CSVTU International Journal of Biotechnology, Bioinformatics and Biomedical

Vol. 7(1), 01-16 2022 ISSN: 2455-5762

Long noncoding RNAs: Novel insights into the diagnostic, prognostic and therapeutic role in oral squamous cell carcinoma

Jyotsna Choubey[1*], Tanushree Chatterjee[1]

[1]Raipur Institute of Technology Raipur (C.G) India, 492001

***Corresponding author, Email: joys.choubey@gmail.com

Received January 28, 2022; received in revised form March 13, 2022; accepted April 2022; Available online April 2022

Abstract

Recent advances in microarray and high throughput sequence analyses show that 87.3% of the human genome is actively transcribed, despite only 3% coding for proteins. This surprising fact suggests that non-coding RNA dominates the transcriptome. High-resolution microarray and massively parallel sequencing data showed that lncRNAs are nonprotein-coding transcripts. LncRNAs are polyadenylated ncRNAs longer than 200 nucleotides. Many lncRNAs are aberrantly expressed in many cancers, making them essential to tumour biology. They play a significant role in the development, spread, and treatment of cancer at multiple stages of the disease's pathogenesis. Even though lncRNAs' functions are poorly understood, there is increasing evidence that they play critical roles in living organisms. To the contrary, it is now widely accepted that their dysregulation plays a role in the initiation and progression of a wide range of human cancers., especially in oral squamous cell carcinoma (OSCC). Consequently, it has the potential to be used as a molecular biomarker in the diagnosis and prognosis of certain forms of cancer. Long non-coding RNAs (lncRNAs) have recently been identified and characterized, revealing their regulatory significance OSCC. We comprehensively reviewed the role of lncRNAs in OSCC biology, highlighting their potential as biomarkers and diagnostic/therapeutic targets.

Research Article

Key words: nonprotein-coding transcripts, long non-coding RNAs, Oral squamous cell carcinoma, molecular biomarkers

1. Introduction

The most common type of malignant tumour found in the mouth is called oral squamous cell carcinoma (OSCC). In fact, more than half a million people around the world are diagnosed with it every year. [1] About 65% of all cancers of the oral cavity occur as a result of tobacco and alcohol use, making these two substances the most important etiologic factors in the development of all head and neck cancers. [2] Recent developments in cancer research have led to the discovery of new information regarding the cellular and molecular processes involved in the development of cancer. This has also led to the discovery of useful biological markers and efficient therapeutic approaches. In addition to this, the majority of patients with OSCC are diagnosed with the disease when it is already in an advanced stage, long-term survival rates remain low, and no early screening strategy has been shown to be effective. The 5-year survival rate for patients with OSCC remains below 50% despite significant advances in diagnosis and combined treatments in recent years. [3–5] For this reason, it is absolutely necessary to discover novel biomarkers and therapeutic targets in order to enhance the outlook for patients with OSCC.

Presently, a great deal of attention is being paid to long noncoding RNAs (lncRNAs), with much of this attention focusing on their potential roles in cancer. Long non-coding RNAs (lncRNAs) are a subset of RNAs that are 200 nucleotides or longer but are not translated into proteins. When first

discovered, lncRNAs were dismissed as "transcriptional garbage" because RNA polymerase II creates them in such large quantities. It was thought that they had no influence over their biological impulses. [6]. Recent studies have shown that long noncoding RNAs that are dysregulated play important roles in the cellular processes that occur during the development and progression of cancer. These processes include cell proliferation, differentiation, and invasion. These long noncoding RNAs also play important roles in the development of tumours and the progression of cancers such as ovarian [7], colorectal, gastrointestinal [8], and lung [9]. It is becoming more and more widely accepted that lncRNAs should be given higher priority as therapeutic targets [10,11]. It has been demonstrated in a number of studies that aberrant lncRNAs play a role in the biological behaviours, clinical diagnosis, prognosis, and treatment options associated with OSCC. Our ultimate goal is to find better ways to diagnose and treat OSCC, and there is promising evidence that lncRNAs can play a role in both of these processes. Therefore, this review offers a condensed summary of the functions of lncRNA and the molecular mechanisms by which they contribute to OSCC.

2. Mechanisms of lncRNAs in cancer

Numerous studies in various types of cancer have implicated LncRNAs as regulators of cellular processes. In addition to epigenetic and transcriptional effects, they also exert post-transcriptional modifications. Many lncRNAs are nuclear, where their expression is typically much lower than that of coding mRNAs. The cellular localization of lncRNAs is critical to their functions. Long noncoding RNAs (lncRNAs) found in the nucleus serve as scaffolds for chromatin-modifying complexes, which in turn trigger chromatin reprogram, imprinting, and histone modification. They can interact with target genes and promoters to increase transcription of enhancers and affect epigenetic events through transcription-dependent mechanisms like DNA methylation. Post-transcriptional regulation, protein activity, mRNA splicing, and degradation are all influenced by lncRNAs in addition to gene expression. Their versatility makes them useful as complex scaffolds, exosomal signalling molecules, and vectors for genetic variation. [12-15] The mechanisms by which lncRNAs perform their functions are illustrated in Figure 1. Researchers Li et al. [16] discovered that lncRNA ROR would increase tumour chemoresistance by inhibiting the P53 signalling pathway. LOC401317 influences the cell cycle by upregulating p21 and downregulating cyclin D1 and cyclin E1 expression and by promoting apoptosis by inducing poly ADP-ribose polymerase (PARP) and caspase-3 cleavage. [17]

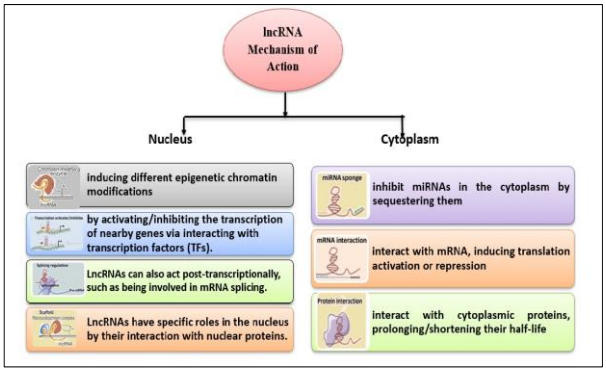

Fig 1. Mechanism of lncRNA

MiRNA sponging has been reported as an important pathway for lncRNA functional mechanisms. Studies have shown that the LncRNA NEAT1 promotes tumour growth by modulating either the miR-107/CDK6 or miR-365/RGS20 pathways. [18,19] One study found that MEG3 induced miR-26a

and miR-21, two microRNAs thought to play a role in tumour suppression. [20] As a molecular scaffold, HOTAIR promotes cancer metastasis by reprogramming chromatin states and focusing on the histone modification complexes PRC2 and LSD1.Together with EZH2 and H3K27me3, it binds to the E-cadherin promoter and inhibits the gene's activity.[21]

3. Biologic functions of lncRNAs in OSCC

OSCC is a complex multi-step process influenced by a number of factors, including genetics, epigenetics, and the environment. The dysregulation of lncRNAs has emerged as a crucial regulatory factor in the emergence of cancer as our understanding of their structure and function has progressed. [22] High-throughput sequencing technologies have led to an exponential increase in the number of lncRNAs with aberrant expression in a wide range of cancers over the past few decades. [23] Functional studies demonstrated the importance of lncRNAs in regulating nearly every aspect of normal cell function, including oncogenesis, tumour suppression, and chemoresistance. (Figure 2). Cell proliferation, apoptosis, invasion, metastasis, [24] EMT, and drug resistance [25] are all influenced by aberrant lncRNAs. Lymph node metastases, distant metastases, and postoperative recurrence are all influenced by lncRNAs. [26] Many upregulated lncRNAs have been shown to act as oncogenes and promote biologically malignant behaviours in OSCC, and this is consistent with previous studies. Proliferation, migration, metastasis, and angiogenesis are all examples of such behaviours. To the contrary, lncRNAs halted both apoptosis and the cell cycle. Suppressing LEF1-AS1 led to a G0/G1 cell cycle arrest and a reduction in cell proliferation and growth in vitro via Hippo signalling. [27] Through control of the small proline-rich protein (SPRR), MALAT-1 promotes distant metastasis. Both tumour growth and metastasis can be suppressed or boosted depending on whether or not a LncRNA is acting as an oncogene or a suppressor. [28]

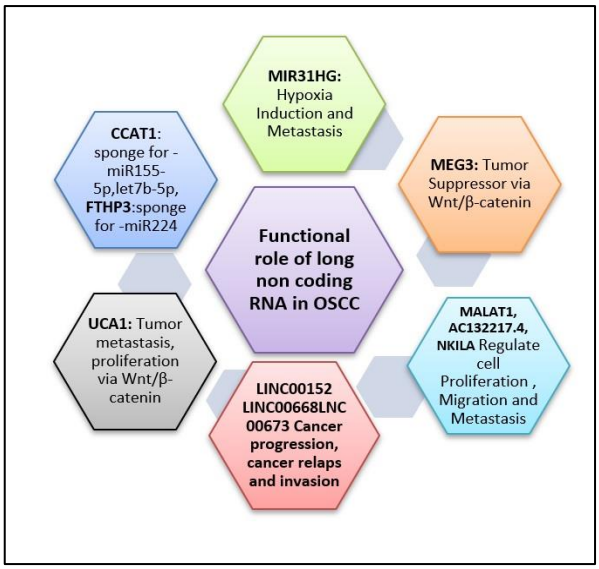

Fig 2. Function of lncRNA in OSCC

Cancer-suppressing lncRNA NKILA is inversely associated with metastasis and survival in breast cancer. [29] Lower NKILA expression was also confirmed by Huang et al. in tongue squamous cell carcinoma (TSCC). When NKILA is overexpressed, the NF-B/Twist signalling pathway is activated, which inhibits EMT and cell migration in Tscca and CAL27 cells. [30] In OSCC, the tumour suppressor gene maternally expressed gene 3 (MEG3) is well-established. Overexpression of MEG3 inhibits SCC15 proliferation and migration while increasing apoptosis in CAL27. In terms of mechanisms, MEG3 has the potential to inhibit the WNT/-catenin signalling pathway and to modulate the JAK-STAT signalling pathway by acting as miRNAs sponge. [31,32] Adjuvant radiation or chemotherapy in combination with

radiation is used to treat OSCC patients, depending on the stage of the disease [3]. One drug derived from platinum used to treat OSCC is cisplatin (CDDP). Tumor relapse and a poor prognosis result from resistance to cisplatin. [33] There is evidence that long noncoding RNAs (lncRNAs) control chemoresistance in OSCC. [34] UCA1 was shown by Fang et al. to increase OSCC cell proliferation and induce cisplatin resistance by regulating the expression of SF1, a target gene of miR-184. [35].

Table 1 Dysregulated lncRNA in OSCC

LncRNA	Location	Cytology	Expression	Associated Targets/Pathway	Function in Tumorigenesis	References
MALAT1	11q13.1	Tca8113, SCC-25, CAL-27 and HN5 cells +	Upregulated	SPRR, miR-125b/STAT3 NF-_B	Biomarker	[36]
CCAT1	8q24.21	OSCC tissues/HIOECs	Upregulated	miR-181a/Wnt/_-catenin DDR2/ERK/AKT, miR155-5p, let7b-5p	Biomarker	[37]
MEG3	14q32.3	OSCC tissues/SCC-15 and CAL-27 cells	downregulated	Wnt/_-catenin signaling miR-548d-3p/JAK–STAT	Biomarker, Tumor suppressor	[38]
UCA1	19p13.12	SCC-15 and CAL-27/Tca8113, TSCCA, CAL-27 and SCC-9 cells	Upregulated	P27, Wnt/_-catenin, miR-184/miR-184/SF1	Biomarker, Oncogene	[39]
AC132217.4	-	UM-SCC6H and SCC-090 cells	Upregulated	IGF2	Biomarker	[40]
HNF1A-AS1	12q24.31	OSCC tissues and cell lines	Upregulated		Oncogene	[41]
HAS2-AS1	8q24.13	SCC-9 and CAL-27 cells	Upregulated	HF-1_, NF-_B signaling	Biomarker	[42]
HOTAIR,	12q13.13	TSCCA, Tca8223, KB and CAL-27 cells,	Upregulated	EZH2/H3K27me3	Biomarker, Oncogene	[21]
Linc-RoR	18q21.31	OSCC tissues	Upregulated	miR-145-5p, c-Myc, Klf4, Oct4, Sox2	Biomarker	[43]
LINC00668	18p11.31	SCC-4, SCC-9, SCC-1, SCC- SNU-1041, SCC-15 cells 25, TU-183, HSU-3, FADU, OEC-M1,	Upregulated	miR-297/VEGFA	Oncogene	[44]
NEAT1	11q13.1	HN-4, Tca-8113, UM-SCC-1, CAL-27, SCC-25 and SCCKN cells	Upregulated	miR-365, RGS20	Biomarker	[45]
DLEU1	13q14.2-	SAS, Ca9–22, HSC-3, KON, MOT, HSC-4, OSC-19 and MON2 cells,	Upregulated	miR-149-5p/CDK6 HA-CD44 signaling	Biomarker,	[46]
CASC2	10q26.11	SCC-090 and SCC-25 cells	downregulated	miR-21	Tumor suppressor	[47]
CASC9	-	CASC9 Upregulated Oncogene AKT/mTOR	Upregulated	AKT/mTOR miR-423-5p/SOX12	Oncogene	[48]

When it comes to effective treatment for OSCC, chemoresistance isn't the only hurdle that needs to be cleared. Radio sensitivity is another major barrier. More and more research has shown that lncRNAs are critically involved in radiotherapy as well. Dysregulated lncRNAs in OSCC their functions are elaborate in Table 1. [36-48].

4. lncRNAs in OSCC

Lips, floor of mouth, tongue, buccal mucosa, lower and upper gingiva, hard palate, retromolar trigone, and retromolar ridges are all potential sites for oral cancer. [49] Studies have shown that lncRNAs have multiple functions in OSCC oncogenesis and progression, including transcriptional regulation, posttranscriptional modulation, and epigenetic modifications. [50] Possible biomarkers or therapeutic targets for the diagnosis, prognosis, and treatment of oral squamous cell carcinoma (OSCC) include LncRNAs involved in migration, epithelial-mesenchymal transition (EMT), metastasis, progression, and invasion. [51] Several oral cancers associated lncRNAs have been identified with the advent of whole transcriptome analyses, which incorporate serial analyses of gene expression, RNA sequencing, and microarray data. A total of 2,294 DE lncRNAs were screened in OSCC (n=72) and adjacent normal tissues by Qiu et al. [52] in 2019. Poor progression-free and overall survival was associated with low expression of four lncRNA nodes. Insight into the role of lncRNAs in OSCC was provided by this study. The OSCC has protein, RNA, and DNA interactions. [50] Hyaluronan synthase 2 antisense 1 (HAS2AS1) is overexpressed in response to hypoxia via the transcription factors hypoxia-inducible factor 1 (HIF1) and nuclear factor-kappa B (NFB). Through its role in stabilising the HAS2 gene, HAS2AS1 promotes EMT and invasiveness in OSCC. The expression of the GDF15 protein was suppressed by LINC01133, which in turn reduced OSCC cell migration and invasion. [53] The adjacent promoter of the gene FOXC1, which was identified by Kong et al. [54] to be a long noncoding RNA, was found to stimulate OSCC proliferation and migration. So much study has uncovered transcriptional regulatory mechanisms for lncRNAs in OSCC. One of the main functions of lncRNAs is posttranscriptional regulation, which can take the form of pre-mRNA alternative splicing, accelerated mRNA decay, mRNA protection, or translational activation or repression. [55] By sponging miR125b, Chang and Hu [56] demonstrated that MALAT1 can function as a ceRNA to regulate STAT3 expression in OSCC. By using a nude mouse xenograft model, we show that MALAT1 promotes OSCC cell viability and growth and confirm the MALAT1/miR125b/STAT3 axis in vivo. Urothelial cancer associated 1 (UCA1), a lncRNA increase splicing factor 1 mRNA expression, promote proliferation, and inhibit apoptosis in OSCC cells by downregulating miR184 expression. Therefore, ceRNA is a potentially useful posttranscriptional regulator of OSCC. There is evidence that lncRNAs play a role in OSCC by influencing chromatin structure, DNA methylation, and imprinting. [57] By interacting with enhancer of zeste homolog 2, a component of the polycomb repressive complex 2 (PRC2), and H3K27me3 at the Ecadherin promoter, the LncRNA HOX transcript antisense RNA (HOTAIR) repressed Ecadherin expression. By interacting with PRC2, lysine-specific

histone demethylase1, and RE1 elements, HOTAIR silenced transcription factors, which in turn resulted in chromatin remodelling and transinhibited the homeobox D cluster gene and promoted tumour occurrence, invasion, and metastasis. [21] The epigenetic changes that drive the progression of OSCC should be accompanied by the discovery of additional lncRNAs as research continues. [58]

5. LncRNAs as a Novel Diagnostic and Prognostic Tools in OSCC

Research shows that the dysregulated lncRNA can be detected in body fluids from primary tumours. [59] The diagnostic potential of circulating lncRNAs in OSCC was confirmed in a study, which found altered expression profiles of lncRNAs in the plasma of OSCC patients. Receivers operating characteristic (ROC) curves demonstrated significant value in detecting plasma CASC2 for OSCC diagnosis (AUC = 0.8445). [47] The plasma level of CASC2 decreased in OSCC patients with local recurrence while it increased in those without recurrence. Additionally, OSCC patients can be distinguished from oral ulcer patients by a second lncRNA, CASC15, which was found to be upregulated in the plasma of OSCC patients. [60] Serum lncRNA lncAC007271.3, discovered by Shao et al., has a higher expression level in patients with OSCC than the traditional tumour marker squamous cell carcinoma antigen (SCCA). [61] Tang et al. found that the lncRNAs HOTAIR and MALAT1 can be found in human saliva. OSCC patients with metastasis had higher levels of HOTAIR in their saliva than those without. [62] Saliva lncRNA detection has the potential to be an easy and noninvvasive method of detecting OSCC. It has been suggested that LncRNAs can be used as biomarkers that can predict whether or not OSCC will spread to the lymph nodes or return to the local level. A higher TNM stage, more metastatic cervical lymph nodes, and postoperative recurrence are all associated with increased expression of LINC00152 [63]. High expression of H19, CCAT2, and TUG1 in OSCC has also been linked to TNM stage and pathological grade [64, 65, 66]. High levels of LINC-RoR expression in tumours with an undifferentiated pathology are predictive of a positive therapeutic outcome in ocular squamous cell carcinoma (OSCC).[44] Previous research has established that lncRNAs are linked to OSCC patients' survival time and are therefore considered prognostic biomarkers, adding to the lncRNAs' diagnostic utility. MALAT1 is highly expressed in tissues from OSCCs. In a study using Kaplan-Meier analysis, Zhou et al. discovered that patients whose MALAT1 expression was lower had a higher 5-year survival rate. [36] Using a multivariate proportional hazards (COX) regression analysis, Yao et al. found that high levels of BANCR expression in OSCC tissues were independently associated with poor overall survival (OS) and disease-free survival (DFS), suggesting that BANCR was an independent prognostic factor in OSCC patients.[67] Using Kaplan-analysis and COX regression analysis, Yang et al. found that patients with OSCC who expressed low levels of CASC9 lived longer overall survival on average than those who expressed high levels of CASC9.[48] Furthermore, the unregulated expression of LINC01234 [68, 69], colon cancer-associated transcript 2 (CCAT2), FOXD2-AS1 [70], and FTH1P3 [71] in OSCC tissues was also linked to a poor prognosis and a shorter OS. Despite its invasive nature, tissue biopsy remains the gold standard for

diagnosing cancer. Because of their long half-lives, low background noise, and non-invasive nature in blood and other bodily fluids, lncRNAs have great potential as biomarkers for the diagnosis and prognosis of cancer. [59] Cancer diagnostic lncRNAs are more readily detectable and reproducible due to their disease and cell-type-specificity. In many contexts, long noncoding RNAs (LncRNAs) are used as a reliable biomarker.

6. LncRNAs as Therapeutic Targets

As a result of their tissue/cell-specific expression and multifaceted carcinogenic roles, lncRNAs hold great potential as drug targets and clinical applications in cancer treatment. lncRNA-targeted therapies may be antitumor. Antisense oligonucleotides (ASOs), small interfering RNAs (siRNAs), short hairpin RNAs (shRNAs), aptamers, and CRISPRCas9 are all effective tools for inhibiting OSCC growth, migration, and invasion in vitro and in vivo by targeting specific lncRNAs. [72] LncRNAs have been studied using conventional methods, such as small interfering RNAs (siRNAs) and shRNAs (small hairpin RNAs), for Tumor growth in a mouse model of Tscca is suppressed by MALAT1-targeting siRNA.[36] In addition, Wang et al. demonstrated that tail vein injection of lnc-p23154-targeting shRNA inhibited tumour metastasis in OSCC mouse model.[73] Interestingly, a novel potential approach for the reversal of cisplatin resistance in OSCC is shRNA-mediated knockdown of lncRNA KCNQ1OT1. This results in increased cisplatin sensitivity and decreased tumour burden in OSCC xenografts.[74] On the other hand, siRNA technology can cause unwanted side effects [75]. It is lncRNAs that are most effectively targeted by ASO methods. When the expression of FOXD2-AS1 is silenced using ASOs, tumour growth in mice suffering from OSCC is reduced. [70] Generally low abundance of lncRNAs in vivo also suggests that off-target effects are possible when targeting lncRNAs with ASO therapeutics. [78] In spite of these setbacks, ASOs have been used to target protein-coding genes. For this reason, the ASO method of targeting lncRNAs in cancer treatment may be promising. As a result of CRISPR-Cas9, lncRNA research has been revolutionised, and novel therapeutic targeting in cancer research has become possible. [76] CRISPR/Cas9-mediated deletion of lncRNA XIST attenuated tumour development in patients with tongue cancer, as previously reported by Zhang et al. [77]. Chang et al. discovered that CRISPR/Cas9 targeting MIR31HG decreased the oncogenicity of OSCC, indicating its therapeutic efficacy. [78] Due to its stability and low off-target effect, CRISPR/Cas9 could pave the way for gene-level cancer therapy. CRISPR/Cas9-based personalised and targeted therapy is likely the future of cancer treatment. Although anti-PD-1/PD-L1 therapy for recurrent and/or metastatic OSCC was recently approved, many patients are resistant. [79]. Anti-PD-1/PD-L1 resistance may be alleviated in OSCC patients if these lncRNAs are targeted. LncRNA acts as an upstream regulator by focusing on the PD-1/PD-L1 axis, which in turn stimulates anti-tumor activity. According to Ma and colleagues, IFN-induced lncMX1-215 inhibited OSCC proliferation and metastasis. To prevent immune escape, LncMX1-215 inhibited PD-L1. According to the findings, PD-1/PD-L1 targeting immune therapies that utilise lncRNAs can improve patient outcomes. Comprehensive research is required to back up the strategy. [80]

7. Application of lncRNA in OSCC as biomarker

It has been hypothesised that particular lncRNAs play a role in carcinogenesis. The vast majority were able to be detected in the plasma and urine of cancer patients. The degree to which lncRNAs are expressed is correlated with cancer malignancy. These features combined to make lncRNAs an attractive therapeutic target and a non-invasive biomarker for cancer. [81] LncRNAs are distinct from protein-coding genes in a variety of respects. First, lncRNAs are more common than protein-coding genes, so changes in their expression levels may serve as biomarkers for a variety of cancers. Secondly, the expression of lncRNAs is highly tissue-specific, which is important for the creation of diagnostic biomarkers and personalised therapy. [82, 83]. Moreover, lncRNAs can be used to develop novel strategies for specific cancer diagnosis and targeting due to their participation in diverse cellular signalling pathways and tissue-specific expression. The expression of the lncRNA C5orf66-AS1 in OSCC was significantly lower than that in the adjacent normal tissues. It has been hypothesised that the long noncoding RNA (lncRNA) EGFR-AS1 is a biomarker for oral squamous cell carcinoma due to its upregulation in this cancer.[84] Consequently, lncRNAs appeared to be promising diagnostic and prognostic markers for a variety of cancers, but their clinical applications posed numerous challenges and required extensive validations. Circulating and salivary lncRNAs may serve as biomarkers for oral cancer. Results from a study of 41 patients with head and neck cancer who were treated with radical chemo radiotherapy found that plasma levels of HOTAIR and two other lncRNAs (lincRNA-p21 and GAS5) were linked to the effectiveness of the therapy.[85] Higher GAS5 expression was observed in patients with progressive disease compared to those who showed good clinical responses, as reported by Maarabouni et al. [86] Saliva and blood samples may provide novel information for identifying OSCC. Using cutting-edge methods, researchers have proven that multiple lncRNAs promote tumour growth. The large size of LncRNAs suggests that they may be able to fold into secondary and tertiary structures and scaffolds, which may play a role in the initiation and progression of cancer. In response to DNA damage, mRNA expression of HOTAIR was upregulated in Tca8113 cells, leading to an increase in cell proliferation. Expression of HOTAIR mRNA inhibits cell proliferation in Tca8113 during the G2/M or M phases [87]. Based on these results, HOTAIR may be a therapeutic target for treating OSCC. There was an upregulation of the angiogenesis factor VEGF-A and the matrix metalloproteinases (MMPs) in patients with OSCC. [54, 88] Upregulation of NEAT1 in OSCC tissues and cells correlate with a more advanced TNM stage and poorer prognosis for the patient. Due to high NEAT1 levels, miR-365 was suppressed (a tumour suppressor or oncogene). Inhibiting cell proliferation and infiltration by lowering NEAT1 levels which suggests that NEAT1/miR-365 levels could be used to treat OSCC.

[18] High levels of H19 expression in OSCC tissues were associated with advanced tumour stage, lymph node invasion, and poorer overall survival. Reduced H19 expression can inhibit the development and spread of OSCC cells. [67] Low and high LINC00152 expression groups had an overall survival of 35 and 28 months, respectively, while the recurrence

free survival was 29 and 26.5 months, as reported by Yu et al. [65]. According to the findings, LINC00152 has the potential to serve as an oncogene in OSCC and as a biomarker for diagnosis, prognosis and treatment. In a case-control study, abnormal levels of AC007271.3 were associated with OSCC clinical stage. Perhaps AC007271.3 can be used as a diagnostic biomarker for OSCC. [89]

8. Research in the Area of LncRNAs in OSCC

The study of lncRNA in OSCC is still in its early stages. The expression and functional mechanisms of lncRNAs in oral cancer have been the subject of some promising studies, but there is still a dearth of evidence supporting their role. Though research in this area is just beginning, the molecules being studied are strong candidates in the development of oral cancer. This is especially crucial as their lack of a reliable marker to distinguish between oral leukoplakia lesions caused by non-progressive and oral leukoplakia lesions caused by cancer. Saliva may be helpful for the early diagnosis of OSCC, salivary gland tumours, or metastatic diseases because lncRNAs are present in body fluids and have a site-specific expression profile. [90] In addition, salivary lncRNA expression can be used as a biomarker for cancer recurrence. Collecting saliva does not necessitate any invasive procedures, which is just one of its many advantages. Different therapeutic strategies can be employed to target lncRNAs in an effort to restore their homeostatic levels. [90] Delivery of small interfering RNAs (siRNAs) that are complementary to their target lncRNA is the most investigated method to inhibit upregulated oncogenic lncRNAs. [61] Short hairpin RNAs, microRNAs, and small molecule inhibitors that interfere with lncRNA function by blocking the binding site of interaction, changing the secondary structure, or preventing lncRNA-protein interactions are other options. Short hairpin RNAs, microRNAs, and small molecule inhibitors that interfere with lncRNA function by blocking the binding site of interaction, changing the secondary structure, or preventing lncRNA-protein interactions are other options. [62] A tumor's growth and spread are controlled by lncRNAs contained in exosome inclusions and serve as Non-invasive cancer biomarkers. Lung cancer exosomes were found to have elevated levels of MALAT-1, according to research by Zhang et al. MALAT-1, which is found in exosomes, promote the spread and development of tumours. The exosomal protein MALAT-1 has diagnostic and prognostic value in non-small cell lung cancer [93]. A lot of attention will be paid to lncRNAs in OSCC exosomes in the future. In cancer immunotherapy, the PD-1/PD-L1 axis is critical, and lncRNAs play a key role in regulating this pathway. As of yet, no lncRNA-targeting therapies to regulate PD-1/PD-L1 have advanced to the clinical trial phase. There is a lack of information regarding the role of lncRNA in modulating the PD-1/PD-L1 axis in OSCC. Perhaps a novel approach to tumour immunotherapy involves targeting lncRNAs in tandem with anti-PD-1/PD-L1.[80] Due to its efficiency and low cost, the novel gene-editing technology CRISPR/Cas9 system has also shown promising clinical applications [76]. There are many methods for bringing lncRNA levels back to homeostasis, but this has not made their delivery in vivo any easier. The first challenge to be overcome is the identification of key lncRNAs that are amenable to being targeted in oral cancer, as

research on lncRNAs and oral cancer has only recently begun to emerge.

Conclusions and future perspectives

The ultimate goal of research into how to increase the survival rate of people with OSCC is the implementation of clinical trials, testing, novel treatment strategies, personalised medicine, and non-invasive specific biomarkers. The study of lncRNA's functional role has come a long way in a short period of time, but the field is still in its infancy, and many questions and challenges remain debatable. The exact role they play in human diseases is still a mystery. In conclusion, the extensive study of lncRNAs has given rise to renewed hope in the fight against cancer. Knowledge of lncRNA's expression, structure, and mechanisms will pave the way for a new intervention, leading to the identification of sensitive biomarkers and potential therapeutic targets.

Conflicts of Interest: None.

References

1. Haddad, R.I. and D.M. Shin, Recent advances in head and neck cancer. N Engl J Med, 2008. 359(11): p. 1143-54.
2. Lubin JH, Purdue M, Kelsey K, et al. Total exposure and exposure rate effects for alcohol and smoking and risk of head and neck cancer: a pooled analysis of case-control studies. Am J Epidemiol. 2009; 170:937-947.
3. Z. Shi and M. S. Stack, "Molecules of cell adhesion and extracellular matrix proteolysis in oral squamous cell carcinoma," Histology and Histopathology, vol. 25, no. 7, pp. 917–932, 2010.
4. N. Yamamoto, K. Sato, T. Yamauchi et al., "A 5-year activity report from the oral cancer center, Tokyo Dental College," The Bulletin of Tokyo Dental College, vol. 54, no. 4, pp. 265– 273, 2013.
5. M. Guttman and J. L. Rinn, "Modular regulatory principles of large non-coding RNAs," Nature, vol. 482, no. 7385, pp. 339– 346, 2012
6. Cabili MN, Trapnell C, Goff L, Koziol M, Tazon-Vega B, Regev A, et al. Integrative annotation of human large intergenic noncoding RNAs reveals global properties and specific subclasses. Genes Dev. 2011; 25:1915–27.
7. L. Ning, Y. C. Hu, S. Wang, and J. H. Lang, "Altered long noncoding RNAs and survival outcomes in ovarian cancer: a systematic review and meta-analysis (PRISMA compliant)," Medicine (Baltimore), vol. 97, no. 32, article e11481, 2018.
8. W. Kang, Q. Zheng, J. Lei, C. Chen, and C. Yu, "Prognostic value of long noncoding RNAs in patients with gastrointestinal cancer: a systematic review and meta-analysis," Disease Markers, vol. 2018, Article ID 5340894, 15 pages, 2018.
9. W. Pan, C. Wu, Z. Su et al., "Genetic polymorphisms of noncoding RNAs associated with increased head and neck cancer susceptibility: a systematic review and meta-analysis," Oncotarget, vol. 8, no. 37, pp. 62508–62523, 2017.
10. Y. Sanchez and M. Huarte, "Long non-coding RNAs: challenges for diagnosis and therapies," Nucleic Acid Therapeutics, vol. 23, no. 1, pp. 15–20, 2013.
11. K. Z. Thin, X. Liu, X. Feng, S. Raveendran, and J. C. Tu, "lncRNA-

DANCR: a valuable cancer related long non- coding RNA for human cancers," Pathology, Research and Practice, vol. 214, no. 6, pp. 801–805, 2018.

12. Kino T, Hurt DE, Ichijo T, Nader N, Chrousos GP. Noncoding RNA gas5 is a growth arrest- and starvation-associated repressor of the glucocorticoid receptor. Sci Signal 2010; 3: ra8.
13. Wang X, Ara i S, Song X, Reichar t D, Du K, Pascual G, Tempst P, Rosenfeld MG, Glass CK, Kurokawa R. Induced ncRNAs allosterically modify RNA-binding proteins in cis to inhibit transcription. Nature 2008; 454: 126-130.
14. Rinn JL, Kertesz M, Wang JK, Squazzo SL, Xu X, Brugmann SA, Goodnough LH, Helms JA, Far nham PJ, Segal E, Chang HY. Functional demarcation of active and silent chromatin domains in human HOX loci by noncoding RNAs. Cell 2007; 129:1311-1323.
15. Brown CJ, Ballab io A, Rupert JL, Lafr eniere RG, Grompe M, Tonlorenzi R, Willar d HF. A gene from the region of the human X inactivation centre is expressed exclusively from the inactive X chromosome. Nature 1991; 349: 38-44.
16. Li L, Gu M, You B, Shi S, Shan Y, Bao L, You Y. Long non-coding RNA ROR promotes proliferation, migration and chemoresistance of nasopharyngeal carcinoma. Cancer Sci 2016; 107: 1215-1222.
17. Gong Z, Zhang S, Zeng Z, Wu H, Yang Q, Xiong F, Shi L, Yang J, Zhang W, Zhou Y, Zeng Y, Li X, Xiang B, Peng S, Zhou M, Li X, Tan M, Li Y, Xiong W, Li G. LOC401317, a p53-regulated long non-coding RNA, inhibits cell proliferation and induces apoptosis in the nasopharyngeal carcinoma cell line HNE2. PLoS One 2014; 9: e110674.
18. Huang G, He X, Wei XL. LncRNA NEAT1 promotes cell proliferation and invasion by regulating miR365/RGS20 in oral squamous cell carcinoma. Oncol Rep 2018; 39: 1948-1956.
19. Wang P, Wu T, Zhou H, Jin Q, He G, Yu H, Xuan L, Wang X, Tian L, Sun Y, Liu M, Qu L. Long noncoding RNA NEAT1 promotes laryngeal squamous cell cancer through regulating miR-107/ CDK6 pathway. J Exp Clin Cancer Res 2016; 35: 22.
20. Zhang L, Hu D, Zou L. Low expression of lncRNA MEG3 promotes the progression of oral squamous cell carcinoma by targeting miR-21. Eur Rev Med Pharmacol Sci 2018; 22: 8315-8323.
21. Wu Y, Zhang L, Zhang L, Wang Y, Li H, Ren X, Wei F, Yu W, Liu T, Wang X, Zhou X, Yu J, Hao X. 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 2015; 46: 2586-2594.
22. Huarte, M. The emerging role of lncRNAs in cancer. Nat. Med. 2015, 21, 1253–1261.
23. Xu, Y.; Jiang, E.; Shao, Z.; Shang, Z. Long noncoding RNAs in the metastasis of oral squamous cell carcinoma. Front. Oncol. 2020, 10, 1–15.
24. Liu, K.; Gao, L.; Ma, X.; Huang, J.; Chen, J.; Zeng, L.; Ashby, C.; Zou, C.; Chen, Z. Long non-coding RNAs regulate drug resistance in cancer. Mol. Cancer 2020, 19, 54.
25. Chandra Gupta, S.; Nandan Tripathi, Y. Potential of long non-coding RNAs in cancer patients: From biomarkers to

therapeutic targets. Int. J. Cancer 2017, 140, 1955–1967.

26. Li, M.; Ding, X.; Zhang, Y.; Li, X.; Zhou, H.; Yang, L.; Li, Y.; Yang, P.; Zhang, X.; Hu, J.; et al. Antisense oligonucleotides targeting lncRNA AC104041.1 induces antitumor activity through Wnt2B/_-catenin pathway in head and neck squamous cell carcinomas. Cell Death Dis. 2020, 11, 672.
27. Zhang, C.; Bao, C.; Zhang, X.; Lin, X.; Pan, D.; Chen, Y. Knockdown of lncRNA LEF1-AS1 inhibited the progression of oral squamous cell carcinoma (OSCC) via Hippo signaling pathway. Cancer Biol. Ther. 2019, 20, 1213–1222.
28. Choudhari, R.; Sedano, M.; Harrison, A.; Subramani, R.; Lin, K.; Ramos, E.; Lakshmanaswamy, R.; Gadad, S. Long noncoding RNAs in cancer: From discovery to therapeutic targets. Adv. Clin. Chem. 2020, 95, 105–147.
29. Liu, B.; Sun, L.; Liu, Q.; Gong, C.; Yao, Y.; Lv, X.; Lin, L.; Yao, H.; Su, F.; Li, D.; et al. A cytoplasmic NF-kappaB interacting long noncoding RNA blocks IkappaB phosphorylation and suppresses breast cancer metastasis. Cancer Cell 2015, 27, 370–381.
30. Huang, W.; Cui, X.; Chen, J.; Feng, Y.; Song, E.; Li, J.; Liu, Y. Long non-coding RNA NKILA inhibits migration and invasion of tongue squamous cell carcinoma cells via suppressing epithelial-mesenchymal transition. Oncotarget 2016, 7, 62520–62532.
31. Liu, Z.;Wu, C.; Xie, N.;Wang, P. Long non-coding RNA MEG3 inhibits the proliferation and metastasis of oral squamous cell carcinoma by regulating the WNT/beta-catenin signaling pathway. Oncol. Lett. 2017, 14, 4053–4058.
32. Tan, J.; Xiang, L.; Xu, G. LncRNA MEG3 suppresses migration and promotes apoptosis by sponging miR-548d-3p to modulate JAK-STAT pathway in oral squamous cell carcinoma. IUBMB Life 2019, 71, 882–890.
33. Wang, X.; Li, H.; Shi, J. LncRNA HOXA11-AS promotes proliferation and cisplatin resistance of oral squamous cell carcinoma by suppression of miR-214-3p expression. Biomed. Res. Int. 2019, 2019, 1–11.
34. Meng, X.; Lou, Q.Y.; Yang, W.Y.; Wang, Y.R.; Chen, R.; Wang, L.; Xu, T.; Zhang, L. The role of non-coding RNAs in drug resistance of oral squamous cell carcinoma and therapeutic potential. Cancer Commun. 2021, 41, 981–1006.
35. Fang, Z.; Zhao, J.; Xie, W.; Sun, Q.; Wang, H.; Qiao, B. LncRNA UCA1 promotes proliferation and cisplatin resistance of oral squamous cell carcinoma by sunppressing miR-184 expression. Cancer Med. 2017, 6, 2897–2908.
36. Zhou X, Liu S, Cai G, Kong L, Zhang T, Ren Y, Wu Y, Mei M, Zhang L, Wang X. Long non coding RNA MALAT1 promotes tumor growth and metastasis by inducing epithelial-mesenchymal transition in Oral squamous cell carcinoma. Sci Rep. 2015; 5:15972.
37. Arunkumar G, Murugan AK. Prasanna Srinivasa Rao H, Subbiah S, Rajaraman R, Munirajan AK. Long non-coding RNA CCAT1 is overexpressed in oral squamous cell carcinomas and predicts poor prognosis. Biomedical Reports. 2017;6(4):455–62.

38. Shiah SG, Hsiao JR, Chang WM, Chen YW, Jin YT, Wong TY, Huang JS, Tsai ST, Hsu YM, Chou ST, et al. Downregulated miR329 and miR410 promote the proliferation and invasion of oral squamous cell carcinoma by targeting Wnt-7b. Cancer Res. 2014;74(24):7560–72.
39. Yang YT, Wang YF, Lai JY, Shen SY, Wang F, Kong J, Zhang W, Yang HY. Long non-coding RNA UCA1 contributes to the progression of oral squamous cell carcinoma by regulating the WNT/beta-catenin signalling pathway. Cancer Sci. 2016;107(11):1581–9.
40. Li X, Ma C, Zhang L, Li N, Zhang X, He J, He R, Shao M, Wang J, Kang L, et al. LncRNAAC132217.4, a KLF8-regulated long non-coding RNA, facilitates oral squamous cell carcinoma metastasis by upregulating IGF2 expression. Cancer Lett. 2017; 407:45–56.
41. Liu Z, Li H, Fan S, Lin H, Lian W. STAT3-induced upregulation of long noncoding RNA HNF1A-AS1 promotes the progression of oral squamous cell carcinoma via activating notch signaling pathway. Cancer Biol Ther. 2018; 1:10.
42. Zhu G, Wang S, Chen J, Wang Z, Liang X, Wang X, Jiang J, Lang J, Li L. Long noncoding RNA HAS2-AS1 mediates hypoxia-induced invasiveness of oral squamous cell carcinoma. Mol Carcinog. 2017;56(10):2210–22.
43. Arunkumar G, Deva Magendhra Rao AK, Manikandan M, Arun K, Vinothkumar V, Revathidevi S, Rajkumar KS, Rajaraman R, Munirajan AK. Expression profiling of long non-coding RNA identifies linc-RoR as a prognostic biomarker in oral cancer. Tumour Biol. 2017;39(4):1010428317698366.
44. Zhang CZ. Long intergenic non-coding RNA 668 regulates VEGFA signalling through inhibition of miR-297 in oral squamous cell carcinoma. Biochem Biophys Res Commun. 2017;489(4):404–12.
45. Yu X, Li Z, Zheng H, Chan MT, Wu WK. NEAT1: A novel cancer-related long non-coding RNA. Cell Prolif. 2017;50(2): e12329.
46. Nishiyama K, Maruyama R, Niinuma T, Kai M, Kitajima H, Toyota M, Hatanaka Y, Igarashi T, Kobayashi J-I, Ogi K, et al. Screening for long noncoding RNAs associated with oral squamous cell carcinoma reveals the potentially oncogenic actions of DLEU1. Cell Death Dis. 2018;9(8):826.
47. Dong Y, Wu W. Downregulation of lncRNA CASC2 promotes the postoperative local recurrence of early oral squamous cell carcinoma. Eur Arch Otorhinolaryngol. 2019;276(2):605–10.
48. Yang, Y.; Chen, D.; Liu, H.; Yang, K. Increased expression of lncRNA CASC9 promotes tumor progression by suppressing autophagy-mediated cell apoptosis via the AKT/mTOR pathway in oral squamous cell carcinoma. Cell Death Dis. 2019, vol. 10, no. 2, p. 41.
49. Huang SH and O'Sullivan B: Oral cancer: Current role of radiotherapy and chemotherapy. Med Oral Patol Oral Cir Bucal 18: e233-e240, 2013.
50. Gomes CC, de Sousa SF, Calin GA and Gomez RS: The emerging role of long noncoding RNAs in oral cancer. Oral Surg Oral Med Oral Pathol Oral Radiol 123: 235-241, 2017.
51. Luo X, Qiu Y, Jiang Y, Chen F, Jiang L, Zhou Y, Dan H, Zeng X, Lei YL and

Chen Q: Long non-coding RNA implicated in the invasion and metastasis of head and neck cancer: Possible function and mechanisms. Mol Cancer 17: 14, 2018.

52. Qiu YL, Liu YH, Ban JD, Wang WJ, Han M, Kong P and Li BH: Pathway analysis of a genome wide association study on a long noncoding RNA expression profile in oral squamous cell carcinoma. Oncol Rep 41: 895-907, 2019.
53. Kong J, Sun W, Zhu W, Liu C, Zhang H and Wang H: Long noncoding RNA LINC01133 inhibits oral squamous cell carcinoma metastasis through a feedback regulation loop with GDF15. J Surg Oncol 118: 1326-1334, 2018.
54. Kong XP, Yao J, Luo W, Feng FK, Ma JT, Ren YP, Wang DL and Bu RF: The expression and functional role of a FOXC1 related mRNA-lncRNA pair in oral squamous cell carcinoma. Mol Cell Biochem 2014, 394: 177-186.
55. Li Y, Zhang J, Pan J, Feng X, Duan P, Yin X, Xu Y, Wang X and Zou S: Insights into the roles of lncRNAs in skeletal and dental diseases. Cell Biosci 8: 8, 2018.
56. Chang SM and Hu WW: Long non-coding RNA MALAT1 promotes oral squamous cell carcinoma development via microRNA-125b/STAT3 axis. J Cell Physiol 233: 3384-3396, 2018.
57. Gonzalez-Ramirez I, Soto-Reyes E, Sanchez-Perez Y, Herrera LA and Garcia-Cuellar C: Histones and long non-coding RNAs: The new insights of epigenetic deregulation involved in oral cancer. Oral Oncol 50: 691-695, 2014.
58. Yang CM, Wang TH, Chen HC, Li SC, Lee MC, Liou HH, Liu PF, Tseng YK, Shiue YL, Ger LP and Tsai KW: Aberrant DNA hypermethylation-silenced SOX21-AS1 gene expression and its clinical importance in oral cancer. Clin Epigenetics 8: 129, 2016.
59. Bolha, L.; Ravnik-Glavaˇc, M.; Glavaˇc, D.J. Long noncoding RNAs as biomarkers in cancer. Dis. Markers 2017, 2017, 1–14.
60. Zhang, X.; Guo, B.; Zhu, Y.; Xu, W.; Ning, S.; Liu, L. Up-regulation of plasma lncRNA CACS15 distinguished early-stage oral squamous cell carcinoma patient. Oral Dis. 2020, 26, 1619–1624.
61. Fang, X.; Tang, Z.; Zhang, H.; Quan, H. Long non-coding RNA DNM3OS/miR-204-5p/HIP1 axis modulates oral cancer cellviability and migration. J. Oral. Pathol. Med. 2020, 49, 865–875.
62. Tang, H.; Wu, Z.; Zhang, J.; Su, B. Salivary lncRNA as a potential marker for oral squamous cell carcinoma diagnosis. Mol. Med. Rep. 2013, 7, 761–766.
63. Yu, J.; Liu, Y.; Guo, C.; Zhang, S.; Gong, Z.; Tang, Y.; Yang, L.; He, Y.; Lian, Y.; Li, X.; et al. Upregulated long non-coding RNA LINC00152 expression is associated with progression and poor prognosis of tongue squamous cell carcinoma. J. Cancer 2017, 8, 523–530.
64. Hong, Y.; He, H.; Sui,W.; Zhang, J.; Zhang, S.; Yang, D. Long non-coding RNA H19 promotes cell proliferation and invasion by acting as a ceRNA of miR138 and releasing EZH2 in oral squamous cell carcinoma. Int. J. Oncol. 2018, 52, 901–912.
65. Ma, Y.; Hu, X.; Shang, C.; Zhong, M.; Guo, Y. Silencing of long non-coding RNA CCAT2 depressed malignancy of oral squamous cell carcinoma via

Wnt/beta-catenin pathway. Tumour. Biol. 2017, 39, 1–9.

66. Liang, S.; Zhang, S.; Wang, P.; Yang, C.; Shang, C.; Yang, J.;Wang, J. LncRNA, TUG1 regulates the oral squamous cell carcinoma progression possibly via interacting with Wnt/beta-catenin signaling. Gene 2017, 608, 49–57.
67. Yao, C.; Kong, F.; Zhang, S.; Wang, G.; She, P.; Zhang, Q. Long non-coding RNA BANCR promotes proliferation and migration in oral squamous cell carcinoma via MAPK signaling pathway. J. Oral Pathol. Med. 2021, 50, 308–315.
68. Huang, W.; Cao, J.; Peng, X. LINC01234 facilitates growth and invasiveness of oral squamous cell carcinoma through regulating the miR-637/NUPR1 axis. Biomed. Pharmacother. 2019, 120, 1–6
69. Liu, D.; Jian, X.; Xu, P.; Zhu, R.;Wang, Y. Linc01234 promotes cell proliferation and metastasis in oral squamous cell carcinoma via miR-433/PAK4 axis. BMC Cancer 2020, 20, 107.
70. Liu, Z.; Zhou, W.; Lin, C.; Wang, X.; Zhang, X.; Zhang, Y.; Yang, R.; Chen, W.; Cao, W. Dysregulation of FOXD2-AS1 promotes cell proliferation and migration and predicts poor prognosis in oral squamous cell carcinoma: A study based on TCGA data. Aging 2020, 13, 2379–2396.
71. Zhang, C.Z. Long non-coding RNA FTH1P3 facilitates oral squamous cell carcinoma progression by acting as a molecular sponge of miR-224-5p to modulate fizzled 5 expression. Gene 2017, 607, 47–55.
72. Liu, S.J.; Dang, H.X.; Lim, D.A.; Feng, F.Y.; Maher, C.A. Long noncoding RNAs in cancer metastasis. Nat. Rev. Cancer 2021, 21, 446–460.
73. Wang, Y.; Zhang, X.; Wang, Z.; Hu, Q.; Wu, J.; Li, Y.; Ren, X.; Wu, T.; Tao, X.; Chen, X.; et al. LncRNA-p23154 promotes the invasion-metastasis potential of oral squamous cell carcinoma by regulating Glut1-mediated glycolysis. Cancer Lett. 2018, 434, 172–183.
74. Zhang, S.; Ma, H.; Zhang, D.; Xie, S.; Wang,W.; Li, Q.; Lin, Z.; Wang, Y. LncRNA KCNQ1OT1 regulates proliferation and cisplatin resistance in tongue cancer via miR-211-5p mediated Ezrin/Fak/Src signaling. Cell Death Dis. 2018, 9, 742.
75. Winkle, M.; El-Daly, S.M.; Fabbri, M.; Calin, G.A. Noncoding RNA therapeutics—Challenges and potential solutions. Nat. Rev. Drug Discov. 2021, 20, 629–651.
76. Yang, J.; Meng, X.; Pan, J.; Jiang, N.; Zhou, C.; Wu, Z.; Gong, Z. CRISPR/Cas9-mediated noncoding RNA editing in human cancers. RNA Biol. 2018, 15, 35–43.
77. Tao, B.; Wang, D.; Yang, S.; Liu, Y.; Wu, H.; Li, Z.; Chang, L.; Yang, Z.; Liu, W. Cucurbitacin B inhibits cell proliferation by regulating x-inactive specific transcript expression in tongue cancer. Front. Oncol. 2021, 11, 1–11.
78. Chang, K.; Hung, W.; Chou, C.; Tu, H.; Chang, S.; Liu, Y.; Liu, C.; Lin, S. MIR31HGLncRNA drives oncogenicity by inhibiting the limb-bud and heart development gene (LBH) during oral carcinoma. Int. J. Mol. Sci. 2021, 22, 8383.
79. Saâda-Bouzid, E.; Defaucheux, C.; Karabajakian, A.; Coloma, V.; Servois, V.; Paoletti, X.; Even, C.; Fayette, J.; Guigay, J.; Loirat, D.; et al.

Hyperprogression during anti-PD-1/PD-L1 therapy in patients with recurrent and/or metastatic head and neck squamous cell carcinoma. Ann. Oncol. 2017, 28, 1605–1611.

80. Nishino, M.; Ramaiya, N.; Hatabu, H.; Hodi, F. Monitoring immune-checkpoint blockade: Response evaluation and biomarker development. Nat. Rev. Clin. Oncol. 2017, 14, 655–668.
81. Kondo Y, Shinjo K, Katsushima K. Long non-coding RNAs as an epigeneticregulator in human cancers. Cancer Sci. 2017;108(10):1927–33.
82. Su X, Malouf GG, Chen Y, Zhang J, Yao H, Valero V, Weinstein JN, Spano JP, Meric-Bernstam F, Khayat D, et al. Comprehensive analysis of long non-coding RNAs in human breast cancer clinical subtypes. Oncotarget. 2014;5(20):9864–76.
83. Melo CP, Campos CB, Rodrigues Jde O, Aguirre-Neto JC, Atalla A, Pianovski MA, Carbone EK, Lares LB, Moraes-Souza H, Octacilio-Silva S, et al. Long non-coding RNAs: biomarkers for acute leukaemia subtypes. Br J Haematol. 2016;173(2):318–20.
84. Bhan A, Mandal SS. LncRNA HOTAIR: A master regulator of chromatin dynamics and cancer. Biochim Biophys Acta. 2015;1856(1):151–64.
85. Tan DSW, Chong FT, Leong HS, Toh SY, Lau DP, Kwang XL, Zhang X, Sundaram GM, Tan GS, Chang MM, et al. Long noncoding RNA EGFR-AS1 mediates epidermal growth factor receptor addiction and modulates treatment response in squamous cell carcinoma. Nat Med. 2017;23(10):1167–75.
86. Fayda M, Isin M, Tambas M, Guveli M, Meral R, Altun M, Sahin D, Ozkan G, Sanli Y, Isin H, et al. Do circulating long non-coding RNAs (lncRNAs) (LincRNA-p21, GAS 5, HOTAIR) predict the treatment response in patients with head and neck cancer treated with chemoradiotherapy? Tumour Biol. 2016;37(3):3969–78.
87. Mourtada-Maarabouni M, Pickard MR, Hedge VL, Farzaneh F, Williams GT. GAS5, a non-protein-coding RNA, controls apoptosis and is downregulated in breast cancer. Oncogene. 2009;28(2):195–208.
88. Yu T, Wu Y, Helman JI, Wen Y, Wang C, Li L. CXCR4 promotes oral squamous cell carcinoma migration and invasion through inducing expression of MMP-9 and MMP-13 via the ERK signalling pathway. Mol Cancer Res. 2011;9(2):161–72.
89. Shao T, Huang J, Zheng Z, Wu Q, Liu T, Lv X. SCCA, TSGF, and the Long non-coding RNA AC007271.3 are effective biomarkers for diagnosing Oral squamous cell carcinoma. Cell Physiol Biochem. 2018;47(1):26–38.
90. Fatima R, Akhade VS, Pal D, Rao SM. Long noncoding RNAs in development and cancer: potential biomarkers and therapeutic targets. Mol Cell Ther. 2015; 3:5.
91. Silva A, Bullock M, Calin G. The clinical relevance of long noncoding RNAs in cancer. Cancers (Basel). 2015; 7:2169-2182.
92. Colley SM, Leedman PJ. SRA and its binding partners: an expanding role for RNA-binding coregulators in nuclear receptor mediated gene regulation. Crit Rev Biochem Mol Biol. 2009;44: 25-33.
93. Zhang R, Xia Y, Wang Z, Zheng J, Chen Y, Li X, Wang Y, Ming H. Serum long non-coding RNA MALAT-1

protected by exosomes is up-regulated and promotes cell proliferation and migration in non-small cell lung cancer. Biochem Biophys Res Commun. 2017;490(2):406–14.