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Role of HOXA10-AS in Oral Squamous Cell Carcinoma: A Systematic Review

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ABSTRACT: Background: Oral squamous cell carcinoma (OSCC) is a common malignancy with high morbidity and mortality globally. Recent studies have highlighted the regulatory function of long non-coding RNAs (lncRNAs) in tumorigenesis, of which HOXA10 antisense RNA (HOXA10-AS) is an emerging candidate oncogenic driver in OSCC. This systematic review assesses the expression profile, molecular mechanisms, and clinical significance of HOXA10-AS in OSCC, noting its promise as a biomarker and therapeutic target.

Materials and Methods: This review was conducted following PRISMA guidelines. Literature searches were made on PubMed, Scopus, and Web of Science databases for original articles published between January 2000 and March 2025. The inclusion criteria included English-language studies assessing HOXA10-AS in OSCC using clinical samples, in vitro or in vivo models, and molecular studies. Important data concerning study design, methodology, results, and implications were extracted and synthesized systematically.

Results: Six studies were finally included in the synthesis. HOXA10-AS was always overexpressed in OSCC tissues and cell lines. Mechanistically, it contributed to oncogenesis through acting as a natural antisense transcript for HOXA10, sponging miR-29a, and binding with RNA-binding proteins like UPF1 to stabilize oncogenic mRNAs. These behaviors led to increased cell proliferation, epithelial–mesenchymal transition (EMT), stemness, and metastasis. Clinically, elevated levels of HOXA10-AS expression were associated with tumor grade progression, lymph node metastasis, and poor prognosis, indicating its prognostic significance.

Conclusion: HOXA10-AS is a wide-ranging lncRNA that has implications in OSCC pathobiology. It regulates significant oncogenic processes at both the transcriptional and post-transcriptional levels, making it a potential diagnostic marker and therapeutic target. Additional prospective and mechanistic studies are needed to ascertain its clinical significance.

Keywords: HOXA10-AS, oral squamous cell carcinoma, long non-coding RNA, epigenetic regulation, TP63, miR-29a, MCL-1, cancer stem cells, PI3K/AKT.

INTRODUCTION

Oral squamous cell carcinoma (OSCC) is responsible for over 90% of malignant tumors occurring in the oral cavity and is a significant worldwide health problem because of its aggressive clinical behavior, high rate of recurrences, and habitual resistance to standard therapy.[1] It is a multifactorial disorder defined by malignant change of stratified squamous epithelium, with significant etiological factors being tobacco smoking, betel quid chewing, chronic alcohol consumption, and infection with high-risk subtypes of human papillomavirus (HPV). OSCC often occurs at late stages and is often linked with locoregional lymph node metastasis and local tissue invasion, underpinning a relentlessly low five-year survival rate of around 50%, in spite of advances in surgical and oncologic therapy.[2] In the midst of the ever-growing field of molecular oncology, there is an increasing recognition of the potential involvement of non-coding RNAs in carcinogenesis. Long non-coding RNAs (lncRNAs), RNA transcripts with more than 200 nucleotides and a non-coding capacity, have come to be recognized more and more for their potential to modulate gene expression at the levels of transcription, post-transcription, and epigenetics.[3] These lncRNAs participate in a range of biological functions, such as chromatin remodeling, RNA splicing, and interaction with other species of RNA or proteins. In cancer, abnormally regulated lncRNA expression has been implicated in the development of hallmarks of malignancy, including continuous proliferative signaling, avoidance of growth suppressors, and activation of metastasis and invasion.[4] One such lncRNA, HOXA10 antisense RNA (HOXA10-AS), or Homeobox A10 Antisense RNA, a long non-coding RNA transcribed in the antisense direction from the HOXA10 gene, has gained significant interest because of its persistent overexpression in many cancers, including OSCC.[5] HOXA10-AS is transcribed from the HOXA10 antisense strand, mapping to chromosome 7p15.2 within the highly investigated HOXA gene cluster. Its proximity to regulatory factors, including miR-196b, and the possibility of modulating the expression of its sense counterpart, HOXA10, make HOXA10-AS an important node in the oncogenic regulatory network.[5] Preclinical experiments have shown that HOXA10-AS is involved in major oncogenic activities in OSCC, such as augmented cellular proliferation, migration, invasion, epithelial-to-mesenchymal transition (EMT), and chemoresistance. Its involvement in cancer stemness regulation and chemotherapy response modulation has also started to surface. Such findings highlight the role of HOXA10-AS in the molecular pathology of OSCC.[6] The present review attempts a systematic aggregation of what is already known about the expression patterns, the regulatory mechanisms, and the clinical relevance of HOXA10-AS in OSCC with the aim of guiding future investigations and, possibly, therapeutic interventions in this lncRNA.

MATERIALS AND METHODS

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[7] (Figure 1). A wide-ranging literature search was conducted in three of the major databases: PubMed, Scopus, and Web of Science. The search strategy entailed the use of various keyword combinations like "HOXA10-AS," "oral squamous cell carcinoma," "lncRNA," "epigenetic regulation," "microRNA sponging," and "tumor progression."

Inclusion Criteria:

- Original research articles in English
- Studies focusing on HOXA10-AS expression or function in OSCC
- Clinical, molecular, or functional studies in cell lines, patient specimens, or animal models.

Exclusion Criteria:

- Review articles, editorials, or commentaries.
- Studies not directly involving OSCC or HOXA10-AS.

All the studies that had been identified were screened by title and abstract and then by full text for eligibility. Data extraction was conducted independently by two reviewers and entailed author information, year of publication, study design, characteristics of the sample, methods, and main findings.

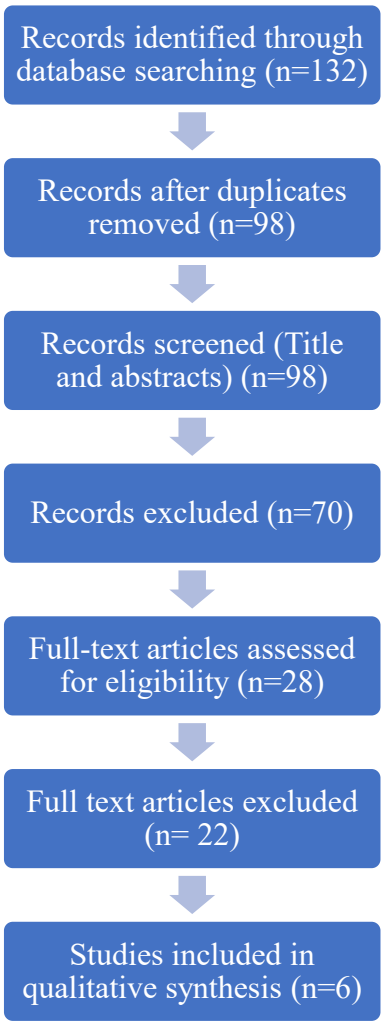

Figure 1: PRISMA Flowchart

RESULTS

Six studies were found to meet the inclusion criteria and were included in the final synthesis. The details of these studies' characteristics and findings are presented in Table 1.

Table 1: Summary of Included Studies

Author	Study	Study Focus	Methodology	Key Findings
Padam et al. (2025)[8]	Natural Antisense Transcript-Mediated Regulation of HOXA10-AS in Oral Squamous Cell Carcinoma	NAT regulation, epigenetics	RT-qPCR, ChIP-qPCR, siRNA knockdown	HOXA10-AS enhances HOXA10 expression via chromatin modifications and promotes EMT and proliferation
Hu et al. (2025)[9]	LncRNA HOXA10-AS as a novel biomarker and therapeutic target in human cancers	Pan-cancer analysis	Transcriptome profiling, survival plots	HOXA10-AS is overexpressed in OSCC and predicts adverse clinical outcomes
Chen et al. (2022)[10]	Modular scaffolding by lncRNA HOXA10-AS promotes oral cancer progression	Scaffold function, TP63 mRNA	RIP, western blot, functional assays	HOXA10-AS stabilizes TP63 transcript via UPF1 interaction, enhancing oncogenic traits
Wang D et al. (2021)[11]	Promotive effects of HOXA10 antisense RNA on the stemness of oral squamous cell carcinoma stem cells through a microRNA-29a/MCL-1/phosphatidyl inositol 3-kinase/protein kinase B axis	Cancer stemness, PI3K/AKT pathway	miRNA analysis, xenograft models	HOXA10-AS sponges miR-29a, upregulates MCL-1, activates PI3K/AKT signaling, and promotes stemness
Yan et al. (2020)[12]	Silencing lncRNA HOXA10-AS decreases cell proliferation of oral cancer and HOXA10-antisense RNA can serve as a novel prognostic predictor	Prognostic relevance	TCGA analysis, proliferation assays	High HOXA10-AS levels associated with tumor grade, poor survival, and cell cycle activation
Carrera et al. (2015)[6]	HOXA10 controls proliferation, migration and invasion in oral squamous cell carcinoma	HOXA10 validation	qPCR, RNA interference, EMT markers	HOXA10 promotes OSCC cell proliferation, migration, and invasion

DISCUSSION

The extensive review of existing literature confirms a robust oncogenic function for HOXA10-AS in OSCC, as repeatedly evidenced by its overexpression in tumor tissues compared to surrounding normal tissues. Such differential expression is of functional significance, since all the reviewed studies offer mechanistic explanations of how HOXA10-AS drives oral carcinogenesis.

Padam et al. (2025)[8] demonstrated that HOXA10-AS enhances its sense gene, HOXA10, via epigenetic regulation. In particular, the study confirmed histone marks in the distal promoter of HOXA10 that enabled transcriptional activation. The unmethylated CpG island and histone mark deposition like H3K4me3 and H3K27ac at the promoter region were associated with enhanced HOXA10 transcription, in turn contributing to epithelial-to-mesenchymal transition (EMT) and cell proliferation—essential processes for tumor progression.

Concomitantly, Chen et al. (2022)[10] proposed a different post-transcriptional process. Their study identified HOXA10-AS as a modular RNA scaffold that is able to bind to UPF1 in order to enhance the processing and stabilization of TP63 mRNA, a survival- and differentiation-related gene transcript. Scaffolding activity resulted in increased expression of TP63 and was associated with enhanced cell proliferation, migration, and invasion. While Padam et al.[8] concentrated on the level of chromatin control, Chen et al. shed light on cytoplasmic RNA processing, thus expanding the functional role of HOXA10-AS.

Wang et al. (2021)[11] extended the mechanistic model even further by proposing the role of HOXA10-AS as a competing endogenous RNA (ceRNA). In this research, it was depicted how HOXA10-AS sponges miR-29a, a tumor-suppressive microRNA, and thus derepresses its downstream target MCL-1. The resultant elevation of MCL-1 levels activates PI3K/AKT signaling pathway, leading to increased survival, proliferation, and stem cell-like characteristics in OSCC cells. This ceRNA behavior is consistent with the epigenetic and scaffolding actions previously described and offers a unifying theme of HOXA10-AS-mediated oncogenic signaling.

The clinical relevance of these molecular events was further confirmed by Yan et al. (2020)[12] and Hu et al. (2025)[9], who used bioinformatics resources and patient sample information to show that overexpression of HOXA10-AS correlates with advanced clinical stage, lymph node metastasis, and poor overall survival. The evidence suggests that HOXA10-AS can be employed as a credible prognostic biomarker. These observations validate and translate molecular findings of in vitro and in vivo studies to clinical environments, underscoring the clinical significance of HOXA10-AS in OSCC.

Carrera et al. (2015)[6] also targeted HOXA10, the HOXA10-AS-regulated sense gene, and demonstrated that HOXA10 silencing resulted in inhibited proliferation, migration, and invasion of OSCC cell lines. The results indirectly prove the oncogenic function of HOXA10-AS because its regulatory roles on HOXA10 expression were found to translate into concrete cellular behaviors that pertain to malignancy.

Overall, these studies portray HOXA10-AS as an oncogenic driver with multiple functions in OSCC. Its various modes of action—chromatin remodeling, mRNA scaffolding, miRNA

sequestration, and proto-oncogene upregulation—come together to promote tumor growth, invasion, metastasis, and stemness. Notably, the convergence of findings from molecular, cellular, and clinical studies highlights the strong consistency of HOXA10-AS as both a biomarker and a potential therapeutic target for the treatment of oral cancer.

CONCLUSION

HOXA10-AS becomes a critical lncRNA possessing oncogenic functions in OSCC. Its expression enables tumor growth under multifactored mechanisms via epigenetic regulation, mRNA splicing, and activation of signaling pathways. HOXA10-AS is also a candidate biomarker for diagnosis and prognosis and therapeutic target in clinic. Translational studies and clinical trials must be performed to explore HOXA10-AS-directed interventions in OSCC management.

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