Molecular Therapy
Oncolytics
Review

# The role of long non-coding RNAs in the pathogenesis of head and neck squamous cell carcinoma

Man Jiang,[1,2,5] Fang Liu,[3,5] An-Gang Yang,[4] Wei Wang,[4] and Rui Zhang[2,4]

[1]School of Life Science and Technology, Xi'an Jiaotong University, Xi'an, Shaanxi 710032, China; [2]State Key Laboratory of Cancer Biology, Department of Biochemistry and Molecular Biology, The Fourth Military Medical University, Xi'an, Shaanxi 710032, China; [3]Department of Dermatology, Xijing Hospital, The Fourth Military Medical University, Xi'an, Shaanxi 710032, China; [4]State Key Laboratory of Cancer Biology, Department of Immunology, The Fourth Military Medical University, Xi'an, Shaanxi 710032, China

**Head and neck cancers are a heterogeneous collection of malignancies of the upper aerodigestive tract, salivary glands, and thyroid. However, the molecular mechanisms underlying the carcinogenesis of head and neck squamous cell carcinomas (HNSCCs) remain poorly understood. Over the past decades, overwhelming evidence has demonstrated the regulatory roles of long non-coding RNAs (lncRNAs) in tumorigenesis, including HNSCC. Notably, these lncRNAs have vital roles in gene regulation and affect various aspects of cellular homeostasis, including proliferation, survival, and metastasis. They exert regulating functions by interacting with nucleic acids or proteins and affecting cancer cell signaling. LncRNAs represent a burgeoning field of cancer research, and we are only beginning to understand the importance and complicity of lncRNAs in HNSCC. In this review, we summarize the deregulation and function of lncRNAs in human HNSCC. We also review the working mechanism of lncRNAs in HNSCC pathogenesis and discuss the potential application of lncRNAs as diagnostic/prognostic tools and therapeutic targets in human HNSCC.**

## BACKGROUND

Head and neck squamous cell carcinoma (HNSCC) is a leading malignant disease and contributes to the global cancer burden.[1] HNSCC develops in the upper airway's epithelial cells and mucosal lining of food passages, such as the oral cavity, oropharynx, larynx, or hypopharynx. The majority of HNSCCs are associated with tobacco and alcohol use.[2,3] Some subgroups, especially oropharynx cancers, are caused by human papillomavirus (HPV) infection.[4] More than half of HNSCC patients are initially diagnosed at a locally advanced stage.[5] Even with combined treatment involving surgery, radiotherapy, chemotherapy, and immunotherapy, the prognosis of HNSCC is still poor. For example, the 5-year survival rates range from approximately 60% in laryngeal carcinoma to roughly 25% in hypopharyngeal carcinoma.[6] Besides the poor outcomes due to specific anatomical structures, patient survival is also threatened by cancer cells' tendency to invade surrounding normal tissue and metastasize to cervical lymph nodes. Despite the therapeutic progress in the past two decades, novel strategies that provide earlier diagnosis, more effective treatment, and prognosis assessment are urgently needed. As the pathogenesis of HNSCC is a multistep process driven by the accumulation of various genetic and epigenetic alterations, a better understanding of the molecular mechanism of HNSCC is in need as a crucial factor for the future development of effective treatment.

Early studies on the molecular mechanism of cancer carcinogenesis have focused on protein-coding genes because proteins are traditionally accepted as the center of molecular biology. However, high-throughput transcriptome studies in the past few years have revealed many non-coding RNAs that outnumber the protein-coding genes in the human genome.[7] These non-coding RNAs have been found to be implicated in diverse biological processes affecting development, differentiation, and physiology.[8] Although some of these non-coding RNAs are small, most of them surpass 200 nucleotides in length and are cataloged as long non-coding RNAs (lncRNAs). It is now recognized that lncRNAs are exquisitely regulated and restricted to specific cell types greater than messenger RNA (mRNA).[9] They frequently have an evolutionarily conserved function, a secondary structure, and microhomology regions, despite sharing minimal overall sequence similarity.[10–12] LncRNAs can control chromatin modifications, chromosomal looping, DNA transcription, and edit and stabilize mRNAs that influence their translation or interact directly with proteins and other RNA species.[11] Concerning cancer disease, lncRNAs are aberrantly expressed in different types of cancer and

https://doi.org/10.1016/j.omto.2021.12.001.

[5]These authors contributed equally

**Correspondence:** An-Gang Yang, PhD, State Key Laboratory of Cancer Biology, Department of Immunology, The Fourth Military Medical University, Xian 710032, China.
**E-mail:** agyang@fmmu.edu.cn
**Correspondence:** Wei Wang, PhD, State Key Laboratory of Cancer Biology, Department of Immunology, The Fourth Military Medical University, Xian 710032, China.
**E-mail:** wwang115@fmmu.edu.cn
**Correspondence:** Rui Zhang, PhD, State Key Laboratory of Cancer Biology, Department of Immunology, The Fourth Military Medical University, Xian 710032, China.
**E-mail:** ruizhang@fmmu.edu.cn

influence cell-cycle regulation, survival, immune response, or pluripotency, among functions altering cancer phenotypes.[13] Several lncRNAs can also be transcriptionally regulated by key tumor suppressors or oncogenes.[14,15] Increasing evidence has shown that lncRNAs are key players in human carcinogenesis, and we are only beginning to understand the importance and complicity of lncRNAs in HNSCC.

In this review, we describe the emerging roles of lncRNAs in HNSCC and outline the current knowledge on the functions and action mechanism of lncRNAs in HNSCC pathogenesis. We also discuss the potential applications of lncRNAs as diagnostic/prognostic tools and therapeutic targets and highlight the possible challenges in future studies.

## BIOLOGICAL ROLES OF lncRNAs IN HNSCC

### LncRNA profile in HNSCC

Multiple profiling studies based on microarray and whole-genome transcriptome sequencing platforms have pinpointed the aberrant expression pattern of lncRNAs in HNSCC. From the etiological aspect, by analyzing lncRNA expression across 426 HNSCC samples from The Cancer Genome Atlas (TCGA), researchers have shown significant associations between lncRNA-based clustering and DNA methylation, HPV infection, and TP53 mutation.[16] A recent study has identified a DNA methylation-dysregulated four-lncRNA signature (DNAMeFourLncSig) from 596 DNA methylation-dysregulated lncRNAs in HNSCC, which could be an independent prognostic factor and may predict the chemotherapy response of HNSCC patients.[17] Other studies have observed the hypomethylated lncRNA H19 as a potential prognostic biomarker in oral squamous cell carcinoma (OSCC) [18] and the hypermethylated lncRNA HNF1A-AS1 as a tumor suppressor in laryngeal squamous cell carcinoma (LSCC),[19] respectively. LncRNAs are also differentially expressed in HPV-positive and HPV-negative HNSCCs.[16] By analyzing databases of the Atlas of Noncoding RNAs in Cancer (TANRIC) and TCGA, researchers have found 140 lncRNA transcripts significantly and differentially expressed between HPV-positive and HPV-negative tumors.[20] Among them, lncRNA HOX transcript antisense RNA (HOTAIR), PROM1, CCAT1, and MUC19 are inversely correlated with the myeloid-derived suppressor cell collection of HPV-associated HNSCC.[21] More recently, Song et al. have identified the lnc-IL17RA-11 transcription factor ER-alpha as the most likely HPV infection-associated factor promoting increased lnc-IL17RA-11 levels.[22] As another critical etiology of HNSCC, over 70% of HNSCC patients carry TP53 oncogenic mutations.[23] Researchers have also found that the expression of tumorigenic lncMIR205HG significantly increased in HNSCC with mutated TP53 compared with matched non-tumoral tissues.[23] Moreover, Chaudhary et al. have found 133 lncRNAs to have differential abundance by 2-fold in the mutant versus wild-type TP53 samples, among which LINC00460 is associated with cancer-related biological pathways, including epithelial-to-mesenchymal transition (EMT) and other inflammatory response pathways.[24] The transcriptional regulation of tumor-suppressive lincRNA-p21 by the mutant p53/nuclear transcription factor Y subunit alpha (NF-YA) complex in HNSCC has also been confirmed, in which knockdown of NF-YA reversed the activation of lincRNA-p21 in mutant p53 cells, not wild-type p53 cells.[25]

From the lifestyle aspect, it is widely accepted that alcohol consumption and tobacco abuse are implicated in the pathogenesis of HNSCC. By comparing the expression of lncRNAs in alcohol drinker and non-alcohol drinker HNSCC patients, researchers have identified a panel of lncRNAs dysregulated due to alcohol consumption. Among them, lnc-PSD4-1 and lnc-NETO-1 have been found differentially expressed due to alcohol consumption, and the low expression of the lnc-PSD4-1 isoform, lnc-PSD4-1:14, has been observed to exhibit a strong correlation with high survival rates of HNSCC patients.[26] In terms of tobacco abuse, a research group from India has proved that out of 11 lncRNAs analyzed, 9 are expressed at a significantly high level in HNSCC patients who are tobacco chewers/smokers. In these 9 lncRNAs, Linc-RoR, a regulator of reprogramming, has shown a strong association with tumor recurrence and poor therapeutic response.[27] Taken together, these findings have shown us the close correlation between the lncRNA profile and etiology factors, as well as the living habits of HNSCC patients.

### Key lncRNAs in the pathogenesis of HNSCC

Numerous lncRNAs have been found dysregulated in cancer cell lines and cancerous tissue of HNSCC. Based on their expression pattern in cancerous tissues and their functions in regulating cell behaviors, lncRNAs promote and suppress tumors. Among the most evaluated HNSCC-related lncRNAs, selected examples will be discussed as follows and are summarized in Figure 1.

#### *HOTAIR*

HOTAIR is coded by the homeobox C gene (HOXC) locus and exerts diverse functions in various malignancies.[22] HOTAIR is aberrantly expressed in multiple human cancers, and it is a potential biomarker for assessing prognosis.[28] HOTAIR functions as an oncogene by recruiting EZH2 to catalyze H3K27 triple-methylation (H3K27me3) to suppress downstream tumor suppressor genes.[29] STAT3 can enhance HOTAIR transcription by interacting with pEZH2-serine21, thus promoting HNSCC cell growth via activation of PI3K/AKT.[30] Targeting HOTAIR and EZH2 can also cause mitochondria-related apoptosis and inhibit the growth of HNSCC.[31] Furthermore, high levels of HOTAIR have been reported to be correlated with poor prognosis in LSCC patients by inducing PTEN methylation.[28] Besides, HOTAIR can upregulate stanniocalcin-2 (STC2) by sponging miR-206 and activating PI3K/AKT signaling pathway, thus promoting HNSCC cell proliferation, invasion, and migration.[32]

#### *HOXA11-AS*

Homeobox A11 antisense (HOXA11-AS) is located on the HOXA gene cluster. It has been reported to be upregulated in various carcinomas.[33] LSCC patients with T3–4 grade, neck nodal metastasis, or advanced clinical stage present a high HOXA11-AS level. Kaplan-Meier analysis has shown that high HOXA11-AS expression could predict a poor prognosis of LSCC patients.[34] HOXA11-AS is also significantly

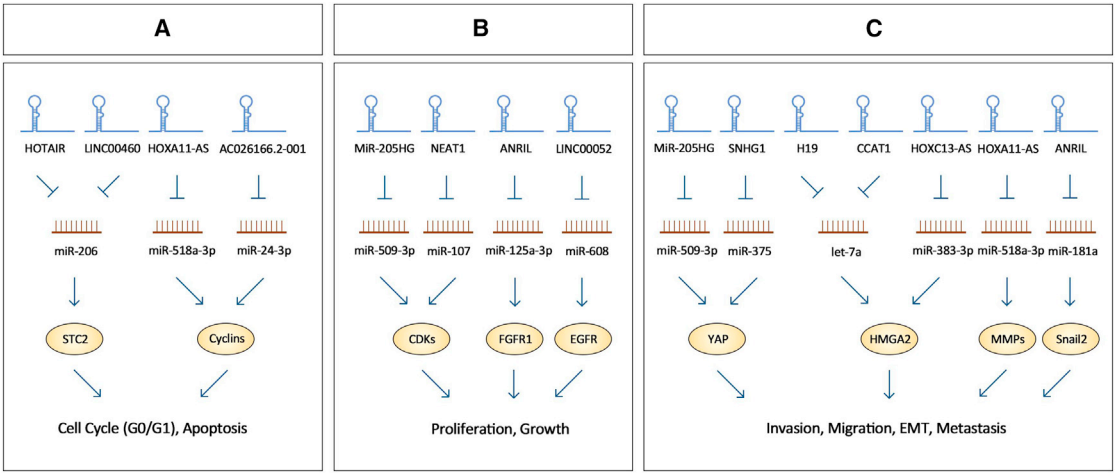


**Figure 1. Role and mechanism of lncRNAs involved in different malignant processes of HNSCC**

The lncRNAs, with the corresponding miRNAs they sponge and the target genes, finally take effect in the cell-cycle distribution (G0/G1 arrest) and apoptosis (A), proliferation *in vitro* and growth *in vivo* (B), and invasion, migration, EMT, and metastasis (C).

upregulated in hypopharyngeal squamous cell carcinoma (HSCC) tumors and is positively associated with lymph node metastasis. HOXA11-AS knockdown suppresses the proliferation and migration ability in HSCC FaDu cells by sponging miR-155.[35] Furthermore, HOXA11-AS also targets miR-518-3p and enhances PDK1 level, thus promoting the malignancy of OSCC both *in vitro* and *in vivo*.[36]

### *MALAT1*

Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) is a nuclear-enriched lncRNA that is generally overexpressed in patients' primary tumors and metastases. Chromatin immunoprecipitation (ChIP) and luciferase reporter assays have revealed that STAT3 could bind to the malat1 promoter region and transcriptionally activate MALAT1 expression. Then MALAT1 can interact reciprocally with miR-30a, thus inducing the EMT and accelerating HNSCC metastasis.[37] MALAT1 targets p21 (RAC1)-activated kinase 1 (PAK1) through suppressing miR-140-5p, thus promoting the proliferation, migration, and invasion of tongue squamous cell carcinoma (TSCC) cells both *in vitro* and *in vivo*.[38] MALAT1 also promotes the migration and invasion of LSCC Hep-2 and HSCC FaDu cells.[39]

### *ANRIL*

LncRNA antisense non-coding RNA in INK4 locus (ANRIL) functions as a competing endogenous RNA (ceRNA) for miR-125a-3p and upregulates fibroblast growth factor receptor-1, which can promote HNSCC growth.[40] ANRIL promotes the proliferation, clonogenicity, and invasion of LSCC via the miR-181a/Snai2 axis.[41] Moreover, it has been reported to activate the transforming growth factor β (TGF-β)/Smad pathway's key molecules and promote the proliferation of OSCC cells.[42]

### *H19*

H19 is significantly overexpressed in a cohort of 65 primary tumor samples and 2 HNSCC cell lines, playing an essential role in tumor growth and progression.[43] The expression of H19 is higher in metastasized tumors than in unmetastasized ones. Consistently, TSCC cells express a higher level of H19 than human squamous cells. H19 functions as a ceRNA to sponge miRNA let-7a, leading to an increase in a let-7a target HMGA2, the key regulator of tumor metastasis.[44] Upregulating in LSCC, H19 targets miR-148a-3p and increases the expression of DNA methyltransferase 1. Therefore, cellular DNA methylation levels are upregulated due to the high level of H19.[45]

## MECHANISM OF lncRNAs IN HNSCC

LncRNAs can form complex secondary and tertiary structures, thus providing multiple binding sites to RNAs and other biological molecules. LncRNAs can exert their functions in HNSCC through the following ways (Figure 2): (1) to regulate gene expression by interacting with chromatin-modifying enzymes or transcription factors; (2) to guide transcription factors and direct their localization to specific sites or block transcription factor binding sites; (3) to be involved in mRNA splicing; (4) to serve as a scaffold to facilitate the intermolecular interaction of target molecules; (5) to bind and sequester RNAs (for example, miRNAs); (6) to assemble with mRNAs to protect them from miRNA targeting and increase their stability; (7) to bind to proteins and regulate their stability (Table 1).

### LncRNAs interact with microRNAs

Due to complementary base pairing, lncRNAs can bind miRNAs and keep them away from their target mRNAs. This function implies that dysregulated lncRNAs in HNSCC can act as ceRNAs, affecting gene expressions and tumor progression.

Increasing evidence has shown that lncRNAs work as miRNA sponges to promote HNSCC cells' unrestrained proliferation. For example, LncMIR205HG is significantly increased in p53-mutated HNSCC and depletes miR-590-3p, leading to upregulated expression of cyclin B, CDK1, and YAP.[23] LncRNA nuclear paraspeckle assembly transcript

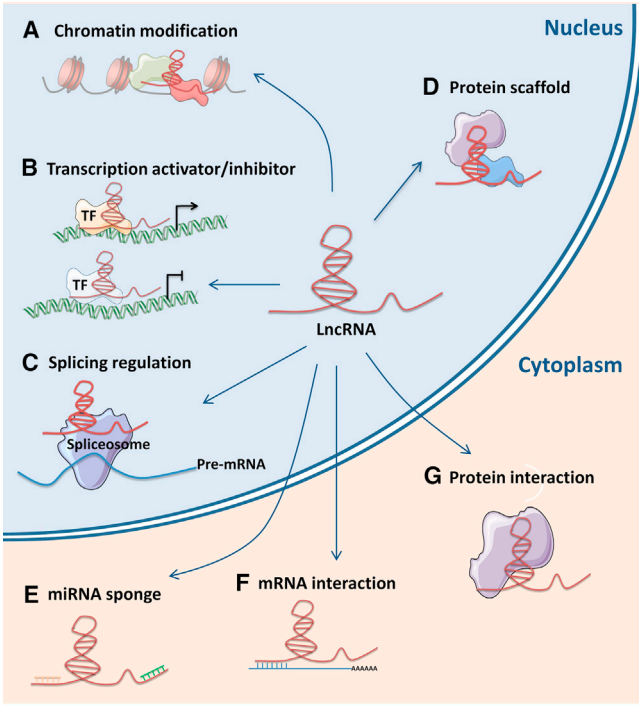


**Figure 2. Diverse molecular mechanism of lncRNAs in HNSCC**

Some lncRNAs act in the nucleus of the cell (A) by inducing different epigenetic chromatin modifications and (B) by activating/inhibiting the transcription of nearby genes via interacting with transcription factors (TFs). (C) LncRNAs can also act post-transcriptionally, such as being involved in mRNA splicing. (D) LncRNAs have specific roles in the nucleus by their interaction with nuclear proteins. (E) Many lncRNAs leave the nucleus and inhibit miRNAs in the cytoplasm by sequestering them, or (F) interact with mRNA, inducing translation activation or repression, and (G) interact with cytoplasmic proteins, prolonging/shortening their half-life.

1 has been found to upregulate CDK6 by targeting miR-107 and inducing the proliferation of LSCC cells.[61] AC026166.2-001 is downregulated in LSCC tissues, acting as a sponge of miR-24-3p, and regulates the expression of p27 and cyclin D1. The *in vivo* results have shown that AC026166.2-001 significantly suppresses LSCC xenografts' growth and promotes apoptosis.[62] LINC00052 sponges miR-608 that regulate epidermal growth factor receptor (EGFR) expression, promoting HNSCC cell proliferation *in vitro* and *in vivo*.[63]

LncRNAs also regulate the invasion of HNSCC cells by targeting microRNAs. For example, LINC00467 enhances HNSCC progression and EMT via the miR-299-5p/ubiquitin-specific protease-48 axis.[64] HNSCC patients with a lower expression of ZFAS1 present a slightly longer disease-free survival and overall survival. ZFAS1 likely regulates the EMT process through miR-150-5p and its downstream target eukaryotic initiation factor 4E.[50]

LncRNAs can exert their functions through targeting several different miRNAs. For example, LncRNA KCNQ1 overlapping transcript 1 (KCNQ1OT1) has been shown to facilitate the proliferation of maxillary sinus squamous cell carcinoma cells through inhibiting miR-204 expression and restoring EphA7 expression.[51] It can also sponge miR185-5p to promote the migration and proliferation of OSCC cells.[65] Besides, KCNQ1OT1 contributes to the cisplatin resistance of TSCC through the miR-124-3p/TRIM14 axis.[66] For other lncRNAs, XIST promotes the progression of LSCC via sponging both miR-144 and miR-125b-5p.[67,68] FAM225A functions as a ceRNA, which sponges miR-590-3p and miR-1275, leading to the upregulation of their target integrin β3. FAK/PI3K/Akt signaling is also activated to promote the proliferation and invasion of nasopharyngeal carcinoma (NPC) cells.[69] In addition, LINC00460 has been found to bind miR-206 and increase the expression of STC2, AKT, and ERK, and the phosphorylation of AKT and ERK, which could inhibit the apoptosis and autophagy of HNSCC cells.[70] LINC00460 also promotes HNSCC cell progression by sponging miR-612 to upregulate AKT2.[71]

On the other hand, key miRNAs or downstream targets in the tumor progression can also be regulated by the lncRNA-microRNA network. For instance, lncRNA maternally expressed 3 (MEG3) and CASC2 can reduce miR-21 expression and restrain the proliferation of HNSCC cells. These two lncRNAs are downregulated in HNSCC and thus promote tumor progression.[52,53] LncRNA H19 and CCAT1 both target miR-let-7 and increase the expression of HMGA2, promoting EMT in HNSCC.[44,54] The level of HMGA2 is also enhanced by HOXC13-AS via sponging miR-383-3p, promoting cell proliferation, migration, and invasion.[72] Small nucleolar RNA host genes (SNHGs), as stable cytoplasmic lncRNAs, have been widely reported to be overexpressed in various tumors and promote disease progression. As an essential member of the SNHG family, SNHG1 promotes YAP1 expression and Hippo signaling activity by competitively sponging miR-375. Moreover, YAP1 can occupy the SNHG1 promoter to enhance its transcription, suggesting a positive feedback regulation loop between YAP1 and SNHG1.[55] Similarly, SNHG12 promotes the proliferation and invasion of LSCC cells via sponging miR-129-5p and potentiating WW domain-containing E3 ubiquitin protein ligase 1 expression.[46] A study also showed that the SNHG20/miR-197/LIN28 axis is vital in OSCC oncogenesis and stemness.[47]

### LncRNAs bind and stabilize mRNAs

LncRNA can also directly interact with mRNAs and regulate the stability of mRNAs. Overexpression of lncRNA zinc finger E-box binding homeobox2 antisense RNA 1 has been found to promote EMT and metastasis of HNSCC. ZEB2-AS1 is a natural antisense transcript corresponding to the 5′ UTR of ZEB2 and might increase their target sense mRNAs' stability by forming an RNA duplex. Researchers have demonstrated that the stability of ZEB2 mRNA is significantly impaired following ZEB2-AS1 inhibition.[48] Another study has reported that aberrant upregulation of lncRNA WWTR1-AS1 is associated with malignant features and unfavorable prognosis of HNSCC by modulating WWTR1 mRNA stability.[56] Leng et al. have found that increased HOXB-AS3 expression is associated with poor prognosis in OSCC. HOXB-AS3 and its encoded protein could promote OSCC cell proliferation and viability by directly binding with IGF2BP2 to maintain c-Myc mRNA stability.[57] Furthermore,

**Table 1. Selected examples of lncRNAs with oncogenic or tumor-suppressive functions**

| LncRNAs (Refs) | Cancer type | Expression | Molecular mechanisms |
|---|---|---|---|
| A) Chromatin modification | | | |
| HORAIR[24] | OSCC | up | binds to EZH2 and H3K27me3, promoting tumor progression and metastasis |
| MXI-215[46] | HNSCC | down | interacts with GCN5 (an H3K27 acetylase) to inhibit PD-L1 and galectin-9 expression |
| B) Transcription activator/inhibitor | | | |
| LINC00460[47] | HNSCC | up | interacts with PRDX1 and facilitates PRDX1 entry into the nucleus. PRDX1 promoted the transcription of LINC00460 and EMT-related genes |
| C) Splicing regulation | | | |
| AC091729.7[48] | HNSCC | up | combines with SRSF2 and promotes HNSCC cell migration, proliferation and invasion, and tumor growth |
| D) Protein scaffold | | | |
| FOXD2-AS1[49] | LSCC | up | binds to STAT3 and augmented STAT3 transcriptional activity by recruiting PRMT5 |
| (E) miRNA sponge | | | |
| lncMIR205HG[41] | HNSCC | up | targets miR-590-3p, upregulating the expression of cyclin B, CDK1, and YAP |
| LncRNA NEAT1[42] | LSCC | up | targets miR-107 and upregulates CDK6, inducing proliferation of LSCC cells |
| LINC00467[45] | HNSCC | up | enhances HNSCC progression and EMT via the miR-299-5p/ubiquitin-specific protease-48 axis |
| LncRNA XIST[50,51] | LSCC | up | sponges both miR-144 and miR-125b-5p |
| LncRNA SNHG1[52] | HNSCC | up | promotes YAP1 expression and Hippo signaling activity by competitively sponging miR-375 |
| LncRNA SNHG12[53] | LSCC | up | sponges miR-129-5p and potentiates WWP1 expression, promoting LSCC proliferation and invasion |
| LncRNA SNHG20[54] | OSCC | up | promotes OSCC oncogenesis and stemness through the miR-197/LIN28 axis |
| (F) mRNA interaction | | | |
| ZEB-AS1[55] | HNSCC | Up | increases the stability of their target sense mRNAs and promotes EMT and metastasis |
| (G) Protein interaction | | | |
| MIR31HG[56] | LSCC | up | targets HIF1A and p21 to regulate cell-cycle progression |
| DANCR[57] | NPC | up | binds to NF90 and NF45 to increase HIF-1α mRNA stability and NPC cell invasion and metastasis |
| ST7-AS1[58] | LSCC | up | be required for the malignancy by interacting with CARM1 and protect CARM1 from ubiquitin-dependent degradation |
| CEBPA-AS1[59] | OSCC | up | interacts with CEBPA and promote tumorigenesis via CEBPA /Bcl2 |
| LincRNA-p21[60] | HNSCC | down | binds to STAT3 to inhibit its phosphorylation, suppressing HNSCC tumor growth |

NEAT1, nuclear paraspeckle assembly transcript 1; SRSF2, serine/arginine-rich splicing factor 2; WWP1, WW domain-containing E3 ubiquitin protein ligase 1; ZEB-AS1, zinc finger E-box binding homeobox 2 antisense RNA 1.

FOXD1-AS1 has been reported to express at a high level in OSCC and promote the malignant phenotypes via regulating the stability of FOXD1.[58] Other studies have focused on DANCR, which is dramatically upregulated in human NPC and can bind to RNA-binding protein 3 and stabilize SOX2 mRNA, resulting in NPC cell proliferation.[59] Besides, DANCER can also increase HIF-1α mRNA stability by interacting with NF90/NF45, leading to NPC metastasis and disease progression.[49]

### LncRNAs interact with proteins

LncRNAs interact with proteins to modulate protein function, directing their localization or regulating protein-protein interaction. Overexpression of lncMX1-215 suppresses HNSCC proliferation and its metastatic capacity both *in vitro* and *in vivo*. The researchers have found that lncMX1-215 directly interacts with GCN5, a known H3K27 acetylase. Therefore, the binding of GCN5 to H3K27 interrupts acetylation and thus inhibits the expressions of PD-L1 and galectin-9.[60] LINC00460 interacts with PRDX1 and facilitates PRDX1 entry into the nucleus. PRDX1 then promotes the transcription of LINC00460 and EMT-related genes, forming a positive feedback loop.[73] Using RNA immunoprecipitation (RIP), lncRNA AC091729.7 has been found to directly combine with the serine/arginine-rich splicing factor 2 and promote HNSCC cell proliferation, migration and invasion, and tumor growth *in vivo*.[74] LncRNA MIR31HG targets HIF-1α and p21, promoting cell-cycle progression and inhibiting cell apoptosis, thus facilitating HNSCC cell proliferation and tumorigenesis.[75] Moreover, lncRNA DANCR is responsible for NPC metastasis and the hypoxia phenotype. NF90, as the most-enriched DANCR-binding protein, is a double-stranded RNA-binding protein, and can complex with NF45 to increase HIF-1α mRNA stability, promoting NPC cell invasion and metastasis both *in vitro* and *in vivo*.[49] In LSCC, lncRNA ST7-AS1 can interact with CARM1 and protect it from ubiquitin-dependent degradation. CARM1 then methylates Sox-2 (a pluripotent transcription factor)

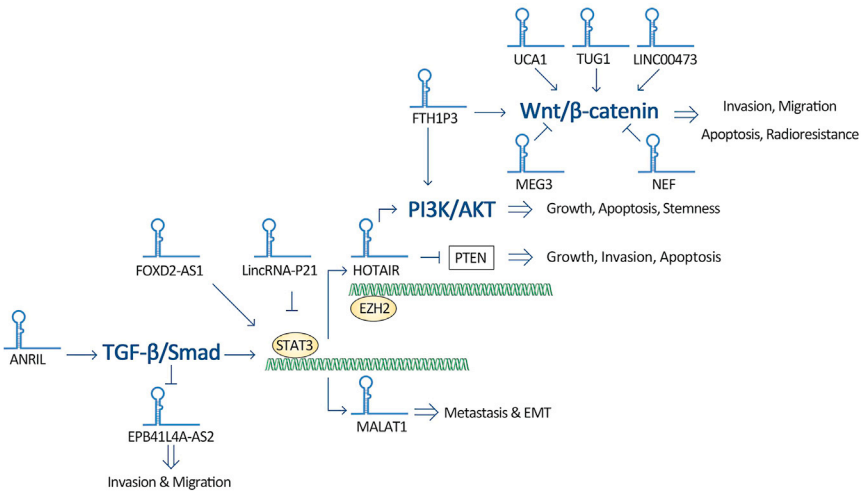


**Figure 3. Interactions of lncRNAs with corresponding signaling pathways in HNSCC**
The interactions of HNSCC-related lncRNAs with corresponding signaling pathways, including JAK/STST3, TGF-β/Smad, and Wnt/β-catenin.

and enhances Sox-2 self-association and transactivation activity. Thus, ST7-AS1 is required for LSCC cells' malignancy through migration, tumorsphere formation assay, and *in vivo* implantation.[76] In OSCC cells, using RNA pull-down assay, CEBPA-AS1 has been demonstrated to directly interact with CEBPA and promote tumorigenesis via CEBPA/Bcl2, and its high expression is correlated with poor prognosis.[77]

## LncRNAs are involved in signaling pathways that synergistically drive tumor progression

Aberrant expression of lncRNAs has been reported to be associated with dysregulation of several signaling pathways in cancerous tissues, such as the JAK/SATA3, TGF-β/Smad, and Wnt/β-catenin pathways (Figure 3).

### *JAK/STAT3 signaling pathway*

STAT3 is frequently activated in cancer progression.[78] STAT3 plays a vital role in the EMT and self-renewal of laryngeal cancer stem cells (CSCs), acting as a mediator that transduces intracellular and extracellular signals to the nucleus. FOXD2-AS1 acts as a scaffold for STAT3 and protein arginine N-methyltransferase 5 (PRMT5) and promotes STAT3 transcriptional activity, thus maintaining cancer stemness and promoting chemotherapy resistance.[79] Conversely, lincRNA-p21 works as a tumor suppressor and its lower expression indicates a worse prognosis. High lincRNA-p21 level inhibits Janus kinase 2 (JAK2)/STAT3 signaling activation by directly binding to STAT3, inducing G1 arrest and apoptosis.[25] Furthermore, activated STAT3 binds to the HOTAIR encoding gene's promoter to increase HOTAIR transcription, thereby enhancing the EZH2-mediated epigenetic silencing of genes in HNSCC.[30]

### *TGF-β/Smad signaling pathway*

The role of TGF-β-induced tumor progression in advanced malignancy is well established.[80] It has been proposed that TGF-β/Smad signaling transduction plays a leading role in inducing EMT of OSCC. The silence of lncRNA ANRIL increases the expression of TGF-β1 and p-Smad2/3 in OSCC cells.[42] TGF-β causes the downregulation of lncRNA EPB41L4A-AS2. Overexpression of this lncRNA inhibits cell migration and invasion in the TGF-β-induced EMT model of HNSCC.[81] Upregulated TGF-β may also promote EMT through STAT3 activation. ChIP and luciferase reporter assays have demonstrated that STAT3 binds to the promoter of lncRNA MALAT1 and upregulates its expression, thus inducing EMT and promoting HNSCC metastasis.[37]

### *Wnt/β-catenin signaling pathway*

The Wnt/β-catenin signaling pathway is one of the classical pathways in cell signaling transduction, promoting cell growth, proliferation, and invasion. Several lncRNAs have been reported to be involved in the Wnt/β-catenin signaling pathway. Higher ferritin heavy chain 1 pseudogene 3 expression in OSCC tissue is associated with T classification, N classification, and TNM staging. It promotes OSCC cell migration and invasion via enhancing the PI3K/Akt/GSK3β/Wnt/β-catenin pathway.[82] In OSCC cell lines, low expression of lncRNA MEG3 leads to activation of the Wnt pathway and a higher expression of β-catenin. LncRNA urothelial cancer-associated 1 (UCA1) could regulate the Wnt/β-catenin pathway's downstream targets, such as MMP9 and cyclin D1 (CCND1).[83] The knockdown of TUG1 in OSCC cells inhibits the mRNA and protein expression of β-catenin, CCND1, and c-myc.[84] In LSCC cells, LncRNA NEF inhibits the Wnt/β-catenin pathway and promotes apoptosis.[85] Moreover, lncRNA LINC00473 is upregulated in HNSCC cells and induces radioresistance through the Wnt/β-catenin pathway.[86]

## LncRNAs and tumor immunity of HNSCC

As the research hotspot in recent years, the role of lncRNAs in the tumor immunity of HNSCC has also been fully investigated. One study has highlighted the value of the 21 immune-related lncRNA pairs signature as a predictor of prognosis and immunotherapeutic response in HNSCC.[87] Also, by pairing immune-related lncRNAs, Yin et al. have established a signature, concerning specific expression levels, to predict the immune landscape of HNSCC, thus guiding the clinical therapy of HNSCC patients.[88] In HNSCC patients with an elevated expression of the m6A-modified lncRNAs, the programmed cell death 1-ligand 1 (PD-L1) immune scores are significantly higher, with more infiltration of $CD8^+$ T cells, Tregs, follicular helper T cells, and naive B cells.[89] More specifically, Ma et al. have observed that ectopic expression of lncMX1-215 markedly inhibits the expression

**Table 2. Selected examples of lncRNAs with a potential prognostic role for patients with HNSCC**

| Cancer type | Patients | Methods of analysis | Diagnostic/prognostic | Up/down | lncRNAs-mRNAs-miRNAs (Refs) |
|---|---|---|---|---|---|
| TSCC | 12 | integrated data analysis | P | up | lncRNA AP001056.1[79] |
| HNSCC | 546 | integrated data analysis | P | up | lncRNA HOTTIP[80] |
| HSCC | 53 | microarray analysis | P | up | lncRNA UCA1[81] |
| HNSCC | 192 | orthogonal partial least-squares discrimination analysis | P | – | 3-lncRNA panel[82] |
| HNSCC | 269 | Gene set enrichment analysis | P | – | 8-lncRNA signature[20] |
| HNSCC | 425 | Cox regression analysis | P | – | 3-lncRNA signature[83] |
| HNSCC | 498 | multivariate Cox regression and stratified analyses | p | – | 15-lncRNA signature[84] |
| HNSCC | 28 | single-factor survival analysis | P | – | 5-lncRNA signature [85] |
| HNSCC | 499 | univariate Cox regression survival analysis, robust likelihood-based survival model, and random sampling iterations | P | – | 4-lncRNA signature [86] |
| HNSCC | 501 | univariate Cox proportional hazards regression analysis | P | – | 4 lncRNAs-3 miRNAs-6 mRNAs[87] |
| HNSCC | 502 | univariate Cox proportional hazards regression | P | – | 71 lncRNAs-8 miRNAs-16 mRNAs[88] |
| HNCC | 755 | univariate Cox regression survival analysis | P | – | 7 lncRNAs-mRNA[89] |

Head and neck squamous cell carcinoma (HNSCC) is a leading malignant disease. Here, we summarize the deregulation and dysfunction of lncRNAs (200-nt to 100-kb transcripts lacking protein-coding potentials) in HNSCC, review their working mechanism in HNSCC pathogenesis, and discuss their potential application as diagnostic/prognostic tools and therapeutic targets.

of interferon-α-induced, immunosuppression-related molecules of PD-L1 and galectin-9. Mechanistically, their study has suggested that lncMX1-215 negatively regulates immunosuppression by interrupting GCN5/H3K27ac binding in HNSCC, thus providing novel insights into immune checkpoint blockade treatment.[60] Another group of researchers has found that lncRNA DCST1-AS1 can activate the NF-κB pathway to promote M2 macrophage polarization, thus advancing OSCC cancer progression.[90] Li et al. have observed that silencing of lncRNA LINC02195 can decrease the MHC I protein expression. High LINC02195 expression is positively correlated with an increased number of $CD8^+$ and $CD4^+$ T cells in the HNSCC microenvironment.[91]

In terms of the tumor microenvironment (TME), researchers have identified an immune-related seven-lncRNA prognostic signature (IRLPS), grouping HNSCC patients into high- and low-IRLPS subgroups. Then they found that low-IRLPS samples have more immune cell infiltration and are enriched in immune-related pathways, while high-IRLPS samples are enriched in metabolic pathways.[92] In another study, based on bioinformatics analyses and functional assays, Zhong et al. have proved that certain lncRNAs (e.g., AL365361.1 and PCED1B-AS1) likely contribute to the modification of TME in the high-immune-score HNSCC patients, achieved by regulating transcription of abundant immune-related genes, including CCR7 and TLR8.[93] More recently, another group of researchers has demonstrated that lncRNA LURAP1L-AS1 plays a vital role in platelet-derived growth factor BB-induced activation of cancer-associated fibroblasts (CAFs) in TME through the positive regulation on NF-κB signaling, which may become a potential target for the treatment of OSCC.[94]

In recent years, studies on the role of lncRNAs and tumor metabolism have also emerged. Wang et al. have reported that lncRNA-p23154 binds to the 3′ UTR of the miR-378a-3p promoter and inhibits miR-378a-3p transcription, thus accelerating OSCC metastasis by regulating the glucose transporter 1 (GLUT-1)-mediated glycolysis.[95] In another study also focusing on OSCC, researchers have shown that, by regulating miR-159-5p and GLUT-1, the lncRNA PVT1 promotes tumor cell proliferation, invasion, and migration, and inhibits apoptosis of cancer cells.[96] Furthermore, Yang et al. have suggested that lncRNA H19 could promote glycolysis pathway in CAFs, thus accelerating the growth of OSCC through the H19/miR-675-5p/6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3 axis.[97] Studies on the role of lncRNAs in the metabolism of other nutrients in HNSCC, including protein and lipid, are relatively low, of which more research is needed in the future.

## POTENTIAL CLINICAL IMPLICATIONS OF lncRNAs IN HNSCC

### LncRNAs as biomarkers for HNSCC

The heterogeneity of HNSCC is high due to the heterogeneity of the causes of the disease, including alcohol abuse, HPV infection, and diet. This makes the prognosis difficult to predict and the therapy challenging in HNSCC patients. The prognosis of HNSCC patients mainly depends on the TNM staging system and histologic grade. However, the therapeutic effect based on this is unfavorable. LncRNAs are involved in the tumorigenesis of HNSCC via different mechanisms. They are often tissue-specifically expressed, stable in human body fluids, and can be obtained with non-invasive methods. Therefore, lncRNAs are promising diagnostic and prognostic tumor biomarkers for HNSCC (Table 2).

Researchers have focused on lncRNAs with enhancer-like functions, which is a subclass of lncRNAs derived from the enhancer region of genes and could contribute to the activation of critical regulators of development and differentiation.[98,99] The TANRIC database and cBioPortal have been used to explore the RNA levels and clinical

data from TCGA project. The most significant survival-associated enhancer lncRNA is AP001056.1, with a ligand for the T cell-specific cell surface receptor ICOS gene encoding an immune checkpoint protein as its regulated target.[100] Researchers have obtained a total of 546 RNA-seq profiles of HNSCC patients with clinical outcome data from the TCGA database. HOTTIP has shown the most significant prognostic value and is significantly correlated with the clinical stage and histological grade of HNSCC patients.[101] Moreover, the upregulation of UCA1 in HSCC is noticed in a cohort of 53 paired tumor and non-tumor samples. The high UCA1 level is significantly associated with advanced T category, later clinical stages, more lymphatic invasion, and worse prognosis.[102]

The markers above have been primarily studied in isolation, but more work has revealed that combining them might improve the predictive power. For example, Cao et al. have analyzed the RNA-seq data derived from the TANRIC database to identify a lncRNA prognostic signature model using the orthogonal partial least-squares discrimination analysis and 1.5-fold expression change criterion methods. A three-lncRNA panel (KTN1-AS1, LINC00460, and RP5-894A10.6) has been achieved to predict the overall survival of HNSCC patients.[103] Using RNA-seq and clinical survival information of 269 patients from the GEO dataset, 8 prognosis-related lncRNAs, including AC010624.1, AC130456.4, LINC00608, LINC01300, MIR99AHG, AC008655.1, AC055758.2, and AC118553.1, have been obtained by univariate analysis, Cox LASSO regression, and multivariate analysis. Combined with clinical information, a nomogram containing an eight-lncRNA signature has been established. Furthermore, gene set enrichment analysis of the signature score has indicated that samples with high scores are mainly enriched in IL6/JAK/SATA3 signaling, complement pathways, and allograft rejection-related genes. This finding implicates that HNSCC patients with a poor prognosis might have dysfunctional immune systems.[78] Another study has obtained a three-lncRNA expression signature with similar strategies, predicting HNSCC patient survival from data of 425 patients.[104] Zhang et al. have assessed lncRNAs expressed in the HNSCC cohort samples in the TCGA database. A risk score model is constructed based on a 15-lncRNA expression signature, effectively predicting the overall survival and facilitating patient stratification in HNSCC.[105] Reports show five-lncRNA[106] and four-lncRNA[107] signatures in HNSCC, suggesting the importance of lncRNAs as prognostic biomarkers.

LncRNAs can act as ceRNAs and sponge miRNAs and mRNAs, therefore playing an essential role in tumor initiation and progression.[7,11] Several studies have analyzed the lncRNA-mediated ceRNA crosstalk to construct a ceRNA network of HNSCC and identify key prognostic markers. For example, an analysis has found that four lncRNAs (RP11-366H4.1, HOTTIP, RP11-865I6.2, and RP11-275N1.1), three microRNAs (miR-99a, miR-337, and miR-137), and six mRNAs (NOSTRIN, TIMP4, GRB14, HOXB9, CELSR3, and ADGRD2) can be used as prognostic genes of HNSCC.[108] Another study has constructed a lncRNA-miRNA-mRNA ceRNA network of HNSCC, including 8 miRNAs, 71 lncRNAs, and 16 mRNAs.[109] There is also a study integrating the expression of mRNAs and lncRNAs to predict the survival in HNSCC. A seven-lncRNA-mRNA-based risk model has been developed, and the model has successfully predicted the survival of 755 HNSCC patient samples.[110]

### LncRNA and therapy resistance in HNSCC

HNSCC patients are frequently treated with surgery, together with radiotherapy or cisplatin-based chemotherapy. Patients with aggressive disease may also be treated with anti-EGFR antibodies or tyrosine kinase inhibitors (TKIs). However, therapy resistance has become the main obstacle to the effective treatment of HNSCC.

Emerging studies have focused on the role of lncRNAs in the chemoresistance of various cancers, including HNSCC. UCA1 is regarded as an oncogene that facilitates proliferation, enhances cisplatin chemoresistance, and suppresses apoptosis in OSCC cells, suggesting a potential therapeutic strategy targeting UCA1 in OSCC patients.[111] Overexpressed MALAT1 can also promote the chemo-resistance of LSCC cell lines TU686 and LSC-1.[112] FOXD2-AS1 acts as a scaffold for STAT3 and PRMT5 and promotes chemo-resistance. Interfering with FOXD2-AS1 using a short hairpin RNA can rescue LSCC's chemotherapeutic sensitivity.[79] The knockdown of LINC00958 expression enhances HNSCC cells' sensitivity to cisplatin treatment as well as ionizing radiation.[113] Furthermore, cisplatin treatment upregulates inflammation-related lnc-IL7R expression in OSCC cells, resulting in decreased chemotherapy sensitivity of patients. TLR3 agonist polyinosine-polycytidylic acid treatment can negatively manipulate the expression of lnc-IL7R and strengthen the low-dose cisplatin-based chemotherapy with reduced side effects.[114]

LncRNAs are also involved in the resistance to radiotherapy. LINC00473 is recognized as an oncogene to promote cell proliferation and inhibit apoptosis. Downregulation of LINC00473 can inhibit the Wnt/β-catenin signaling pathway and enhance the sensitivity of HNSCC cells to radiotherapy.[86] LncRNA BLACAT1 promotes cell viability and inhibits cell apoptosis by modulating the presenilin-1 (PSEN1) gene. The knockdown of BLACAT1 improves the radiosensitivity of HNSCC cells.[115] In HPV-positive HNSCC, HPV infection-induced expression of transcription factor ER-alpha can upregulate lnc-IL17RA-11 and its co-expressed genes that enhance HNSCC cells' sensitivity to radiotherapy.[22]

Therapeutics targeting the EGFR pathway have shown potential clinical activity in HNSCC. Despite the solid evidence that some HNSCCs are dependent on the EGFR signaling pathway,[116] only moderate success has been achieved via treatment with anti-EGFR monoclonal antibodies or TKIs. Researchers have identified a synonymous mutation in EGFR, c.2361G > A (encoding p.Gln787Gln) in two HNSCC patients. This A/A genotype has shown greater sensitivity to TKIs than the G/A and G/G genotypes. Mechanically, G > A mutation decreases the stability of the lncRNA EGFR-AS1 and increases the sensitivity to TKIs. Overexpression of this lncRNA is sufficient to induce resistance to TKIs, while EGFR-AS1 knockdown could cause sensitivity to TKIs both *in vitro* and *in vivo*.[117]

## CONCLUSIONS AND FUTURE PERSPECTIVES

Over the past decades, lncRNA has emerged pivotal to understanding tumorigenesis. The advancement of high-throughput sequencing technology has greatly facilitated the expression profiling of lncRNAs in normal and cancer cells. Accumulating evidence has suggested that the deregulation of lncRNAs is closely associated with HNSCC carcinogenesis and metastasis. Functional analyses integrated with clinical data have shown that lncRNAs interact with RNAs/proteins and exert regulatory roles via controlling intracellular pathways, communication between cancer cells, and other cell types in the microenvironment. Further investigations may advance our knowledge of more functions of lncRNAs and unravel the sophisticated crosstalk in different cancer-related processes, such as EMT and CSC formation. In addition, how deregulation of lncRNA contributes to cancer heterogeneity remains to be clarified. Studies in these areas will better explain the pathway regulation and produce more therapeutic targets for this lethal and aggressive disease.

LncRNAs hold a great promise with regard to therapeutic applications for HNSCC, either by inhibiting or restoring lncRNAs that fine-tune cancer cells' regulatory networks in a cancer-type-specific manner. The challenge now is that lncRNAs can simultaneously regulate multiple targets and be involved in complicated feedback mechanisms. To avoid adverse effects due to off-targeting, a thorough understanding of lncRNA functions and mechanisms in HNSCC-specific content is required to identify proper therapeutic lncRNA targets or mimics. Moreover, further investigations are needed in chemical technology, which may improve the stability of the therapeutic oligonucleotides and prolong their half-life *in vivo*, and nanotechnology, which can improve the efficiency of *in vivo* delivery.[118]

The application of lncRNAs as non-invasive biomarkers for early detection and prognostication for HNSCC has been proposed in the past few years. The challenges still exist and remain to be explored. The most important limitation is the varying results among studies, which may arise due to the lack of a consensus regarding the analytic methods used in different studies. Therefore, it is essential to validate the results in multiple laboratories on diverse populations to reach reproducibility. Further effort is required to validate these biomarkers' specificity and sensitivity in prospective studies with larger patient cohorts and standardized methodology. In particular, it would be interesting to explore the potential values of employing lncRNA markers to predict treatment response and guide therapeutic decisions for personalized medicine.

In summary, lncRNA is emerging as an important regulator involved in HNSCC initiation and progression. A better understanding of the regulation and deregulation of lncRNA will shed light on the molecular mechanisms of HNSCC carcinogenesis. The opportunities for utilizing lncRNAs as novel diagnostic and therapeutic modalities for patients with HNSCC are fascinating and have been exemplified by the studies summarized in this review. Indeed, further investigations are required to translate the research findings into clinical applications.

## ACKNOWLEDGMENTS

This work was supported by the National Natural Science Foundation of China (nos. 81630069, 31771439, 81773262, 81902897, and 82173046), the Independent Program of the State Key Laboratory of Cancer Biology, China (CBSKL2019ZZ21), the Natural Science Foundation of Shaanxi Province, China (2020JQ-448), and the Promotion Project of Xijing Hospital, Fourth Military Medical University (XJZT19MJ18).

## AUTHOR CONTRIBUTIONS

M.J. searched and reviewed the literature and wrote the original draft. F.L. validated the results, revised and edited the draft. A.-G.Y. conceptualized the idea and supervised the whole work. W.W. conceptualized the idea and supervised the whole work. R.Z. conceptualized the idea, supervised the whole work, and administrated the project.

## DECLARATION OF INTERESTS

The authors declare no competing interests.

## REFERENCES

1. Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R.L., Torre, L.A., and Jemal, A. (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J. Clin. *68*, 394–424.
2. Wyss, A., Hashibe, M., Chuang, S.C., Lee, Y.C., Zhang, Z.F., Yu, G.P., Winn, D.M., Wei, Q., Talamini, R., Szeszenia-Dabrowska, N., et al. (2013). Cigarette, cigar, and pipe smoking and the risk of head and neck cancers: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. Am. J. Epidemiol. *178*, 679–690.
3. Maier, H., Dietz, A., Gewelke, U., Heller, W.D., and Weidauer, H. (1992). Tobacco and alcohol and the risk of head and neck cancer. Clin. Invest. *70*, 320–327.
4. Chaturvedi, A.K., Engels, E.A., Pfeiffer, R.M., Hernandez, B.Y., Xiao, W., Kim, E., Jiang, B., Goodman, M.T., Sibug-Saber, M., Cozen, W., et al. (2011). Human papillomavirus and rising oropharyngeal cancer incidence in the United States. J. Clin. Oncol. *29*, 4294–4301.
5. Gatta, G., Botta, L., Sánchez, M.J., Anderson, L.A., Pierannunzio, D., Licitra, L., and EUROCARE Working Group. (2015). Prognoses and improvement for head and neck cancers diagnosed in Europe in early 2000s: the EUROCARE-5 population-based study. Eur. J. Cancer *51*, 2130–2143.
6. Budach, V., and Tinhofer, I. (2019). Novel prognostic clinical factors and biomarkers for outcome prediction in head and neck cancer: a systematic review. Lancet Oncol. *20*, e313–e326.
7. Schmitt, A.M., and Chang, H.Y. (2016). Long noncoding RNAs in cancer pathways. Cancer Cell *29*, 452–463.
8. Wong, C.M., Tsang, F.H., and Ng, I.O. (2018). Non-coding RNAs in hepatocellular carcinoma: molecular functions and pathological implications. Nat. Rev. Gastroenterol. Hepatol. *15*, 137–151.
9. Cabili, M.N., Trapnell, C., Goff, L., Koziol, M., Tazon-Vega, B., Regev, A., and Rinn, J.L. (2011). Integrative annotation of human large intergenic non-coding RNAs reveals global properties and specific subclasses. Genes Dev. *25*, 1915–1927.
10. Hezroni, H., Koppstein, D., Schwartz, M.G., Avrutin, A., Bartel, D.P., and Ulitsky, I. (2015). Principles of long non-coding RNA evolution derived from direct comparison of transcriptomes in 17 species. Cell Rep. *11*, 1110–1122.
11. Quinn, J.J., and Chang, H.Y. (2016). Unique features of long non-coding RNA biogenesis and function. Nat. Rev. Genet. *17*, 47–62.
12. Ulitsky, I., Shkumatava, A., Jan, C.H., Sive, H., and Bartel, D.P. (2011). Conserved function of lincRNAs in vertebrate embryonic development despite rapid sequence evolution. Cell *147*, 1537–1550.

13. Guttman, M., Amit, I., Garber, M., French, C., Lin, M.F., Feldser, D., Huarte, M., Zuk, O., Carey, B.W., Cassady, J.P., et al. (2009). Chromatin signature reveals over a thousand highly conserved large non-coding RNAs in mammals. Nature *458*, 223–227.

14. Huarte, M., Guttman, M., Feldser, D., Garber, M., Koziol, M.J., Kenzelmann-Broz, D., Khalil, A.M., Zuk, O., Amit, I., Rabani, M., et al. (2010). A large intergenic non-coding RNA induced by p53 mediates global gene repression in the p53 response. Cell *142*, 409–419.

15. Zheng, G.X., Do, B.T., Webster, D.E., Khavari, P.A., and Chang, H.Y. (2014). Dicer-microRNA-Myc circuit promotes transcription of hundreds of long non-coding RNAs. Nat. Struct. Mol. Biol. *21*, 585–590.

16. de Lena, P.G., Paz-Gallardo, A., Paramio, J.M., and García-Escudero, R. (2017). Clusterization in head and neck squamous carcinomas based on lncRNA expression: molecular and clinical correlates. Clin. Epigenetics *9*, 36.

17. Wang, Q., Yang, W., Peng, W., Qian, X., Zhang, M., and Wang, T. (2021). Integrative analysis of DNA methylation data and transcriptome data identified a DNA methylation-dysregulated four-lncRNA signature for predicting prognosis in head and neck squamous cell carcinoma. Front. Cell. Dev. Biol. *9*, 666349.

18. Lee, E.Y., Song, J.M., Kim, H.J., and Park, H.R. (2021). Hypomethylation of lncRNA H19 as a potential prognostic biomarker for oral squamous cell carcinoma. Arch. Oral Biol. *129*, 105214.

19. Shi, Y., Zhang, Q., Xie, M., Feng, Y., Ma, S., Yi, C., Wang, Z., Li, Y., Liu, X., Liu, H., et al. (2020). Aberrant methylation-mediated decrease of lncRNA HNF1A-AS1 contributes to malignant progression of laryngeal squamous cell carcinoma via EMT. Oncol. Rep. *44*, 2503–2516.

20. Nohata, N., Abba, M.C., and Gutkind, J.S. (2016). Unraveling the oral cancer lncRNAome: identification of novel lncRNAs associated with malignant progression and HPV infection. Oral Oncol. *59*, 58–66.

21. Ma, X., Sheng, S., Wu, J., Jiang, Y., Gao, X., Cen, X., Wu, J., Wang, S., Tang, Y., Tang, Y., et al. (2017). LncRNAs as an intermediate in HPV16 promoting myeloid-derived suppressor cell recruitment of head and neck squamous cell carcinoma. Oncotarget *8*, 42061–42075.

22. Song, L., Xie, H., Tong, F., Yan, B., Zhang, S., Fu, E., Jing, Q., and Wei, L. (2019). Association of lnc-IL17RA-11 with increased radiation sensitivity and improved prognosis of HPV-positive HNSCC. J. Cell. Biochem. *120*, 17438–17448.

23. Di Agostino, S., Valenti, F., Sacconi, A., Fontemaggi, G., Pallocca, M., Pulito, C., Ganci, F., Muti, P., Strano, S., and Blandino, G. (2018). Long non-coding MIR205HG depletes hsa-miR-590-3p leading to unrestrained proliferation in head and neck squamous cell carcinoma. Theranostics *8*, 1850–1868.

24. Chaudhary, R., Wang, X., Cao, B., De La Iglesia, J., Masannat, J., Song, F., Hernandez-Prera, J.C., Gimbrone, N.T., Slebos, R.J.C., and Chung, C.H. (2020). Long non-coding RNA, LINC00460, as a prognostic biomarker in head and neck squamous cell carcinoma (HNSCC). Am. J. Transl. Res. *12*, 684–696.

25. Jin, S., Yang, X., Li, J., Yang, W., Ma, H., and Zhang, Z. (2019). p53-targeted lincRNA-p21 acts as a tumor suppressor by inhibiting JAK2/STAT3 signaling pathways in head and neck squamous cell carcinoma. Mol. Cancer *18*, 38.

26. Yu, V., Singh, P., Rahimy, E., Zheng, H., Kuo, S.Z., Kim, E., Wang-Rodriguez, J., and Ongkeko, W.M. (2016). RNA-seq analysis identifies key long non-coding RNAs connected to the pathogenesis of alcohol-associated head and neck squamous cell carcinoma. Oncol. Lett. *12*, 2846–2853.

27. Arunkumar, G., Rao, A.K.D.M., Manikandan, M., Arun, K., Vinothkumar, V., Revathidevi, S., Rajkumar, K.S., Rajaraman, R., and Munirajan, A.K. (2017). Expression profiling of long non-coding RNA identifies linc-RoR as a prognostic biomarker in oral cancer. Tumour Biol. *39*, 1010428317698366.

28. Li, D., Feng, J., Wu, T., Wang, Y., Sun, Y., Ren, J., and Liu, M. (2013). Long intergenic non-coding RNA HOTAIR is overexpressed and regulates PTEN methylation in laryngeal squamous cell carcinoma. Am. J. Pathol. *182*, 64–70.

29. Wu, Y., Zhang, L., Zhang, L., Wang, Y., Li, H., Ren, X., Wei, F., Yu, W., Liu, T., Wang, X., et al. (2015). Long non-coding RNA HOTAIR promotes tumor cell invasion and metastasis by recruiting EZH2 and repressing E-cadherin in oral squamous cell carcinoma. Int. J. Oncol. *46*, 2586–2594.

30. Sun, S., Wu, Y., Guo, W., Yu, F., Kong, L., Ren, Y., Wang, Y., Yao, X., Jing, C., Zhang, C., et al. (2018). STAT3/HOTAIR signaling axis regulates HNSCC growth in an EZH2-dependent manner. Clin. Cancer Res. *24*, 2665–2677.

31. Kong, L., Zhou, X., Wu, Y., Wang, Y., Chen, L., Li, P., Liu, S., Sun, S., Ren, Y., Mei, M., et al. (2015). Targeting HOTAIR induces mitochondria related apoptosis and inhibits tumor growth in head and neck squamous cell carcinoma in vitro and in vivo. Curr. Mol. Med. *15*, 952–960.

32. Li, T., Qin, Y., Zhen, Z., Shen, H., Cong, T., Schiferle, E., and Xiao, S. (2019). Long non-coding RNA HOTAIR/microRNA-206 sponge regulates STC2 and further influences cell biological functions in head and neck squamous cell carcinoma. Cell Prolif. *52*, e12651.

33. Wang, Q., Zhang, J., Liu, Y., Zhang, W., Zhou, J., Duan, R., Pu, P., Kang, C., and Han, L. (2016). A novel cell cycle-associated lncRNA, HOXA11-AS, is transcribed from the 5-prime end of the HOXA transcript and is a biomarker of progression in glioma. Cancer Lett. *373*, 251–259.

34. Qu, L., Jin, M., Yang, L., Sun, C., Wang, P., Li, Y., Tian, L., Liu, M., and Sun, Y. (2018). Expression of long non-coding RNA HOXA11-AS is correlated with progression of laryngeal squamous cell carcinoma. Am. J. Transl. Res. *10*, 573–580.

35. Xu, J., Bo, Q., Zhang, X., Lei, D., Wang, J., and Pan, X. (2020). lncRNA HOXA11-AS promotes proliferation and migration via sponging miR-155 in hypopharyngeal squamous cell carcinoma. Oncol. Res. *28*, 311–319.

36. Li, B., Wang, W., Miao, S., Li, G., Lv, Y., Xiang, C., and Pei, R. (2019). HOXA11-AS promotes the progression of oral squamous cell carcinoma by targeting the miR-518a-3p/PDK1 axis. Cancer Cell Int. *19*, 140.

37. Wang, Y., Wu, C., Zhang, C., Li, Z., Zhu, T., Chen, J., Ren, Y., Wang, X., Zhang, L., and Zhou, X. (2018). TGF-β-induced STAT3 overexpression promotes human head and neck squamous cell carcinoma invasion and metastasis through malat1/miR-30a interactions. Cancer Lett. *436*, 52–62.

38. Zhu, M., Zhang, C., Chen, D., Chen, S., and Zheng, H. (2019). lncRNA MALAT1 potentiates the progression of tongue squamous cell carcinoma through regulating miR-140-5p-PAK1 pathway. Onco Targets Ther. *12*, 1365–1377.

39. Xu, E., Liang, X., Ji, Z., Zhao, S., Li, L., and Lang, J. (2020). Blocking long non-coding RNA MALAT1 restrained the development of laryngeal and hypopharyngeal carcinoma. Eur. Arch. Otorhinolaryngol. *277*, 611–621.

40. Zhang, L.M., Ju, H.Y., Wu, Y.T., Guo, W., Mao, L., Ma, H.L., Xia, W.Y., Hu, J.Z., and Ren, G.X. (2018). Long non-coding RNA ANRIL promotes tumorgenesis through regulation of FGFR1 expression by sponging miR-125a-3p in head and neck squamous cell carcinoma. Am. J. Cancer Res. *8*, 2296–2310.

41. Hao, Y.R., Zhang, D.J., Fu, Z.M., Guo, Y.Y., and Guan, G.F. (2019). Long non-coding RNA ANRIL promotes proliferation, clonogenicity, invasion and migration of laryngeal squamous cell carcinoma by regulating miR-181a/Snai2 axis. Regen. Ther. *11*, 282–289.

42. Liu, L., Ning, S.B., Fu, S., Mao, Y., Xiao, M., and Guo, B. (2019). Effects of lncRNA ANRIL on proliferation and apoptosis of oral squamous cell carcinoma cells by regulating TGF-β/Smad pathway. Eur. Rev. Med. Pharmacol. Sci. *23*, 6194–6201.

43. Guan, G.F., Zhang, D.J., Wen, L.J., Xin, D., Liu, Y., Yu, D.J., Su, K., Zhu, L., Guo, Y.Y., and Wang, K. (2016). Overexpression of lncRNA H19/miR-675 promotes tumorigenesis in head and neck squamous cell carcinoma. Int. J. Med. Sci. *13*, 914–922.

44. Kou, N., Liu, S., Li, X., Li, W., Zhong, W., Gui, L., Chai, S., Ren, X., Na, R., Zeng, T., et al. (2019). H19 facilitates tongue squamous cell carcinoma migration and invasion via sponging miR-let-7. Oncol. Res. *27*, 173–182.

45. Wu, T., Qu, L., He, G., Tian, L., Li, L., Zhou, H., Jin, Q., Ren, J., Wang, Y., Wang, J., et al. (2016). Regulation of laryngeal squamous cell cancer progression by the lncRNA H19/miR-148a-3p/DNMT1 axis. Oncotarget *7*, 11553–11566.

46. Li, J., Sun, S., Chen, W., and Yuan, K. (2019). Small nucleolar RNA host gene 12 (SNHG12) promotes proliferation and invasion of laryngeal cancer cells via sponging miR-129-5p and potentiating WW domain-containing E3 ubiquitin protein ligase 1 (WWP1) expression. Med. Sci. Monit. *25*, 5552–5560.

47. Wu, J., Zhao, W., Wang, Z., Xiang, X., Zhang, S., and Liu, L. (2019). Long non-coding RNA SNHG20 promotes the tumorigenesis of oral squamous cell carcinoma via targeting miR-197/LIN28 axis. J. Cell. Mol. Med. *23*, 680–688.

48. Diao, P., Ge, H., Song, Y., Wu, Y., Li, J., Li, Z., Yang, J., Wang, Y., and Cheng, J. (2019). Overexpression of ZEB2-AS1 promotes epithelial-to-mesenchymal transition and metastasis by stabilizing ZEB2 mRNA in head neck squamous cell carcinoma. J. Cell. Mol. Med. *23*, 4269–4280.

49. Wen, X., Liu, X., Mao, Y.P., Yang, X.J., Wang, Y.Q., Zhang, P.P., Lei, Y., Hong, X.H., He, Q.M., Ma, J., et al. (2018). Long non-coding RNA DANCR stabilizes HIF-1α and promotes metastasis by interacting with NF90/NF45 complex in nasopharyngeal carcinoma. Theranostics *8*, 5676–5689.

50. Kolenda, T., Guglas, K., Kopczyńska, M., Teresiak, A., Bliźniak, R., Mackiewicz, A., Lamperska, K., and Mackiewicz, J. (2019). Oncogenic role of ZFAS1 lncRNA in head and neck squamous cell carcinomas. Cells *8*, 366.

51. Sun, Y., Xu, C., Wu, Q., Zhang, L., and Wang, P. (2020). Long non-coding RNA KCNQ1OT1 promotes proliferation, migration, and invasion in maxillary sinus squamous cell carcinoma by regulating miR-204/EphA7 axis. J. Cell. Biochem. *121*, 2962–2969.

52. Zhang, L.L., Hu, D., and Zou, L.H. (2018). Low expression of lncRNA MEG3 promotes the progression of oral squamous cell carcinoma by targeting miR-21. Eur. Rev. Med. Pharmacol. Sci. *22*, 8315–8323.

53. Dong, Y., and Wu, W. (2019). Downregulation of lncRNA CASC2 promotes the postoperative local recurrence of early oral squamous cell carcinoma. Eur. Arch. Otorhinolaryngol. *276*, 605–610.

54. Zhuang, K., Wu, Q., Jiang, S., Yuan, H., Huang, S., and Li, H. (2016). CCAT1 promotes laryngeal squamous cell carcinoma cell proliferation and invasion. Am. J. Transl. Res. *8*, 4338–4345.

55. Gao, L., Cao, H., and Cheng, X. (2018). A positive feedback regulation between long non-coding RNA SNHG1 and YAP1 modulates growth and metastasis in laryngeal squamous cell carcinoma. Am. J. Cancer Res. *8*, 1712–1724.

56. Li, J., Li, Z., Wu, Y., Diao, P., Zhang, W., Wang, Y., Yang, J., and Cheng, J. (2019). Overexpression of lncRNA WWTR1-AS1 associates with tumor aggressiveness and unfavorable survival in head-neck squamous cell carcinoma. J. Cell. Biochem. *120*, 18266–18277.

57. Leng, F., Miu, Y.Y., Zhang, Y., Luo, H., Lu, X.L., Cheng, H., and Zheng, Z.G. (2021). A micro-peptide encoded by HOXB-AS3 promotes the proliferation and viability of oral squamous cell carcinoma cell lines by directly binding with IGF2BP2 to stabilize c-Myc. Oncol. Lett. *22*, 697.

58. Ma, Y., Han, J., and Luo, X. (2021). FOXD1-AS1 upregulates FOXD1 to promote oral squamous cell carcinoma progression. Oral Dis. https://doi.org/10.1111/odi.14002.

59. Li, Q., Jiang, Y., Zhong, G., Lu, Y., Song, T., Zhang, Y., Wu, J., Zhang, M., Liang, X., Zhou, L., et al. (2020). Long noncoding RNA DANCR regulates cell proliferation by stabilizing SOX2 mRNA in nasopharyngeal carcinoma. Am. J. Pathol. *190*, 2343–2354.

60. Ma, H., Chang, H., Yang, W., Lu, Y., Hu, J., and Jin, S. (2020). A novel IFNα-induced long non-coding RNA negatively regulates immunosuppression by interrupting H3K27 acetylation in head and neck squamous cell carcinoma. Mol. Cancer *19*, 4.

61. Wang, P., Wu, T., Zhou, H., Jin, Q., He, G., Yu, H., Xuan, L., Wang, X., Tian, L., Sun, Y., et al. (2016). Long non-coding RNA NEAT1 promotes laryngeal squamous cell cancer through regulating miR-107/CDK6 pathway. J. Exp. Clin. Cancer Res. *35*, 22.

62. Shen, Z., Hao, W., Zhou, C., Deng, H., Ye, D., Li, Q., Lin, L., Cao, B., and Guo, J. (2018). Long non-coding RNA AC026166.2-001 inhibits cell proliferation and migration in laryngeal squamous cell carcinoma by regulating the miR-24-3p/p27 axis. Sci. Rep. *8*, 3375.

63. Ouyang, T., Zhang, Y., Tang, S., and Wang, Y. (2019). Long non-coding RNA LINC00052 regulates miR-608/EGFR axis to promote progression of head and neck squamous cell carcinoma. Exp. Mol. Pathol. *111*, 104321.

64. Chen, Y., and Ding, Y. (2020). LINC00467 enhances head and neck squamous cell carcinoma progression and the epithelial-mesenchymal transition process via miR-299-5p/ubiquitin specific protease-48 axis. J. Gene Med. *22*, e3184.

65. Bao, Q., Liao, X., Li, R., and Ding, N. (2019). KCNQ1OT1 promotes migration and inhibits apoptosis by modulating miR-185-5p/Rab14 axis in oral squamous cell carcinoma. Dev. Growth Differ *61*, 466–474.

66. Qiao, C.Y., Qiao, T.Y., Jin, H., Liu, L.L., Zheng, M.D., and Wang, Z.L. (2020). LncRNA KCNQ1OT1 contributes to the cisplatin resistance of tongue cancer through the KCNQ1OT1/miR-124-3p/TRIM14 axis. Eur. Rev. Med. Pharmacol. Sci. *24*, 200–212.

67. Liu, C., Lu, Z., Liu, H., Zhuang, S., Guo, P.. LncRNA XIST promotes the progression of laryngeal squamous cell carcinoma via sponging miR-125b-5p to modulate TRIB2. Biosci. Rep. 40, BSR20193172.

68. Cui, C.L., Li, Y.N., Cui, X.Y., and Wu, X. (2020). lncRNA XIST promotes the progression of laryngeal squamous cell carcinoma by sponging miR-144 to regulate IRS1 expression. Oncol. Rep. *43*, 525–535.

69. Zheng, Z.Q., Li, Z.X., Zhou, G.Q., Lin, L., Zhang, L.L., Lv, J.W., Huang, X.D., Liu, R.Q., Chen, F., He, X.J., et al. (2019). Long noncoding RNA FAM225A promotes nasopharyngeal carcinoma tumorigenesis and metastasis by acting as ceRNA to sponge miR-590-3p/miR-1275 and upregulate ITGB3. Cancer Res. *79*, 4612–4626.

70. Xue, K., Li, J., Nan, S., Zhao, X., and Xu, C. (2019). Downregulation of LINC00460 decreases STC2 and promotes autophagy of head and neck squamous cell carcinoma by upregulating microRNA-206. Life Sci. *231*, 116459.

71. Xie, X., Xiong, G., Wang, Q., Ge, Y., and Cui, X. (2019). Long non-coding RNA LINC00460 promotes head and neck squamous cell carcinoma cell progression by sponging miR-612 to upregulate AKT2. Am. J. Transl. Res. *11*, 6326–6340.

72. Gao, C., Lu, W., Lou, W., Wang, L., and Xu, Q. (2019). Long non-coding RNA HOXC13-AS positively affects cell proliferation and invasion in nasopharyngeal carcinoma via modulating miR-383-3p/HMGA2 axis. J. Cell. Physiol. *234*, 12809–12820.

73. Jiang, Y., Cao, W., Wu, K., Qin, X., Wang, X., Li, Y., Yu, B., Zhang, Z., Wang, X., Yan, M., et al. (2019). LncRNA LINC00460 promotes EMT in head and neck squamous cell carcinoma by facilitating peroxiredoxin-1 into the nucleus. J. Exp. Clin. Cancer Res. *38*, 365.

74. Yu, B., Qu, L., Wu, T., Yan, B., Kan, X., Zhao, X., Yang, L., Li, Y., Liu, M., Tian, L., et al. (2020). A novel lncRNA, AC091729.7 promotes sinonasal squamous cell carcinomas proliferation and invasion through binding SRSF2. Front. Oncol. *9*, 1575.

75. Wang, R., Ma, Z., Feng, L., Yang, Y., Tan, C., Shi, Q., Lian, M., He, S., Ma, H., and Fang, J. (2018). LncRNA MIR31HG targets HIF1A and P21 to facilitate head and neck cancer cell proliferation and tumorigenesis by promoting cell-cycle progression. Mol. Cancer *17*, 162.

76. Qin, H., Xu, J., Gong, L., Jiang, B., and Zhao, W. (2019). The long non-coding RNA ST7-AS1 promotes laryngeal squamous cell carcinoma by stabilizing CARM1. Biochem. Biophys. Res. Commun. *512*, 34–40.

77. Guo, Y., Ma, Y., Hu, X., Song, R., Zhu, L., and Zhong, M. (2018). Long non-coding RNA CEBPA-AS1 correlates with poor prognosis and promotes tumorigenesis via CEBPA/Bcl2 in oral squamous cell carcinoma. Cancer Biol. Ther. *19*, 205–213.

78. Yang, B., Shen, J., Xu, L., Chen, Y., Che, X., Qu, X., Liu, Y., Teng, Y., and Li, Z. (2019). Genome-wide identification of a novel eight-lncRNA signature to improve prognostic prediction in head and neck squamous cell carcinoma. Front. Oncol. *9*, 898.

79. Li, R., Chen, S., Zhan, J., Li, X., Liu, W., Sheng, X., Lu, Z., Zhong, R., Chen, L., Luo, X., et al. (2020). Long non-coding RNA FOXD2-AS1 enhances chemotherapeutic resistance of laryngeal squamous cell carcinoma via STAT3 activation. Cell Death Dis. *11*, 41.

80. Cantelli, G., Crosas-Molist, E., Georgouli, M., and Sanz-Moreno, V. (2017). TGFB-induced transcription in cancer. Semin. Cancer Biol. *42*, 60–69.

81. Huang, T., Huang, W., Lu, H., Zhang, B.Y., Ma, J., Zhao, D., Wang, Y.J., Yu, D.H., and He, X. (2018). Identification and validation a TGF-β-associated long non-coding RNA of head and neck squamous cell carcinoma by bioinformatics method. J. Transl. Med. *16*, 46.

82. Liu, M., Gao, X., and Liu, C.L. (2018). Increased expression of lncRNA FTH1P3 promotes oral squamous cell carcinoma cells migration and invasion by enhancing PI3K/Akt/GSK3b/Wnt/β-catenin signaling. Eur. Rev. Med. Pharmacol. Sci. *22*, 8306–8314.

83. Sun, S., Gong, C., and Yuan, K. (2019). LncRNA UCA1 promotes cell proliferation, invasion and migration of laryngeal squamous cell carcinoma cells by activating Wnt/β-catenin signaling pathway. Exp. Ther. Med. *17*, 1182–1189.

84. Liang, S., Zhang, S., Wang, P., Yang, C., Shang, C., Yang, J., and Wang, J. (2017). LncRNA, TUG1 regulates the oral squamous cell carcinoma progression possibly via interacting with Wnt/β-catenin signaling. Gene *608*, 49–57.

85. Cui, X., Fang, N., Cui, Y., Xiao, D., and Wang, X. (2019). Long non-coding RNA NEF inhibits proliferation and promotes apoptosis of laryngeal squamous cell carcinoma cells by inhibiting Wnt/β-catenin signaling. Oncol. Lett. *17*, 4928–4934.

86. Han, P.B., Ji, X.J., Zhang, M., and Gao, L.Y. (2018). Upregulation of lncRNA LINC00473 promotes radioresistance of HNSCC cells through activating Wnt/β-catenin signaling pathway. Eur. Rev. Med. Pharmacol. Sci. *22*, 7305–7313.

87. Wang, X., Cao, K., Guo, E., Mao, X., Guo, L., Zhang, C., Guo, J., Wang, G., Yang, X., Sun, J., et al. (2021). Identification of immune-related LncRNA pairs for predicting prognosis and immunotherapeutic response in head and neck squamous cell carcinoma. Front. Immunol. *12*, 658631.

88. Yin, J., Li, X., Lv, C., He, X., Luo, X., Li, S., and Hu, W. (2021). Immune-related lncRNA signature for predicting the immune landscape of head and neck squamous cell carcinoma. Front. Mol. Biosci. *8*, 689224.

89. Feng, Z.Y., Gao, H.Y., and Feng, T.D. (2021). Immune infiltrates of m6A RNA methylation-related lncRNAs and identification of PD-L1 in patients with primary head and neck squamous cell carcinoma. Front. Cell. Dev. Biol. *9*, 672248.

90. Ai, Y., Liu, S., Luo, H., Wu, S., Wei, H., Tang, Z., Li, X., and Zou, C. (2021). lncRNA DCST1-AS1 facilitates oral squamous cell carcinoma by promoting M2 macrophage polarization through activating NF-κB signaling. J. Immunol. Res. *2021*, 5524231.

91. Li, H., Xiong, H.G., Xiao, Y., Yang, Q.C., Yang, S.C., Tang, H.C., Zhang, W.F., and Sun, Z.J. (2020). Long non-coding RNA LINC02195 as a regulator of MHC I molecules and favorable prognostic marker for head and neck squamous cell carcinoma. Front. Oncol. *10*, 615.

92. Chen, Y., Luo, T.Q., Xu, S.S., Chen, C.Y., Sun, Y., Lin, L., and Mao, Y.P. (2021). An immune-related seven-lncRNA signature for head and neck squamous cell carcinoma. Cancer Med. *10*, 2268–2285.

93. Zhong, Z., Hong, M., Chen, X., Xi, Y., Xu, Y., Kong, D., Deng, J., Li, Y., Hu, R., Sun, C., et al. (2020). Transcriptome analysis reveals the link between lncRNA-mRNA co-expression network and tumor immune microenvironment and overall survival in head and neck squamous cell carcinoma. BMC Med. Genomics *13*, 57.

94. Ren, X., Li, L., Wu, J., Lin, K., He, Y., and Bian, L. (2021). PDGFBB regulates the transformation of fibroblasts into cancer-associated fibroblasts via the lncRNA LURAP1L-AS1/LURAP1L/IKK/IκB/NFκB signaling pathway. Oncol. Lett. *22*, 537.

95. Wang, Y., Zhang, X., Wang, Z., Hu, Q., Wu, J., Li, Y., Ren, X., Wu, T., Tao, X., Chen, X., et al. (2018). LncRNA-p23154 promotes the invasion-metastasis potential of oral squamous cell carcinoma by regulating Glut1-mediated glycolysis. Cancer Lett. *434*, 172–183.

96. Li, X., and Ren, H. (2020). Long non-coding RNA PVT1 promotes tumor cell proliferation, invasion, migration and inhibits apoptosis in oral squamous cell carcinoma by regulating miR-150-5p/GLUT-1. Oncol. Rep. *44*, 1524–1538.

97. Yang, J., Shi, X., Yang, M., Luo, J., Gao, Q., Wang, X., Wu, Y., Tian, Y., Wu, F., and Zhou, H. (2021). Glycolysis reprogramming in cancer-associated fibroblasts promotes the growth of oral cancer through the lncRNA H19/miR-675-5p/PFKFB3 signaling pathway. Int. J. Oral Sci. *13*, 12.

98. Ørom, U.A., Derrien, T., Beringer, M., Gumireddy, K., Gardini, A., Bussotti, G., Lai, F., Zytnicki, M., Notredame, C., and Huang, Q. (2010). Long non-coding RNAs with enhancer-like function in human cells. Cell *143*, 46–58.

99. Zhang, L., Peng, D., Sood, A.K., Dang, C.V., and Zhong, X. (2018). Shedding light on the dark cancer genomes: long noncoding RNAs as novel biomarkers and potential therapeutic targets for cancer. Mol. Cancer Ther. *17*, 1816–1823.

100. Gu, X., Wang, L., Boldrup, L., Coates, P.J., Fahraeus, R., Sgaramella, N., Wilms, T., and Nylander, K. (2019). AP001056.1, a prognosis-related enhancer RNA in squamous cell carcinoma of the head and neck. Cancers (Basel) *11*, 347.

101. Yin, X., Yang, W., Xie, J., Wei, Z., Tang, C., Song, C., Wang, Y., Cai, Y., Xu, W., and Han, W. (2019). HOTTIP functions as a key candidate biomarker in head and neck squamous cell carcinoma by integrated bioinformatic analysis. Biomed. Res. Int. *2019*, 5450617.

102. Qian, Y., Liu, D., Cao, S., Tao, Y., Wei, D., Li, W., Li, G., Pan, X., and Lei, D. (2017). Upregulation of the long non-coding RNA UCA1 affects the proliferation, invasion, and survival of hypopharyngeal carcinoma. Mol. Cancer *16*, 68.

103. Cao, W., Liu, J.N., Liu, Z., Wang, X., Han, Z.G., Ji, T., Chen, W.T., and Zou, X. (2017). A three-lncRNA signature derived from The Atlas of ncRNA in Cancer (TANRIC) database predicts the survival of patients with head and neck squamous cell carcinoma. Oral Oncol. *65*, 94–101.

104. Wang, P., Jin, M., Sun, C.H., Yang, L., Li, Y.S., Wang, X., Sun, Y.N., Tian, L.L., and Liu, M. (2018). A three-lncRNA expression signature predicts survival in head and neck squamous cell carcinoma (HNSCC). Biosci. Rep. *38*, BSR20181528.

105. Zhang, B., Wang, H., Guo, Z., and Zhang, X. (2019). Prediction of head and neck squamous cell carcinoma survival based on the expression of 15 lncRNAs. J. Cell. Physiol. *234*, 18781–18791.

106. Liu, G., Zheng, J., Zhuang, L., Lv, Y., Zhu, G., Pi, L., Wang, J., Chen, C., Li, Z., Liu, J., et al. (2018). A prognostic 5-lncRNA expression signature for head and neck squamous cell carcinoma. Sci. Rep. *8*, 15250.

107. Diao, P., Song, Y., Ge, H., Wu, Y., Li, J., Zhang, W., Wang, Y., and Cheng, J. (2018). Identification of 4-lncRNA prognostic signature in head and neck squamous cell carcinoma. J. Cell. Biochem. *120*, 10010–10020.

108. Pan, Y., Liu, G., Wang, D., and Li, Y. (2019). Analysis of lncRNA-mediated ceRNA crosstalk and identification of prognostic signature in head and neck squamous cell carcinoma. Front. Pharmacol. *10*, 150.

109. Fang, X.N., Yin, M., Li, H., Liang, C., Xu, C., Yang, G.W., and Zhang, H.X. (2018). Comprehensive analysis of competitive endogenous RNAs network associated with head and neck squamous cell carcinoma. Sci. Rep. *8*, 10544.

110. Zhang, Z.L., Zhao, L.J., Chai, L., Zhou, S.H., Wang, F., Wei, Y., Xu, Y.P., and Zhao, P. (2017). Seven LncRNA-mRNA based risk score predicts the survival of head and neck squamous cell carcinoma. Sci. Rep. *7*, 309.

111. Fang, Z., Zhao, J., Xie, W., Sun, Q., Wang, H., and Qiao, B. (2017). LncRNA UCA1 promotes proliferation and cisplatin resistance of oral squamous cell carcinoma by suppressing miR-184 expression. Cancer Med. *6*, 2897–2908.

112. Jiang, Q., Liu, S., Hou, L., Guan, Y., Yang, S., and Luo, Z. (2020). The implication of LncRNA MALAT1 in promoting chemo-resistance of laryngeal squamous cell carcinoma cells. J. Clin. Lab. Anal. *34*, e23116.

113. Huang, S., Zhan, Z., Li, L., Guo, H., Yao, Y., Feng, M., Deng, J., and Xiong, J. (2019). LINC00958-MYC positive feedback loop modulates resistance of head and neck squamous cell carcinoma cells to chemo- and radiotherapy in vitro. Onco Targets Ther. *12*, 5989–6000.

114. Ding, L., Ren, J., Zhang, D., Li, Y., Huang, X., Ji, J., Hu, Q., Wang, H., Ni, Y., and Hou, Y. (2017). The TLR3 agonist inhibit drug efflux and sequentially consolidates low-dose cisplatin-based chemoimmunotherapy while reducing side effects. Mol. Cancer Ther. *16*, 1068–1079.

115. Gou, C., Han, P., Li, J., Gao, L., Ji, X., Dong, F., Su, Q., Zhang, Y., and Liu, X. (2020). Knockdown of lncRNA BLACAT1 enhances radiosensitivity of head and neck squamous cell carcinoma cells by regulating PSEN1. Br. J. Radiol. *93*, 20190154.

116. Cramer, J.D., Burtness, B., Le, Q.T., and Ferris, R.L. (2019). The changing therapeutic landscape of head and neck cancer. Nat. Rev. Clin. Oncol. *16*, 669–683.

117. Tan, D.S.W., Chong, F.T., Leong, H.S., Toh, S.Y., Lau, D.P., Kwang, X.L., Zhang, X., Sundaram, G.M., Tan, G.S., Chang, M.M., et al. (2017). Long non-coding RNA EGFR-AS1 mediates epidermal growth factor receptor addiction and modulates treatment response in squamous cell carcinoma. Nat. Med. *23*, 1167–1175.

118. Adams, B.D., Parsons, C., Walker, L., Zhang, W.C., and Slack, F.J. (2017). Targeting non-coding RNAs in disease. J. Clin. Invest. *127*, 761–777.