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EXPLORING LNC- MEG3 EXPRESSION AS DIAGNOSTIC BIOMARKERS ORAL SQUAMOUS CELL CARCINOMA (OSCC)

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Abstract

Background: According to previous studies, aberrant expression of various non-coding RNAs, including microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), plays undeniable roles in the development and progression of different types of cancer, including OSCC. This study aimed to investigate long non-coding RNA Maternally Expressed 3 (LNC- MEG3) expression patterns as a potential diagnostic biomarker for oral squamous cell carcinoma (OSCC).

Method: In this cross-sectional study, LNC- MEG3 expression patterns were examined using real-time PCR method. Firstly, tumor tissue and margins were separated during surgery in 100 patients. Then total RNA was extracted and transcribed to cDNA from the obtained to measure the transcription level of lnc-MEG3 by qRT-PCR. GraphPad 6 Prism v.8 was used to perform the statistical analyses. Comparisons between groups in internal samples were conducted by paired student's t-test ($P < 0.05$).

Results: Our results indicated that the lncRNA MEG3 is downregulated in oral squamous cell carcinoma (OSCC) tumor samples compared to adjacent marginal tissue. These changes were significantly associated with lymph node invasion, tissue differentiation, and metastasis. Also, using receiver operating characteristic curve analysis, the MEG-3 expression pattern was found as a possible diagnostic biomarker for OSCC (The area under the curve was 0.62 and p-value:0.012).

Conclusion: We identified lncRNA MEG-3 downregulation in OSCC tumorigenesis. Our findings suggest lncRNA MEG-3 as a possible biomarker for OSCC.

Keywords*:* lncRNA MEG-3, Gene expression, oral squamous cell carcinoma, biomarker, Neoplasm.

Introduction

Oral squamous cell carcinoma (OSCC) ranks as the eighth most prevalent cancer worldwide (1-2). In keratinocyte DNA mutations can occur spontaneously, yet the existence of mutagens can elevate the mutation rate. Typically, OSCC affects the lips, with frequent incidents also found on the tongue and mouth floor (3-4). Moreover, OSCC is one of the few malignancies that have different prevalence in two sexes, its incidence is higher in men than women. Smoking, alcohol and diet are the most known risk factors for OSCC. Genetic variation in enzymes, which affect carcinogen metabolism, DNA repair, and other protective mechanisms, may help explain differential susceptibility to OSCC. Indeed, various risk factors for OSCC seem to act mainly by increasing the mutation rate. While various driver genes have been associated with OSCC pathogenesis, (5-6) the molecular mechanisms underlying tumorigenesis are not fully clarified. Therefore, further exploration of molecular changes in OSCC

progression is essential to identify novel therapeutic targets and molecular biomarkers for early diagnosis and treatment of Oral squamous cell carcinoma (7-8).

Genome sequencing projects determined that only 2 percent of the expressed genomic sequences have the capability to encode proteins and numerous genome positions are transcribed into non-coding RNAs. Based on the length of the transcript Non-coding RNAs are divided into two categories: short non-coding RNAs with a length of less than 200 nucleotides and long non-coding RNAs with a length of more than 200 nucleotides. The biogenesis of long non-coding RNAs is similar to messenger RNAs and they are usually transcribed by RNA polymerase II. Non-coding RNAs originated from exonic, intronic regions of coding genes and non-coding regions of the genome. Lnc-RNAs are located in the nucleus or cytoplasm of eukaryotic cells and are involved in biological processes including regulation of gene expression, transcription, translation, cell cycle control, chromatin modification and cell differentiation. Current evidence shows that the aberrant expression of these genes can affect cancer-related mechanisms such as metastasis, tumor cell proliferation, apoptosis, epithelial-mesenchymal transition (EMT), invasion, metastasis, and drug resistance, in some cases their expression is correlated with poor patient prognosis (10-15).

lnc-MEG-3 is one of the most well-known human long non-coding RNAs located at chromosomal locus 14q32. The transcript of this gene is 1.4 kilobytes long and has 10 exons. In addition, because of its promoter design epigenetics variations affect the expression of the lnc-MEG3. According to previous studies, it seems that lnc-MEG3 plays an important role in the progression and development of various human diseases, including cancer (16-17). Various studies have shown that suppressing or inducing the expression of lnc-MEG3 can affect various characteristics of malignant cells, including growth, metastasis, migration, and apoptosis (18). Previous molecular studies have identified that several cancer-related gene cascades, including pathways that are associated with BCL-2 and PTEN expression, are affected by dysregulation of lnc-MEG3 expression. In addition, lnc-MEG3 can act as a sponge of several micro-RNAs like miR-21 and miR-9 to reduce or prevent their functions (19-21). Considering the gaps in our understanding of the molecular mechanisms driving OSCC tumorigenesis and the importance of novel molecular biomarkers and therapeutic targets, further study of key molecular players like lnc-MEG3 in Oral squamous cell carcinoma is imperative. Despite advancements in identifying driver genes associated with OSCC, the intricate interactions and regulatory networks that involve non-coding RNAs such as lnc-MEG3 still lack comprehensive understanding. This study aimed to investigate the dysregulation of the gene in OSCC, specifically focusing on clarifying its diagnostic values to further understand the pathogenesis of OSCC for early and effective diagnosis.

Material and Method

Preparation of patient samples

The current study is a cross-sectional study, during which 100 tumor samples and tumor margins were collected as control from eligible patients. In the current study, not having chronic diseases, not taking long-term medication, signing an ethical consent form, and having Oral squamous cell carcinoma (OSCC) of patients entering the study. in Imam Reza Hospital from 2019 to 2023. All participants in this research were of the Turkish population living in the northwest of Iran. The subjects with prior radiotherapy or chemotherapy or patients who refused to participate in this study were excluded. After obtaining the written informed consent from all participants, tissues of patients were collected by the surgery as the routine parts of the patient diagnostic approach. The tissue samples were preserved in liquid nitrogen before they were subjected to total RNA extraction. Clinic pathological features of patients with OSCC are summarized in table 1.

Extraction of total RNA

The AllPrep DNA/RNA/Protein kit (Qiagen, Hilden, Germany) was used to isolate genomic total RNA to company instructions. Briefly, after grinding the tissue samples in lysis buffer provided by the kit. In lysis buffer, the samples were homogenized by using a needle and syringe and then subjected to RNA isolation by silica RNA spin columns. Subsequently, the quality and concentration

of extracted nucleic acids were evaluated according to optical density by using the ThermoFisher's NanoDrop (Scientific Life Sciences, USA).

The synthesis of cDNA and real-time PCR

Utilizing the BioFACT cDNA synthesis kit (BioFACT, Korea), 1 microgram of the extracted total RNA was employed to synthesize cDNA following the provided protocols. Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) was used as internal controls for normalizing transcript levels of lnc-MEG3 respectively. Primer sequences are presented in Table 2.

Statistical analysis

Data were presented as the mean ± standard error of the experiments and GraphPad 6 Prism v.8 (GraphPad Software, San Diego, CA) was used to conduct the statistical analyses. The Livak method (comparative 2-ΔΔCT) was employed to evaluate relative lnc-MEG3 expression levels. Paired Student's t-test, independent sample t-test, or ANOVA test was used for comparing the groups in internal samples. Pearson's correlation test was implemented to assess the potential correlation between scale variables. P values that were less than 0.05 were considered statistically significant. The Receiver operating characteristic (ROC) curve analysis was performed to investigate whether lnc-MEG3 expression possessed a potential as the diagnostic biomarker by assessing the ability of this molecule to distinguish the groups. Then, the expression values for OSCC tumor samples and normal marginal tissue samples were considered as patient and control values. Then, GraphPad 6 Prism software was employed to perform ROC curve analysis to evaluate the area under the curve (AUC) at a confidence interval (CI) equal to 95%.

Results

We have assessed the expression of the lnc-MEG3 gene in 100 OSCC tissue samples compared to margin samples. Subsequently, lnc-MEG3 expression relation with the clinicopathological characteristics of OSCC patients, such as gender, age, smoking status, tumor stage, tumor location, differentiation and distant metastasis, were also analyzed. The results showed that the expression level of lnc-MEG3 was significantly downregulated in tumor samples compared to tumor border samples (fold change = 0.78 and p-value= 0.0030) (Figure 1). Furthermore, lnc-MEG3 expression level was significantly associated with some clinicopathological characteristics of patients, such as lymph node metastasis (p-value= 0.0021), differentiation (p-value= 0.0061), and distant metastases (p-value= 0.0001), while no significant association was found between lnc-MEG-3 expression level and gender, age, smoking and tumor location. All the data obtained are presented in detail in Table 1.

The Capability of lnc-MEG3 for the Diagnosis of OSCC

The ROC curve functioned to evaluate the sensitivity and specificity of lnc-MEG3 as a potential novel biomarker for OSCC. The resulting ROC area (AROC) for the lnc-MEG3 gene in OSCC patients was 0.627. The ROC curve data can be seen in Fig. 2.

Discussion

The study has revealed significant molecular changes in OSCC tumor tissues compared to normal marginal samples. We observed the downregulation of lnc-MEG3. Additionally, we found that the alteration in lnc-MEG3 expression was not only linked to the presence of cancer, but also associated with differentiation, metastasis, and lymph node invasion, suggesting that this long non-coding RNA could serve as a prognostic indicator. Furthermore, our investigation identified these molecular changes as potential diagnostic biomarkers for OSCC. Through ROC curve analysis, we determined that lnc-MEG3 expression could effectively distinguish OSCC from normal tissue. These findings underscore the diagnostic value of lnc-MEG3 in detecting OSCC and highlight its potential for clinical use in cancer diagnostics and patient management. Oral squamous cell carcinoma (OSCC) is the most prevalent type of the oral cancer. OSCC is the eighth most common cancer worldwide and is more common in low-income communities with high prevalence in men over 45 years of age. In terms of

clinical manifestations, involvement mostly occurs in the lip area and ranks second after intraoral cancer, which mainly affects the tongue. The main source of this malignancy is mutated keratinocyte cells. Lifestyle, especially tobacco and alcohol consuming is the main risk factor for the OSCC, in addition exposure to sunlight and ionizing radiation, human papillomavirus (HPV) or other infections like immune deficiency viruses can also contribute to the development of the disease

Oral squamous cell carcinoma (OSCC) is the most prevalent type of oral cancer. OSCC is the eighth most common cancer worldwide and is more common in low-income communities with high prevalence in men over 45 years of age. In terms of clinical manifestations, involvement mostly occurs in the lip area and ranks second after intraoral cancer, which mainly affects the tongue. The main source of this malignancy is mutated keratinocyte cells. Lifestyle, especially tobacco and alcohol consumption are the main risk factor for the OSCC. in addition, exposure to sunlight and ionizing radiation, human papillomavirus (HPV), or other infections like immune deficiency viruses can also contribute to the development of the disease (1,22).

At the molecular level, various regulatory genes play key roles in oral squamous cell carcinoma development. lncRNA, as a significant regulatory factor, provides a new avenue for studying malignant tumors and streamlines OSCC management. Maternally expressed gene 3 (MEG3), a recently discovered lncRNA, is implicated in multiple cancers. Reduced lnc-MEG3 levels in malignant cells impact cell proliferation, advancement, and prognosis. Additionally, increasing lnc-MEG3 expression inhibits in vivo and in vitro tumorigenesis of pancreatic cancer cells by influencing cell growth, invasion, and migration (24). Previous research has shown reduced lnc-meg3 expression in lung tumor cells and tissues. Moreover, studies indicate that increasing lnc-MEG3 levels can trigger apoptosis and hinder the growth of non-small cell lung cancers (NSCLC) (25). Examining lnc-MEG-3 roles in leukemia cell lines highlights its downregulation across various leukemia cell lines. Additionally, lnc-MEG-3 governs key malignant cell traits by sponging miR-181. Further investigations reveal significant depletion of lnc-MEG3 in AML cell lines, with this decrease linked to WT-1 protein mutations (26-28).

Previous research on the clinical implications of lnc-MEG3 in various cancers, such as ovarian cancer, has yielded conflicting results regarding its correlation with patient prognosis. Discrepancies in findings may be due in part to variations in patient demographics and sample types analyzed. Nonetheless, the Cancer LncRNA Census (CLC) ranks lnc-MEG3 as one of the top tumor suppressors lncRNAs. Mechanistically, the bulk of evidence indicates that MEG3 functions as a tumor suppressor by enhancing p53 protein levels and subsequently activating its downstream target genes (30). On the other hand, recent studies indicate that MEG3 plays a role in regulating oncogenic and tumor suppressor gene networks, possibly by serving as a molecular sponge for cancer-related microRNAs. A notable mechanism involves lnc-MEG3 positively influencing PTEN expression in certain cancer types. While the precise pathways of this regulation are not entirely understood, it is suggested that MEG3 competes as an endogenous RNA for miR-214, which consequently leads to the negative regulation of PTEN protein expression (32).

In our study, we explored the diagnostic potential of lnc-MEG3 expression, for OSCC. Our findings from ROC curve analysis demonstrated that the downregulation of lnc-MEG3 showed promising diagnostic capability in distinguishing OSCC tumors from normal samples. These results suggest that the expression status of lnc-MEG3 could serve as valuable diagnostic biomarkers for OSCC, potentially facilitating earlier detection and improved management of this disease. Further validation studies are warranted to confirm these findings and assess its clinical utility in OSCC diagnosis and patient management.

While we conducted well-designed experiments to produce strong results, it is crucial to recognize the limitations of the current study. We did not explore the downstream targets of lnc-MEG3 in our samples. Furthermore, we did not conduct confirmatory mechanistic assays, like overexpressing this gene in OSCC cell lines, to elucidate its role in driving tumor behaviors. These limitations underscore the need for additional research to improve our comprehension of the molecular mechanisms that lead to lnc-MEG3 dysregulation in OSCC.

Conclusion

The findings of our study confirm and build upon existing knowledge about the molecular characteristics of OSCC. Our research showed that the downregulation of lnc-MEG3 is a simultaneous event in OSCC carcinogenesis. Importantly, these molecular changes were found to correlate with clinical features in OSCC patients. Furthermore, our study emphasizes the potential of lnc-MEG3 as a promising diagnostic marker for OSCC, providing a better understanding of its clinical significance. Although our results have meaningful implications for OSCC diagnosis and understanding of its underlying mechanisms, further validation studies are needed to explain the exact roles of lnc-MEG3 in pathogenesis. Future studies should focus on unraveling the mechanistic basis of these molecular variations and exploring their therapeutic effects to improve patient prognosis in OSCC.

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Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request

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Conflict of Interest

None declared.

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Table 1. Sequence of primers used for q-PCR

Gene	Primer sequence	Annealing temp (°C)
Lnc-MEG3	F: 5′- CTGCCCATCTACACCTCACG -3′ R: 5′- CTCTCCGCCGTCTGCGCTAGGGGCT -3′	59
GAPDH	F: 5′-CAAGATCATCAGCAATGCCTCC-3′ R: 5′-GCCATCACGCCACAGTTTCC-3′	59

GAPDH: Glyceraldehyde-3-phosphate dehydrogenase, Lnc-MEG3: long non-coding RNA Maternally Expressed 3

Table 2. Association of transcript levels of lnc-MEG3 and clinicopathological features of patients.

Cilinicopathological Character	Number		P value lnc-MEG-3
Age	>60	76	0.23
	<60	24	
Sex	Female	32	0.22
	Male	68	
Family Story	Positive	9	0.13
	Negative	91	
Smoking	Positive	62	0.112
	Negative	38	
Lymph node Invasion	Positive	57	0.0021
	Negative	43	
Distant Metastasis	Positive	8	0.0001
	Negative	92	
Differentiation	Poor	39	0.0061
	Intermediate & Good	61	

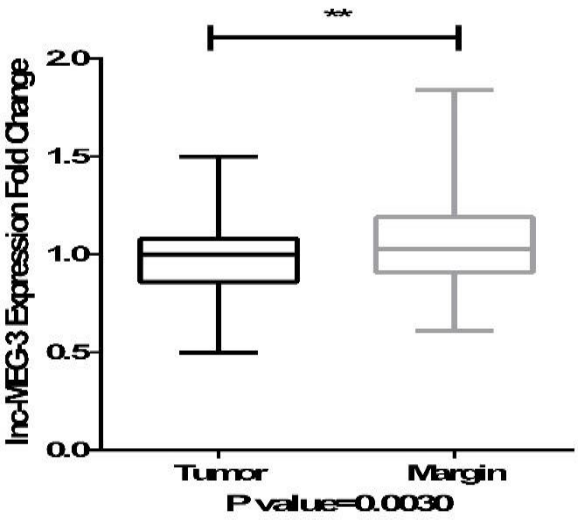

Figure 1. Expression of lnc-MEG3 in OSCC

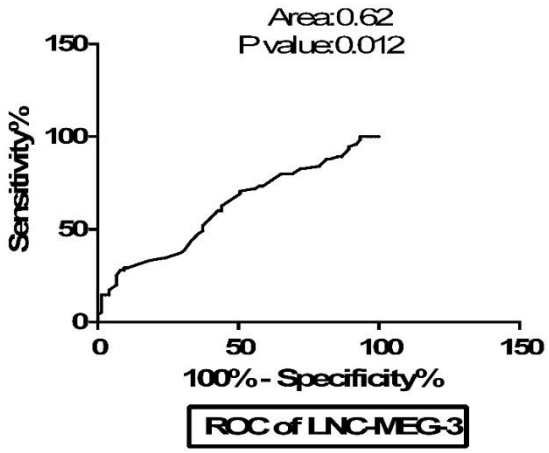

Figure 2. ROC curve analysis of lnc-MEG3 expression in OSCC.