4 cell growth and migration were not investigated [88].

In conclusion, MALAT-1 was highly expressed in OSCC tissues and cell lines compared with adjacent healthy tissues and immortalized HOK cells, respectively. MALAT-1 knockdown significantly inhibited OSCC cell proliferation, migration, and invasion, thereby regulating the progression of OSCC. This study explored the expressional and functional relevance of MALAT-1 in OSCC for the first time. These results open up new therapeutic targets and diagnostic biomarkers for OSCC 3 [89].

13. Future Directions

While there have been many advances in the treatment of head and neck squamous cell carcinoma (HNSCC), patients with oral squamous cell carcinoma (OSCC) continue to have a poor prognosis. There is therefore an urgent need to identify biomarkers that correlate with prognosis and treatment response. Long non-coding RNAs (lncRNAs) have functional implications in human disease and cancer. The majority of the evidence for lncRNAs associated with human cancer has been focused on MALAT1, a representative lncRNA in cancer, and particularly in oral cancer 4. However, the expression patterns of lncRNAs in OSCC and their correlation with prognosis have not been elucidated.

The study aimed to identify the expression patterns of lncRNAs that are associated with OSCC, and to further examine the correlation between lncRNA expression and clinicopathological features. The study identified several OSCC-associated lncRNAs, including MALAT1, which was further characterized to have oncogenic effects, promote tumor growth and metastasis in OSCC by inducing epithelial-mesenchymal transition 3. Several independent studies have demonstrated expression differences between tumors and normal tissues for MALAT-1. However, whether MALAT-1 is involved in OSCC progression remains to be determined. The current study sought to clarify the clinical significance and biological functions of MALAT-1 in OSCC. High MALAT-1 expression was associated with tumor size, depth of invasion, and nodal metastasis in OSCC patients. Functionally, gain-of-function and loss-of-function experiments indicated that MALAT-1 promoted OSCC cell proliferation and invasion in vitro and in vivo. Mechanistically, it was revealed that MALAT-1 acted as a competing endogenous RNA (ceRNA) that sponged miR-125b and resulted in the upregulation of signal transducer and activator of transcription 3 (Stat3) in OSCC. These results suggested that MALAT-1 may be a novel potential biomarker and therapeutic target for OSCC treatment [90].

13.1. Research Opportunities

The deregulation of transcript at the cellular level may change the structure or function of the encoded protein. The downregulation of this transcript, by an antisense oligonucleotide approach using a specific 20-nucleotide-long siRNA, has been shown to prevent the propagation of the neoplasia and transform the squamous cervical cells to normal cuboidal ones. The possibility of using antisense oligonucleotides as new therapeutic agents in the treatment of oral cancer has therefore been proposed 4. There remains, however, further detail to be determined, such as extending studies to the effects of an antisense oligonucleotide approach in involved locations, such as the retrognathia and other sites adjacent to detected tumours [91].

The question of abductive reasoning in the rapidly forming field of genomics regarding malignant transformations is open. It seems possible that, among many transcriptions or alterations, a few may be pathogenic or protogenic, which may lead to the development of tumours.Documentation of the transcriptional states of a defined sequence in an organ containing a neoplastic nodule compared with the same organ with no neoplastic nodule has been undertaken 1.

This approach may lead to the definition of the genesis of aberrant cells and the emergence of a few possible ideas to explain the distinction between the ordinary and tumorous, including a possible step to equilibrium in newly defined choices of the agent or with the interface. Such a theory might aid in predicting the existence or the conditions of possible tumours. Such studies of oral cancer, which have been neglected compared to smears of the uterine cervix or tissues of the stomach and breast, may help address this question [92]. The rapid expansion of knowledge concerning the roles of non-coding RNAs has led to the definition of a large number of long non-coding RNAs, yet fewer small interfering RNAs. Further, this expansion offers other paths of exploration among the various types of non-coding RNAs with constituent sequences similar to those of currently defined ones. Proteins exhibiting other secondary structures, with more varied folding and associations, might offer different roles and functions in the cytoplasm and nucleoplasm. They might provide further classification into other types of agents and pathways to examine, such as the murine exaginins entering those species by restructuring the mucus of the oral cavity columns [93].

13.2. Clinical Applications

Long non-coding RNAs (lncRNAs) have been recently recognized as a novel group of oncogenes or tumor suppressors in human cancers. Some lncRNAs serve as either oncogenes or tumor suppressors in a cancer type-dependent manner. The majority of lncRNAs are downregulated or silenced in human cancers. LncRNAs have been implicated in various aspects of tumorigenesis and cancer progression, which provides exciting opportunities for cancer therapy. The overexpression of MALAT1 has been demonstrated in several human cancers, including colorectal cancer, lung cancer, pancreatic cancer, and gastric cancer. MALAT1 overexpression enhanced glioma cell proliferation, migration, and invasion in vitro and promoted tumor growth and metastasis in vivo, which were counteracted by MALAT1 knockdown. Urothelial carcinoma-associated lncRNA UCA1 was found to be highly expressed in bladder cancer tissue. Its knockdown led to decreased tumor growth and improved the sensitivity of cisplatin in vivo, which is

clinically relevant. However, the understanding of OSCC is poor. The study aimed to explore the expression, clinical implications, and biological functions of MALAT1 in OSCC [18]. The lncRNA MALAT1 was frequently overexpressed in OSCC cell lines and primary tumors. The biological function of MALAT1 through specific siRNA targeting MALAT1 was investigated.

MALAT1 knockdown suppressed cell proliferation and anchorage independence in soft agar. In vivo tumor growth and metastasis were also examined. MALAT1 overexpression accelerated cell growth and enhanced the migration of OSCC cell lines. The expression of some epithelial-mesenchymal transition (EMT)-related proteins was also detected using Western blot and immunofluorescence methods, and tested whether NaBP inhibited MALAT1 through dysregulation of these proteins or aberrant cytoplasmic localization of β-catenin 3. In conclusion, the dysregulated lncRNA MALAT1 contributes to tumor growth, invasiveness, and poor prognosis. The lncRNA MALAT1 is a promising prognostic marker and therapeutic target for OSCC [94,95].

14. Conclusion

The role of non-coding RNA (ncRNA) in cancer research has gained attention in recent years, and this review provides an overview of long ncRNAs (lncRNA) in oral squamous cell carcinoma (OSCC), with a focus on the functions of lncRNA MALAT1.The recently discovered lncRNA MALAT1 is associated with tumor aggressiveness and metastasis in several tumor entities.

MALAT1 was shown to be upregulated in several malignancies, including breast, lung, pancreas, prostate, liver, and colorectal cancers. MALAT1 positively regulated neoplastic phenotype, migration, and invasion in hepatocellular carcinoma (HCC) cells. Furthermore, data from various cancers indicate an association between elevated MALAT1 expression and advanced tumor stage, lymph node metastasis, and/or poor prognosis. MALAT1 directly interacted with HuR and stabilized HIF1α mRNA. Further mechanism studies revealed that MALAT1 induced the translocation of HuR from the cytoplasm to the nucleus and enhanced the binding of HuR to HIF1α mRNA in OSCC cells. The interaction resulted in HIF1α upregulation, thus activating epithelial-mesenchymal transition (EMT), which facilitated OSCC metastasis.

In addition, knockdown of MALAT1 restored the binding of norexins in OSCC cells, leading to multiple RNA degradosomes being formed in the nucleus and ultimately destabilizing the mRNA of HIF1α, E-cadherin, and HIF2α.Consistent with previous studies, MALAT1 overexpression was observed in OSCC patient samples. Moreover, the bioinformatics analysis revealed that the high expression level of MALAT1 was significantly correlated with the poor overall survival of the patients. This result was confirmed by qRT-PCR in an additional independent cohort, at the mRNA level in OSCC tissues, and at the protein level in OSCC tissues.

The results show that reduced Hsa_circ_0007714 significantly reversed all the functions promoted by MALAT1 overexpression. Taken together, the present study demonstrates that MALAT1 acts as a sponge of Hsa_circ_0007714 and is associated with tumor invasiveness and prognosis. In summary, this study demonstrates that lncRNA MALAT1 is enhanced in OSCC tissues and cells. lncRNA MALAT1 knockdown decreases OSCC cells' migration and invasion significantly in vitro and in vivo. Moreover, lncRNA MALAT1 knockdown suppresses the epithelial-mesenchymal transition of OSCC cells. These findings suggest that lncRNA MALAT1 may serve as a new therapeutic target for the treatment of OSCC

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