Long non-coding RNAs are novel players in oral inflammatory disorders, potentially premalignant oral epithelial lesions and oral squamous cell carcinoma (Review)

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Abstract. In recent years, a large number of studies have shown that the abnormal expression of long non-coding (lnc)RNAs can lead to a variety of different diseases, including inflammatory disorders, cardiovascular disease, nervous system diseases, and cancers. Recent research has demonstrated the biological characteristics of lncRNAs and the important functions of lncRNAs in oral inflammation, precancerous lesions and cancers. The present review aims to explore and discuss the potential roles of candidate lncRNAs in oral diseases by summarizing multiple lncRNA profiles in diseased and healthy oral tissues to determine the altered lncRNA signatures. In addition, to highlight the exact regulatory mechanism of lncRNAs in oral inflammatory disorders, potentially premalignant oral epithelial lesions and oral squamous cell carcinoma. The detection of lncRNAs in oral samples has the potential to be used as a diagnostic and an early detection tool for oral diseases. Furthermore, lncRNAs are promising future therapeutic targets in oral diseases, and research in this field may expand in the future.

Contents

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1. Introduction

Oral inflammatory disorder is a series of processes associated with microbial infections (such as periodontal, endodontic and periapical diseases) and immune-mediated damage [for example Sjögren's syndrome (SS)] (1). Numerous factors, including non-coding (nc)RNAs, leukocytes, cytokines and complement components, are involved in this process (2,3). Long non-coding (lnc)RNAs affect oral inflammation by sponging microRNAs (miRNA/miR) (4) or activating downstream target miRNAs (5). Research on competing endogenous (ce)RNA mechanisms, in which lncRNAs sponge specific miRNAs to suppress their target genes, has increased in numbers in over the last 2 years (6). For example, lncRNA metastasis associated lung adenocarcinoma transcript 1 (MALAT1) acts as a sponge of miR-20a to induce Toll-like receptor 4 (TLR4) signaling and results in an inflammatory reaction from human gingival fibroblasts (HGFs) (7).

Several potentially premalignant oral epithelial lesions (PPOELs) are associated with the disease process of chronic inflammatory disorders (8,9). PPOEL is a broad term to define both histological and clinical oral lesions that have malignant potential, including oral lichen planus (OLP), oral submucous fibrosis (OSF), and oral dysplasia (10). In addition, other vital epigenetic and subcellular regulatory non-coding transcripts, such as lncRNAs and miRNAs are also known to regulate the mRNA expression of inflammation-related cytokines, and disturbance of the miRNA-mRNA-cytokine regulatory network is one of the common pathological features of PPOELs (11,12). For example, the significant upregulation of miR-31 and downregulation of its target gene, C-X-C motif chemokine ligand 12 (CXCL12) contributed to progression of PPOELs (13).

As the 7th hallmark of cancer, chronic inflammation has been linked to various stages of tumorigenesis (14). Several studies have reported that numerous regulators, including inflammatory cytokines and ncRNAs, facilitate tumor development (15,16). LncRNAs participate in the transformation of chronic inflammation into cancer by altering the expression of various inflammatory signaling pathways such as NF-κB and STAT3 and proinflammatory cytokines [such as tumor necrosis factor (TNF) family]. Interleukin (IL)-6-dependent STAT3 signaling activation contributes to the occurrence of colorectal cancer (17). The major histological type of oral cancer is oral

squamous cell carcinoma (OSCC) (18). Jia *et al* (19), identified that differentially expressed (DE) lncRNAs and genes between OSCC, oral dysplasia, and normal oral tissues may control the initiation and development of OSCC through phosphatidylinositol-3-kinases (PI3K)/Akt signaling and mast cell NF-κB functional pathways.

LncRNAs play an essential role in the occurrence and development of inflammation and cancer (20,21). The oral diseases associated with the function of lncRNAs are shown in Fig. 1. According to previous reports, the DE lncRNAs between healthy and pathological oral tissues may affect the occurrence and process of oral diseases (Table I). The present review outlines the current understanding of the established functions and underlying mechanisms of lncRNAs in various oral inflammatory disorders, PPOELs and OSCC.

2. LncRNA biogenesis

LncRNAs are a class of RNA molecules whose transcript length is >200 nucleotides (22). Different lncRNA classifications have been established based on different criteria. The first criteria was presented by Jarroux *et al* (23), and lncRNAs which are >10 kb belong to the groups of very long intergenic RNAs and macro lncRNAs. Examples of macro lncRNAs include antisense of IGF2R non-protein coding RNA, KCNQ1 opposite strand/antisense transcript 1 and GNAS antisense RNA1, which act as cis-silencers in mouse genomic imprinting (24). The second criterion, location with respect to protein coding genes, is commonly used. In this classification, 5 types (sense, antisense, bidirectional, intronic and intergenic) of lncRNAs are included (23). An example of nature antisense transcripts, which is one type of antisense lncRNAs, is antisense non-coding RNA in the *INK4* locus, which is encoded by the NK4b-ARF-INK4a locus on chromosome 9p21 (25). According to the classification based on association with other DNA regulatory elements and loci, lncRNAs are divided into pseudogenes, enhancer lncRNAs and promoter-associated lncRNAs and 3'-untranslated region-associated RNAs (23). Long intergenic non-coding (LINC)RNA-p21 is an enhancer RNA, which originates from a p53 binding site associated with regulation of cyclin-dependent kinase inhibitor 1A (26). The associated biochemical pathways or stability of lncRNAs serve as characteristics for their classification, as demonstrated by stable unannotated transcripts (27), Xrn1 sensitive unstable transcripts (XUTs) (such as 5'-long terminal repeat antisense TY1 RNA and XUT1678) (28), Nrd1-unterminated transcripts (29) and cryptic unstable transcripts (for example promoter upstream transcript) (30). Furthermore, several subgroups of lncRNAs with a precise subcellular localization have been defined. Long non-coding mitochondrial RNAs (ncmtRNAs) are cytoplasmic lncRNAs while GAA repeat-containing RNAs and chromatin-enriched RNAs (cheRNAs) locate in the nucleus (23). For example, antisense mitochondrial non-coding RNA-2 and hemin-induced chromatin-enriched RNA downstream of fetal hemoglobin are ncmtRNAs and cheRNAs, respectively (31,32). Lastly, hypoxia-induced non-coding ultra-conserved transcripts (HINCUTs), stress-induced lncRNA (si-lncRNA), senescence-associated lncRNA (SAL), non-annotated stem transcript, prostate cancer-associated transcripts serve as subgroups of another attribute used for lncRNA classification: Association with specific biological processes (23). Hypoxia-inducible factor (HIF) induces HINCUTs to elevate transcription of nearby genes, which are involved in cellular signaling pathways and processes, such as glucose metabolism (33). Oxidative stress causes rapid and transient dynamics of si-lncRNAs in the nucleus and the cytosol, leading to their accumulation at polysomes, which subsequently induces transcription (34). Antisense very long intergenic ncRNA (*VAD*), one type of SAL, modulates chromatin structure in *cis* and increases gene expression in *trans* at the INK4 locus, which encodes cell cycle inhibitors, that are important to senescence-associated cell proliferation arrest (35). The schematic diagram illustrating various classes of lncRNAs are presented in Fig. 2.

LncRNA can also be classified according to their function. LncRNAs exert or execute their functions in four main ways: Signal, decoy, guide, and scaffold. They have been shown to impact cell macromolecular (protein, RNA and DNA) stability (36). The regulatory mechanism of lncRNAs vary based on their locations within the cells. They participate in chromatin modification and transcription in the nucleus, while they interact with RNA-binding proteins or modulate mRNA translation in the cytoplasm (37,38). There are a variety of mutual regulatory mechanisms for lncRNAs and miRNAs. LncRNAs can not only be mediated by miRNAs but also act as miRNA precursors. It is noteworthy that the ceRNA network is one of the common sites of posttranscriptional regulation (12). In the last 5 years, it has been demonstrated that lncRNAs are important in the regulation of a healthy immune system, which in turn is important for healthy oral tissue (39,40,41). An increasing number of lncRNAs have been reported to regulate the differentiation and activation of immune cells. The differentiation of granulocytes is partly mediated by HOX antisense intergenic RNA myeloid 1 (HOTAIRM1), an antisense lncRNA within the HOXA gene locus. Hallmark myeloid maturation-associated genes such as HOXA1/A2 would be inhibited by silencing HOTAIRM1 (42). The potential importance of lncRNAs in the immune response, inflammation and even cancers is emerging (43-45).

3. Role of lncRNAs in oral inflammatory disorders

Pulpitis. Pulpitis is a state of inflammation of the dental pulp. Most cases are due to penetration of a carious lesion into the pulp chamber (46). Pulpitis is classified as either reversible or irreversible (47). Huang and Chen (48) conducted a microarray analysis to establish lncRNA profiles of inflamed (n=7) and normal (n=5) pulp tissues. A total of 752 lncRNAs (338 upregulated and 414 downregulated) were significantly expressed. A total of 460 significantly upregulated genes were enriched in biological processes, such as immune system processes, immune and defense response, the response to stress, and cell activation. The results indicated that most lncRNAs might play roles in the immune system and inflammatory responses of dental pulp. Lei *et al* (49), performed a comprehensive analysis of a lncRNA-miRNA-mRNA ceRNA network by integrating the lncRNA profile from Huang and Chen (48), the miRNA profile from Zhong *et al* (50) and the gene expression profile from Galicia *et al* (51). A ceRNA regulatory network was created, which was composed of the lncRNA

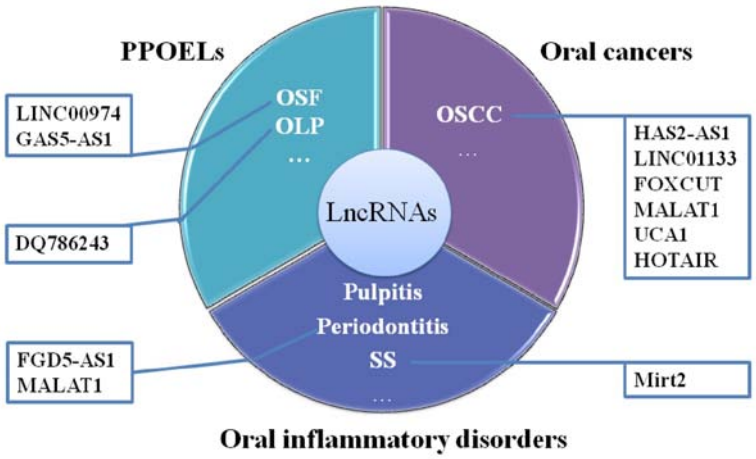

Figure 1. Oral diseases involving lncRNAs. PPOELs, potentially premalignant oral epithelial lesions; OLP, oral lichen planus; OSF, oral submucous fibrosis; OSCC, oral squamous cell carcinoma; SS, Sjögren's syndrome; lnc, long non-coding.

plasmacytoma variant translocation 1, miR-455-5p, and the mRNAs, suppressor of cytokine signaling 3 and Plexin C1. To the best of our knowledge, only one lncRNA microarray has been performed with a comprehensive analysis (49). There has been no mechanistic study focusing on specific lncRNAs in pulpitis. Thus, more research is required to explore the regulatory role of specific lncRNAs in pulpitis.

Periodontitis. Periodontitis is an inflammatory disease, which is primarily caused by bacterial infection (52). It can cause inflammation of the gingivae, loss of alveolar bone and loss of attachment (53). Tooth loss, which occurs in adults is largely due to periodontitis (54). In 2015, Zou *et al* (55) revealed for the first time that lncRNAs have critical roles in the pathogenesis of periodontitis. A total of 2 pairs of chronic periodontitis gingival samples and adjacent healthy samples were collected for lncRNA analysis and 8,925 DE lncRNAs were detected, of which 4,313 were upregulated and 4,612 were downregulated. Functional analysis of the nearby protein-coding genes revealed that different lncRNAs can regulate a common gene, and a single lncRNA can be regulated by different genes. Thus, lncRNAs might play crucial and dual roles in periodontitis.

Chen *et al* (4) found that lncRNA FGD5 antisense RNA1 (FGD5-AS1) was downregulated in the gingival samples from patients with chronic periodontal compared with that in healthy samples. FGD5-AS1 inhibited NF-κB signaling via the FGD5-AS1/miR-142-3p/suppressor of cytokine signaling 6 (SOCS6) ceRNA network and subsequently reduced the secretion of TNF-α, IL-6, IL-1β and IL-8. Thus, the axis may provide a promising strategy for the treatment of periodontitis.

Several lncRNAs inhibit periodontitis; however, results from recent research have revealed that lncRNAs could promote the inflammatory process of periodontal-derived cells, including MALAT1 (7) and papillary thyroid carcinoma susceptibility candidate 3 (56). Li *et al* (7), explored the role of MALAT1 in inflammatory cytokine production in HGFs. The study indicated that MALAT1 bound to miR-20a, as a ceRNA and consequently led to increased mRNA levels of TLR4, which contributed to the activation of inflammation. Therefore, the effect and mechanism of MALAT1 in periodontal inflammation have been characterized.

SS. SS is a chronic systemic autoimmune disease characterized by reduced secretions of the salivary and lacrimal glands and associated neuroendocrine disturbances (57). The disturbances of neuroendocrine include release of hormones (i.e., glucocorticoids) via the hypothalamic-pituitary-adrenal axis stimulation, production of mediators within the sympathetic innervation of immune organs (i.e., thymus) and production of proinflammatory cytokines (i.e., IL-2 and TNF-α) during the inflammatory response (58). The primary hallmark of SS is the infiltration of inflammatory mediators and cells, particularly T and B cells into the salivary and lacrimal glands (59). In addition, gland tissues have damaged acinar cells, fibrosis and increased adiposity with severe inflammatory lesions (60,61). Therefore, exploration into the relevant molecular mechanisms underlying SS is required.

In 2019, Dolcino *et al* (62) performed a high-throughput gene and lncRNA expression profiling in peripheral blood mononuclear cell samples from 8 patients with primary SS (pSS) and 8 healthy subjects. Among the 199 lncRNAs that were identified, CTD-2020K17.1, LINC00511 and LINC00657 and their target genes were found to be involved in apoptosis, immune response, cell proliferation, and several proinflammatory pathways. Shi *et al* (63), compared the expression profiles of lncRNAs from labial salivary glands between patients with pSS and healthy individuals. The gene ontology and pathway analysis results found 28 DE mRNAs associated with 8 DE lncRNAs were involved in chemokine signaling pathways, the NF-κB signaling pathway, and the TNF signaling pathway. Taken together, the results suggest that samples from multiple tissues could be utilized for investigating the same oral autoimmune disease. A comparison of DE lncRNA sets from different sample types of the same disease could provide valuable clues to the discovery of novel therapeutic targets to treat oral autoimmune diseases.

Subsequently, Xin *et al* (5) demonstrated that lncRNA myocardial infarction associated transcript 2 (Mirt2) reduces apoptosis and inflammatory levels in interferon (IFN)-γ-induced inflammation in salivary gland epithelial cells. It is hypothesized that Mirt2 might block NF-κB, and Janus kinase (JAK)/STAT3 signaling by increasing miR-377 expression levels.

Table I. Expression profile of lncRNAs in diseased oral tissues.

Disease	No. of sample/subjects	Method	Confirmation	Findings	Comments	(Refs.)
Pulpitis	7 inflamed pulp tissues and 5 healthy pulp tissues	Microarray	RT-qPCR; 10 normal human pulp tissue and 10 inflamed samples	338 upregulated and 414 downregulated lncRNAs; FC>2; P<0.05	Inflamed pulp samples were collected from patients with pulpitis, to reflect the real pathological state	(31)
Periodontitis	Inflamed and healthy adjacent gingival tissue from two patients with chronic periodontitis	Microarray	RT-qPCR; 15 normal tissue samples and 30 chronic periodontitis tissue samples	4313 upregulated and 4612 downregulated lncRNAs; FC≥2.0; P≤0.05	First time to analyze DE lncRNAs between chronic periodontitis tissues samples and adjacent normal tissues	(36)
SS	PBMCs from 8 patients with pSS and 8 healthy subjects	Microarray	qRT-PCR; No sample size reported	199 dysregulated lncRNAs; FC≥1.5; P≤0.01[a]	No validation; first time to analyze DE lncRNAs in PBMCs of pSS	(43)
SS	LSGs from 4 pSS patients and 4 healthy individuals	Microarray	RT-qPCR; 30 pSS patients and 16 controls	890 upregulated lncRNAs and 353 downregulated lncRNAs; FC>2; P<0.05	First time to analyze DE lncRNAs in LSGs of pSS	(44)
OSF	20 OSCC samples, 10 OSF samples and 13 normal mucous samples	RNA-sequencing	RT-qPCR; 20 OSCC samples, 10 OSF samples and 13 normal mucous samples	231 upregulated lncRNAs and 456 downregulated lncRNAs; FC>2; P<0.05	LncRNAs involved in the malignant transformation process were firstly analyzed and assessed	(56)
OLP	1 papillomavirus-related OSCC tissue, one OLP tissue and 1 normal oral mucosa tissue samples	RNA-sequencing	-	76.2% intergenic lncRNAs and 16.5% sense lncRNAs; A coding potential calculator score <0, and CPAT probability ≤0.364	3 types of tissues samples but sample numbers were too small; lncRNAs involved in the malignant transformation process were firstly analyzed and assessed	(70)
OSCC	72 OSCC tissues and adjacent normal tissues	Microarray	RT-qPCR; 72 OSCC tissues and adjacent normal tissues	933 upregulated and 1361 downregulated lncRNAs; FC>2.0; P<0.05	3 types of OSCC tissues (tongue cancer, gingival carcinoma and carcinoma of the buccal mucosa) were analyzed and compared, and 4 critical lncRNA nodes were identified	(62)

[a]Bonferroni corrected P-value. lnc, long non-coding; SS, Sjögren's syndrome; pSS, primary SS; OSCC, oral squamous cell carcinoma; OLP, oral lichen planus; OSF, oral submucous fibrosis; PBMCs, peripheral blood mononuclear cells; LSGs, labial salivary glands; RT-qPCR, reverse transcription-quantitative PCR; FC, fold change; CPAT, Coding Potential Assessment Tool; DE, differentially expressed.

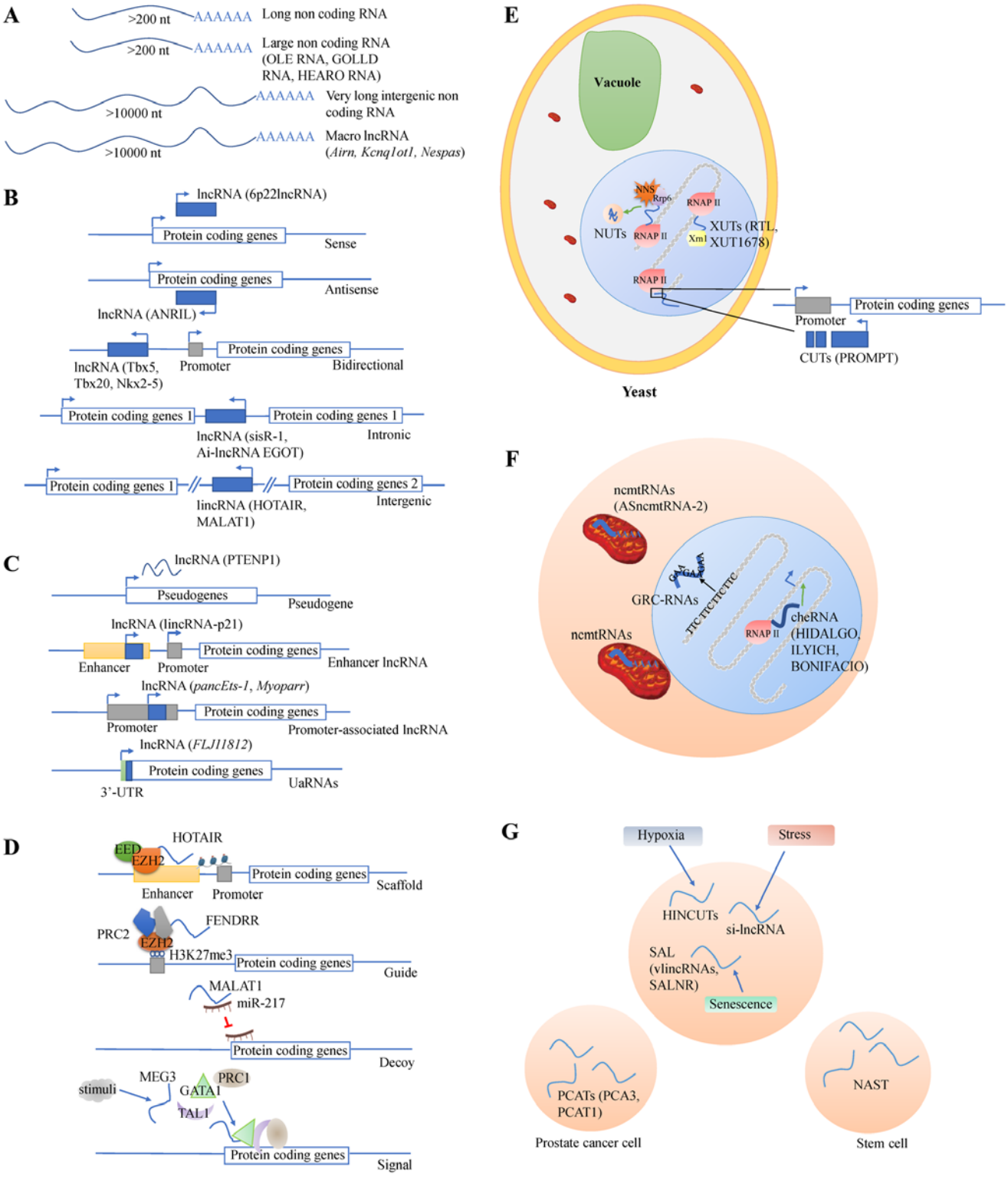

Figure 2. Schematic diagram of the various classes of lncRNAs. Classification according to lncRNAs (A) length, (B) location with respect to protein coding genes, (C) location with specific DNA regulatory elements and loci, (D) lncRNAs function, (E) biogenesis pathway and stability, (F) subcellular localization or origin. (G) association with specific biological processes. The green arrow indicates induction, and the red T indicates inhibition. HOTAIR, HOX transcript antisense RNA; MALAT1, metastasis associated lung adenocarcinoma transcript 1; UTR, untranslated region; uaRNAs, 3'-untranslated region-associated RNAs; EED, embryonic ectoderm development; EZH2, enhancer of zeste homolog 2; PRC2, polycomb repressive complex 2; RNAPII, RNA polymerase II; NUTs, Nrd1-unterminated transcripts; CUTs, cryptic unstable transcripts; XUTs, Xrn1-sensitive unannotated transcripts; PROMPT, promoter upstream transcript; ncmtRNAs, long noncoding mitochondrial RNAs; GRC-RNAs, GAA repeat-containing RNAs; cheRNA, chromatin-enriched RNA; si-lncRNA, stress-induced lncRNA; SAL, senescence-associated lncRNA; vlincRNAs, very long intergenic non-coding RNAs; SALNR, senescence-associated long non coding RNA; PCATs, prostate cancer-associated transcripts; PCA3, prostate cancer antigen 3; NAST, non-annotated stem transcript.

Research investigating lncRNAs typically involves the fields of medicine and biology; however, research regarding lncRNAs in oral inflammatory disorders is still in the early stages. To date, the collection of clinical oral tissue samples

and subsequent microarray or sequencing analysis has been the primary method of investigation in this field. In periodontitis, the majority of lncRNAs serve as ceRNAs (4,6,7). There are a high number of research models investigating oral tissue-derived cells treated with related inflammatory stimuli (i.e., lipopolysaccharide and IFN-γ) (5,7). Periodontitis animal models and lncRNAs have been well-established (64-66), while animal models involving lncRNAs in other oral inflammatory disorders requires further investigation. Thus, additional research is required to determine the mechanism of lncRNAs in oral inflammatory disorders.

4. Role of lncRNAs in PPOELs

OSF. OSF is a chronic, occult oral mucosal disease associated with chewing betel nut, characterized by a juxta-epithelial inflammatory response followed by generalized submucosal fibrosis (67,68). As a result, OSF typically leads to difficulty in opening the mouth and an increased malignant transformation rate (69,70). Therefore, the identification of molecules associated with OSF pathological progression is urgent. In the course of OSF, endothelial dysfunction may be accompanied by the dysregulation of multiple lncRNAs (71). For example, lncRNA growth arrest specific 5 antisense 1 (GAS5-AS1) was inhibited, while lncRNA hypoxia-inducible factor 1-α antisense RNA 1 (HIF1A-AS1) was upregulated during the development of OSF (72,73). Research into lncRNAs has increased in the last 5 years; however, the function of numerous lncRNAs in OSF remains unclear. To date, only four articles have illustrated the relative issues (72-75).

The lncRNA sequencing conducted in 2019 by Zhou *et al* (75) included 13 normal mucous samples, 10 OSF samples, and 20 OSCC samples. A total of 5 DE candidate lncRNAs were found to participate in the inflammatory signaling pathway and contributed to inflammatory and fibroelastic pathogenetic changes by deregulating their cis-target and trans-target genes in OSF malignant development. Further functional analysis of these lncRNAs is required to provide conclusive evidence supporting an underlying regulatory mechanism during OSF.

Fang *et al* (74), determined that arecoline-induced myofibroblast trans-differentiation occurred via LINC00974-mediated activation of the transforming growth factor-β (TGF-β)/Smad signaling pathway. According to their study, collagen gel contractility and myofibroblast migration ability was increased in fibrotic buccal mucosal fibroblasts (fBMFs) overexpressing LINC00974. Increased expression of another lncRNAHIF1A-AS1 also positively modulates the TGF-β/Smad signaling pathway, similar to LINC00974 (72). However, the lncRNA GAS5-AS1 presented contrary results in arecoline-treated BMFs and fBMFs (73).

OLP. OLP is a chronic inflammatory disease affecting the oral mucosa with characteristic relapses and remissions (76-78). Emerging evidence shows that OLP may be premalignant (79). Unstable molecular changes can induce the production of several inflammatory cytokines and subsequently contribute to the course of OLP (77,80). For example, pathogen associated molecular patterns and adaptor molecules (i.e., myeloid differentiation factor 88) activation leads to nuclear translocation of NF-κB and augments the transcription of inflammatory genes (i.e., IL-6 and IL-8) (81). As with OSF, there have only been two studies on the role of lncRNAs in OLP to date.

Yang *et al* (82), examined DE genes and lncRNA targets in human papillomavirus-related OSCC (n=1), normal (n=1), and OLP (n=1) samples. Of the identified lncRNAs, most (697; 76.2%) were intergenic lncRNAs, followed by 151 sense lncRNAs (16.5%). Keratinization and MHC class I antigen processing and presentation were significantly enriched by OSCC-associated DE genes and lncRNA targets, and the olfactory transduction pathway was enriched by OLP- and OSCC-related DE genes. To the best of our knowledge, this has been the only study investigating the lncRNA profile of OLP so far; however, the number of tissue samples was too small to guarantee the validity of these findings. In addition, there is evidence suggesting that lncRNA DQ786243 significantly enhances the expression levels of miR-146a by inducing Forkhead box P3 (Foxp3), which subsequently blocks NF-κB signaling during OLP. Moreover, $Foxp3^+$ regulatory T cells significantly suppressed the function of other $CD4^+$ T cells, such as $CD4^+IL\text{-}1^+$ helper T cells and $CD4^+IL\text{-}17^+$ helper T cells, by inhibiting the mRNA expression levels of IFN-γ and IL-17 (83).

LncRNA microarray analysis is considered a reasonable option for comparing and determining DE lncRNAs in normal, PPOEL and OSCC tissues, which are difficult to simultaneously acquire in one patient. Animal models which investigate both lncRNAs and PPOELs are expected to be explored extensively, and to primarily include fBMFs treated with related stimuli (i.e., arecoline). Mechanistically, the classical signaling pathways in PPOELs focus on the TGF-β/Smad and NF-κB signaling pathways. Therefore, it is worth exploring more regulatory mechanisms [i.e., p38/MAPK and JAK/STAT3 signaling pathways] in subsequent studies on PPOELs.

5. Role of lncRNAs in OSCC

Oral cancers are cancers that exist in the oral cavity, such as the mucosal surfaces of the lips, floor of the mouth, tongue, buccal mucosa, lower and upper gingival surfaces, hard palate, and retromolar trigone (84). The histology of oral cancers varies widely; the majority of them are OSCCs (84). An increasing number of reports have revealed that lncRNAs play a broad role in the oncogenesis and progression of OSCC through transcriptional regulation, posttranscriptional modulation and epigenetic modifications (85). LncRNAs, functioning in oral cancer migration, epithelial-mesenchymal transition (EMT), metastasis, progression and invasion (86), could serve as biomarkers or therapeutic targets for OSCC diagnosis, prognosis and treatment (87).

With the development of whole transcriptome analyses, including serial analyses of gene expression, RNA sequencing and microarray data, several oral cancer-associated lncRNAs have been identified. In 2019, Qiu *et al* (88) screened 2,294 DE lncRNAs (933 upregulated and 1,361 downregulated) in OSCC tissues (n=72) compared with paired adjacent normal tissues. A total of four lncRNA-mRNA coexpression networks were constructed, and low expression levels of the four lncRNA nodes contributed to poor median progression-free survival and overall survival. This study provided novel insights into the role of lncRNAs in OSCC.

Table II. Regulatory effect of lncRNAs in oral inflammatory disorders, PPOELs and OSCC.

lncRNA	Cell category	Cell stimulation (bacteria)	Disease	Effects	Modes of action	Associated targets or pathways	(Refs.)
FGD5-AS1	PDLCs	LPS (*P. g*)	Periodontitis	Inhibit apoptosis and reduce inflammatory cytokine production	Sponging miR-142-3p	SOCS6 and NF-κB	(37)
MALAT1	HGFs	LPS (*P. g* or *E. coli*)	Periodontitis inflammatory	Enhance cytokine production	Sponging miR-20a	TLR4	(7)
Mirt2	SGECs	IFN-γ	SS	Repress apoptosis inflammatory cytokine production	Facilitate miR-377 and enhance	JAK/STAT3 and NF-κB	(5)
LINC00974	fBMFs	-	OSF	Increase myofibroblasts activation	-	TGF-β/Smad	(55)
HIF1A-AS1	fBMFs	-	OSF	Increase myofibroblasts activation	-	-	(53)
GAS5-AS1	fBMFs	Arecoline	OSF	Inhibit myofibroblasts activities in OSF	Inhibiting p-Smad and α-SMA	TGF-β/Smad	(54)
DQ786243	CD4+ Treg cells	-	OLP	Suppress the function of CD4+ T cells such as Th1 and Th17	Elevating Foxp3	miR-146a/NF-κB	(63)
HAS2-AS1	Human OSCC cell lines	Hypoxia	OSCC	Mediate hypoxia-induced EMT and invasiveness of OSCC	Stabilizing HAS2	HF-1α and NF-κB	(69)
LINC01133	Human OSCC cell lines	-	OSCC	Inhibit OSCC cell migration and invasion	-	GDF15	(70)
FOXCUT	Human OSCC cell lines	-	OSCC	Promote OSCC proliferation and migration ability	-	FOXC1	(71)
MALAT1	Human OSCC cell lines	-	OSCC	Accelerates EMT and development of OSCC	Sponging miR-125b	STAT3	(73)
UCA1	Human OSCC cell lines	-	OSCC	Facilitate proliferation, enhance CDDP chemoresistance, and suppresses apoptosis	Sponging miR-184	SF1	(74)
HOTAIR	Human OSCC cell lines	-	OSCC	Promote occurrence, invasion and metastasis	EZH2 and H3K27me3	E-cadherin	(76)

lnc, long non-coding; miR, microRNA; PDLCs, periodontal ligament cells; HGFs, human gingival fibroblasts; SGECs, salivary gland epithelial cells; fBMFs, fibrotic buccal mucosal fibroblasts; OSCC, oral squamous cell carcinoma; OLP, oral lichen planus; OSF, oral submucous fibrosis; SS, Sjögren's syndrome; LPS, lipopolysaccharide; IFN, interferon; HIF1-α, hypoxia-inducible factor 1-α; Mirt2, myocardial infarction associated transcript 2; FGD5-AS1, FGD5 antisense RNA 1; MALAT1, metastasis associated lung adenocarcinoma transcript 1; HOTAIR, HOX transcript antisense RNA; TLR4, Toll-like receptor 4; HAS2, hyaluronan synthase 2; FOXC1, Fork head box C1; SOCS6, suppressor of cytokine signaling 6; NF-κB, nuclear factor-κ B; TGF-β, transforming growth factor-β; EMT, epithelial-mesenchymal transition; CDDP, cis-diamine dichloroplatinum; p, phosphorylated.

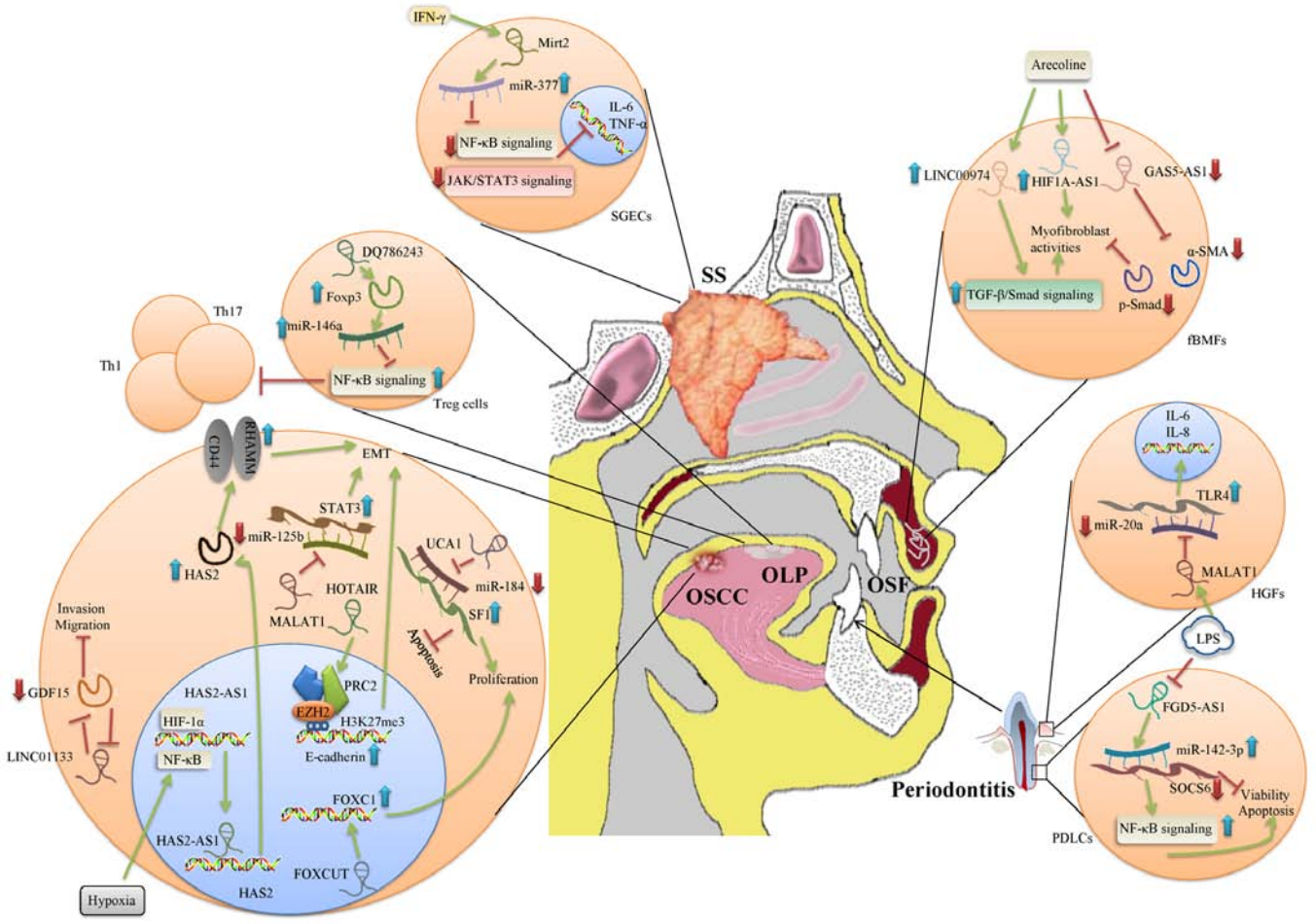

Figure 3. Schematic view of the biological processes involving lncRNAs in multiple oral diseases. The green arrow indicates induction, and the red T indicates inhibition. The blue arrow indicates an increase in expression levels of molecules or activation of pathways. The red arrow indicates a decrease in expression levels of molecules or inhibition of pathways. Lnc, long non-coding; HGFs, human gingival fibroblasts; SGECs, salivary gland epithelial cells; fBMFs, fibrotic buccal mucosal fibroblasts; SS, Sjögren's syndrome; OSCC, oral squamous cell carcinoma; OLP, oral lichen planus; OSF, oral submucous fibrosis; IFN, interferon; HIF1-α, hypoxia-inducible factor 1-α; Mirt2, lncRNA Myocardial infarction associated transcript 2; FGD5-AS1, FGD5 antisense RNA 1; MALAT1, lncRNA Metastasis Associated Lung Adenocarcinoma Transcript 1; HOTAIR, lncRNA HOX transcript antisense RNA; α-SMA, myofibroblasts α-smooth muscle actin; Foxp3, Forkhead box P3; HAS2, Hyaluronan Synthase 2; GDF15, growth and differentiation factor 15; FOXC1, Fork head box C1; SF1, splicing factor 1; TNF-α, tumor necrosis factor-α; RHAMM, receptor for hyaluronan-mediated motility; IL, interleukin; NF-κB, nuclear factor-κ B; TGF-β, transforming growth factor-β; EMT, epithelial mesenchymal transition.

LncRNAs could transcriptionally regulate the progression of OSCC via interactions with proteins or interactions with RNA and DNA molecules (85). Zhu *et al* (89), verified that hypoxia induces the overexpression of hyaluronan synthase 2 antisense 1 (HAS2-AS1) in a HIF-1α- and NF-κB-dependent manner. HAS2-AS1 mediates hypoxia-induced EMT and invasiveness of OSCC cells by binding and stabilizing the HAS2 gene. Additional research found that LINC01133 inhibited OSCC cell migration and invasion by inhibiting growth and differentiation factor 15 (GDF15) protein expression and formed a feedback regulatory loop with GDF15 (90). Kong *et al* (91), found that expression of lncRNA FOXC1 upstream transcript, which is the adjacent promoter upstream of the Fork head box C1 (FOXC1) gene, was positively correlated with FOXC1 mRNA expression and promoted OSCC proliferation and migration. Thus, a vast amount of research has elucidated transcriptional regulatory mechanisms to address the role of lncRNAs in OSCC.

Posttranscriptional regulation through pre-mRNA alternative splicing, mRNA decay acceleration, mRNA protection, or translational activation or repression is also one of the primary mechanisms of lncRNAs (92). Chang and Hu (93), demonstrated that MALAT1 could function as a ceRNA to mediate STAT3 expression by sponging miR-125b in OSCC. OSCC cell viability and growth were enhanced by increasing expression levels of MALAT1, and a role of MALAT1/miR-125b/STAT3 axis was confirmed *in vivo* using a nude mouse xenograft model with OSCC Tca8113 cells. Fang *et al* (94), found that lncRNA urothelial cancer associated 1 (UCA1) facilitated proliferation, enhanced cisplatin chemoresistance, and suppressed apoptosis in OSCC cells by suppressing miR-184 expression to increase the mRNA expression levels of splicing factor 1. Thus, ceRNA appears to be a promising posttranscriptional regulatory mechanism in OSCC.

In addition, lncRNAs could affect the characteristics of OSCC through epigenetic modifications, including DNA methylation, chromatin modification and imprinting (95). LncRNA HOX transcript antisense RNA (HOTAIR) repressed the expression of E-cadherin by binding to enhancer of zeste homolog 2, the enzymatic component of polycomb

repressive complex 2 (PRC2) and H3K27me3 at the E-cadherin promoter (96). HOTAIR silenced transcription factors by interacting with PRC2, lysine-specific histone demethylase-1 and RE-1 elements, leading to chromatin remodelling, thus trans-inhibiting the expression of the homeobox D cluster gene and promoting the occurrence, invasion and metastasis of tumors (96). Additional lncRNAs, participating in the progression of OSCC through epigenetic modifications, are expected to be detected, as there is an increasing number of the research being performed (95,97).

Accumulating evidence has shown that lncRNAs modulate the metastasis, proliferation, invasiveness and migration of oral cancer, especially OSCC, in cellular physiological processes (86,98,99). As aforementioned, lncRNAs interact with different cellular macromolecules, including chromatin, protein and RNA (36). According to the aforementioned studies, unstimulated OSCC cell lines are typically used for external models. Animal models are also well-established to provide more convincing evidence to confirm the role of lncRNAs in OSCC (89,93,94). This suggests that lncRNAs have the potential to be prognostic and therapeutic markers, providing valid approaches for clinical treatment.

6. Conclusion

With the advent of genomic technologies, including microarrays and RNA sequencing, investigations of lncRNA genomic profiles have been widely performed in the last 5 years (6,100,101). A large number of studies include microarray analyses of clinical tissue samples, which enhances the clinical value and significance of the findings (48,55,88). The present review not only summarized the lncRNA profiles but also elucidated the potential underlying mechanisms of lncRNAs in oral diseases (Table II and Fig. 3). These mechanisms may be significant to the clinical diagnosis and therapy of oral diseases. Moreover, the present review focused on the identification and associations of oral inflammatory disorders, PPOELs and OSCC and discussed the functions of lncRNAs in the pathological process. By summarizing the studies involving the mechanisms of lncRNAs in oral diseases, ceRNA regulation was found to be the most common, while lncRNAs interacting with proteins is relatively rare. Thus, additional research is required to expand the early findings and characterize the mechanisms of DE lncRNAs. Overall, lncRNAs, the novel candidates in oral inflammatory disorders, PPOELs and oral cancer, should be investigated further, and their diagnostic and therapeutic functions may have significant value.

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Availability of data and materials

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Authors' contributions

FF and BW contributed to the conception and design of the review. KZ contributed to the writing and drafting of the manuscript. FF and WQ contributed to the critical revision of the manuscript for important intellectual content. All the authors have given approval of the final version to be published and agree to be accountable for all aspects of the work.

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Competing interests

The authors declare that they have no competing interests.

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