PROFESSOR MONICA PENTENERO (Orcid ID : 0000-0003-3972-1203)

PROFESSOR CAMILE S FARAH (Orcid ID : 0000-0002-1642-6204)

DR ILIAS ALEVIZOS (Orcid ID : 0000-0001-5331-1652)

Article type : WWOM proceedings

World Workshop on Oral Medicine VII

Clinical evidence of differential expression of lncRNAs in oral squamous cell carcinoma: a scoping review

^a Pentenero M, ^b Bowers LM, ^c Jayasinghe R, ^d Yap T, ^e Cheong SC, ^f Kerr AR, ^g Farah CS, ^h Alevizos I

^a Department of Oncology, Oral Medicine and Oral Oncology Unit, University of Turin, Italy

^b Department of Stomatology, Division of Oral Medicine, Medical University of South Carolina, Charleston, SC, USA

^c Department of Oral Medicine and Periodontology, Faculty of Dental Sciences, University of Peradeniya, Sri Lanka

^d Melbourne Dental School, University of Melbourne, Australia

^e Head and Neck Cancer Research Team, Cancer Research Malaysia, No. 1, Jalan SS12/1A, Subang Jaya, Selangor, Malaysia

^f New York University College of Dentistry, New York, NY, USA

^g Australian Centre for Oral Oncology Research & Education, UWA Dental School, Faculty of Health and Medical Sciences, University of Western Australia, Perth WA 6009 Australia

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/ODI.13076](https://doi.org/10.1111/ODI.13076)

This article is protected by copyright. All rights reserved

^h Sjogren's Syndrome and Salivary Gland Dysfunction Unit, NIDCR/NIH, Bethesda, MD, 20892, USA

Running title: lncRNAs' differential expression in OSCC

Word count: 4470

Correspondence

Prof. Monica Pentenero

Department of Oncology, Oral Medicine and Oral Oncology Unit, University of Turin, Italy

Regione Gonzole 10, 10043 Orbassano (TO) – ITALY

e-mail: monica.pentenero@unito.it

Funding information

The study group which realized the present review was supported by the World Workshop on Oral Medicine

Abstract

Background. Long non-coding RNAs (lncRNAs) have important roles in regulating gene expression pertaining to cell proliferation, survival, migration and genomic stability. Dysregulated expression of lncRNAs is implicated in cancer initiation, progression and metastasis.

Objectives. Explore, map and summarize the extent of evidence from clinical studies investigating the differential expression of lncRNAs in oral/tongue squamous cell carcinoma.

Methods. PubMed, Scopus, and Web of Science were used as search engines. Clinical, full-length, English language studies were included. PRISMA-ScR protocol was used to evaluate and present results. The present scoping review summarizes relationships of the differential expression of lncRNAs with the presence of tumour and with clinico-pathological features including survival.

Results. Almost half of the investigated transcripts have been explored in more than one study, yet not always with consistent results. The collected data were also compared to the limited studies investigating oral epithelial dysplasia. Data are not easily comparable, first because of different methods used to define what differential expression is, and second because only a limited number of studies performed multivariate analyses to identify clinico-pathological features associated with the differentially expressed lncRNAs.

Conclusions. Standard methods and more appropriate data analyses are needed in order to achieve reliable results from future studies.

Abstract word count: 200

Key words: oral squamous cell carcinoma, lncRNA, epigenetics, GAS5, H19, HIFCAR, HOTAIR, HULC, LINC00152, LINC00673, MALAT1, MEG3, NEAT1, UCA1

Introduction

Cancer is a clonal genetic disease of somatic cells based on the random development and accumulation of genetic and epigenetic changes. Even if the central dogma of molecular biology mainly focuses on the protein-coding genome, at least 80% of the genome encodes regulatory information through non-coding (nc) RNA transcripts.

Among ncRNAs, long non-coding RNAs (lncRNA) play important roles in gene regulation pertaining to cell proliferation, survival, migration and genomic stability. Dysregulation of expression of lncRNAs has been implicated in cancer initiation, progression and metastasis.

Dysregulation of lncRNAs expression due to the presence of cancer can be assessed through different methods such as RNASeq, array or PCR depending on the research target. Conversely, when looking at cancer patients it can be argued that high or low expression of lncRNAs could serve as a tissue-specific biomarker associated with clinico-pathological features including survival. Given the large number of lncRNAs reported, coupled with heterogeneous methodology and patient populations investigated in the clinical studies, a scoping review was selected to map such emerging evidence.

The present scoping review aims to summarize evidence from the literature about the differential expression of lncRNAs in oral/tongue squamous cell carcinoma (OSCC/TSCC) and about the role of lncRNAs in OSCC/TSCC contrasting clinico-pathological features with differentially expressed (DE)-lncRNAs. The present review focuses solely on clinical studies reporting such correlations in order to determine both the extent of the available research and the methodology employed. Methods and the work-flow are fully described in the supplementary data file (**Suppl file**).

The reference standard to define differential expression

Almost the entirety of the publications examined the differential expression associated with the presence of disease, comparing tumour tissue (TT) versus adjacent “control” normal mucosa (ANM) sampled at the time of tumour excision from the normal appearing tissue unconnected to

the excised cancer specimen. Nevertheless, ANM was inconsistently defined. Even if only 4 out of 60 studies did not use paired samples from the same patient, a clear definition of what was considered as ANM can be found in only 11 studies where it was often reported as a distance from TT of 15 mm (ranging from 10 to 30 mm) (**Suppl Tab 1**). The quantifiable levels of the lncRNA transcript “strands” detectable in tissue were investigated. Most studies defined the presence of DE-lncRNA based on the relative expression of the transcript normalized to the expression of a reference-standard gene (e.g. β -actin mRNA) comparing TT and ANM. Only a limited number of studies (11 out of 60) applied a fold-change not always including a false discovery rate cut-off (**Suppl Tab 1**). Finally, the use of different techniques aiming to detect the lncRNA expression could represent a potential bias when comparing studies investigating the expression of same transcript through RNASeq, or array, or PCR (**Suppl Tab 1**). These different methods rendered the results comparison difficult and could be responsible for inconsistent and contradicting results. Moreover, it is unknown if the ANM used harboured DE-lncRNAs as a consequence of a field cancerization effect, thus altering the results.

Presence of disease; dysplasia or SCC versus normal mucosa

In 2013 Tang *et al.* first reported data on the expression profile of lncRNAs in OSCC and assessed a group of previously established cancer-associated transcripts: HOTAIR; MALAT- 1; NEAT-1; HULC; MEG- 3; UCA1 (Tang *et al.*, 2013). They compared four TT-ANM pairs: even if DE trends were observed, the authors were unable to demonstrate significant DEs. The same transcripts were subsequently explored in several studies with larger sample sizes, thereby improving knowledge about their potential involvement in OSCC and TSCC. Supplementary Table 1 summarizes current data about DE-lncRNAs in presence of OSCC/TSCC.

DE of HOTAIR has been assessed in six independent studies analysing 323 patients with results supporting its overexpression (Arunkumar *et al.*, 2017a; Fang *et al.*, 2014; Lu *et al.*, 2017; Wu and Xie, 2015; Wu *et al.*, 2015; Zou *et al.*, 2015). Conversely, the only study that examined HOTAIR expression in dysplastic lesions did not find significant DE (Gibb *et al.*, 2011). Even if these are to be considered preliminary results still to be validated, they may suggest a potential shift to the overexpression of this transcript along with the progression towards malignant transformation.

The expression of MALAT1 has been addressed by six studies finding a significant overexpression in four of these. Three studies addressing TSCC (overall 159 patients) found significant overexpression (Fang *et al.*, 2014; Fang *et al.*, 2016; Liang *et al.*, 2017a). When dealing with OSCC, two studies with similar sample size showed contrasting results, as only one was able to find significant DE (Arunkumar *et al.*, 2017a; Zhou *et al.*, 2015). One report analysing The Cancer

Genome Atlas (TCGA) dataset found no significant DE neither for OSCC (15 cases) nor for TSCC (13 cases) (Zou *et al*, 2015). The only study that addressed MALAT-1 expression in dysplastic lesions found a significant underexpression (Gibb *et al*, 2011), suggesting that the overexpression in OSCC, if proven, could be related to the progression from dysplasia to carcinoma.

Two studies following the first lncRNA report of Tang *et al*. in OSCC (Tang *et al*, 2013); one on a TSCC cohort of 94 patients (Fang *et al*, 2014) and another on a report addressing TCGA data (Zou *et al*, 2015) failed to establish NEAT1 and HULC as DE. Two studies, investigating 58 and 30 OSCC patients respectively, found a significant overexpression of NEAT1 (Liu *et al*, 2018a; Huang *et al*, 2018a). Interestingly, these results demonstrated a downregulation of NEAT1 in presence of dysplasia, thus suggesting a potential shift in its expression during tumourigenesis (Gibb *et al*, 2011; Jia *et al*, 2018).

Three studies assessed DE of UCA1 with quite consistent results, irrespective of the oral anatomical subsite. The significant overexpression of UCA1 was the most significant DE observed by Fang in a cohort of 95 TSCCs ($p < .0001$) (Fang *et al*, 2014) and significant DE was reported in two groups of 124 TSCCs and 30 OSCCs respectively (Yang *et al*, 2016; Fang *et al*, 2017). Of interest UCA1 overexpression was not observed in presence of dysplasia (Gibb *et al*, 2011).

The expression of MEG3 has been assessed in five studies and a significant underexpression is consistently reported in both OSCC and TSCC (Fang *et al*, 2014; Jia *et al*, 2014; Liu *et al*, 2017b; Zou *et al*, 2015). Non-significant DE was found in a study examining 60 OSCCs compared to a limited number of controls (8 cases) (Arunkumar *et al*, 2017a). Of interest a study addressing the TCGA dataset identified a significant underexpression in OSCC but not in TSCC (Zou *et al*, 2015).

Data on GAS5 expression are scant; an analysis of a TCGA dataset (28 patients) and data from an array study (13 cases) both suggested an underexpression in both OSCC and TSCC (Zou *et al*, 2015; Yang *et al*, 2017). Conversely GAS5 DE was not observed in dysplastic lesions (Gibb *et al*, 2011).

Yu *et al*. validated the overexpression in TSCC of LINC00152 (Yu *et al*, 2017b) and LINC00673 (Yu *et al*, 2017a). The overexpression of these two long intergenic ncRNAs had previously been reported to be highly significant ($p < 0.001$) in two independent gene expression profiling studies addressing 26 TSCCs (GEO datasets GSE9844 (Ye *et al*, 2008)) and 167 oral or oropharyngeal SCCs (GSE30784 (Chen *et al*, 2008)). The overexpression of LINC00152 was later found also in 40 OSCCs ($p < 0.01$) (Li *et al*, 2018).

Other DE-lncRNAs reported in independent OSCC studies included overexpression of FTH1P3 (Zhang, 2017b; Zhang *et al*, 2015b; Peng *et al*, 2011), overexpression of HIFCAR (Peng *et al*, 2011; Shih *et al*, 2017), and overexpression of CCAT2 (Ma *et al*, 2017; Zhou *et al*, 2016).

The overexpression of LINC00511 in TSCC has been reported in two independent array studies analysing tissues from 46 patients (Ding *et al*, 2018; Ye *et al*, 2008); while the underexpression of C14orf132, C17orf76-AS1, EPB41L4A-AS1, LINC00341, OTTHUM00000159695 and the overexpression of LINC00094, LINC00520, SNHG15/SNORA9 have been reported in one microarray study (Ye *et al*, 2008). Of note the same differential expressions were previously reported in a microarray study investigating a mixed cohort of oral and oropharyngeal SCCs, where data from OSCCs cannot be separated (Chen *et al*, 2008).

PTENp1 was nearly absent in OSCC compared with adjacent normal tissues (Gao *et al*, 2017) resulting in a significant underexpression also found in the presence of dysplasia (Gibb *et al*, 2011), thus suggesting an early involvement of this transcript in tumorigenesis.

The lncRNA colon cancer associated transcripts CCAT1 and CCAT2 have been reported to behave differently in OSCC; CCAT1 was found to be overexpressed in only 27% of OSCC (Arunkumar *et al*, 2017b), while CCAT2 was found to be significantly overexpressed (Ma *et al*, 2017; Zhou *et al*, 2016).

Anatomical subsite as a potential confounding factor

A large survey of lncRNA expression within 64 solid cancers found dysregulated transcripts differentially expressed across distinct cancer types thus suggesting that many lncRNAs may serve as tissue-specific biomarkers (Brunner *et al*, 2012). Indeed, when addressing the overall HNSCC cohort from TCGA, Zou *et al*. were unable to find any significant dysregulation of many lncRNAs previously linked to cancer, including HOTAIR, MALAT1, ANRIL, NEAT1, and UCA1. Of interest however, was the finding that HOTAIR was significantly overexpressed in tumours arising from oral subsites other than tongue, and conversely GAS5 was downregulated only in TSCCs but not in tumours arising from other oral subsites.

Finally, none of the aforementioned lncRNAs were determined to be dysregulated in laryngeal SCC (Zou *et al*, 2015). Similarly, Arunkumar *et al*. assessed lncRNA expression in OSCCs finding that H19, AP5M1 and MALAT1 showed different expression levels when compared with data from the TCGA HNSCC cohort (Arunkumar *et al*, 2017a). Such evidence once more highlights the tissue-specific expression of lncRNA and the fact that HNSCC is a heterogeneous group of tumours with different epigenetic alterations.

When considering the overexpression of HOTAIR, analyses also addressing the anatomical subsite revealed quite contrasting results. When dealing only with TSCC, three studies overall addressed

149 TSCCs (Fang *et al*, 2014; Zou *et al*, 2015; Wu *et al*, 2015), with only one of them able to find significant overexpression of HOTAIR (Wu *et al*, 2015).

Two OSCC cohorts including TSCC, analysing 126 patient samples, were able to detect a significant overexpression of HOTAIR (Wu and Xie, 2015; Wu *et al*, 2015). In a cohort where TSCC accounted for just 20% of cases (with 38% of lesions involving the buccal mucosa), the overexpression of HOTAIR was found in patients with betel quid with tobacco chewing habit but not in patients with a smoking habit (Arunkumar *et al*, 2017a). This could suggest adjunctive potential interconnections among known risk habits and oral anatomical subsite. DE may be affected by the different risk factors that are associated with subsite; betel quid use associated with buccal mucosa and heavy alcohol consumption/tobacco smoking associated with tongue.

Similarly, there is heterogeneity in the results from studies assessing H19 expression, most likely due to the analysis of lesions from different anatomical subsites. In TSCC, one study investigating 26 patients showed significant underexpression in TT when compared to ANM (Ye *et al*, 2008), while two studies with a “mixed” OSCC cohort reported a significant overexpression, and one showed an absence of DE (Arunkumar *et al*, 2017a; Hong *et al*, 2018).

PTENp1 was nearly absent in OSCC compared with ANM and its down-regulation also seems to be influenced by anatomical subsite. In a group of 62 OSCCs under expression of PTENp1 was observed in all the lesions from buccal mucosa or gingiva, in 71% of lesions from the lip and in 77% of lesions from the tongue (Gao *et al*, 2017).

Arunkumar *et al*. reported that overexpression of CCAT1 was found in only 27% of 60 OSCC cases, but the majority of the CCAT1 overexpressing samples (62.5%) were tumours from buccal mucosa. Moreover, in the presence of tobacco smoking or tobacco chewing/smoking a high expression of CCAT1 was observed. Despite the lack of statistical analyses supporting significant differences, such data suggest that the anatomical subsite and exposure to different environmental risk factors could mediate the differential expression of CCAT1. Additionally, these data were consistent with evidence from the TCGA database where a similar CCAT1 overexpression was observed in cases with a history of tobacco abuse ($p < 0.0001$), suggesting the role of tobacco smoking/chewing in determining a DE of CCAT1 (Arunkumar *et al*, 2017b).

The observed heterogeneity in the DE of lncRNAs in SCCs arising from different anatomic sites, suggests that changes in lncRNA expression may contribute to the emergence of site-specific characteristics in HNSCCs, even in OSCCs arising from different intraoral subsites. In particular, the tongue and the buccal mucosa had distinctive signatures in lncRNA expression. Overall, only four

studies fully described the anatomical site of OSCC and investigated such feature in the light of DE-lncRNAs (Gao *et al*, 2017; Ma *et al*, 2017; Guo *et al*, 2018; Liu *et al*, 2017a), two studies just compared OSCCs and TSCCs (Wu *et al*, 2015; Arunkumar *et al*, 2018) and one study compared anatomical subsite from TSCCs (Ding *et al*, 2018). Therefore, evidence for the potential DE of lncRNAs across anatomical subsites, and the environmental risk factors linked to such subsite cancers, should be precisely assessed in larger and better-defined cohorts, stratifying patients according to exposure to risk habits.

DE-lncRNAs and clinico-pathological features

More than half of the studies (41 out of 60) searched for associations between DE-lncRNA transcripts and clinico-pathological features, including age/gender, risk habits, staging and survival. Most of these divided SCC tissues into high-expression and low-expression groups according to the median expression level of all samples; others based their analyses on relative expression levels (**Table 1**). Regardless, these varying approaches complicate interstudy comparisons of the reported results.

Age-gender

Potential links of lncRNA expression and demographical data of cancer patients such as age or gender have been assessed in 31 studies which assessed 29 different lncRNA transcripts including HOTAIR, MALAT1, MEG3, NEAT1, PTENp1, and UCA1. Significant DE was never observed, with the exception of the overexpression of HIFCAR in patients aged over 50 years of age ($p=0.037$) (**Table 2**).

Risk habits

lncRNAs have a low to moderate expression level which depends on cell differentiation, is tissue- and cell-type specific, and can vary spatially, temporally, or in response to exogenous stimuli such as the known environmental risks for cancer development (i.e. tobacco and alcohol). Data on the relationship between lncRNAs and tobacco use are still preliminary and mainly come from studies addressing human bronchial epithelial (HBE) cells. The two most extensively studied lncRNAs in lung cancer in regard to tobacco use are HOTAIR and MALAT1 which were shown to be upregulated in smokers (Soares do Amaral *et al*, 2016), but risk factor data from OSCC/TSCC cohorts are sparse. One study using RNA-seq analysis identified lncRNAs potentially related to alcohol-associated HNSCC, but the study did not stratify patients according to anatomical subsite and these finding may not necessary apply to OSCC alone (Yu *et al*, 2016). The present review found only 17 studies investigating lncRNA DE related to risk habits (tobacco smoking, betel quid

with tobacco chewing, alcohol exposure) and they assessed 28 transcripts overall. Tobacco smoking has never been found to be related to DE of lncRNA and alcohol exposure has been shown to be related only to a reduced expression of AC012456.4 in OSCCs (Hu *et al*, 2018). Conversely, one study from India identified DE of more than one lncRNA in relation to betel quid with tobacco chewing (**Table 3**). Of note, six studies included patients with TSCC, but the other 11 studies on OSCC performed analyses without any stratification of the risk habit with respect to the oral anatomical subsite (**Table 3**).

Tumour size, nodal involvement, grading and TNM staging

Studies examining the links between lncRNA expression and TNM staging have assessed 37 lncRNAs, with particular emphasis on the association with regional metastasis (i.e. nodal involvement). Results from these studies are summarized in **Table 1**.

When considering individual lncRNAs, most potential associations have been reported only once and lack validation. Of interest is that only 15 out of 33 lncRNAs were found to be up/down regulated in presence of nodal involvement. In 2013, Tang *et al*. reported that in presence of nodal involvement the expression of HOTAIR, NEAT1 and UCA1 was significantly upregulated, while MEG3 was downregulated (Tang *et al*, 2013). Two subsequent studies investigating 58 and 30 OSCC patients respectively confirmed that NEAT1 overexpression is significantly correlated with nodal metastasis ($p=0.009$) (Liu *et al*, 2018a; Huang *et al*, 2018a) and two studies addressing TSCC confirmed UCA1 overexpression ($p=0.0379$ and $p=0.011$ when addressing 94 and 124 patients respectively) (Fang *et al*, 2014; Yang *et al*, 2016). One author hypothesised that UCA1 overexpression promoted the metastatic but not the proliferative ability of TSCC cells (Fang *et al*, 2014). HOTAIR was assessed in two studies collectively with about 100 patients and both studies supported a significant link between the overexpression of this transcript and the presence of nodal metastasis (Tang *et al*, 2013; Wu *et al*, 2015). In a small cohort of 15 OSCCs, a significantly increasing trend of expression of HOTAIR was observed when comparing non-tumour tissue, tumour tissue, and tissue from metastatic nodes ($p<0.05$). Such a trend associated with metastases has been related to enhanced cancer stemness and metastasis due to overexpression of HOTAIR in oral carcinoma stem cells (Lu *et al*, 2017).

Conversely, the link between nodal involvement and underexpression of MEG3 was not confirmed by two subsequent studies (Arunkumar *et al*, 2017a; Jia *et al*, 2014). Three studies reported contrasting results when addressing MALAT1, overall suggesting that a significant overexpression in presence of nodal involvement could be found only in TSCC (Liang *et al*, 2017a) but further validation is needed (Arunkumar *et al*, 2017a; Tang *et al*, 2013).

Most studies addressing TNM stage compared lesions with stage I-II versus lesions with stage III-IV disease. When both TNM staging and nodal involvement were assessed, a few transcripts (CCAT2, EGFR, HOTTIP, PTENp1) appeared to be associated with tumour size rather than with nodal involvement (Gao *et al*, 2017; Ma *et al*, 2017; Zhang *et al*, 2015a; Sun *et al*, 2018), while others seemed related with nodal involvement but not to tumour size (CEBPA-AS1, HAS2-AS1, MBL2-4:3, TUG1, UCA1) (Gao *et al*, 2014; Zhu *et al*, 2017; Guo *et al*, 2018; Liang *et al*, 2017b; Yang *et al*, 2016; Fang *et al*, 2014).

Of note, among the 20 transcripts assessed for their association with both nodal involvement and tumour size, only LINC00152 (Yu *et al*, 2017b), Inc-p23154 (Wang *et al*, 2018a) and NKILA (Huang *et al*, 2016) showed significant DE with the same direction: overexpression for LINC00152 and Inc-p23154, underexpression for NKILA.

Outcome: relapse and survival

Most of the studies addressed the potential role of lncRNA expression as predictors of poor prognosis, mainly focusing on overall survival (OS) and occasionally on both OS and relapse-free survival (RFS). When a significant link between lncRNA expression and OS was found, it was consistent with significant links relating the transcript expression to the presence of nodal involvement or at least to a higher TNM stage. Nevertheless, as reported below, only a subset of studies performed a multivariate analysis in order to adjust for these potential confounding factors.

Several studies acquired data from public transcriptome datasets. When analysing merged data from three datasets, the TCGA and 2 GEO datasets (GSE9844 (Ye *et al*, 2008) and GSE13601 (Estilo *et al*, 2009)), multivariate Cox regression analysis identified three lncRNAs as independent prognostic markers for OS in OSCC patients ($p < 0.05$), namely overexpressed C10orf91 (chromosome 10 open reading frame 91) and C2orf48 (chromosome 2 open reading frame 48) and underexpressed TTTY14 (testis-specific transcript, Y-linked 14) (Li *et al*, 2017). An univariate analysis of 42 OSCCs from the GSE3524 dataset (Toruner *et al*, 2004) revealed that the overexpression of H19 was significantly related to poorer OS (Hong *et al*, 2018). Kaplan-Meier survival analysis of OSCC patients from TCGA database demonstrated that higher HOTAIR expression led to poor survival ($p=0.0024$) (Lu *et al*, 2017). A multivariate Cox regression analysis for OS in OSCC patients from TCGA showed that poor survival was independently associated with low expression of AC012456.4 ($p = 0.002$), nodal involvement and age (Hu *et al*, 2018).

HOTAIR was the only transcript whose prognostic role has been assessed in multiple independent cohorts of OSCC patients. Despite with contrasting results from studies exploring the association between HOTAIR expression and nodal involvement or tumour grading, in univariate analyses, two studies found a negative impact of HOTAIR overexpression related to OS in cohorts of 50 and 76 patients ($p = 0.023$ and $p = 0.002$ respectively) (Wu and Xie, 2015; Wu *et al*, 2015) and to RFS ($p = 0.027$) (Wu *et al*, 2015).

Yu *et al*. investigated the expression of LINC00673 and LINC00152 in a cohort of about 200 TSCC patients finding significant associations with the outcome parameters in univariate analyses. The median RFS in patients with low and high expression of LINC00673 was 39 and 25 months, respectively ($p=0.008$) (Yu *et al*, 2017a), while the median RFS time of patients with low and high expression of LINC00152 was 29 and 26.5 months, respectively ($p=0.007$) (Yu *et al*, 2017b). The median OS time was 39.5 and 29 months with low and high expression of LINC00673 respectively ($p = 0.009$). Similar results were reported for LINC00152; the median OS time was 35 and 28 months with low and high expression of LINC00152, respectively ($p = 0.006$) (Yu *et al*, 2017b). The prognostic value of LINC00152 overexpression was also found when investigating a group of 40 OSCCs ($p < 0.05$) (Li *et al*, 2018).

In another study assessing 103 TSCCs, high expression of AFAP-AS1 was found to be correlated to both lower RFS and OS in univariate analyses ($p = 0.009$ and $p = 0.033$ respectively) (Wang *et al*, 2018b).

Univariate Kaplan-Meier analyses also found the expression of several other lncRNAs to be positively correlated with poorer survival in OSCC including MALAT1 ($p < 0.05$; 54 patients) (Zhou *et al*, 2015), NEAT1 ($p=0.042$; 58 patients and $p=0.01$; 30 patients) (Liu *et al*, 2018a; Huang *et al*, 2018a), LINC00668 ($p < 0.05$; 50 patients) (Zhang, 2017a), FTH1P3 ($p = 0.0032$; 70 patients) (Zhang, 2017b), CCAT2 ($p = 0.028$; 62 patients) (Ma *et al*, 2017), PDIA3P ($p = 0.0211$; 58 patients) (Sun *et al*, 2017) and ANRIL ($p = 0.013$; 130 patients) (Chai *et al*, 2018). When analysing only TSCC patients, higher expression associated with poor OS was found for GIHCG ($p < 0.05$ from a 20 patients cohort) (Ma *et al*, 2018). Conversely an underexpression of PTENp1 ($p = 0.04$; 62 patients) (Gao *et al*, 2017) and LINC01133 ($p = 0.013$; 50 patients) (Kong *et al*, 2018) correlated with a reduced survival rate.

Multivariate analyses were performed in 10 studies: three addressing TSCC (Jia *et al*, 2014; Zhang *et al*, 2015a; Huang *et al*, 2016) and seven addressing OSCC (Shih *et al*, 2017; Guo *et al*, 2018; Liu *et al*, 2017a; Huang *et al*, 2018b; Zhou *et al*, 2016; Hu *et al*, 2018; Liu *et al*, 2018b). In a cohort of

96 TSCCs, a multivariate Cox regression analysis including tumour size, identified the decreased expression of NKILA as the only significant item related to OS ($p = 0.042$) and lower RFS ($p = 0.002$) (Huang *et al*, 2016). In presence of poor OS, HOTTIP was found to be overexpressed in 86 patients ($p = 0.023$) (Zhang *et al*, 2015a), while MEG3 was found to be underexpressed in 76 patients ($p = 0.013$) (Jia *et al*, 2014). In OSCC, a multivariate analysis was not able to determine a significant association between OS and the expression of HIFCAR (42 patients) (Shih *et al*, 2017), while a Cox regression analysis including tumour size, staging, nodal involvement, grading and oral anatomical subsite showed that an increased expression of CEBPA-AS1 ($p < 0.001$) and nodal involvement ($p = 0.001$; 60 patients) were the only significant parameters related to survival (Guo *et al*, 2018). Cox regression analyses performed in OSCC groups showed that an increased expression of ANRIL ($p < 0.001$; 116 patients) (Liu *et al*, 2017a), PANDAR ($p < 0.001$; 92 patients) (Huang *et al*, 2018b), CCAT2 ($p < 0.001$; 102 patients) (Zhou *et al*, 2016), and HNF1A-AS1 ($p = 0.014$; 62 patients) (Liu *et al*, 2018b) were significantly related to survival.

One step back: oral potentially malignant disorders

Very few studies have investigated the presence of DE lncRNAs in oral potentially malignant disorders (OPMD). In 2011 Gibb *et al*. reported the first lncRNA expression map for normal and dysplastic human oral mucosa (GEO dataset: GSE31021) (Gibb *et al*, 2011). They described the expression of 325 lncRNAs finding that about 60%, including lncRNAs previously associated with other human cancers, showed aberrant expression in oral dysplasia. A significant fold-change either greater or lower than 3-fold was found for 85 transcripts. The high rate of dysregulated transcripts suggests that quite a large number of alterations might be required to drive the onset of dysplasia.

Interestingly, when addressing multiple lesions in the same patient, consistent changes were observed, thus suggesting epigenomic support to the concept of field cancerization. This is of interest when compared to genomic studies which conversely found that dysplasia and invasive tumours with a close spatial relationship do not have linearly related mutational changes (Wood *et al*, 2015).

When comparing transcripts dysregulated in presence of dysplasia or SCC, it can be observed that several transcripts dysregulated in cancer (e.g. HOTAIR, GAS5) do not exhibit altered expression in dysplasia suggesting a potential role in tumour progression rather than in oncogenesis (Gibb *et al*, 2011).

Han *et al.* (Han *et al.*, 2015), analysed the GEO dataset created by Gibbs aiming to compare Serial Analysis of Gene Expression (SAGE) data from patients with oral epithelial dysplasia with healthy controls, in order to identify differentially expressed mRNAs and lncRNAs, as well as the regulatory relationships between them. The authors compared two mild dysplasia, four moderate dysplasia and four severe dysplasia samples to six healthy oral samples used as normal controls. In presence of dysplasia, irrespective of its grade, 108 lncRNAs were differentially expressed: 87 were upregulated (e.g., LINC00675, HCG22, MIR17HG, FAM3D, LINC00152, FAM45A, FAM129B, and NEAT1) and 21 were downregulated (e.g., SNHG6, HCG11, and LINC00116) (Han *et al.*, 2015). The same dataset was addressed by Jia *et al.* (Jia *et al.*, 2018) who created a lncRNA-gene co-expression network aiming to decipher the role of lncRNAs in the molecular pathogenesis of oral premalignant lesions.

Conclusions

The study of lncRNA expression in oral dysplasia and SCC may facilitate the identification of biomarkers useful to improve the diagnosis and the identification of lesions with higher risk of malignant transformation.

OSCC and TSCC are considered a subset of head and neck squamous cell carcinoma (HNSCC). Nevertheless, it is a heterogeneous group of tumours with growing evidence of different genetic alterations and aetiology based on the anatomical subsite. For these reasons, the present review included only studies on OSCC/TSCC and data reported in this study support the need for a strict selection of patients in order to have reliable results.

Limitations of the present review rely on the lack of a direct assessment performed within the present review of data from RNASeq or array datasets publically deposited and on a potentially inconsistent definition of OSCC (site of tumour) when not clearly reported in the studies. Moreover, the use of different techniques (RNASeq, array, PCR) aiming to detect the lncRNA expression could represent a potential bias when comparing studies investigating the expression of same transcript.

Despite the fact that all studies analysed relied on the same techniques for assessing lncRNA (array or PCR mainly performed on fresh frozen tissue samples), attempts to merge the data and consider the studies as a whole proved difficult. Current evidence is heterogeneous for the inconsistent choice of normal tissue to be used as control, and for the different bioinformatic approaches to define thresholds of lncRNA expression and therefore differential expression. For

these reasons designing meta-analyses on such data could imply a potentially high risk of bias. Moreover, analyses assessing the potential role of risk habits are scant.

Strict selection of patients, standard methods to assess differential expression and appropriate data analyses including all clinico-pathological features are required in order to achieve reliable results from future studies. Oral medicine specialist might collaborate on this type of research improving the selection of homogeneous cohort of patients and the collection of complete clinico-pathological dataset to be contrasted with lncRNA expression.

Acknowledgements

The authors would like to thank Dr. Bruce Baum for his critical review, guidance, comments and suggestions during the development of the manuscript.

The authors gratefully acknowledge the following organizations, individuals, and companies that provided unrestricted financial support for WWOM VII: American Academy of Oral Medicine, European Association of Oral Medicine, The British Society for Oral Medicine, The National Institute of Dental and Craniofacial Research, Oral Diseases, Henry Schein Cares, Colgate, Xerostom, Dermotreat, The World Dental Education Foundation, and Unilever. In addition, the authors, including selected members of the WWOM VII Steering Committee, express their sincere appreciation for the opportunity to collaborate with the full WWOM VII Steering Committee over the past 2 years. This committee provided the conceptual framework and logistical support to produce the WWOM VII Conference in September 2018 in Gothenburg, Sweden. In addition, the Steering Committee provided scientific and editorial critique of this manuscript. The entire Steering Committee is listed below, in alphabetical order: Martin S. Greenberg (USA), Timothy A. Hodgson (UK), Siri Beier Jensen (Denmark), A. Ross Kerr (USA), Peter B. Lockhart (USA), Giovanni Lodi (Italy), Douglas E. Peterson (USA).

Conflict of interest

None to declare.

References

Arunkumar G, Anand S, Raksha P, Dhamodharan S, Prasanna Srinivasa Rao H, Subbiah S, Murugan AK and Munirajan AK (2018). lncRNA OIP5-AS1 is overexpressed in undifferentiated oral tumors and integrated analysis identifies as a downstream effector of stemness-associated transcription factors. *Sci Rep* **8**: 7018.

Arunkumar G, Deva Magendhra Rao AK, Manikandan M, Arun K, Vinothkumar V, Revathidevi S, Rajkumar KS, Rajaraman R and Munirajan AK (2017a). Expression profiling of long non-coding RNA identifies linc-RoR as a prognostic biomarker in oral cancer. *Tumor Biology* **39**: 101042831769836.

Arunkumar G, Murugan AK, Prasanna Srinivasa Rao H, Subbiah S, Rajaraman R and Munirajan AK (2017b). Long non-coding RNA CCAT1 is overexpressed in oral squamous cell carcinomas and predicts poor prognosis. *Biomedical reports* **6**: 455-462.

Brunner AL, Beck AH, Edris B, Sweeney RT, Zhu SX, Li R, Montgomery K, Varma S, Gilks T, Guo X, Foley JW, Witten DM, Giacomini CP, Flynn RA, Pollack JR, Tibshirani R, Chang HY, van de Rijn M and West RB (2012). Transcriptional profiling of long non-coding RNAs and novel transcribed regions across a diverse panel of archived human cancers. *Genome Biol* **13**: R75.

Chai L, Yuan Y, Chen C, Zhou J and Wu Y (2018). The role of long non-coding RNA ANRIL in the carcinogenesis of oral cancer by targeting miR-125a. *Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie* **103**: 38-45.

Chen C, Mendez E, Houck J, Fan W, Lohavanichbutr P, Doody D, Yueh B, Futran ND, Upton M, Farwell DG, Schwartz SM and Zhao LP (2008). Gene expression profiling identifies genes predictive of oral squamous cell carcinoma. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology* **17**: 2152-62.

Ding J, Yang C and Yang S (2018). LINC00511 interacts with miR-765 and modulates tongue squamous cell carcinoma progression by targeting LAMC2. *J Oral Pathol Med* **47**: 468-476.

Estilo CL, P Oc, Talbot S, Socci ND, Carlson DL, Ghossein R, Williams T, Yonekawa Y, Ramanathan Y, Boyle JO, Kraus DH, Patel S, Shaha AR, Wong RJ, Huryn JM, Shah JP and Singh B (2009). Oral tongue cancer gene expression profiling: Identification of novel potential prognosticators by oligonucleotide microarray analysis. *BMC Cancer* **9**: 11.

Fang Z, Wu L, Wang L, Yang Y, Meng Y and Yang H (2014). Increased expression of the long non-coding RNA UCA1 in tongue squamous cell carcinomas: a possible correlation with cancer metastasis. *Oral surgery, oral medicine, oral pathology and oral radiology* **117**: 89-95.

Fang Z, Zhang S, Wang Y, Shen S, Wang F, Hao Y, Li Y, Zhang B, Zhou Y and Yang H (2016). Long non-coding RNA MALAT-1 modulates metastatic potential of tongue squamous cell carcinomas partially through the regulation of small proline rich proteins. *BMC Cancer* **16**: 706.

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 sunppressing miR-184 expression. *Cancer medicine* **6**: 2897-2908.

Gao L, Ren W, Zhang L, Li S, Kong X, Zhang H, Dong J, Cai G, Jin C, Zheng D and Zhi K (2017). PTENp1, a natural sponge of miR-21, mediates PTEN expression to inhibit the proliferation of oral squamous cell carcinoma. *Mol Carcinog* **56**: 1322-1334.

Gao W, Chan JY and Wong TS (2014). Long non-coding RNA deregulation in tongue squamous cell carcinoma. *BioMed research international* **2014**: 405860.

Gibb EA, Enfield KS, Stewart GL, Lonergan KM, Chari R, Ng RT, Zhang L, MacAulay CE, Rosin MP and Lam WL (2011). Long non-coding RNAs are expressed in oral mucosa and altered in oral premalignant lesions. *Oral Oncol* **47**: 1055-61.

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 biology & therapy* **19**: 205-213.

Han X, Wei YB, Tian G, Tang Z, Gao JY and Xu XG (2015). Screening of crucial long non-coding RNAs in oral epithelial dysplasia by serial analysis of gene expression. *Genetics and molecular research : GMR* **14**: 11729-38.

Hong Y, He H, Sui W, Zhang J, Zhang S and Yang D (2018). Long non-coding RNA H1 promotes cell proliferation and invasion by acting as a ceRNA of miR138 and releasing EZH2 in oral squamous cell carcinoma. *Int J Oncol* **52**: 901-912.

Hu X, Qiu Z, Zeng J, Xiao T, Ke Z and Lyu H (2018). A novel long non-coding RNA, AC012456.4, as a valuable and independent prognostic biomarker of survival in oral squamous cell carcinoma. *PeerJ* **6**: e5307.

Huang G, He X and Wei XL (2018a). lncRNA NEAT1 promotes cell proliferation and invasion by regulating miR365/RGS20 in oral squamous cell carcinoma. *Oncology reports* **39**: 1948-1956.

Huang W, Cui X, Chen J, Feng Y, Song E, Li J and Liu Y (2016). Long non-coding RNA NKILA inhibits migration and invasion of tongue squamous cell carcinoma cells via suppressing epithelial-mesenchymal transition. *Oncotarget* **7**: 62520-62532.

Huang Z, Sang T, Zheng Y and Wu J (2018b). Long non-coding RNA PANDAR overexpression serves as a poor prognostic biomarker in oral squamous cell carcinoma. *Int J Clin Exp Pathol* **11**: 2728-2734.

Jia H, Wang X and Sun Z (2018). Exploring the molecular pathogenesis and biomarkers of high risk oral premalignant lesions on the basis of long noncoding RNA expression profiling by serial analysis of gene expression. *European journal of cancer prevention : the official journal of the European Cancer Prevention Organisation (ECP)* **27**: 370-378.

Jia LF, Wei SB, Gan YH, Guo Y, Gong K, Mitchelson K, Cheng J and Yu GY (2014). Expression, regulation and roles of miR-26a and MEG3 in tongue squamous cell carcinoma. *Int J Cancer* **135**: 2282-93.

Kong J, Sun W, Zhu W, Liu C, Zhang H and Wang H (2018). Long noncoding RNA LINC01133 inhibits oral squamous cell carcinoma metastasis through a feedback regulation loop with GDF15. *Journal of surgical oncology*.

Li M, Ning J, Li Z, Wang J, Zhao C and Wang L (2018). LINC00152 promotes the growth and invasion of oral squamous cell carcinoma by regulating miR-139-5p. *OncoTargets and therapy* **11**: 6295-6304.

Li S, Chen X, Liu X, Yu Y, Pan H, Haak R, Schmidt J, Ziebolz D and Schmalz G (2017). Complex integrated analysis of lncRNAs-miRNAs-mRNAs in oral squamous cell carcinoma. *Oral Oncol* **73**: 1-9.

Liang J, Liang L, Ouyang K, Li Z and Yi X (2017a). MALAT1 induces tongue cancer cells' EMT and inhibits apoptosis through Wnt/beta-catenin signaling pathway. *J Oral Pathol Med* **46**: 98-105.

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

Liu F, Liu S, Chen L, Lei Z, Wu J and Wu J (2017a). Up-regulation of the long non-coding RNA ANRIL indicates poor prognosis and promotes tumorigenesis in oral squamous cell carcinoma. *Int J Clin Exp Pathol* **10**: 6900-6905.

Liu XH, Shang WZ and Zheng FJ (2018a). Long non-coding RNA NEAT1 promotes migration and invasion of oral squamous cell carcinoma cells by sponging microRNA-365. *Experimental and Therapeutic Medicine* **16**: 2243-2250.

Liu Z, Li H, Fan S, Lin H and Lian W (2018b). STAT3-induced upregulation of long noncoding RNA HNF1A-AS1 promotes the progression of oral squamous cell carcinoma via activating Notch signaling pathway. *Cancer biology & therapy*: 1-10.

Liu Z, Wu C, Xie N and Wang P (2017b). Long non-coding RNA MEG3 inhibits the proliferation and metastasis of oral squamous cell carcinoma by regulating the WNT/beta-catenin signaling pathway. *Oncology letters* **14**: 4053-4058.

Lu MY, Liao YW, Chen PY, Hsieh PL, Fang CY, Wu CY, Yen ML, Peng BY, Wang DP, Cheng HC, Wu CZ, Shih YH, Wang DJ, Yu CC and Tsai LL (2017). Targeting LncRNA HOTAIR suppresses cancer stemness and metastasis in oral carcinomas stem cells through modulation of EMT. *Oncotarget* **8**: 98542-98552.

Ma L, Wang Q, Gong Z, Xue L and Zuo Z (2018). Long noncoding RNA GIHCG enhanced tongue squamous cell carcinoma progression through regulating miR-429. *Journal of cellular biochemistry*.

Ma Y, Hu X, Shang C, Zhong M and Guo Y (2017). Silencing of long non-coding RNA CCAT2 depressed malignancy of oral squamous cell carcinoma via Wnt/beta-catenin pathway. *Tumour Biol* **39**: 1010428317717670.

Peng CH, Liao CT, Peng SC, Chen YJ, Cheng AJ, Juang JL, Tsai CY, Chen TC, Chuang YJ, Tang CY, Hsieh WP and Yen TC (2011). A novel molecular signature identified by systems genetics approach predicts prognosis in oral squamous cell carcinoma. *PloS one* **6**: e23452.

Shih JW, Chiang WF, Wu ATH, Wu MH, Wang LY, Yu YL, Hung YW, Wang WC, Chu CY, Hung CL, Changou CA, Yen Y and Kung HJ (2017). Long noncoding RNA LncHIFCAR/MIR31HG is a HIF-1alpha co-activator driving oral cancer progression. *Nature communications* **8**: 15874.

Soares do Amaral N, Cruz e Melo N, de Melo Maia B and Malagoli Rocha R (2016). Noncoding RNA Profiles in Tobacco- and Alcohol-Associated Diseases. *Genes* **8**: 6.

Sun CC, Zhang L, Li G, Li SJ, Chen ZL, Fu YF, Gong FY, Bai T, Zhang DY, Wu QM and Li DJ (2017). The lncRNA PDIA3P Interacts with miR-185-5p to Modulate Oral Squamous Cell Carcinoma Progression by Targeting Cyclin D2. *Molecular therapy. Nucleic acids* **9**: 100-110.

Sun T, Tang L and Zhang M (2018). Long noncoding RNA LncEGFR promotes cell proliferation and inhibits cell apoptosis via regulating the expression of EGFR in human tongue cancer. *Molecular medicine reports* **17**: 1847-1854.

Tang H, Wu Z, Zhang J and Su B (2013). Salivary lncRNA as a potential marker for oral squamous cell carcinoma diagnosis. *Mol Med Rep* **7**: 761-6.

Toruner GA, Ulger C, Alkan M, Galante AT, Rinaggio J, Wilk R, Tian B, Soteropoulos P, Hameed MR, Schwalb MN and Dermody JJ (2004). Association between gene expression profile and tumor invasion in oral squamous cell carcinoma. *Cancer genetics and cytogenetics* **154**: 27-35.

Wang Y, Zhang X, Wang Z, Hu Q, Wu J, Li Y, Ren X, Wu T, Tao X, Chen X, Li X, Xia J and Cheng B (2018a). lncRNA-p23154 promotes the invasion-metastasis potential of oral squamous cell carcinoma by regulating Glut1-mediated glycolysis. *Cancer letters* **434**: 172-183.

Wang ZY, Hu M, Dai MH, Xiong J, Zhang S, Wu HJ, Zhang SS and Gong ZJ (2018b). Upregulation of the long non-coding RNA AFAP1-AS1 affects the proliferation, invasion and survival of tongue squamous cell carcinoma via the Wnt/beta-catenin signaling pathway. *Molecular cancer* **17**: 3.

Wood HM, Conway C, Daly C, Chalkley R, Berri S, Senguen B, Stead L, Ross L, Egan P, Chengot P, Graham J, Sethi N, Ong TK, High A, MacLennan K and Rabbitts P (2015). The clonal relationships between pre-cancer and cancer revealed by ultra-deep sequencing. *The Journal of pathology* **237**: 296-306.

Wu J and Xie H (2015). Expression of long noncoding RNA-HOX transcript antisense intergenic RNA in oral squamous cell carcinoma and effect on cell growth. *Tumour Biol* **36**: 8573-8.

Wu Y, Zhang L, Zhang L, Wang Y, Li H, Ren X, Wei F, Yu W, Liu T, Wang X, Zhou X, Yu J and Hao X (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**: 2586-94.

Yang M, Xiong X, Chen L, Yang L and Li X (2017). Identification and validation long non-coding RNAs of oral squamous cell carcinoma by bioinformatics method. *Oncotarget* **8**: 107469-107476.

Yang YT, Wang YF, Lai JY, Shen SY, Wang F, Kong J, Zhang W and Yang HY (2016). Long non-coding RNA UCA1 contributes to the progression of oral squamous cell carcinoma by regulating the WNT/beta-catenin signaling pathway. *Cancer Sci* **107**: 1581-1589.

Ye H, Yu T, Temam S, Ziober BL, Wang J, Schwartz JL, Mao L, Wong DT and Zhou X (2008). Transcriptomic dissection of tongue squamous cell carcinoma. *BMC Genomics* **9**: 69.

Yu J, Liu Y, Gong Z, Zhang S, Guo C, Li X, Tang Y, Yang L, He Y, Wei F, Wang Y, Liao Q, Zhang W, Li X, Li Y, Li G, Xiong W and Zeng Z (2017a). Overexpression long non-coding RNA LINC00673 is associated with poor prognosis and promotes invasion and metastasis in tongue squamous cell carcinoma. *Oncotarget* **8**: 16621-16632.

Yu J, Liu Y, Guo C, Zhang S, Gong Z, Tang Y, Yang L, He Y, Lian Y, Li X, Deng H, Liao Q, Li X, Li Y, Li G, Zeng Z, Xiong W and Yang X (2017b). Upregulated long non-coding RNA LINC00152 expression is associated with progression and poor prognosis of tongue squamous cell carcinoma. *Journal of Cancer* **8**: 523-530.

Yu V, Singh P, Rahimy E, Zheng H, Kuo SZ, Kim E, Wang-Rodriguez J and Ongkeko WM (2016). RNA-seq analysis identifies key long non-coding RNAs connected to the pathogenesis of alcohol-associated head and neck squamous cell carcinoma. *Oncology letters* **12**: 2846-2853.

Zhang CZ (2017a). Long intergenic non-coding RNA 668 regulates VEGFA signaling through inhibition of miR-297 in oral squamous cell carcinoma. *Biochemical and biophysical research communications* **489**: 404-412.

Zhang CZ (2017b). 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* **607**: 47-55.

Zhang H, Zhao L, Wang YX, Xi M, Liu SL and Luo LL (2015a). Long non-coding RNA HOTTIP is correlated with progression and prognosis in tongue squamous cell carcinoma. *Tumour Biol* **36**: 8805-9.

Zhang S, Tian L, Ma P, Sun Q, Zhang K, GuanchaoWang, Liu H and Xu B (2015b). Potential role of differentially expressed lncRNAs in the pathogenesis of oral squamous cell carcinoma. *Archives of oral biology* **60**: 1581-7.

Zhou H, Zhang ZQ, Wu Y and Zhao JJ (2016). Effect of the long non-coding RNA AC007392.4 on growth, invasion and migration for tongue squamous cell carcinoma. *International Journal of Clinical and Experimental Medicine* **9**: 5805-5812.

Zhou X, Liu S, Cai G, Kong L, Zhang T, Ren Y, Wu Y, Mei M, Zhang L and Wang X (2015). Long Non Coding RNA MALAT1 Promotes Tumor Growth and Metastasis by inducing Epithelial-Mesenchymal Transition in Oral Squamous Cell Carcinoma. *Sci Rep* **5**: 15972.

Zhu G, Wang S, Chen J, Wang Z, Liang X, Wang X, Jiang J, Lang J and Li L (2017). Long noncoding RNA HAS2-AS1 mediates hypoxia-induced invasiveness of oral squamous cell carcinoma. *Mol Carcinog* **56**: 2210-2222.

Zou AE, Ku J, Honda TK, Yu V, Kuo SZ, Zheng H, Xuan Y, Saad MA, Hinton A, Brumund KT, Lin JH, Wang-Rodriguez J and Ongkeko WM (2015). Transcriptome sequencing uncovers novel long noncoding and small nucleolar RNAs dysregulated in head and neck squamous cell carcinoma. *RNA (New York, N.Y.)* **21**: 1122-34.

Tables

Table 1. Differential expression of lncRNAs in SCC related to clinico-pathological features.

PMID	First Author	year	lncRNA	N° of patients	Anatomical site	Cut-off for expression assessment	T size	N+	TNM stage	grading
30128179	Hu X(Hu <i>et al</i> , 2018)	2018	AC012456.4	329	OSCC	MEL	NS			
29310682	Wang Z(Wang <i>et al</i> , 2018b)	2018	AFAP1-AS1	103	TSCC	MEL	over p = 0.036		over p = 0.025	
25045670	Gao W(Gao <i>et al</i> , 2014)	2014	AL355149.1-1	32	TSCC	REL	under p < 0.001	NS		
29635126	Chai L(Chai <i>et al</i> , 2018)	2018	ANRIL	130	OSCC			over p = 0.003	over p = 0.004	
NA	Liu F(Liu <i>et al</i> , 2017a)	2017	ANRIL	116	OSCC	MEL	NS		over p = 0.027	over p = 0.009
28443494	Arunkumar G(Arunkumar <i>et al</i> , 2017a)	2017	AP5M1	60	OSCC	REL		NS	NS	NS
28413645	Arunkumar G(Arunkumar <i>et al</i> , 2017b)	2017	CCAT1	60	OSCC	DE versus non DE	NS	NS		NS
28671055	Ma Y(Ma <i>et al</i> , 2017)	2017	CCAT2	62	OSCC	MEL	over p = 0.035	NS	over p = 0.016	over p < 0.001
NA	Zhou NG(Zhou <i>et al</i> , 2016)	2016	CCAT2	102	OSCC	MEL	NS		over p < 0.001	over p < 0.001
28443494	Arunkumar G(Arunkumar <i>et al</i> , 2017a)	2017	CDKN2B-AS1	60	OSCC	REL		NS	NS	NS
29281558	Guo Y(Guo <i>et al</i> , 2018)	2018	CEBPA-AS1	60	OSCC	MEL	NS	over	over	over

								p < 0.0001	p = 0.039	p = 0.013
29138845	Sun T(Sun <i>et al</i> , 2018)	2018	EGFR	50	TSCC	MEL	over p < 0.001	NS	NS	
28443494	Arunkumar G(Arunkumar <i>et al</i> , 2017a)	2017	FALEC	60	OSCC	REL		NS	NS	NS
28443494	Arunkumar G(Arunkumar <i>et al</i> , 2017a)	2017	H19	60	OSCC	REL		NS	NS	NS
29344674	Hong Y(Hong <i>et al</i> , 2018)	2018	H19	42	OSCC	REL		over	over p < 0.01	
28485478	Zhu G(Zhu <i>et al</i> , 2017)	2017	HAS2-AS1	96	OSCC	MEL	NS	over p = 0.025		NS
28639619	Shih J(Shih <i>et al</i> , 2017)	2017	HIFCAR	42	OSCC	maximum sum of sensitivity and specificity for RFS analysis	NS	NS	NS	over p = 0.01
30404566	Liu Z(Liu <i>et al</i> , 2018b)	2018	HNF1A-AS1	62	OSCC	MEL		over p = 0.009		over p < 0.001
28443494	Arunkumar G(Arunkumar <i>et al</i> , 2017a)	2017	HOTAIR	60	OSCC	REL		NS	NS	NS
23292713	Tang H(Tang <i>et al</i> , 2013)	2013	HOTAIR	16	OSCC	REL		over p = 0.002		
26036760	Wu J(Wu and Xie, 2015)	2015	HOTAIR	50	OSCC	MEL	over p = 0.023	NS	over p = 0.021	NS
25901533	Wu Y(Wu <i>et al</i> , 2015)	2015	HOTAIR	76	OSCC		NS	over	over	over

								p < 0.0001	p = 0.001	p = 0.019
26058875	Zhang H(Zhang <i>et al</i> , 2015a)	2015	HOTTIP	86	TSCC	MEL	over p = 0.023	NS p = 0.053	over p = 0.018	NS
23292713	Tang H(Tang <i>et al</i> , 2013)	2013	HULC	16	OSCC	REL		NS		
30310293	Li M(Li <i>et al</i> , 2018)	2018	LINC00152	40	OSCC	MEL		over p < 0.01	over p < 0.01	NS
28367232	Yu J(Yu <i>et al</i> , 2017b)	2017	LINC00152	197	TSCC	ISH	over p = 0.009	over p = 0.036	over p = 0.017	
28443494	Arunkumar G(Arunkumar <i>et al</i> , 2017a)	2017	LINC00312	60	OSCC	REL		NS	NS	NS
29315846	Ding J(Ding <i>et al</i> , 2018)	2018	LINC00511	20	TSCC	Mean expression level			NS	
28039470	Yu J(Yu <i>et al</i> , 2017a)	2017	LINC00673	202	TSCC	ISH	over p = 0.034		over p = 0.018	
28443494	Arunkumar G(Arunkumar <i>et al</i> , 2017a)	2017	linc-RoR	60	OSCC	REL		NS	NS	over p = 0.022
30026052	Wang Y(Wang <i>et al</i> , 2018a)	2018	lnc-p23154	49	OSCC		over p = 0.042	over p = 0.03	over p = 0.012	NS
28443494	Arunkumar G(Arunkumar <i>et al</i> , 2017a)	2017	MALAT1	60	OSCC	REL		NS	NS	NS
27353727	Liang J(Liang <i>et al</i> , 2017a)	2017	MALAT1	32	TSCC	MEL	NS	over p = 0.026		NS
23292713	Tang H(Tang <i>et al</i> , 2013)	2013	MALAT1	16	OSCC	REL		NS		
26522444	Zhou X(Zhou <i>et al</i> , 2015)	2015	MALAT1	54	OSCC	MEL				NS
25045670	Gao W(Gao <i>et al</i> , 2014)	2014	MBL2-4:3	32	TSCC	REL	NS	over p = 0.002		

28443494	Arunkumar G(Arunkumar <i>et al</i> , 2017a)	2017	MEG3	60	OSCC	REL		NS	NS	NS
24343426	Jia LF(Jia <i>et al</i> , 2014)	2014	MEG3	76	TSCC	mean fold changes	under p < 0.001	NS		NS
23292713	Tang H(Tang <i>et al</i> , 2013)	2013	MEG3	16	OSCC	REL		under p = 0.034		
29484420	Huang G(Huang <i>et al</i> , 2018a)	2018	NEAT1	30	OSCC	REL		over p = 0.009	over p = 0.018	NS
30186464	Liu X(Liu <i>et al</i> , 2018a)	2018	NEAT1	58	OSCC	MEL			over p = 0.009	NS
23292713	Tang H(Tang <i>et al</i> , 2013)	2013	NEAT1	16	OSCC	REL		over p = 0.001		
27613832	Huang W(Huang <i>et al</i> , 2016)	2016	NKILA	96	TSCC	ISH	under p = 0.001	under p = 0.001	under p = 0.001	NS
29728583	Arunkumar G(Arunkumar <i>et al</i> , 2018)	2018	OIP5-AS1	60	OSCC	REL	NS	NS	NS	NS
28443494	Arunkumar G(Arunkumar <i>et al</i> , 2017a)	2017	PANDAR	60	OSCC	REL		NS	NS	NS
NA	Huang Z(Huang <i>et al</i> , 2018b)	2018	PANDAR	92	OSCC	MEL	NS		over p = 0.004	NS
28443494	Arunkumar G(Arunkumar <i>et al</i> , 2017a)	2017	POU3F3	60	OSCC	REL		NS	NS	NS
25045670	Gao W(Gao <i>et al</i> , 2014)	2014	PPP2R4-5	32	TSCC	REL	NS	NS		
27862321	Gao L(Gao <i>et al</i> , 2017)	2017	PTENp1	62	OSCC		under p < 0.001	NS	under p < 0.001	
25045670	Gao W(Gao <i>et al</i> , 2014)	2014	SPRR2D-1	32	TSCC	REL	NS	NS		
28119088	Liang S(Liang <i>et al</i> , 2017b)	2017	TUG1	96	OSCC	MEL	NS	over p < 0.001	over p < 0.001	over p = 0.015

24332332	Fang Z(Fang <i>et al</i> , 2014)	2014	UCA1	94	TSCC	REL	NS	over p = 0.0379		
23292713	Tang H(Tang <i>et al</i> , 2013)	2013	UCA1	16	OSCC	REL		over p = 0.005		
27560546	Yang YT(Yang <i>et al</i> , 2016)	2016	UCA1	124	TSCC		NS	over p = 0.011	over p = 0.042	

Over or underexpression is as reported in the individual study

OSCC: oral squamous cell carcinoma

TSCC: tongue squamous cell carcinoma

NA: not available

NS: not significant

MEL: median expression level used as cut-off value

REL: relative expression level

Table 2. Studies addressing potential relation between lncRNA differential expression and demographical data in OSCC/TSCC patients.

PMID	First Author	year	lncRNA	N° of patients
30128179	Hu X(Hu <i>et al</i> , 2018)	2018	AC012456.4	329
29310682	Wang Z(Wang <i>et al</i> , 2018b)	2018	AFAP1-AS1	103
25045670	Gao W(Gao <i>et al</i> , 2014)	2014	AL355149.1-1	32
29635126	Chai L(Chai <i>et al</i> , 2018)	2018	ANRIL	130
NA	Liu T(Liu <i>et al</i> , 2017a)	2017	ANRIL	116
28413645	Arunkumar G(Arunkumar <i>et al</i> , 2017b)	2017	CCAT1	60
28671055	Ma Y(Ma <i>et al</i> , 2017)	2017	CCAT2	62
NA	Zhou NG(Zhou <i>et al</i> , 2016)	2016	CCAT2	102
29281558	Guo Y(Guo <i>et al</i> , 2018)	2018	CEBPA-AS1	60
29138845	Sun T(Sun <i>et al</i> , 2018)	2018	EGFR	50
28639619	Shih J(Shih <i>et al</i> , 2017)	2017	HIFCAR*	42
30404566	Liu Z(Liu <i>et al</i> , 2018b)	2018	HNFI1A-AS1	62
23292713	Tang H(Tang <i>et al</i> , 2013)	2013	HOTAIR	16
25901533	Wu J(Wu and Xie, 2015)	2015	HOTAIR	50
26036760	Wu Y(Wu <i>et al</i> , 2015)	2015	HOTAIR	76
26058875	Zhang H(Zhang <i>et al</i> , 2015a)	2015	HOTTIP	86
23292713	Tang H(Tang <i>et al</i> , 2013)	2013	HULC	16
30310293	Li M(Li <i>et al</i> , 2018)	2018	LINC00152	40
28367232	Yu J(Yu <i>et al</i> , 2017b)	2017	LINC00152	197
29315846	Ding J(Ding <i>et al</i> , 2018)	2018	LINC00511	20
28039470	Yu J(Yu <i>et al</i> , 2017a)	2017	LINC00673	202
30026052	Wang Y (Wang <i>et al</i> , 2018a)	2018	lnc-p23154	49
23292713	Liang J(Liang <i>et al</i> , 2017a)	2017	MALAT1	32
27353727	Tang H(Tang <i>et al</i> , 2013)	2013	MALAT1	16
25045670	Gao W(Gao <i>et al</i> , 2014)	2014	MBL2-4:3	32
23292713	Jia LF(Jia <i>et al</i> , 2014)	2014	MEG3	76
24343426	Tang H(Tang <i>et al</i> , 2013)	2013	MEG3	16
23292713	Tang H(Tang <i>et al</i> , 2013)	2013	NEAT1	16
29484420	Huang G(Huang <i>et al</i> , 2018a)	2018	NEAT1	30
30186464	Liu X(Liu <i>et al</i> , 2018a)	2018	NEAT1	58
27613832	Huang W(Huang <i>et al</i> , 2016)	2016	NKILA	96
29728583	Arunkumar G(Arunkumar <i>et al</i> , 2018)	2018	OIP5-AS1	60

NA	Huang Z(Huang <i>et al</i> , 2018b)	2018	PANDAR	92
25045670	Gao W(Gao <i>et al</i> , 2014)	2014	PPP2R4-5	32
27862321	Gao L(Gao <i>et al</i> , 2017)	2017	PTENp1	62
25045670	Gao W(Gao <i>et al</i> , 2014)	2014	SPRR2D-1	32
28119088	Liang S(Liang <i>et al</i> , 2017b)	2017	TUG1	96
23292713	Tang H(Tang <i>et al</i> , 2013)	2013	UCA1	16
27560546	Yang YT(Yang <i>et al</i> , 2016)	2016	UCA1	124

* HIFCAR was upregulated in patients older than 50 years

NA: not available

Table 3. Differential expression of lncRNAs in SCC related to exposure to risk habits.

PMID	First Author	year	lncRNA	N° of patients	Anatomical site	Tobacco	Betel quid with tobacco chewing	Alcohol
30128179	Hu X(Hu <i>et al</i> , 2018)	2018	AC012456.4	329	OSCC	NS		under
29310682	Wang Z(Wang <i>et al</i> , 2018b)	2018	AFAP1-AS1	103	TSCC		NS	
25045670	Gao W(Gao <i>et al</i> , 2014)	2014	AL355149.1-1	32	TSCC	NS		NS
28443494	Arunkumar G(Arunkumar <i>et al</i> , 2017a)	2017	AP5M1	60	OSCC	NS	over	NS
28413645	Arunkumar G(Arunkumar <i>et al</i> , 2017b)	2017	CCAT1	60	OSCC	NS	NS	
28671055	Ma Y(Ma <i>et al</i> , 2017)	2017	CCAT2	62	OSCC	NS		NS
28443494	Arunkumar G(Arunkumar <i>et al</i> , 2017a)	2017	CDKN2B-AS1	60	OSCC	NS	over	NS
29281558	Guo Y(Guo <i>et al</i> , 2018)	2018	CEBPA-AS1	60	OSCC	NS		NS
28443494	Arunkumar G(Arunkumar <i>et al</i> , 2017a)	2017	FALEC	60	OSCC	NS	over	NS
28443494	Arunkumar G(Arunkumar <i>et al</i> , 2017a)	2017	H19	60	OSCC	NS	under	NS
28443494	Arunkumar G(Arunkumar <i>et al</i> , 2017a)	2017	HOTAIR	60	OSCC	NS	over	NS
26036760	Wu J(Wu and Xie, 2015)	2015	HOTAIR	50	OSCC	NS		NS
25901533	Wu Y(Wu <i>et al</i> , 2015)	2015	HOTAIR	76	OSCC	NS		NS
26058875	Zhang H(Zhang <i>et al</i> , 2015a)	2015	HOTTIP	86	TSCC	NS		NS
28367232	Yu J(Yu <i>et al</i> , 2017b)	2017	LINC00152	197	TSCC	NS	NS	
28443494	Arunkumar G(Arunkumar <i>et al</i> , 2017a)	2017	LINC00312	60	OSCC	NS	over	NS
28039470	Yu J(Yu <i>et al</i> , 2017a)	2017	LINC00673	202	TSCC	NS	NS	
28443494	Arunkumar G(Arunkumar <i>et al</i> , 2017a)	2017	linc-RoR	60	OSCC	NS	over	NS

30026052	Wang Y(Wang <i>et al</i> , 2018a)	2018	lnc-p23154	49	OSCC	NS		NS
28443494	Arunkumar G(Arunkumar <i>et al</i> , 2017a)	2017	MALAT1	60	OSCC	NS	over	NS
25045670	Gao W(Gao <i>et al</i> , 2014)	2014	MBL2-4:3	32	TSCC	NS		NS
28443494	Arunkumar G(Arunkumar <i>et al</i> , 2017a)	2017	MEG3	60	OSCC	NS	NS	NS
29484420	Huang G(Huang <i>et al</i> , 2018a)	2018	NEAT1	30	OSCC	NS		
29728583	Arunkumar G(Arunkumar <i>et al</i> , 2018)	2018	OIP5-AS1	60	OSCC	NS	NS	
28443494	Arunkumar G(Arunkumar <i>et al</i> , 2017a)	2017	PANDAR	60	OSCC	NS	over	NS
28443494	Arunkumar G(Arunkumar <i>et al</i> , 2017a)	2017	POU3F3	60	OSCC	NS	over	NS
25045670	Gao W(Gao <i>et al</i> , 2014)	2014	PPP2R4-5	32	TSCC	NS		NS
25045670	Gao W(Gao <i>et al</i> , 2014)	2014	SPRR2D-1	32	TSCC	NS		NS
24332332	Fang Z(Fang <i>et al</i> , 2014)	2014	UCA1	94	TSCC	NS		

Over or underexpression is as reported in the individual study

NS: not significant

Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:

Pentenero, M;Bowers, LM;Jayasinghe, R;Yap, T;Cheong, SC;Kerr, AR;Farah, CS;Alevizos, I

Title:

World Workshop on Oral Medicine VII: Clinical evidence of differential expression of lncRNAs in oral squamous cell carcinoma: A scoping review

Date:

2019-06-01

Citation:

Pentenero, M., Bowers, L. M., Jayasinghe, R., Yap, T., Cheong, S. C., Kerr, A. R., Farah, C. S. & Alevizos, I. (2019). World Workshop on Oral Medicine VII: Clinical evidence of differential expression of lncRNAs in oral squamous cell carcinoma: A scoping review. ORAL DISEASES, 25 (Suppl 1), pp.88-101. <https://doi.org/10.1111/odi.13076>.

Persistent Link:

<http://hdl.handle.net/11343/285918>