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Eminence Grise of the Genome: Long Non-Coding Ribonucleic Acids in Oral Squamous Cell Carcinomas

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I. Introduction

Oral Squamous cell carcinoma (OSCC) is a heterogenous malignancy which results in decreased survival rates due to local recurrence and lymph node metastases [1]. Various other cancers like lymphomas and certain sarcomas possess relatable gene alterations for which effective target drug therapies are developed, but due to complex genomic and epigenomic changes and interactions in OSCC, use of an effective chemotherapeutic agent is still a challenge. Recent research has now focused on epigenomic modifications that effect the gene expression rather than gene mutations to understand these complex mechanisms [2,3,4]. In context to this, non-coding ribonucleic acids (ncRNAs, previously considered as "junk or transcriptional noises") that are transcripts not translated to proteins but are potential effectors of target gene expression have gained additional interest [5,6].

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Statistics of Ensemble 1 show that around 34% of the human genome are protein-coding genes. Among which 66% of genes encode ribonucleic acids (RNAs) that are not translated into proteins [5,6]. The Encyclopedia of DNA Elements Consortium (ENCODE) revealed that humans have 60554 genes out of which 19815 are protein-coding genes, and the rest represents ncRNAs that regulate gene expression involved in vital physiological and pathological processes [4,7].

They are grouped as house-keeping ncRNAs and regulatory ncRNAs. The house-keeping RNAs include ribosomal [rRNAs], transfer RNAs [tRNAs], small nuclear RNAs [snRNAs] and small nucleolar RNAs [snoRNAs]. The regulatory ncRNAs are divided into: a) Short ncRNAs: size < 200 base pairs (bp); b) Long nc 25 RNAs (lncRNA): size > 200 bp; c) Pseudogenes; d) Circular RNAs; e) Intronic RNAs [7,5,6].

The small ncRNAs include small interfering RNAs (siRNAs), PIWI-interacting RNAs (piRNAs), micro RNAs (mi RNAs) and transcription initiator RNAs (tiRNAs) [5,3].

There are about 16,000 lncRNA genes that encode 28,000 lncRNAs. Five types of lncRNA are identified based on the position of DNA protein-coding strands [Figure 1a] from which they are synthesized.

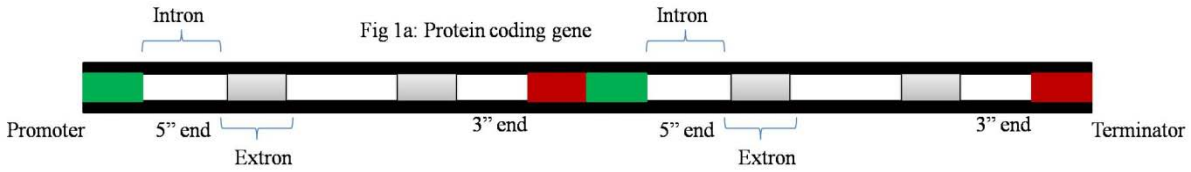

Figure 1a: Protein coding gene

They are grouped as: *a) sense lncRNAs:* overlap the nearest protein-coding genes on the same strand; *b) antisense lncRNAs:* located across the exons of protein- coding genes from the opposite strand [Figure 1b];

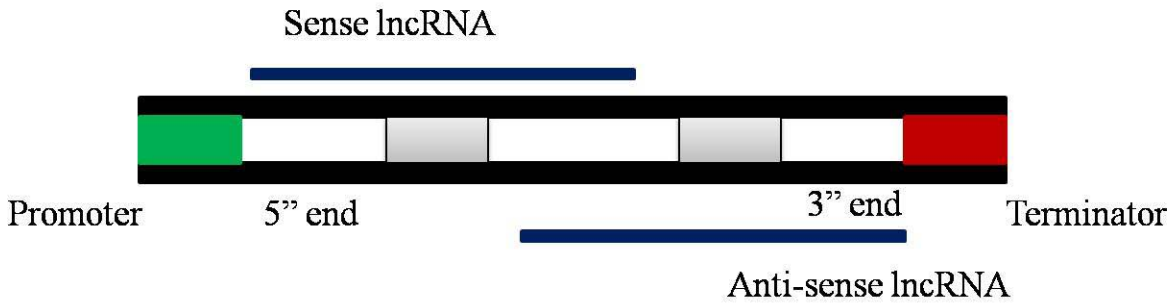

Figure 1b: Sense lncRNA on same strand overlapping the protein coding gene and antisense lncRNA on the opposite strand of protein coding gene

c) Bidirectional lncRNAs: transcribed on the opposite strand within 1 kilobyte (kb) from the nearest protein-coding gene [Figure 1c];

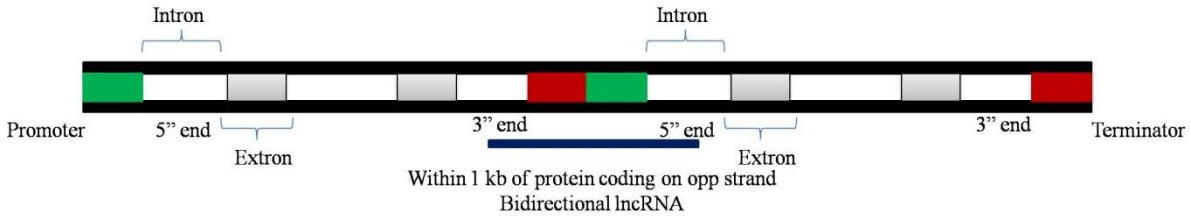

Figure 1c: Bidirectional lncRNA formed from within 1 kb of protein coding on opposite strand

d) Intergenic lncRNAs: located at least 1 kb far from the closest protein-coding gene, in-between the protein-coding genes [Figure 1d]. They form the largest group;

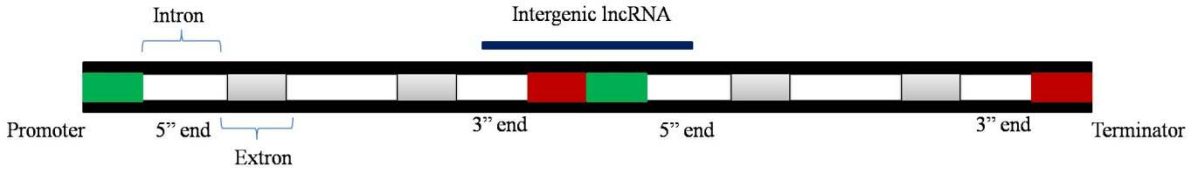

Figure 1d: Intergenic lncRNA synthesized from within 1 kb of protein coding on same strand

e) Intronic lncRNAs: overlapping either the sense or antisense intronic areas of the protein-coding genes (Figure 1e) [7,8,9].

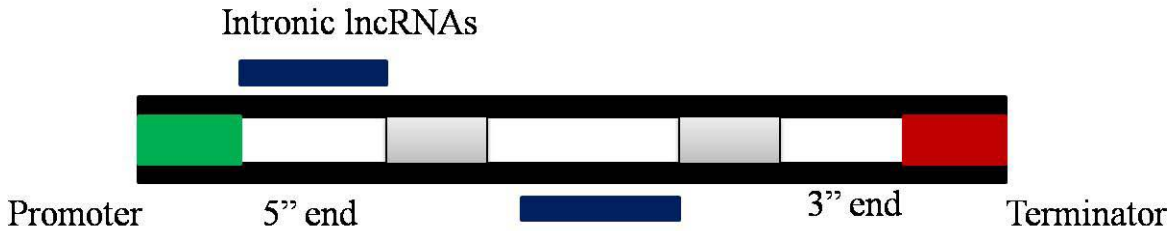

Figure 1e: Intornic lncRNA synthesized from intronic region of coding gene either same or opposite side

LncRNAs regulate gene expression through epigenetic regulation (chromatin modification & DNA methylation), transcription, and post transcription processing by acting as scaffolds, guides, decoys or repressors, sponges serving as competing endogenous RNAs (ceRNAs) for signaling pathways, and enhancer RNAs. They are involved in pre- mRNA splicing [Table 1] [1,4, 6, 9, 7, 10, 11,12, 13].

Table 1: Actions of Long non-coding RNA

Sl no	Action type Long non-coding RNA	Function
1.	LncRNAs scaffolds	Platforms on which multiple enzymatic proteins can be transiently assembled in functional units such as ribonucleoprotein complex (RNP), heterogenous nuclear ribonucleoproteins (hnRNAs) etc. Their interaction is dynamic and exerts regulatory functions during mRNA processing.
2.	LncRNAs guides	Physically direct the RNAs to specific genomic region by binding to regulatory or enzymatically active proteins such as transcription factors, chromatin modifiers etc and regulate gene expression either in cis or trans sites.
3.	LncRNA decoys	Limit the availability of specific regulatory factors by acting as a molecular sink and sequester RNA-binding proteins, transcription factors, microRNAs, catalytic proteins and subunits of larger modifying complexes. They titrate these factors away from interacting with their native targets, decreasing their bioavailability, inhibiting their normal functions
4.	LncRNA sponges	Impair miRNAs, explained by competing endogenous RNA (ceRNA) hypothesis. According to which lncRNAs sequester miRNAs and reduce the availability of miRNA for the target mRNAs. The miRNAs play an important role in post transcriptional regulation of protein coding genes and mRNAs. LncRNAs actively compete with specific protein-coding mRNA that interact with intracellular pool of miRNAs acting as sponges or ceRNA for miRNAs, silence them and reduce the post-transcriptional activity.
5.	Signalling lncRNAs	Associated with specific signalling pathways or events such as cellular stress leading to transcription activation of specific genes.
6.	Enchancer lncRNAs	Enhance and promote gene activity by altering the 3 dimensional configuration of DNA.

LncRNAs act in nucleus or cytoplasm or both, exhibiting three types of interactions: RNA-RNA, RNA-DNA, and 52 RNA-proteins. Their partners of communication include RNA binding proteins (RBPs), transcription factors, chromatin- modifying complexes, nascent RNA transcripts, mature mRNA, microRNA, DNA, and chromatin. [1, 7, 9, 14]

In the nucleus where they are mainly localized, they regulate epigenetics of protein-coding genes and alter their expression through chromatin remodeling complexes [such as polycomb repressive complex 2 (PRC 2), H3K9 methyl transferases] and DNA methylation patterns. They control the gene expression at the transcription level, act as decoys, bind to the DNA target sequences, act as alternative splicing regulators (antisense transcripts), are involved in splicing malfunctioning, and act as decoys for splicing [7,15]. The cis-acting lncRNAs are close to transcription site, and trans-acting lncRNAs are on distant genes of chromosomes [1].

In the cytoplasm, they interact with target mRNAs or miRNAs through miRNA response elements via base paring. They may stabilize or decoy the target transcripts, thus promoting or repressing the translation of transcripts to proteins [7]. Cytoplasmic lncRNAs act as sponges and promote micro peptide formation [10, 16].

a) Synthesis of LncRNA

LnRNAs originate and are predominantly located in the nucleus. Tissue specific RNA polymerase I, II or III transcribe lncRNAs.They are 5' capped, 3' polyadenylated, have exon/intron length, and undergo splicing of multiple exons through canonical genomic splice motifs. They resemble protein-coding mRNAs, but lack or have a small number of open reading frames. The exon length of lncRNA is the same as protein-coding mRNAs but has fewer exons that are less expressed than protein-coding mRNAs. As the span of lncRNA is more than 200 bp, they can fold into more complex three dimensional structures unlike, miRNA. The complex structure of lncRNAs determines their specific interaction with transcription factors, histone and chromatin-modifying genes affecting the expression level of a broad spectrum of genes [9, 8,10,17].

b) Functions of LncRNA

LncRNAs affect numerous biological processes such as embryological development, stem-cell biology, development, and differentiation [6]. They are tissue or cell type-specific as indicated by gene expression profiling, possessing a varied expression to different pathophysiological conditions, and tumors. They regulate cell proliferation, survival, apoptosis, invasion, metastases, glycolysis, angiogenesis, growth, tumor-

stroma signaling or genomic stability, thus serving as potential diagnostic, prognostic biomarkers, and therapeutic targets [5,8,10,13,18,19,20].

LncRNAs are dysregulated in several neurological disorders and cancers, demonstrating both oncogenic and tumor-suppressive roles [12,21]. LncRNA Hox antisense intergenic RNA (HOTAIR), for example, functions as an oncogene in breast cancer, colorectal cancer, pancreatic cancer, etc, and increased levels are associated with reduced survival rates [20]. On the other hand, maternally expressed gene 3 (MEG3) is up-regulated in breast, hepatic cancer, and plays an oncogenic role. In contrast, it is down-regulated in tongue squamous cell carcinoma (TSCC) and plays a tumor-suppressor role [4]. The present article reviews the expression of lncRNAs in OSCC mainly, with a note on its presentation in oral potentially malignant disorders (OPMDs).

Gibb et al. state that in the normal oral mucosa 325 lncRNAs are expressed. In OPMDs, around 164 lncRNAs are aberrantly expressed. Jia et al. studied 3590 differently expressed lncRNAs in TSCC, and found that 1785 were up-regulated, and 1805 were down-regulated [3,4,22]. Yu et al. detected 1572 abnormally expressed lncRNAs with 882 up-regulated, and 690 down-regulated lncRNAs [4]. A study on head and neck squamous cell carcinoma (HNSCC) showed that 84 out of 3199 lncRNAs had an impact on survival rates of the patients [1]. Studies done by Gao et al. showed six upregulated lncRNAs such as lnc 122-PPP2R4-5, SPRR2D-1, FAM46A-1, BL2-4:1, and MBL2-4:3 (associated with high nodal status) in TSCC and two down-regulated lncRNA viz AL355149.1-1 and STXBP5-1[17].

II. LNCRNAs Upregulated during OSCC Progression

a) LncRNA H19

First identified long non-coding RNA, coded by gene H19 located in chromosome 11p15.5 in close association with insulin growth factor (IGF) 2 gene. LncRNA H19 is a transcription factor of the H19/IGF 2 genome blotting cluster, directly activated by c-MYC and down-regulated by p53 contributing to cell growth and proliferation [23].

The combination of H19 and enhancer of zest homolog 2 (EZH2) affects signal transduction of b-catenin/glycogen synthase kinase three beta (GSK 3b)/epithelial- mesenchymal transition (EMT) in TSCC, promoting lymph node metastasis and poor prognosis. MiRNA-138 and 630 down-regulate EZH2 and are suppressed by lncRNA H19. Thus H19 and Hox antisense intergenic RNA (HOTAIR) can up-regulate EZH2 decreasing the E-cadherin levels, enhancing the invasive potential of SCC cells with H19 expression being higher in metastatic tumors than non-metastatic [23].

H19 acts as a ceRNA increasing the level of miRNA lethal(let)-7a targets, a chief regulator of high-mobility group AT-hook 2 (HMGA 2) in the process of tumor metastasis. H19 / let-7a/HMGA2 / EMT axis plays a principal role in the regulation of invasion, metastasis, and is associated with poor prognosis in TSCC [4]. H19 over-expression in endothelial cells stimulated angiogenesis. H19 regulates expression of tumor growth factor (TGF)-b, which promotes cancer cell migration through enhanced adhesion with extracellular molecules. Notch and hepatocyte growth factor regulated signaling of H19.

Blocking of Notch and HGF inhibited H19. The inhibition of H19 decreased cell resistance to Fulvestrant and Tamoxifen [10,22,24]. Thus H19 plays a role in reducing the susceptibility of cells to chemotherapeutic drugs.

b) Hox antisense intergenic RNA- HOTAIR

HOTAIR is highly conserved nuclear lncRNA, a transcript of 2.2 kb, transcribed from the (Homeobox C) HOX C locus at chromosome 12 but functions at transit close to HOX D locus on chromosome 2 that induces silencing of transcription [3].

The domain 5' of HOTAIR binds PCR 2, which includes EZH2, SUZ 12, and EED (both polycomb proteins) to the HOX D locus and inhibits its expression. EZH2 is a histone H3 lysine 27 methyl transferase (H3K27me 3) enzyme that catalyzes trimethylation of H3K27, a histone modification associated with long-term transcription repression [23]. EZH2 is a critical epigenetic regulator for various biological processes such as cell proliferation, cell cycle, metastases, and oncogenesis [6,16].

HOTAIR prefers to occupy a guanine-adenine (GA)-rich DNA motif on chromatin, which allows direct interaction of lncRNA transcript to specific genomic sites (has both cis and trans-regulatory mechanism) [20, 23]. Also, the 3' domain of HOTAIR binds the histone demethylase lysine-specific histone demethylase (LSD)1. This evidence suggests that HOTAIR serves as a platform for two different histone modification complexes [3].

It promotes tumor cell invasion and metastasis by recruiting EZH2 and repressing E-cadherin in OSCC [11]. HOTAIR is differently expressed in the saliva of patients with OSCC with metastases and without metastases [3]. According to Dai et al., HOTAIR 7 is highly expressed in TSCC associated with cell proliferation, apoptosis, metastases, and invasion [4].

High expression of HOTAIR in laryngeal SCC is associated with tumor size greater than 0.9 cm, poor differentiation, lymph node metastasis, resistance to apoptosis, advanced clinical stages, and also drug

resistance with EZH2 serving as a potential mediator [3,8,20].

HOTAIR is highly expressed in hypoxia and regulates angiogenesis through vascular endothelial growth factor A (VEGF A) directly through its promoter sequence or by modifying the levels of glucose-regulated protein- 78 (GRP 78) and angiopoietin 2 (ANG-2) in nasopharyngeal carcinoma [10].

c) Ferritin Heavy Chain 1 Pseudogene 3: FTH1P3

FTHIP3 is mapped to chromosome 2p23.3 with a length of 954 nucleotides, it is ferritin pseudogene with a misannotated 3' un-translated region (UTR), which is closely associated with iron-responsive elements (IREs). It affects the post-transcriptional structured cis-acting RNA regulatory elements in the 5' or 3' UTRs of mRNAs. FTH1P3 harbors miR-224-5p cognate site, sponging miRNA 224-5p and consequently modulates the expression of frizzled class receptor five, which acts as an oncogene in OSCC. miRNA 224-5p is a potential tumor suppressor that is suppressed by FTHIP3 in OSCC, contributing to oncogenesis.

FTH1P3 is coexpressed with plasminogen activator urokinase (PLAU) and targets OSCC associated genes, including matrix metallopeptidase (MMP) 1, 3, 9, PLAU and interleukin 8 (IL 8) which are essential regulators of tumorigenesis. Ectopic and overexpression of FTH1P3 facilitates cell proliferation, colony formation, tumor progression, metastases, and worsens survival rate in OSCC cases [6,11,22,23,24].

d) Urothelial Cancer-associated 1- UCA1

Located on chromosome 19p13.12, UCA1 regulates the expression of various genes mainly through wingless-homeobox gene (WNT)/ b-catenin signaling pathway. The lncRNA is upregulated in OSCC, promoting cellular proliferation and tumor-lymph node-metastasis (TNM) staging. UCA1 functions as a sponge to miR-184 inhibiting it, miRNA-184, in turn, has an inhibitory effect on phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of Rapamycin (mTOR) signaling pathway. As a ceRNA, UCA 1 represses the effect of miRNA-184 promoting tumor progression, suppressing the influence of cisplatin-induced apoptosis and chemosensitivity in TSCC cells. UCA1 acts by inhibiting the cisplatin-activated PI3K/Akt signaling pathway, though, in TSCC, UCA1 promotes lymph node metastases more than cell proliferation.

In OSCC, it is co-expressed with numerous metabolism- related genes. UCA1 enhances the Warburg effect via mTOR activation followed by activation of signal transducer and activator of transcription 3 (STAT 3) and repression of miR-143. The Warburg effect results in increased hexokinase 2 (HK2) levels and a consequent increase in glycolysis.

Tonghan Zhang et al. discovered the regulation effects of UCA1/miR-124/Jagged 1 (JAG1) axis on tongue cancer which activates Notch pathway [4,5,8,12,13,14,21,25,23].

e) Metastases associated lung adenocarcinoma transcript 1- MALAT1

MALAT1 or nuclear enriched abundant transcript 2 (NEAT2), is a long intergenic non-coding RNA that maps on chromosome 11q13 [23] and is 8.7 kb 203 long. It is very stable due to its triple-helical and nuclear retention element (ENE) like structure located in the nucleus and plays a role in RNA metabolism. Expression of cell cycle genes such as E2F1 transcription factors and the G1/S phase requires MALAT 1. It promotes mitosis through transcription factor B-MYB. MALAT-1 depleted cells are sensitive to p53 levels, indicating that p53 is one of the key molecules involved in the downstream effects of MALAT1.

MALAT 1 acts as a sponge to miRNA- 125 b, which upregulates STAT 3 expression promoting OSCC development. It plays a role in EMT in OSCC cells, promoting cell migration and invasion. Its knockdown suppressed N-cadherin and vimentin but induced E-cadherin expression in vitro. In a tongue cancer cell line, MALAT1 targeted miRNA-124 and promoted cancer growth through modulation of JAG1. Studies have shown that upregulated MALAT 1 induced cervical lymph node metastasis in TSCC by increasing BCL2 associated X (BAX) expression.

Upregulated MALAT 1 interacts with EZH2 inducing b-catenin expression activating Wnt/b-catenin signaling pathway, upregulating MMP-7, inducing EMT, enhancing the invasion, and inhibiting apoptosis capacity of TSCC cells. Down-regulation of apoptosis-related genes BNIP3L (pro-apoptotic BCL-2 family protein) and Neuregulin 1 (NRG1) is noted. Increased levels of MALAT 1 also incite mitogen activated protein kinase (MAPK) and PI3K/Akt.

MALAT 1 functions as ceRNA for miRNA-320a, which suppresses forkhead box M1 (FOXMI). FOXM1 is involved in new vessel growth in hypoxic conditions associated with fibroblast growth factor-2 (FGF-2) expression [4,6,14,19,21,25].

f) Opa-interacting protein five antisense RNA 1-OIP5-AS1

Emerges from chromosome 15q15.1 on the strand opposite to OIP5 gene and is involved mainly in the regulation of neurogenesis during development. OIP5-AS1 is an oncogene that serves as a ceRNA by sponging multiple miRNAs such as miR-340-5p, miR-217, miR-200b-3p, miR-223, miR-410, miR- 378a, and miR-338-3p. miRNA 338-3p is a tumor suppressor that modulates the expression of neuropilin 1(NRP1). NRP1 is a co-receptor for VEGF and functions as an oncogene in multiple types of cancers. OIP5-AS1 functions as miR-338-3p 'sponge' to trigger NRP1 expression and thus the progression of OSCC. Overexpression of NRP1

promotes EMT by stimulating the nuclear factor-kappa B (NF-kb) pathway.

Knockdown of OIP5-AS1 decreased the levels of NRP1 and significantly inhibited OSCC cell proliferation, migration, invasion, retarded tumor growth, and colony formation [19].

g) Colon cancer-associated transcript-1-CCAT1-S or cancer-associated region long non-coding RNA-5-CARLO-5

CCAT1-S is a 2628 nucleotide lncRNA located on chromosome 8q24.21. CCAT1 mediates cell proliferation by inhibiting expression of cyclin-dependent kinase (CDK) inhibitor 1A (CDK N1A) mRNA, the main regulator of G0-G1 phase by increasing the expression of p16, p21, and p27 and thus cell proliferation. Silencing of CCAT1 by siRNA leads to induction of phase 1 cell cycle arrest, increased levels of E-cadherin, and decreased levels of fibronectin and vimentin required for EMT. CCAT1 interacts with transcriptional enhancer c-MYC promoter region through chromatin looping and increases its expression. CCAT1 functions as a ceRNA for miRNA-155-5p, let-7b-5p, and miRNA-490-3p by sequestration and miRNA-218- 5p by epigenetic regulation.

27% of oral tumor show overexpression of CCAT1 associated with increased expression of c-MYC; and down-regulation of miRNA-155-5p and let 7b-5p. Oral cancer patients with an increased level of CCAT1 are associated with tobacco use, poor prognosis, and aggressive phenotype [6].

h) THOR- CG8846 gene product from transcript CG8846-RA

IGF 2 mRNA binding protein 1 (IGF2BP1), an oncogene belongs to a conserved family of RNA-binding proteins present mainly in the cytoplasm. They bind to mRNAs that regulate protein synthesis of k-RAS, MYC gene family, CD44, phosphatase and tensin homolog (PTEN) and IGF 2. It plays a pivotal role in cell proliferation, polarization, metabolism, morphology, differentiation, and migration. IGF2BP1 regulates the radio-/chemo-resistance of cancer cells by increasing the expression of multidrug resistance mutation 1 (MDR1).

THOR stabilizes the binding of IGF 2 mRNA with IGF2BP1. It regulates IGF2/mitogen activated kinase/extracellular signal-regulated kinases (IGF2/MEK/ERK) signal pathway in TSCC cells by increasing cell cycle-related proteins cyclin D 1 and E1. THOR functions as a negative prognostic marker by increasing cell proliferation; attenuates cisplatin sensitivity in nasopharyngeal carcinoma; regulates osteosarcoma stemness and mobility [26].

i) Long Intergenic Non-Protein Coding RNA, Regulator of Reprogramming- lncRNA-ROR

Located on chromosome 18q21.31, LncRNA-ROR is 2.6 kb long non-coding RNA and consists of retrotransposons elements such as long interspersed nuclear elements (LINE), short interspersed nuclear elements (SINE) and long terminal repeater (LTR) elements. The location of lncRNA-ROR is a binding site for pluripotency transcription factors such as Sox2, Oct4, and Nanog. LncRNA-ROR acts as ceRNA for miRNA 145-5p at post-transcriptional level, modulating the expression of target genes c-MYC, KI, SOX2, and Oct 4 impacting the differentiation of human embryonic stem cells. It also sponges miRNA-205 increasing the half-life of Zinc Finger E-Box Binding Homeobox 2 (ZEB2), thus promoting EMT. LncRNA-ROR is a suppressor of p53 during DNA damage by interacting with hnRNP I, thus directly inhibiting p53 mediated cell cycle arrest and apoptosis [6].

The other lncRNAs associated with OPMDs is presented in table 2 [4,27,28,29]; and OSCC progression in relation to angiogenesis in table 3 [4,6,10,18,21,23,25,29], cell proliferation in table 4 [4,15,19,23,25,27,30,31,32], metastasis in table 5 [1,4,6,8,16,18,22,25,31,33,35], and chemoresistance in table 6 [4,13,29].

Table 2: Long-coding RNAs involved in OPMDs

Sl no	Name of Lnc RNA	Function	Expression in OPMDS/OSCC
1.	Nuclear enriched abundant transcript 1-NEAT 1	Oncogene regulates miR365/ Regulator of G protein signalling 20 (RGS20) pathway and up regulates cyclin dependent kinase (CDK) 6 through miRNA-107	Over expression: transformation of OPMD to OSCC. Elevating proliferation, invasion, nodal metastases and inhibiting apoptosis in OSCC. *Not found in saliva.*
2.	Long intergenic non-protein coding RNA 974-LINC00974	Oncogene- Areca nut constituents have shown to activate the TGF-/p-Smad2 pathway mediated by LINC00974, leading to enhanced myofibroblastic activity	Higher expression: increases oral fibrinogenesis in OSF and mediates progression of OSF to OSCC.
3.	Long intergenic non-protein coding RNA 511-LINC00511	ceRNA for miRNA 765 increasing the expression of Laminin subunit gamma 2 (LAMC2), weakening the inhibitory effect of miRNA-765	High expression: Higher grades of dysplasia in leukoplakia and progression to malignancy. Increases cell proliferation and invasion in TSCC. *An early biomarker*.

Table 3: Long-coding RNAs affecting angiogenesis

1.	Hyaluronan synthase 2 antisense 1-Lnc HAS2-AS1	Marker for hypoxia	Increased HAS2-AS1induces HIF-1a increased production of hyaluronan synthase which inturn increases EMT and OSCC tumour metastases.
2.	HIF-1a co-activating RNA- lncRNA HIFCAR	Complexes with HIF-1a, recruitment of HIF1a and p300 that target promoters in OSCC.	Complex is induced by hypoxia, stabilizing and activating HIF1-a resulting in angiogenesis
3.	Long intergenic non-coding RNA 668-LINCO 0668	Acts as a ceRNA for miRNA-297 which inhibits VEGF A promoting angiogenesis	Up regulation: Associated with cell proliferation, tumor invasion of OSCC. Knockdown suppressed tumor growth and reduced the expression of proliferation antigen ki-67
4.	FOX C1 upstream transcript-FOXCUT or long intergenic non-protein coding RNA 1379- LINC01379	Influences the expression of matrix metalloproteins (MMP) 2, 7, 9 and VEGF A	Over-expressed in OSCC, associated with cell proliferation, angiogenesis, colony formation and invasion.
5.	Long non-coding RNA MIR31	Hypoxia-inducible lncRNA and acts as HIF-1α co-activator increasing angiogenesis	Enhanced levels are associated with poor clinical outcomes and poor prognosis in oral cancer.
6.	Long non coding RNA p 21- LncRNA-p21	Binds to hnRNP-K complex and suppresses the expression of p53 regulated genes. Induced by hypoxia inducible factor-1a (HIF 1a) directly during hypoxia, increases levels of GLUT-1 and lactate dehydrogenase in turn increasing glycolysis in cancer cells.	Up regulated in OSCC

Table 4: Long non-coding RNAs affecting Cell proliferation

1.	Colon Cancer Associated Transcript 2-CCAT2	Regulates WNT/b-catenin/ GSK-3b	Increased expression: Cell proliferation, higher grade of tumour cell and pathological stage (stage II/III) of OSCC, but does not affect metastases.
2.	Long intergenic non-protein coding RNA 939 or lncRNA RP5-916L7.2	Targets miR-328-5p and miR-939-5p	Up regulation enhances cell proliferation and inhibits cell apoptosis in TSCC.
3.	Cancer Susceptibility 9- CA SC 9	Regulation of p-AKT, p-mTOR, P62 and BCL-2	Over expression: Inhibition of apoptosis, promotes cell proliferation, increases local recurrence in OSCC cases.
4.	MYC-induced long non-coding RNA-MINCR	Oncogene: activates the Wnt/β-catenin signalling pathway	High expression: promotes cell proliferation and regulates G0/G1 stage in OSCC.
5.	Long non-coding RNA Protein Disulfide Isomerase Family A Member 3 Pseudogene 1-LncRNA PDIA3P	Up regulates miR-185-5p target gene cyclin D2 (CCND2) by competitively sponging miR-185-5p and then activating CCND2 signalling pathways involved in cell cycle progression from G1 to S phase	Up-regulation results in OSCC cell proliferation, tumor growth, increased Ki-67 index and decreased the survival rates. *Prognostic biomarker* to distinguish patients with higher risks of OSCC progression.
6.	Long non-coding RNA Taurine upregulated gene 1-LncRNA TUG 1 & 338	Induced by higher levels of notch 1. Acts a sponge of miR-145 that regulates Wnt/b-catenin signalling pathway. TUG 338 dysregulated down stream factors STAT 1, ATK and caspase 3.	Upregulated TUG increased cell proliferation and decreased apoptosis.
7	Long Intergenic non-coding RNA 261-LINC00261	Regulates expression of Ectonucleotide Pyrophosphatase/ Phosphodiesterase (ENPP) 4 and ENPP5 that are involved in tumor development. Low expression of ENPP2 increases reactive oxygen species level that promotes tumor cell apoptosis.	Up-regulation inhibits apoptosis. Decreased expression shows better prognosis in TSCC

Table 5: Long non-coding RNAs affecting metastases

1	HOXA transcript at the distal tip- HOTTIP	Activation of HOX A gene	High expression: advanced clinical stage, tumour size and metastases. Independent prognostic factor
2	A disintegrin and metalloproteinase with a thrombospondin type 1 motif 9 antisense 2- ADAMTS9-AS2	ce RNA for miRNA 600 which reduces EZH2 levels	Up regulation decreased miR-600 levels, increasing EZH2 function, promoting migration and invasion through TGF-b1 mediated EMT process in TSCC. Expression being more in lymph node metastatic TSCC than non-metastatic TSCC.
3	Krueppel-like factor 8 (KLF 8) regulated Long non coding AC132217.4	KLF8 binds to the upstream sequence of AC132217.4, activating its expression and interacts with the 3' UTR of IGF2 mRNA increasing its stability, leading to increased IGF2 levels	Upregulation: promoted cell migration and EMT by upregulating IGF2, activating AKT signalling in OSCC promoting lymph node metastases.
4.	Long Intergenic Non-Protein Coding RNA 958- LINC00958	ceRNA for miRNA 185-5p, silencing YWHAZ, that promotes apoptosis and inhibits cell proliferation.	Up regulation of LINC00958 downregulates YWHAZ promoting proliferation and metastases of OSCC.
5.	Long intergenic non-protein-coding RNA 673- LINC00673	Action in OSCC yet to be determined.	Up regulation: increases tumour size, muscle infiltration, clinical stage, survival and recurrence rate in TSCC. *Early biomarker for OSCC*.
6.	Long intergenic non-coding RNA 00152- LINC00152	Binds to EZH2, silences the expression of p15 and p21 inducing tumor cell cycle progression	High expression: correlates with TSCC progression, advanced stage, relapse and invasion.
7.	Small nucleolar RNA host gene 20- LncRNA SNHG20	Regulates SNHG20/miR-197/LIN 28 axis	Over expression: higher TNM stage, lesser tumor differentiation and poor overall survival in OSCC.
8.	Long non coding RNA small nucleolar RNA host gene 1- lncRNA SNHG 12	Sponge for miR-195-5p leading to over expression of Notch2 and Hes	Up regulation: enhances cell growth, invasion and EMT in esophageal squamous cell cancer.
9.	Long non coding HNF1A antisense RNA 1-LncHNF1A-AS1	Promotes mechanical expression of Notch 1 and Hes 1	High levels associated with cell proliferation, migration and poor prognosis in OSCC.
10.	Colorectal Neoplasia Differentially Expressed-CRNDE	decreases expression of miRNA 384 which targets Kristen rat sarcoma (K-RAS), cell division cycle (CDC) 42 and insulin receptor substrate 1 (IRS 1) genes	Up-regulation: Accelerates the cell cycle, promotes the proliferation and invasion in TSCC.
11.	Cancer Susceptibility 15- CA SC 15	inhibits miRNA- 33a-5p	Increased levels promotes proliferation and migration in TSCC cells
12.	Lnc GIF2IRD2P1 and lnc PDIA3F	Targets MMP 3, 9, PLAU, IL-8 and PDIA3P	Over expression: progression and metasatses of OSCC.
13.	Lnc RNA GIHCG	GIHCG is the gene inhibitor of miR-200b/200a/429 expression and inhibits expression of miRNA 429	Up-regulation: accelerates cell cycle, promotes proliferation and metastasis in TSCC.
14.	X-inactive specific transcript-XIST	regulates oncogene E2F3 by spongeing miR-34a-5p and miR-137	Up-regulation: promotes cell growth, EMT and poor overall survival of HNSCC.
15.	Deleted in lymphocytic leukemia 1 (DLEU 1)	Increases the expression of hyaluronan synthase 3 (HAS 3) and CD 44 and interacts with HA-CD44 signalling. upregulates CDH1 that codes for E-cadherin.	Over expression: increases proliferation, migration, invasion, metastasis, xenograft formation, inhibits apoptosis and leads to progression in OSCC cells.
16.	Long intragenic non-coding RNA 312- LINC00312 or NAG7	NAG7 transcript is translated into protein—estrogen receptor repressor-10 (ERR-10) and functions as both coding and non-coding RNA	Up-regulation: inhibits proliferation (G1/S arrest) and increases cell adhesion, motility and invasion. Positively correlates with lymphnode metastases and negatively correlates with clinical stage and tumour size.

17.	Long Intergenic Non-Protein Coding RNA 460- LINC00460.	Acts as a sponge to miR-206, a tumour suppressor that down regulates AKT/ERK signalling pathway. miR-206 also regulates the expression of Stanniocalcin 2 (STC 2) which is associated with poor cancer prognosis.	High expression of LINC00460, STC2 and poor expression of miR-206 was associated with high nodal metastases in HNSCC
18	KTNI- antisense 1-KTN1-AS1or C14orf33	Acts as a ceRNA and sponges miR-153-3p which dysregulates SNAI1 and ZEB2 involved in EMT	Up regulation promotes cell proliferation, migration, EMT and invasion in OSCC. *Used as a biomarker to identify high risk cases*.
19.	LOC541471	unknown	Up regulation results in increased lymphnode metastases and perineural invasion.
20.	RP5-894A10.6	unknown	Upregulation results in poor prognosis in OSCC cases. Can be used as a *biomarker to identify high risk cases* of OSCC

Table 6: Long non-coding RNAs affecting chemoresistance

1.	Chemotherapy-induced lncRNA 1-CILA1	Activates Wnt/b catenin pathway	High levels of CILA-1 and low levels of phosphorylated b-catenin increased cisplatin resistance in TSCC patients, promoted EMT and invasiveness.
2.	KCNQ1 overlapping transcript 1-KCNQ1OT1	Transcriptionally silences KCNQ1 locus by regulating histone methylation, ceRNA to miRNA 211-5p that regulates Ezrin (also known as cytovillin or villin-2) /focal adhesion kinase (Fak)/Src (non receptor tyrosine kinase) signalling pathway	High expression: chemoresistance in TSCC
3.	Long non coding RNA-lnc-p23154	Possess complementary sequence to miR-378a-3p promoter region. miRNA 378-3p targets 3′UTR of Glut1, inhibiting its expression & in turn glycolysis. Lnc-p23154 interacts with miR-378a-3p promoter to repress its transcription, and then increases Glut1 expression.	Over expression: Increased tumor size, clinical stage, lymph node metastasis and decreased sensitivity of phenformin in OSCC patients.

III. lncRNAs Down-Regulated during OSCC Progression

a) Maternally expressed gene 3- MEG3

Mapped to chromosome 14q32.2, MEG 3 is expressed in normal human tissues and posses tumor suppressor properties. Its expression is lost, especially in cases of HPV-related OSCC due to gene deletion and promoter hypomethylation or hypermethylation of intergenic differentially methylated region. Decreased expression of MEG 3 results in the upregulation of the WNT pathway increasing the levels of b catenin. MEG3 increases the levels of p53 protein and regulates the downstream expression of p53 target genes. Notch 1 and Hes 1 are inhibited by MEG 3 blocking cell proliferation and metastasis.

Studies have revealed that miRNA-26a can increase the expression of MEG3 in TSCC tissues by targeting DNA methyltransferase 3B (DNMT3B) transcript inhibiting cell proliferation and triggering apoptosis. Down-regulation of MEG3 and miRNA-26a results in the increased malignant potential of OPMDs and poor OSCC prognosis [1,4,5,6,23].

b) Nuclear 270 factor- kappa beta interacting long non-coding 271 RNA- NKILA

NKILA helps in phosphorylation of nuclear factor of kappa light polypeptide gene enhancer in B cells inhibitor α (Ikβα) and inhibits activation of NF-kβ. Low levels in cancer promote EMT through TNF-α signaling and increase malignant potential in OPMDs. Reduced levels of NKILA are associated with decreased disease-free survival rates and overall survival rates [2,4,6].

c) Long non-coding ribo-nucleic acid phosphatase and tensin homolog pseudogene 1- lnc RNA PTENP 1:

LncRNA PTENP1 modulates PTEN expression by acting as a sponge for miRNA-17, miRNA-21, miRNA-214, miRNA-19, and miRNA-26, which suppress PTEN expression. Enhanced expression of PTEN can reverse the Warburg effect by PI3K independent or dependent mechanisms inhibiting glycolysis in cancer cells.

Decreased expression of lncRNA PTENP1 is observed in progressive OPMDs [5].

d) Growth Arrest-Specific Transcript 5 antisense 1- GAS 5- AS1

GAS 5 induces apoptosis, is down-regulated in HNSCC, and is associated with poor prognosis. It predicts the response to radical chemotherapy and plays an essential role in the pathogenesis of oral submucous fibrosis (OSF) and its progression to malignancy [4,3,8,22].

e) Prostate Androgen Regulated Transcript 1- PART 1

Located on chromosome 5q12, PART 1 functions as a ceRNA for miRNA- 301b, which regulates Nuclear Receptor Subfamily 3 Group C Member 2 (NR3C2). Down-regulated NR3C2 promotes cell proliferation, EMT, and metastases. PART1/mir-301b/NR3C2 axis may be associated with TSCC. Androgens regulate PART 1 which is a tumor suppressor. Studies have found less expression of androgen receptor (AR) mRNA in OSCC specimens compared to healthy tissues. ARs might be involved in lessening the progression of OSCC and PART 1 is regulated by androgens, PART 1 study may also be involved in the pathogenesis of OSCC [32,38].

f) Long Intergenic Non-Protein Coding RNA 472- LINC00472

LINC00472 acts as a sponge to miRNA-503 that regulates the expression of Gremlin 2, DAN Family BMP Antagonist (GREM2), which is an antagonist of bone morphogenetic proteins (BMP). BMP activates the Notch signaling pathway and Wnt/b-catenin signaling. Higher expression of LINC00472 is associated with a better prognosis [32].

IV. Applications

Identification of up-regulated or down-regulated lncRNAs in the progression of OSCC is essential as their expression can be altered using appropriate RNA interference machinery such as short hairpin RNAs, miRNAs, siRNAs, oligonucleotides that are complimentary to target lncRNAs, etc. Molecule inhibitors that act by preventing the interaction of lncRNAs with the protein partners, blocking the binding or changing the secondary structure of the lncRNAs are tried. For instance, silencing of MALAT1 in TSCC, lung adenocarcinoma, cervical cancer, etc. by short hairpin RNA reduced the migration and invasive abilities of cancer cells. Blocking of MALAT1 increased the levels of miRNA 195, which decreased PDL-1 expression in B-cell lymphoma cases, decreasing apoptosis of CD 8+ cells; proliferative and metastatic abilities of the cancerous cells [39]. Down-regulation of UCA1, MALAT1, HOTAIR, and FOXCUT by using siRNAs resulted in decreased cell proliferation and increased apoptosis in OSCC [8]. lncRNAs are used as gene therapy drugs to deplete cancer stem cells or reverse their phenotype, thus increasing their sensitivity to radiation and chemotherapy [2].

V. Conclusion

LncRNAs function as regulators in the conversion of OPMDs to OSCC, affect angiogenesis, cell proliferation, metastases, and predict chemoresistance. Through reverse-transcriptase polymerase chain reaction, they can be detected in plasma and saliva, and thus serve as biomarkers. Identification of PAC3 in saliva helps in early diagnosis of OSCC, salivary gland tumors, and metastatic disease [8]. Markers such as LINC00974 and NEAT 1 etc, predict the progression of OPMDs. Expression of lncRNAs such as HOTAIR, MALAT 1, etc. found in saliva can help predict metastatic status in OSCC cases. High levels of CILA 1, KCNQ1OT1, etc. predict chemoresistance in OSCC cases. Studies have found that specific siRNAs are used to alter the lncRNAs, regulating their expression in OSCC cases that works for a better prognosis. These features facilitate a thought to research these lncRNAs for good treatment options.

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