REVIEW ARTICLE

The Role of Long Non-Coding RNAs HOTTIP, HOTAIR, and MALAT1 in Oral Squamous Cell Carcinoma

Abikshyeet Panda [1], Harish Kumar[2], Tathagata Bhattacharjee[3], T. Maheswaran[4], Kailash Chandra Dash[5], Aishwariya Mohanty[6]

ABSTRACT

Abstract

When it comes to cancers of the head and neck, oral squamous cell carcinoma (OSCC) ranks high. Its complicated and poorly known molecular pathways underlie its genesis and progression. An essential role in cancer aetiology is played by long non-coding RNAs (lncRNAs), which have recently come to light as key regulators of gene expression. The purpose of this article is to offer a thorough analysis of the functions of three long non-coding RNAs (lncRNAs) in relation to oral squamous cell carcinoma: HOTTIP, HOTAIR, and MALAT1.

Keywords

Oral squamous cell carcinoma, long non-coding RNA, lncRNA, HOTTIP, HOTAIR, MALAT1, gene regulation, oral cancer, biomarkers, therapeutic targets.

INTRODUCTION

Among the several types of oral cancers, squamous cell carcinoma (OSCC) accounts

for over 90%. It ranks ninth in incidence among head and neck cancers. Poses a significant cost on public health on a global scale, accounting for 2.1% of all cancer-related fatalities. Because OSCC is often diagnosed at a late stage and there are limited therapeutic alternatives, the 5-year life expectancy rate of patients is still about 50%, even if medical developments have improved detection and therapy[1]. Thus, in order to discover new biomarkers for early detection and complete treatment targets, it is essential to comprehend the molecular mechanisms behind OSCC growth and progression.

Multiple factors, including unique genetic and epigenetic changes, contribute to OSCC aetiology[2]. Recent advances in molecular biology have piqued the attention of researchers in the nucleotide methylation, histone protein modifications, and non- coding RNA (ncRNA) expression components of epigenetic alterations[3]. With the advancement of whole-genome and transcriptome sequencing, the role of long non-coding RNA (lncRNA) has become increasingly apparent. A subset of the RNA family known as long non-coding RNAs (LncRNAs) contain

1. "Professor, Dept of Oral Pathology and Microbiology, Kalinga Institute of Dental Sciences, KIIT deemed to be University, Patia, Bhubaneswar -751024, abikshyeet.panda@kids.ac.in
2. Professor and HOD, Dept of Oral Pathology and Microbiology, KIIT deemed to be University, Patia, Bhubaneswar -751024, harishmaslekar@gmail.com
3. Associate Professor, Department of Oral Pathology and Microbiology, Dr.R.Ahmed Dental College and Hospital. Kolkata,West Bengal., drtatha.dent@gmail.com
4. Professor, Department of Oral Pathology, Vivekanandha Dental College for Women, Tiruchengode-637205, maheswaranmds@gmail.com
5. Reader, Department of Oral and Maxillofacial Pathology, Kalinga Institute of Dental Sciences, KIIT deemed to be University, Patia, Bhubaneswar -751024, kcdash1986@gmail.com
6. Senior Resident, Dept of Oral and Maxillofacial Pathology, S.C.B Dental College and Hospital, Cuttack-753007 aishwariya260794@gmail.com

Correspondence:
Abikshyeet Panda, Professor, Department of Oral and Maxillofacial Pathology, KIIT (Deemed to be University) Kalinga Institute of Dental Sciences, Bhubaneswar
Email: abikshyeet.panda@kids.ac.in,

DOI: https://doi.org/10.3329/bjms.v24i10.79173

more than 200 nucleotides yet cannot code for proteins.

Research has shown that they modulate chromatin, regulate transcription, and affect gene expression after transcription has already taken place[4]. Oral cancer is just one of several diseases that have been linked to the start, development, and outcome of abnormal lncRNA expression and dysregulation[5,6,7].

Novel insights into the pathophysiology of OSCC and possible treatment targets may be revealed by understanding the activities and processes of lncRNAs in this disease. "Research has looked at how certain long non- coding RNAs (lncRNAs) are related to OSCC clinicopathologic variables like overall survival time and metastatic disease presence, including HOTTIP (HOXA transcript at the distal tip), HOTAIR (HOX transcript antisense RNA), MALAT-1 (Metastasis-associated lung adenocarcinoma transcript 1), UCA1 (urothelial carcinoma associated 1), and FOXCUT (Fork head box C1 upstream transcript) [8,9,10,11,12]. Their potential as biomarkers and therapeutic interventions stems from the fact that their

abnormal expression is linked to either tumor-suppressing or carcinogenic actions. Several lnRNAs, including GAS5 (growth arrest specific transcript 5), MEG3, f lnc- SPRR2 D-1, lnc-PPP2 R4-5, lncMBL2-4:3,

and f lncAL355149.1-1, have been found to have altered expression in OSCC [13].

Compelling evidence has proven crosstalk between lnRNAs regulate overlapping molecular pathways in OSCC providing new innovative concepts for understanding of the lncRNAs network and uncovering innovative concepts towards the therapeutic strategies [14]. Therefore this article aims to explore the functional role, molecular mechanisms and clinical significance of HOTTIP, HOTAIR, MALAT-1 in pathophysiology of OSCC. It also discusses the interplay and Crosstalk among HOTTIP, HOTAIR, and MALAT1.

2. HOTTIP and OSCC

2.1 HOTTIP: An Overview

Embryonic development and cancer are two of the many biological processes impacted by HOTTIP, a well-studied lncRNA that controls gene expression. Its scaffolding role is to facilitate the recruitment of chromatin- modifying complexes to particular genomic loci, which in turn activate target genes through transcription[8].

2.2 Aberrant Expression of HOTTIP in OSCC

Several studies have reported dysregulated expression of HOTTIP in OSCC tissues compared to normal mucosa. It is commonly upregulated and correlates with clinicopathological features such as tumor stage, nodal involvement, and metastasis, suggesting its involvement in OSCC progression [15].

2.3 Functional Roles of HOTTIP in OSCC

Through its effects on gene expression, HOTTIP enhances OSCC cell motility, invasion, and proliferation as well as epithelial-mesenchymal transition (EMT). In preclinical models, its overexpression increases tumour growth and metastasis, indicating that it may have oncogenic potential in OSCC[16].

Molecular Mechanisms of HOTTIP in OSCC

In order to cause cancer in OSCC, HOTTIP activates genes involved in cell proliferation, invasion, and metastasis through molecular mechanisms such as interacting with complexes that modify histones, such as the MLL/SET1 histone methyltransferase complex. By influencing the expression of crucial signalling pathways such the Wnt/Ō- catenin and PI3K/Akt pathways, HOTTIP enhances oncogenic signalling in OSCC cells. [8,15,16].

2.4 Clinical Implications and Prognostic Value of HOTTIP in OSCC

A worsening of clinical outcomes, such as overall survival and disease-free survival, has been linked to the abnormal expression of HOTTIP in OSCC tissues. To help with risk stratification and therapeutic decision-making, HOTTIP expression levels could be used as predictive biomarkers for OSCC patients. Moreover, targeting HOTTIP or its downstream effectors could represent a noveltherapeutic approach for OSCC management

3. HOTAIR and OSCC

3.1 HOTAIR: An Overview

HOTAIR is a well-studied lncRNA that plays a significant role in gene regulation, chromatin remodelling, and cancer progression. It enlists chromatin-modifying complexes such polycomb repressive complex 2 (PRC2) and lysine-specific demethylase 1 (LSD1) to alter epigenetics and inhibit transcription of target genes.[9,17].

3.2 Dysregulation of HOTAIR in OSCC

HOTAIR is frequently dysregulated in OSCC, with both upregulation and downregulation reported in different studies. Its expression levels correlate with clinicopathological features, including tumor size, lymph node metastasis, and overall survival, suggesting its involvement in OSCC pathogenesis and progression [18].

3.3 Functional Roles of HOTAIR in OSCC

HOTAIR promotes OSCC cell proliferation, migration, invasion, and EMT by modulating the expression of genes associated with these processes. It enhances tumor aggressiveness and metastatic potential through its interactions with chromatin-modifying complexes and transcription factors, driving oncogenic signaling pathways in OSCC cells[9,18].

3.4 Molecular Mechanisms of HOTAIR in OSCC

The oncogenic functions of HOTAIR in OSCC are mediated through its interaction with PRC2 and LSD1, leading to repressive histone modifications and transcriptional silencing of tumor suppressor genes. HOTAIR also regulates the expression of key signaling molecules, such as Snail, Twist, and MMPs, involved in cancer metastasis and invasion [19].

3.5 Clinical Significance of HOTAIR in OSCC

According to research, higher levels of HOTAIR expression are associated with more advanced tumour stage, lymph node metastases, and worse overall survival in patients with OSCC. Higher levels of HOTAIR expression are linked to unfavourable clinical outcomes and treatment resistance in OSCC, suggesting its potential as a therapeutic target and prognostic indicator[18,19].

4. MALAT1 and OSCC

4.1 MALAT1: An Overview

Gene expression regulation, alternative splicing, and cancer metastasis are just a few of the many biological processes that include MALAT1, a highly conserved lncRNA. It is abundantly expressed in the nucleus and cytoplasm, where it exerts diverse functions in cellular homeostasis and disease pathogenesis [10].

4.2 Altered Expression of MALAT1 in OSCC

Multiple studies have shown either an increase or a decrease in MALAT1 expression in OSCC tissues when contrasted with normal mucosa. Clinicopathological variables including tumour stage, lymph node metastasis, and patient prognosis are correlated with its expression levels, indicating that it may be involved in the course of OSCC [20].

4.3 Functional Roles of MALAT1 in OSCC

In order to facilitate OSCC cell motility, invasion, proliferation, and EMT, MALAT1 regulates the expression of genes linked to these activities. It increases tumour aggressiveness and metastatic potential via controlling cellular signalling pathways that are implicated in cancer development and spread, including as the PI3K/Akt, MAPK/ERK, and Wnt/β-catenin pathways[21].

4.4 Molecular Mechanisms of MALAT1 in OSCC

The oncogenic functions of MALAT1 in OSCC are mediated through its interactions with RNA-binding proteins, transcription factors, and chromatin-modifying complexes, leading to epigenetic modifications and transcriptional activation of target genes. Through its regulation of alternative splicing mechanisms, MALAT1 affects the expression of genes involved in cell migration, invasion, and proliferation[22].

4.5 Prognostic and Diagnostic Potential of MALAT1 in OSCC

The possibility for MALAT1 expression levels to serve as diagnostic and prognostic biomarkers is supported by the fact that they are correlated with OSCC clinical outcomes and patient survival. It is suggested that MALAT1 could be a potential therapeutic target and prognostic indicator due to the substantial association between high MALAT1 expression and poor OSCC prognosis and treatment responsiveness [23].

5. Interplay and crosstalk among HOTTIP, HOTAIR, and MALAT1 in OSCC

5.1 Co-expression and Interactions

HOTTIP, HOTAIR, and MALAT1 exhibit complex interplay and regulatory interactions in OSCC. Co-expression analyses have revealed correlations among these lncRNAs, suggesting potential regulatory relationships and shared molecular pathways in OSCC pathogenesis [14,24,25].

5.2 Synergistic Effects and Functional Crosstalk

Synergistic effects and functional crosstalk between HOTTIP, HOTAIR, and MALAT1 contribute to enhanced oncogenic phenotypes in OSCC. These

lncRNAs may cooperatively regulate common target genes and signaling pathways, amplifying their individual effects on tumor progression, metastasis, and therapeutic resistance [25].

5.3 Shared Molecular Pathways and Mechanisms

HOTTIP, HOTAIR, and MALAT1 regulate overlapping molecular pathways and mechanisms involved in the pathogenesis, including cell proliferation, migration, invasion, and EMT. They interact with common effector molecules, such as transcription factors, chromatin modifiers, and signaling proteins, to orchestrate complex gene regulatory networks driving tumorigenesis and metastasis [26,27].

6. Therapeutic Targeting of HOTTIP, HOTAIR, and MALAT1 in OSCC

6.1 Strategies for Targeting lncRNAs

A number of strategies have been proposed for targeting HOTTIP, HOTAIR, and MALAT1 in OSCC, including the use of antisense oligonucleotides, small interfering RNAs (siRNAs), and CRISPR/Cas9- mediated gene editing. These approaches aim to inhibit lncRNA expression or activity, thereby attenuating their oncogenic functions and sensitizing tumor cells to conventional therapies [28].

6.2 Current and Potential Therapeutic Approaches

Emerging preclinical studies have demonstrated the therapeutic efficacy of targeting HOTTIP, HOTAIR, and MALAT1 in OSCC using RNA-based therapeutics and small molecule inhibitors [29]. Combination therapies targeting multiple lncRNAs or their downstream effectors may enhance treatment responses and overcome therapeutic resistance in OSCC patients [30,31].

7. Challenges and Future Perspectives

Despite promising preclinical findings, several challenges need to be addressed for the clinical translation of lncRNA-targeted therapies in OSCC. These include off-target effects, delivery strategies, and patient stratification based on lncRNA expression profiles. Future research efforts should focus on developing safe and effective lncRNA- targeted therapies and biomarkers for personalized treatment approaches in OSCC.

CONCLUSION

"Important roles in oral squamous cell carcinoma development and progression are played by long non-coding RNAs HOTTIP, HOTAIR, and MALAT1. Through a number of molecular pathways, carcinogenic processes such as cell migration, invasion,metastasis, and proliferation are aided by dysregulation of these lncRNAs." The complex communication and interaction between these lncRNAs, as well as their utility as OSCC diagnostic biomarkers and treatment targets, need more investigation. Future research into the functions of lncRNAs in OSCC has the potential to lead to more targeted treatments and better health outcomes for patients.

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