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OVERVIEW

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Noncoding RNAs in oral cancer

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Abstract

Oral cancer (OC) is the most prevalent subtype of cancer arising in the head and neck region. OC risk is mainly attributed to behavioral risk factors such as exposure to tobacco and excessive alcohol consumption, and a lesser extent to viral infections such as human papillomaviruses and Epstein–Barr viruses. In addition to these acquired risk factors, heritable genetic factors have shown to be associated with OC risk. Despite the high incidence, biomarkers for OC diagnosis are lacking and consequently, patients are often diagnosed in advanced stages. This delay in diagnosis is reflected by poor overall outcomes of OC patients, where 5-year overall survival is around 50%. Among the biomarkers proposed for cancer detection, noncoding RNA (ncRNA) can be considered as one of the most promising categories of biomarkers due to their role in virtually all cellular processes. Similar to other cancer types, changes in expressions of ncRNAs have been reported in OC and a number of ncRNAs have diagnostic, prognostic, and therapeutic potential. Moreover, some

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ncRNAs are capable of regulating gene expression by various mechanisms. Therefore, elucidating the current literature on the four main types of ncRNAs namely, microRNA, lncRNA, snoRNA, piwi-RNA, and circular RNA in the context of OC pathogenesis is timely and would enable further improvements and innovations in diagnosis, prognosis, and treatment of OC.

This article is categorized under:
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diagnosis, noncoding RNA, oral cancer, prognosis, therapeutics

1 | INTRODUCTION

It is believed that our earth is about 4.54 billion years old, and evidence suggests that ribonucleic acid (RNA) or some other chemically similar molecule to RNA is considered the first living molecule during evolution and supports the RNA world concept (Higgs & Lehman, 2015). In 1968, Crick and Orgel have recognized that RNA contains both a genotype and a phenotype and is probably the precursor of the complex DNA–RNA–protein system (Crick, 1968; Orgel, 1968). In eukaryotes, RNAs are synthesized by various RNA polymerases. RNA is a linear polymer made up of four different nucleotides (adenosine, guanine, cytosine, and uracil) containing a ribose sugar attached to a nitrogen base and a phosphate group. During protein synthesis, ribosomes translate the genetic information present in RNA into protein. The chief function of RNAs is to synthesize proteins through translation. This is carried out by ribosomal RNA (rRNA), transfer RNA (tRNA), and messenger RNA (mRNA). In addition, a group of RNAs known as noncoding RNAs (ncRNAs) have been reported to be involved in RNA editing, regulating gene expression, and acting as RNA interferences.

Over the past century, ncRNAs have been considered as by-products of protein synthesis with a less or no biological and/or functional significance (P. Zhang, Wu, et al., 2019). However, accumulating evidence suggests that despite their inability to code for proteins, they are capable of interacting with other coding/ncRNA, DNA, and proteins and thereby partake in integrated networks of interactions, regulating gene expression at the epigenetic, transcriptional, and post-translational levels (Luisa Statello et al., 2020; P. Zhang, Wu, et al., 2019). As a result, ncRNAs have been reported to involve complex biological processes, which include modulation of physiological and developmental processes (P. Zhang, Wu, et al., 2019).

Recent developments in high throughput genome sequencing and computational analysis have revealed that approximately 80% of the human genome is capable of transcribing into ncRNAs (Peschansky & Wahlestedt, 2013). This highly heterogeneous group of transcripts can be sub-divided based on their size and biological functions into various categories and these include microRNA (miRNA), small nuclear RNA (snRNA), small nucleolar RNA (snoRNA), long noncoding RNA (lncRNA), circular RNA (circRNA), PIWI-interacting RNAs (piRNA), small interfering (siRNA), extracellular RNA (exRNA), and small Cajal body-specific RNA (scaRNA) (Y. Li, Shan, et al., 2020).

Due to the dynamic involvement of ncRNAs in cellular processes, changes in ncRNA expression patterns are often observed in diseases including non-alcoholic fatty liver diseases, cardiovascular diseases, neurologic diseases, and more importantly cancers (Y. Li, Shan, et al., 2020). Studies have revealed ncRNA expression changes across these diseases and in certain instances, ncRNAs have been demonstrated to be directly involved in disease pathogenesis (Y. Li, Shan, et al., 2020). Cancers are among these diseases where active or passive changes of ncRNA expression levels have been consistently reported. Studies across different cancer types have identified many ncRNAs that are capable of promoting or suppressing cellular transformation (Y. F. Chen, Wei, et al., 2019; Sun & Zhang, 2017). Moreover, several ncRNAs have been experimentally confirmed to modulate tumor characteristics such as aggressiveness, ability to metastasize, and treatment response (He et al., 2019; N. Jia, Tong, et al., 2019; Sheng et al., 2019). Owing to these findings, ncRNAs have gained significant attention as diagnostic, prognostic, and therapeutic targets for a range of cancer types.

Similar to other cancer types, oral cancer (OC), the cancer type in the focus of this review, has also been shown to have dysregulated ncRNA profiles. Indicating that some of these changes are triggered even before tumorigenesis, in

which disrupted ncRNA expression patterns have also been observed in oral potentially malignant disorders (OPMD); (Aghbari et al., 2018; Chang et al., 2018; Chen et al., 2018). More importantly, these expression changes can also be detected in surrounding body fluids and circulation, allowing them to be used as liquid biopsy-based biomarkers for OC detection (Nagadia et al., 2013; Punyadeera & Slowey, 2019; Romani et al., 2021). Despite these observations, currently, there are no ncRNA-based diagnostic strategies or therapeutic interventions currently in clinical practice to manage patients with OC. As such, a systematic evaluation of available literature is necessary to identify strategies to translate these findings into clinical practice. As such, this review article focuses on five main types of ncRNAs namely, microRNA, lncRNA, snoRNA, piRNA, and circular RNA, and summarizes and critically evaluates their possible utility in the context of OC.

2 | ORAL CANCER

Head and neck cancer (HNC) is the seventh most common cancer type in the world (Mody et al., 2021). It encompasses a group of malignancies originating from the oral cavity, sinonasal cavities, pharynx, larynx, and salivary glands (Min et al., 2015). Among them, OC is the most prevalent subtype of HNC (Min et al., 2015). Oral squamous cell carcinoma (OSCC), accounts for about 90% of all oral cavity malignancies (L. He et al., 2020; Rivera, 2015).

In 2020, World Health Organization (WHO), reported that the global incidence of lip and oral cavity cancers was 2% and deaths was 1.8% of all cancers (Ferlay et al., 2020). The global 5-year survival rate of OC is about 50% (Gupta et al., 2016). Asian regions dominate in terms of newly diagnosed OC cases, with incidence and mortality rates of 65.8% and 74%, respectively (Ferlay et al., 2020). Although OC is more prevalent in developing countries recent studies suggest that the incidence of OC is also rising in developed countries (Sarode et al., 2020). In the United Kingdom, there has been on average 2.7% increase in the age-standardized incidence of OC since 1989 (Gupta et al., 2016). Furthermore, in Australia and New Zealand, the age-standardized incidence and mortality rates were 6.0 and 0.76 per 100,000 population, respectively (Ferlay et al., 2020). Similar to most other HNC types, OC is more prevalent in men where age-standardized global incidence rates for men and women is around 8.5 and 3.6 per 100,000, respectively (Ferlay et al., 2020).

2.1 | Risk factors of OC

Oral oncogenesis is a complex, multistep process resulting in qualitative and quantitative alterations of genetic and epigenetic events promoting cellular transformation (Williams, 2000). Epidemiological studies have reported that the development of OC has a diverse range of risk factors as classified by the International Agency for the Research on Cancer of the World Health Organization. Alcohol and tobacco consumption are the main risk factors for OC. Similarly, poor oral hygiene, chronic irritation related to loose-fitting dentures or sharp teeth, nutritional deficiencies, ultraviolet light, radiation exposure, viral infections including Human Papillomavirus (HPV), Epstein-Barr virus (EBV), Herpes Simplex virus (HSV), and fungal infections, including *Candida albicans* have been reported to increase the risk of OC (Cancer, 2008). In addition, genetic and epigenetic susceptibility also increase the risk of OC (Cancer, 2008; Kumar et al., 2016) Among the risk factors, exposure to tobacco continues to be the most significant causative factor of OC and the leading cause of high mortality rates (Kumar et al., 2016). Tobacco smoking not only promotes OC but also causes cancers of the lungs, larynx, pharynx, esophagus, and pancreas. The aromatic hydrocarbon benzopyrene and other tobacco-specific nitrosamines present in tobacco smoke are potential carcinogens (Kumar et al., 2016). It has been estimated that the risk of developing OC is three times higher in smokers when compared with nonsmokers (Rivera, 2015). Studies show that even involuntary smoking (passive smoking) increases the risk of developing OC (Mariano et al., 2021; Rivera, 2015). In addition to smoking, tobacco use in the form of oral snuff and betel quid chewing are known to promote OC risk (Krishna et al., 2015; Kumar et al., 2016). Betel quid is the mixture of betel leaves, sliced areca nut, tobacco, and slacked lime (Gupta & Warnakulasuriya, 2002). Among the commonly used psychoactive substances, betel nut chewing is listed as the fourth and is considered a leading risk factor for OC, especially in Asia and the Pacific regions. The major chemical components of betel nut are polyphenols including tannins and alkaloids (Arecoline which is the primary active substance of areca nut and is categorized as a "Group 1" carcinogen; Marques et al., 2021). In contrast, consumption of alcohol is believed to promote the development of OC, however, there is no evidence to suggest that alcohol consumption alone can lead to the development of OC. However, in conjunction with tobacco use, it synergistically increases the risk of developing OC (Kumar et al., 2016).

In terms of genetic predisposition, a genome-wide study has revealed that two loci single nucleotide polymorphisms (SNPs) rs10462706 in *CLPTM1L* at 5p15.33 region and rs1049055 in *HLA-DQB1* are associated with an increased risk of developing OC (Shete et al., 2020). Concurrently, polymorphisms in *CYP1A1* M2 or *GSTM1* and *GSTT1* null genotype are associated with a high risk of OC, especially in Indian population (Sreelekha et al., 2001). Huang et al., reported that mutations in proto-oncogenes, such as *VAV2* and *IQGAP1* are closely related to the development of familial OC (Huang et al., 2019). Therefore, consumption of tobacco and exposure to other potential risk factors may increase the possibility of developing OC in genetically susceptible individuals.

2.2 | Pathogenesis of OC

Carcinogenesis is a complex multistep process driven by the accumulation of genetic and epigenetic alterations. Genetic alterations (point mutations, deletions, amplifications, and chromosomal rearrangements, and the accumulation of these genetic changes) promote tumorigenesis and tumor progression (Blagosklonny, 2005; Jain & Daaboul, 2019). These epi(genetic) alterations are found not only in cancer cells but also in pre-cancer cells offering a strong intimation in the detection of cancer at their early and pre-cancer cells offering a great opportunity to early detect pre-cancer before transforming to OC (Takeshima & Ushijima, 2019).

In the context of OC, genetic instability is a common feature, where gain or loss of chromosomal regions 3, 4, 8, 9, 11, 13, and 17 are frequently observed. Among them, chromosome 11 is the most commonly altered region in OC. It has been reported that loss of some fragile sites in chromosome 11q from FRA11F (11q14.2) to 11qter is observed in more than 50% of OC. Similarly, loss of heterozygosity in chromosome 17p is also reported in many human cancers including OC (Papadimitrakopoulou et al., 1997). p53 mutation (17p13.1) which is one of the most reported mutations in all human cancers, is also reported in more than 50% of HNSCC including OC. Furthermore, other mainly affected genes include well-known tumor suppressor genes such as*CDKN2A* (9p21.3) and *RB1* (13q14.2) (Usman et al., 2021). More importantly, loss of heterozygosity at 9q210 and loss of p16 INK4a have also been reported in advanced stages of OPMD (Papadimitrakopoulou et al., 1997). A genome-wide study based on the Japanese population has reported that the top five mutations associated with OSCC were TP53 (42%), TERT (29%), FAT1 (28%), NOTCH1 (19%), and CASP8 (19%) (X. Chen, Zhao, et al., 2021).

Similarly, amplification of chromosomal band 11q13 is observed in ≈45% of OC and is associated with poor prognosis. Amplification of oncogenes such as epidermal growth factor receptor (EGFR) (7p11.2), K-ras, c-myc, int-2, parathyroid adenomatosis 1 (PRAD-1), and B-cell lymphoma (bcl) have frequently been reported in oral carcinogenesis (Ram et al., 2011). In addition, accumulation of epigenetic alterations such as DNA methylation, histone modifications, and changes in ncRNA expression may disrupt normal cellular physiological mechanisms, and thereby promote cellular transformation (Baylin & Jones, 2016; Jain, 2019). It is also reported that aberrant promoter hyper methylation of *p16*, *hMLH1*, *MGMT*, *and E-cad*, ectopic expression of miR-125b, miR-199a-5p are associated with the development of OC (Y. F. Chen, Wei, et al., 2019; Viswanathan et al., 2003; Wei et al., 2019).

The gain and loss of chromosomal regions encoding for ncRNAs may result in aberrant expression of the relevant ncRNAs and possibly affect the expression of the genes regulated by those ncRNAs. It has been reported that, in humans, microRNA-rich chromosomal bands were 4q32 and 19q13 (Kamanu et al., 2013). More importantly, miRNAs associated with cancer and cardiovascular diseases are frequently located in chromosomes 1, 14, 19, and X (Ghorai & Ghosh, 2014). Chromosome X has 18 miRNA clusters whereas, chromosome 19 has 46 miRNA clusters (largest cluster), when dysregulated may cause the development of cancer and cardiovascular diseases. Concurrently, the band 8q24.21 which is a fragile region on chromosome 8, is a well-known hotspot for genetic variants associated with increased risk of cancer and this locus is rich in genes encoding for lncRNAs. More importantly, this region codes for *MYC* gene which is reported to be involved in about 20% of all cancer types (Wilson & Kanhere, 2021). Also, lncRNA-CCAT2 which is found in this region is reported to be involved in regulating the expression of *MYC* gene. *c-MYC* is one of the well-known oncogenes driving tumorigenesis in many cancers including OC. Therefore, gain/loss of chromosomal material in regions associated with any ncRNAs may lead to their aberrant expression. For instance, loss of chromosomal region 11q is associated with OC and the expression of miR-100 and miR-125b is significantly reduced due to the loss of genes coding for these miRNAs. This observation is further supported by the fact that most genes encoding for microRNAs are located in the fragile sites of the chromosome that are more prone to breakage and gain/loss and may lead to aberrant expression of miRNAs (Ghorai & Ghosh, 2014; Kamanu et al., 2013; Wilson & Kanhere, 2021).

A significant number of OC cases are preceded by OPMD characterized by oral lesions with potential for malignant transformation (Jäwert et al., 2021). In the initial stages, these lesions often display hyperplastic changes and with the acquisition of further genetic and epigenetic changes, these lesions may progress toward dysplasia and invasive cancer (Figure 1; Jain, 2019).

3 | ORAL POTENTIALLY MALIGNANT DISORDERS

Potentially malignant disorders of the oral cavity are a heterogeneous group of lesions, which are associated with a variable risk of malignant transformation to OC (Mithani et al., 2007). The most common OPMDs include: Leukoplakia (LE), lichen planus (LP), oral lichenoid lesions (OLL), oral erythroplakia (OE), oral submucous fibrosis (OSF), and proliferative verrucous leukoplakia (PVL) (Mithani et al., 2007; Parakh et al., 2020). Similarly, oral dysplasia defined as a mucosal area characterized by cellular and architectural derangement, and this may lead to the development of OPMDs (Mithani et al., 2007).

3.1 | Leukoplakia

Leukoplakia is defined as "predominantly white lesion of the oral mucosa that cannot be characterized as any other detectable lesion" (Mithani et al., 2007). The malignant transformation of the lesion depends on its heterogeneity

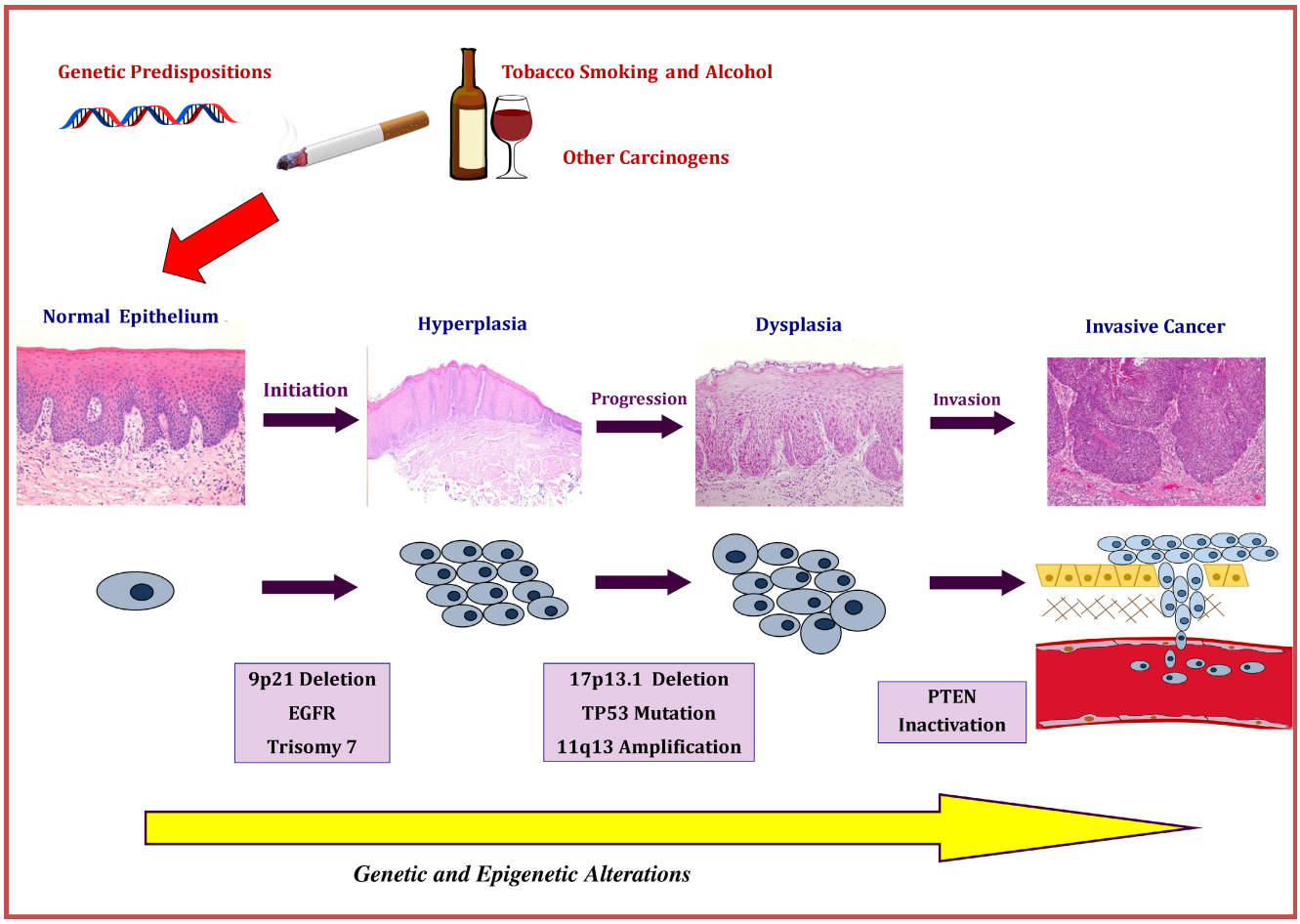

FIGURE 1 Pathogenesis of oral cancer (OC). The normal oral epithelia undergoes molecular changes following considerable exposure to carcinogens. More importantly, individuals with genetic and epigenetic predisposition are more prone for these epithelial transformations. Furthermore, genetic and epigenetic alterations, chromosomal abnormalities and other molecular interactions would lead to initiation, promotion, and progression to invasive OC.

(Mithani et al., 2007). Leukoplakia is the most frequently encountered pre-malignant lesion in the oral cavity and approximately 36% of cases with dysplastic features subsequently develop to OC. In contrast, around 15% of leukoplakia patients without dysplasia develop OC. Among the premalignant lesions, patients with leukoplakia are prone to malignant transformation driven by chromosomal aberrations, *TP53* mutations, epigenetic alterations, and mitochondrial alterations (Chang et al., 2018; Chen et al., 2018; Mithani et al., 2007).

3.2 | Erythroplakia

Erythroplakia usually presents as a discrete, velvety red macule or plaque, with a diameter of more than 1.5 cm, found on the floor of the mouth, the soft palate or the buccal mucosa in which the lesion "cannot be characterized clinically or pathologically as any other recognizable condition" (Kramer et al., 1978; Mithani et al., 2007). The development of oral erythroplakia is often associated with tobacco chewing, alcohol and smoking. It is reported that approximately 85%–90% of OSCC which are diagnosed at late stages were initially developed from erythroplakia. Qin et al., reported that the tumor suppressor gene *TP53*, which encodes *TP53*, is mutated in 46% of erythroplakia (Qin et al., 1999).

3.3 | Oral lichen planus

Oral lichen planus (OLP) is a benign lesion demonstrating a characteristic whitish, lacy, reticular pattern that classically presents on the buccal mucosa of the oral cavity. It can be sub-divided into papular and atrophic or erosive lesions in which the latter lesions are quite painful and result in multiple complications, including secondary infections (predominantly *Candida* species), poor nutrition, and dehydration due to pain. Studies have reported that the overall risk of malignant transformation to be approximately 0.4%–5.6% (Mithani et al., 2007).

3.4 | Oral submucous fibrosis

Oral submucous fibrosis is a region-specific chronic disease that is exclusively found in South Asia. The regional specificity is believed to be due to betel quid chewing (mixture of areca nut, betel leaf, tobacco, and slack lime). It is characterized by irreversible fibrotic changes of the soft tissues of the oral cavity. Oral submucous fibrosis is a collagen-metabolic disorder. Transforming growth factor-beta (TGF-β) is a multifunctional cytokine that plays a major role in the assembly and remodeling of extracellular matrix (ECM). The autoregulatory process of TGF-β triggers the increased production and decreased degradation of collagen, leading to collagen deposition and ultimately resulting in fibrosis (Rajalalitha & Vali, 2005).

3.5 | Oral lichenoid lesions

The term "Oral lichenoid lesions" (OLL) was introduced by Finne in 1982 and was described as eruptions in oral mucosa resembling OLP clinically and histologically but has less morphologic characteristic and distribution when compared with OLP (Mravak-Stipetić et al., 2014). These lesions are associated with dental restorative materials, systemic diseases, drug intake, food or flavor allergies (Cobos-Fuentes et al., 2009; Rotaru et al., 2020). It is often associated with several clinical types depending on the causative agent such as dental restorative materials (most frequently mercury amalgam) resulting in allergic immune stomatitis, temporal contact with certain undigested drugs such as oral hypoglycemics, nonsteroidal anti-inflammatory drugs (NSAIDs), and acute graft versus host disease and systemic lupus erythematosus associated ones (Cobos-Fuentes et al., 2009).

3.6 | Proliferative verrucous leukoplakia

Proliferative verrucous leukoplakia (PVL) is a rare form of oral leukoplakia, which was first reported by Hansen et al., in 1985. It is referred to as a chronic progressive condition that initially develops from a hyperkeratotic white lesion

and eventually transforms into an irreversible, multifocal, exophytic lesion (Munde & Karle, 2016). PVL presents with unique features, including a tendency toward multifocality, being biologically more aggressive than other types of leukoplakia, a high probability for recurrence and being more prone to malignant transformation (40%–100% in a follow-up period of 4.4–11.6 years) (Cobos-Fuentes et al., 2009; Rotaru et al., 2020).

4 | CURRENT DIAGNOSTIC METHODS OF OC AND OPMD

At present, OC and OPMD screening are conducted by the dentist during routine dental oral cavity mucosa examination. OC screening is defined as the process by which the medical practitioner evaluates an asymptomatic person to determine if the individual is likely or unlikely to have a potentially malignant or malignant lesion (Charanya et al., 2016). During screening, the identification of suspected lesions is further investigated by exfoliative cytology in which the oral epithelial cells are collected with the aid of a cytology brush (Sugerman & Savage, 1996). The potential of screening methods can be enhanced by the use of optical adjunctive aids. These aids include vital tissue staining using Toluidine blue or Lugol's iodine or acetic acid (3%–5%). In addition, light-based detection systems, namely chemiluminescence, autofluorescence, VELscope system, narrow-band imaging, and biopsies such as brush biopsy can be used as optical adjunctive aids (Charanya et al., 2016). However, the degree of consent given by the patient affects the effectiveness of the screening procedures. Screening plays a major role in the early detection of OC and OPMD thus, providing early treatment and subsequent monitoring of relevant patients.

Detection of OC at an early stage is believed to be the most effective strategy to improve overall survival, reduce mortality and improve quality of life (Baykul et al., 2010). Early detection of OC aims to identify not only early-stage OC lesions but also OPMD at the earliest possible stage. According to www.cancer.net, it has been stated that, when OC is diagnosed at an early stage the overall 5-year survival is improved (85%), however, only 28% of the OC patients are diagnosed at this stage. Similarly, 50% of OC patients are diagnosed when primary cancer has spread to locoregional lymph nodes and adjacent tissue. It is also documented that poor overall 5-year survival of 40% is associated with OC patients who have developed metastasis at the point of diagnosis. Unfortunately, ≈18% of the patients are diagnosed at this stage (American Society of Clinical Oncology (ASCO), 2005-2022). Therefore, more than 65% of OC patients are diagnosed at a stage with at least locoregional metastasis. In 1995, Anderson et al., proposed a model to conceptualize the stages of patient delay in diagnosis and treatment of cancer. The Anderson model has reported that the total patient delay in cancer diagnosis has five stages, namely appraisal, illness, behavioral, scheduling and treatment (Andersen et al., 1995). A delay in any of these stages would negatively impact the management of cancer patients, thus decreasing 5-year patient survival rates (Walter et al., 2012). A study evaluated the effect of delay in diagnosis with regards to mortality in 183 OC patients and reported that the mean overall time interval between the first symptom to the start of treatment was 107.1 days (±85.2) with an overall survival rate of 58.4% (Lopez-Cedrún et al., 2020). More importantly, the mortality of the patients with short overall time interval (24–55.5 days) was lower than for those patients with long (127.5–420 days) and medium (55.5–127.5 days) overall time intervals (Lopez-Cedrún et al., 2020). Therefore, as one of the strategies to reduce the delay in patient diagnosis, the detection of molecular biomarkers either in tumor biopsy or in liquid biopsy would be a promising way forward in the management of OC.

5 | MOLECULAR BIOMARKERS OF OC

Over the past decades the emergence of cancer biomarkers has turned out to be a promising avenue in clinical oncological diagnosis. Biomarkers, also known as molecular markers or signature molecules, are defined as biological molecules found in blood, or other body fluids, or tissues that can be a sign of normal or abnormal processes, or of a condition or disease (http://www.cancer.gov). Biomarkers can be used to assess the status of a patient in various clinical stages, such as estimating the risk of disease development, screening of primary cancers, differentiating benign from malignant tumors, prognosis, monitoring response to therapy and detecting recurrence. Biomarkers can be classified into genomic, transcriptomic, proteomics, metabolites, and carbohydrates (Quezada et al., 2017). Epigenetic mechanisms that regulate gene expression are DNA methylation, histone modifications, nucleosome positioning, and the action of microRNAs and piRNAs which are a type of ncRNA (Sharma et al., 2009). The role of ncRNAs in OC development is the main focus of this review article.

More importantly, epigenetic dysregulation, existing genetic mutations, amplifications, or polymorphisms may lead to nucleic acid-based modifications that pave the way to aberrant expression of cancer-related genes offering them to be used as potential biomarkers (Cervino et al., 2019).

As mentioned earlier, oncogenesis is driven by the accumulation of alterations influencing the structure and function of the genome. Accumulation allows the cells to escape from tightly regulated mechanisms involving cell proliferation and cell death/ apoptosis (Hanahan & Weinberg, 2011). Consequently, genes (oncogenes) enhancing cell division and resisting cell death will be promoted (Baylin & Jones, 2016). Alternatively, or additionally, the inactivation of tumor suppressor genes also paves the way for tumorigenesis. Genetic changes and epigenetic alterations ([epi]genome) are two well-established alterations leading to pathogenesis of cancer (Hanahan & Weinberg, 2011). Historically, many studies have explored the impact of genetic changes in carcinogenesis. In contrast, more recently, researchers are evaluating the effects of epigenetic alterations in oncogenesis. Both genetic and epigenetic changes occur at each stage of carcinogenesis, from initiation to progression and ultimately to malignancy, including metastasis (Herceg & Hainaut, 2007). It is now well-established that, except for few cancer types (cervical cancer, prostate cancer, breast cancer) where there are screening programs, cancers can be detected in asymptomatically individuals. As an example, Tang et al., were able to diagnose a 2 mm occult HPV driven oropharyngeal cancer in an asymptomatic healthy person using a saliva sample (Tang et al., 2020). Unfortunately, this is not the case for OC, in most occasions the primary tumor has metastasized to adjacent tissues at the time of diagnosis. Delayed clinical presentation of these neoplastic changes prevent early detection of cancer leading to an increase in morbidity and mortality (Herceg & Hainaut, 2007). The discovery of epigenetic biomarkers will likely assist in early diagnosis and prevention of further complications. The epigenetic mechanisms that regulate gene expression are DNA methylation, histone modifications, nucleosome positioning, and the action of microRNAs and piRNAs which are a type of ncRNA (Sharma et al., 2009). The role of ncRNAs in OC development is the main focus of this review article.

At present, there are very few clinically validated biomarker tests approved by either the Food and Drug Administration (FDA) or Conformitè Europëenne (CE) or Clinical Laboratory Improvement Amendments (CLIA) for the detection of OC. The available tests include biomarkers of proteins, mRNA-based and DNA-methylation (Momen-Heravi & Bala, 2018; Table 1). However, development of biomarkers for diagnosis and prognosis of OC is hampered by the heterogeneous nature of this cancer. Recently, a US-based company, Viome developed an algorithm to predict OC noninvasively, using a salivary metatranscriptomic signature (Banavar et al., 2021). Their diagnostic classifier yielded sensitivity up to 83% (92.3% for stage 1 cancer) and specificity up to 97.9% with an area under the curve (AUC) of 0.9. Their metatranscriptomic signature incorporated both taxonomic and functional microbiome features, and includes previously known and novel taxa and functional OC related pathways. The company received FDA approval under emergency use authorization in May 2021 (Banavar et al., 2021).

To date, several studies have detected aberrant expression of ncRNAs such as miRNAs, lncRNAs, snoRNAs, circRNAs, and piRNAs suggesting that they may be used as biomarkers for the early detection, diagnosis and monitoring of OC and as potential therapeutic targets. Noncoding RNAs are being considered a potential biomarker of cancer because of their high stability in tumor and body fluids, tumor and tissue-specific expression profiles, and possible characterization by polymerase chain reaction (PCR). However, using a single ncRNA as a biomarker might not be sufficient due to the heterogeneity of cancer and the ubiquitous expression of most ncRNAs. Therefore, using panel of ncRNAs could increase the sensitivity and specificity (Rishabh et al., 2021). Moreover, the fact that a single ncRNA can regulate more than one gene, it is easier to use as a therapeutic target in which a single ncRNA could reverse the expression of more than one altered gene. For instance, Yu et al., reported that lncRNA-LINC00673 was overexpressed in Oral tongue squamous cell carcinoma (OTSCC) tissues, and can be used as a potential biomarker for early detection and prognosis, as it was associated with poor overall survival of patients (Yu et al., 2017). Additionally, a validation study was performed using oral cytology and tissue samples from OTSCC patients. They reported that a combination of miR-21 and miR-375 can be used as a biomarker for the early detection of OTSCC in tissue samples, with a sensitivity and specificity of 83% and in oral cytology samples with a sensitivity of 100% and specificity of 65% (He et al., 2016). Another study reported that miR-9 was downregulated in OSCC tissues and the cell cycle regulator CDK6 was identified as a functional target of miR-9. The cells transfected with miR-9 showed low CDK6 protein levels. Therefore, it was reported that the antiproliferative activity of miR-9 can be used as a biomarker of early detection of OSCC (Shang et al., 2018). A study by our team has shown that overexpression of miRNA-9 in OC cell lines resulted in a significant reduction in cell proliferation and migration, and an increase in apoptosis, which was associated with an increase in Galectin-3 secretion and export of Galectin-3 protein (Wan et al., 2021). We concluded that both miR-9-5p and Galectin-3 are critical biomarkers involved in the progression of OC. In addition, Zhang et al., reported that

TABLE 1 A summary of biomarkers that have received FDA, CE, or CLIA approval for clinical use

No.	Type of biomarker	Biomarker	Specimen	Approval	Application	References
1	DNA methylation	ZNF582-PAX1	Oral exfoliated tissue	CE	Detection of oral dysplasia (Adjunct test) and OC. Prediction of OC recurrence. MIDY+ Sensitivity: 81.93% Specificity: 67.86% MODY+ Sensitivity: 96.97% Specificity: 42.31%	Cheng et al. (2016); Cheng et al. (2018)
2	mRNA	Multi-panel mRNA OAZ1, SAT, DUSP	Saliva	CLIA	Risk stratification test. Sensitivity + Specificity = 150.7%	Martin et al. (2015)
3	Proteins	CD44	Saliva	CE	Risk stratification, CD44 and total protein Sensitivity: 80% Specificity: 48.7%	Pereira et al. (2016)
4		S100A7	Tissue	CE	Risk stratification measuring S100A7 levels Over expressed in high-risk dysplastic lesions Sensitivity: 95% Negative predictive value: 78%	Hwang et al. (2017)
5	Microbial gene expression signature	Meta-transcriptomic signature	Saliva	FDA	Noninvasive prediction of OC. Sensitivity: 83% Specificity: 97.9%	Banavar et al. (2021)

Abbreviations: CE, Conformitè Europëenne; CLIA, Clinical Laboratory Improvement Amendments; DNA, deoxyribonucleic acid; FDA, Food and Drug Administration; mRNA, messenger ribonucleic acid.

miR-103a-3p was upregulated in OC tissue (Zhang et al., 2020). RCAN1, One of the antitumor genes, was identified as a downstream target of miR-103a-3p, causing the downregulation of RCAN1 leading to the development of cancer cells. Furthermore, lncRNA-LINC00675 acted as a sponge for miR-103a-3p leading to its downregulation and overexpression of RCAN1 (Zhang et al., 2020).

6 | NONCODING RNAs

It has been reported that only 2% of the total DNA encodes for proteins and 70% of the remaining is transcribed into ncRNAs (Huang et al., 2020). These ncRNAs do not encode for proteins, however, they have the ability to deliver housekeeping functions in number of biological processes by regulating gene expression through several mechanisms at the transcriptional, post-transcriptional, and epigenetic level (Dahariya et al., 2019; Momen-Heravi & Bala, 2018). The value of ncRNAs as key biomarkers for disease pathogenesis is increasingly being recognized (Momen-Heravi & Bala, 2018). ncRNAs are involved in a number of biological functions, including regulation of chromosome dynamics, RNA editing, splicing, translational inhibition, and mRNA destruction. There is evidence to support that ncRNAs are dysregulated in many cellular processes (initiation, progression, migration, invasion, and drug resistance) leading to

cancer development (Wang et al., 2019). Even though ncRNAs do not encode proteins, alterations in ncRNAs can lead to oncogenesis (Huang et al., 2020).

To date there is a large number of published reviews on the biogenesis and regulation of ncRNAs in diseases (Gebert & MacRae, 2019; Iwasaki et al., 2015; Kristensen et al., 2019; Ozata et al., 2018; Saliminejad et al., 2018; Selbach et al., 2008; Statello et al., 2020; Yao et al., 2019). More importantly, there are large number of publications on OC as well. However, most reports are documenting one type of ncRNA in OC. This review article focuses on five major types of ncRNAs in the context of OC.

6.1 | microRNA

It is now apparent that the regulation of gene expression is a fundamental, dynamic, and complex biological process. Therefore, alterations in key regulatory mechanisms may lead to abnormal phenotypes and diseases, including cancers. Transcription factors and miRNAs are important regulators of gene expression that can result in either oncogenic or tumor-suppressive activity alterations (Qin et al., 2020). However, under certain circumstances, miRNAs are also involved in the activation of gene expression. Increasing evidence suggests that miRNAs are aberrantly expressed in multiple human tumors and involved in critical oncogenesis processes, such as cell proliferation, differentiation, migration, invasion, survival, metabolism, genomic instability, inflammation, and angiogenesis (Lin & Gregory, 2015).

miRNAs are small single-stranded ncRNAs of approximately 19–22 nucleotides in length (Nagadia et al., 2013; Salazar et al., 2014; Satapathy et al., 2017). The first miRNA was discovered in 1993 in *Caenorhabditis elegans* which was coded by the gene *lin-4* and it was post-transcriptionally repress lin-14 mRNA. Subsequently, in 2000, let-7 was discovered as the first microRNA in humans. Studies show that the human genome encodes for more than 2500 miRNAs and 60% of the total human genes are regulated by these miRNAs (Friedman et al., 2009). Based on the genomic origin, miRNAs can be categorized into intergenic, intronic, exonic, and others. They regulate protein-coding gene expression by guiding the Argonaute (AGO) proteins to the target region and binding to the complementary sequences in the 3′ untranslated region (UTR) of target mRNAs. This results in mRNA (messenger RNA) degradation or translational inhibition by the miRNA-induced silencing complex (miRISC) (Lin & Gregory, 2015).

Recent studies suggest that miRNAs are shuttled between various subcellular compartments to control the rate of transcription and translation activities (Dai et al., 2020). Therefore, miRNAs are crucial to ensure the normal biological process of cell development. Abnormal expression of miRNAs is encountered in various disease conditions, including cancer. Generally, in cancer cells, oncomiRs (i.e., miR-21 cluster, targeting a large number of tumor suppressor genes associated with proliferation, apoptosis, and invasion) are amplified or over-expressed, whereas tumor suppressor miRNAs (i.e., miR-100) are under-expressed due to deletion or suppression (Condrat et al., 2020; Manasa & Kannan, 2017; Scapoli et al., 2010). Therefore, miRNAs have a significant role in regulating gene expression and alterations in their actions may lead to carcinogenesis (Dioguardi et al., 2020; Quirico & Orso, 2020). One of the main roles of miRNAs is to regulate mRNA gene expression by mediating the degradation of mRNA and regulation of transcription and translation via canonical and noncanonical mechanisms. The canonical mechanism progresses as the miRNAs within the RNA-induced silencing complex (RISC) guide the complex to the specific mRNA targets resulting in complementary binding to the mRNA sequences in the 3′ UTR. Repression of the mRNA post-transcriptionally is achieved through binding to the 3′ UTR of the mRNA with the miRNA seed region (5′). Furthermore, it has been purported that longer seed regions have a greater efficacy on mRNA repression. In contrast, miRNAs have been reported to bind to 5′ UTR, coding sequence which represses gene expression and their interaction within promoter regions result in enhancement of transcription. This leads to the suppression of mRNA expression by inhibiting translation at the initiation step through the release of eukaryotic initiation factor 4A-I (eIF4A-I) and eIF4A-II. The majority (66%–90%) of the gene regulation is by cleavage of mRNA through deadenylation and decapping and the remaining by repression (Gebert & MacRae, 2019; Min et al., 2015). In contrast, about 60% of the interactions between miRNA-induced silencing complex (miRISC) and mRNAs are via noncanonical mechanisms in which the strands are not completely complementary to each other. Therefore, a single miRNA could target more than one mRNA, while one mRNA allows the binding of more than one miRNA. The cooperative repression is achieved by miRNA binding with closely spaced target sites. In the miRNA sequence, 2–8 nucleotides from the 5′ end form the seed sequence and which is the deciding factor for the mRNA recognition. In addition, individual miRNAs or miRNA clusters can regulate entire cellular pathways and this interaction enables the miRNA to regulate several biological processes such as cell proliferation, differentiation,

migration, apoptosis, and signal transduction (Condrat et al., 2020; Min et al., 2015). These biological interactions of miRNAs serve as the key regulators in different diseases, including cancers (Kulkarni et al., 2017; Quirico & Orso, 2020).

It is now evident that miRNAs play a key role in regulating gene expression facilitated by binding of miRNA seed sequence to mRNA target. The miRNA seed sequence is the crucial player in its function. Moreover, RNA secondary structures that mediate the interactions with RNA binding proteins (RBPs) could possibly affect the biogenesis of miRNAs. The regulation of miRNA biogenesis, activity and turnover is carried out by cellular processes that alter the seed sequence of miRNA or its precursor (Gebert & MacRae, 2019; Lee et al., 1993; Wightman et al., 1993). The activity of miRNA is determined by the modification of miRNA sequence which is achieved through isomer formation, miRNA precursor editing by deamination, nontemplated nucleotide addition, and post-translational modification of AGO. Similarly, miRNA turnover is regulated by sequestration and regulation of miRNA target sites and controlling the transport of miRNAs from cytoplasm (Gebert & MacRae, 2019).

6.1.1 | Biogenesis of microRNAs

Biogenesis of miRNA is a multistep sequential process. It begins in the cell nucleus and ends in the cytoplasm (Yete & Saranath, 2020). About 50% of currently identified miRNAs are mostly processed from introns and very few of the miRNAs are derived from exons of protein coding genes. The rest are intergenic, which are transcribed independently of a host gene and regulated by their own promoters. miRNA clusters are one long transcript possibly with similar seed regions and can be considered as a family. Figure 2 shows an overview of the biogenesis of miRNA.

6.1.2 | Role of microRNAs in OPMD

Several studies have reported the association between OPMD and microRNA. Aghbari et al., reported low levels of miR-27b and miR-137 in both tumor tissues and saliva samples 20 patients diagnosed with Oral Lichen Planus (OLP) and 20 healthy controls (Aghbari et al., 2018). Tissue miR-27b was reported to be the best diagnostic biomarker for OLP (AUC = 0.98) with a sensitivity and specificity of 100% and 65%, respectively, whereas salivary miR-27b was reported to be a fair diagnostic marker (AUC = 0.78) with a sensitivity and specificity of 75% and 100%, respectively. The tissue miR-137 was reported as the best predictor of malignant transformation (AUC = 1.00) with 100% sensitivity and 100% specificity and salivary miR-137 with 100% sensitivity and 80% specificity (AUC = 0.97) (Aghbari et al., 2018). Cheng et al., has reported that miR-222-3p was down-regulated in OL compared with OC and healthy individuals. Furthermore, both miR-150-5p and miR-423-5p were upregulated in OSCC compared with normal. Combining three miRNAs as a panel, they were able to differentiate OC from OL with 83.6% sensitivity and 85% specificity (AUC = 0.916). Furthermore, miR-222-3p and miR-423-5p were reported as prognostic biomarkers of tumor progression (Chang et al., 2018). Chen et al., has proposed a panel of three miRNAs (miR-129-5p, miR-450b-5p, and miR-296-5p) that can predict the transformation of OL ($N = 30$) to OSCC ($N = 25$). The combination of these three miRNAs was able to discriminate between OL and OL-OSCC with an AUC of 0.872 (Chen et al., 2018).

6.1.3 | Role of microRNAs during oral carcinogenesis

The expressions of miRNAs can be tumor and tissue specific. Past studies have revealed that numerous miRNA expression profiles have been reported in oral neoplastic tissues and in cell lines in vitro. In the context of carcinogenesis, miRNAs function by controlling the expression of oncogenes through tumor suppressor miRNAs and by controlling the expression of tumor suppressor genes by oncogenic miRNAs (Manasa & Kannan, 2017). Dysregulation of miRNAs can be due to one or a combination of causes, such as alterations in biogenesis driven by epigenetics, alterations in miRNA genes, altered transcription factors and abnormalities in enzymes (Drosha, Dicer). In addition, chromosomal instability, genomic instability, genetic mutations, SNPs, deletions or duplications in miRNA genes, loss of miRNA binding sites, and redirection of the miRISC to multiple competitive miRNA binding sites present in ceRNAs. Dysregulation of miRNAs by any of the above mechanism/s result in activation of oncogenic genes or proteins and deactivation of tumor suppressor genes. Gradually, the alterations in miRNA expression cause transformation of a normal cell into a

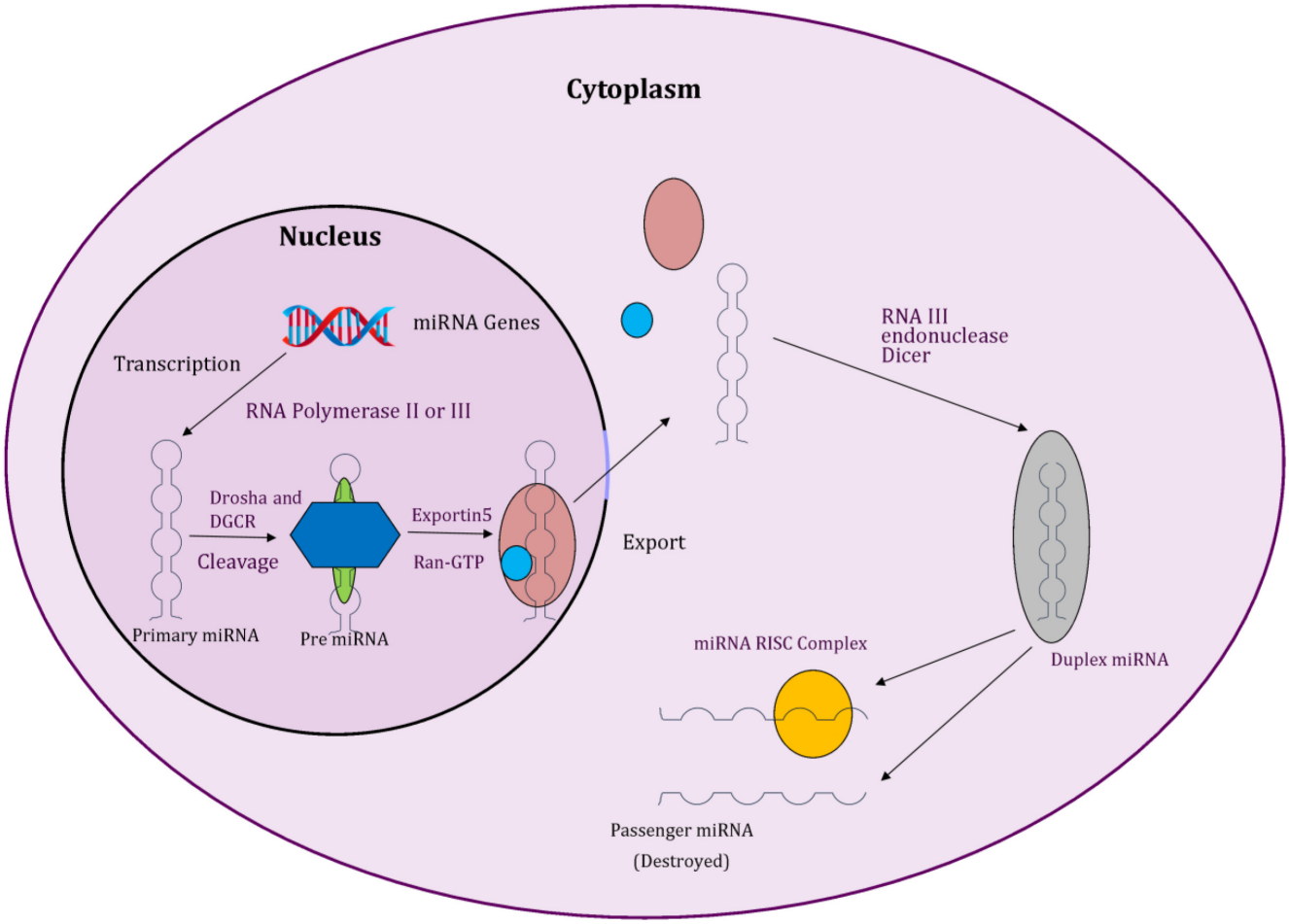

FIGURE 2 An overview of biogenesis of microRNA. The initial step of miRNA biogenesis is the production of primary miRNA (pri-microRNA) from transcription of miRNA genes by RNA polymerase II or RNA polymerase III. The specific hairpin loop of pri-microRNA is recognized and cleaved by Drosha, Dicer along with DGCR8, forming a microprocessor complex generating 70–100 nucleotide pre-microRNA. Consequently, the pre-microRNAs are transported to the cytoplasm from the nucleus by Exportin5 and Ran-GTP complex and converted to microRNA duplexes (19–24 nucleotides) by the RNA III endonuclease Dicer. The double-stranded miRNA is unwound by a helicase enzyme to form mature miRNA. Consequently, the mature miRNA is combined with the Argonaute family of proteins giving rise to the RISC. This complex is responsible for the biogenesis of functional miRNAs. The other single strand of the mature miRNA duplex, known as passenger miRNA, is usually degraded, but on some occasions, these passenger miRNAs escape the degradation process and act as mature miRNAs themselves

neoplastic cell (Ghosh et al., 2020). Several miRNA profiling studies revealed that mature miRNAs are either upregulated or downregulated in the tumor tissue (Ghosh et al., 2020). Therefore, miRNA expression levels can be used to explain the pathogenesis, metastasis, and chemo-resistance of OC (Manasa & Kannan, 2017). There is a plethora of miRNAs that are involved in the carcinogenesis of OC. Expression changes of miRNA have also been reported to be associated with clinical outcomes of OC patients. Several reports highlight that upregulation of miR-125b in OC tissue indicates poor prognosis (Y. F. Chen, Wei, et al., 2019). Similarly, miR-199a-5p, a well-known tumor suppressor across several cancer types, has shown to predict OC prognosis where downregulation is indicative of poor overall survival (Wei et al., 2019). In addition, studies that associate miRNAs with the development of OC document in the Table 2.

Concurrently, researchers have examined the use of miRNA-based therapies for the treatment of cancer. Some studies have provided promising outcomes emphasizing that miRNAs could be used as a potential therapeutic agent in the context of cancer therapy. Mainly, there are two possible techniques to achieve this goal. First, silencing of miRNAs that are associated with carcinogenesis using miRNA inhibitors to block the functions of miRNAs. Second, the use of miRNA mimics as therapeutic agents to replace particular miRNAs that are expressed at low levels in cancers (Komatsu et al., 2018). Despite the great potential of miRNAs in the treatment of cancer, further in vivo studies focused

TABLE 2 microRNAs whose aberrant expression is associated with OC development

No.	miRNA	Population/ *sample*	Up/down	Clinical association	Functional regulation	Target gene	Function	Clinical application	References
1	miR-125b	*OSCC cell lines*	Down	Low expression of tissue miR-125b associated with worse prognosis	Low expression of miR-125b leads to increased cell proliferation, migration, invasion, ROS, CDDP resistance	↑ Peroxiredoxin like 2A (*PRXL2A*)	miR-125b represses PRXL2A expression. Increased PRXL2A expression in SAS cells contributes to oncogenesis, tumorigenesis, reactive oxygen species scavenging and chemo-resistance.	Protection of cancer cells from oxidative stress by downregulating *PRXL2A*	Y. F. Chen, Wei, et al. (2019)
2	miR-21, miR-375	19 OTSCC 20 Normal Tissue *Oral cytology*	miR-21—Up miR-375—Down	Not determined	Not determined	Not determined	Sensitivity 100% Specificity 64%	Early detection of OTSCC	He et al. (2016)
3	miR-9	21 OSCC *Tissue*	Down	Not determined	Underexpression of miR-9 leads to increased cell proliferation, migration, invasion and reduced apoptosis	↑ *CDK6/Cyclin D1*	Overexpression of miR-9 downregulates CDK6 and Cyclin D1	Diagnosis and therapy	Shang et al. (2018)
4	miR-143	15 OSCC 15 Normal *Tissue*	Down		Underexpression of miR-143 leads to increased cell migration, cellular glucose metabolism, proliferation, colony formation, invasion and reduced apoptosis, inhibited cell cycle arrest	↑ *Hexokinase 2*	miR-143 acts as a tumor suppressor. miR-143-mediated cancer suppression through the direct inhibition of Hexokinase 2. Inhibits of glycolysis in vitro and in vivo.	Therapeutic target	Sun and Zhang (2017)
5	miR-199a-5p	40 OSCC *Tissue*	Down	Under expression of miR-199a-5p associated with poor overall survival.	Underexpression of miR-199a-5p increases cell proliferation, invasion, migration, induces epithelial–mesenchymal	↑ EMT-related transcription factor *SRY-box 4*	miR-199a-5p may inhibit cell invasion and migration in OSCC cells via modulating EMT. miR-199a-5p inhibits SOX4 expression. SOX4 may act as an oncogene	Prognostic biomarker and therapeutic target	Wei et al. (2019)

(Continues)

TABLE 2 (Continued)

No.	miRNA	Population/ *sample*	Up/down	Clinical association	Functional regulation	Target gene	Function	Clinical application	References
				Associated with tumor size,	transition (EMT) cascade,		in OSCC via modulating cell proliferation, migration and invasion.		
6	miR-103a-3p	OSCC cell lines	Up		Increased expression of miR-103a-5p lead to increased cell proliferation and reduced apoptosis and necrosis	↓ *RCAN1* ↑ *PCNA*, cyclin D1, and cyclin B1 protein level ↓ *PTEN* ↓ cleaved caspase-9 and cleaved caspase-3	miR-103a-3p inhibition suppressed the proliferation and induced apoptosis in OSCC cells through regulating RCAN1 LINCRNA00675 acted as a sponge of miR-103a-3pOver expression of LINCRNA00675 led to increased RCAN1 and PTEN	Diagnostic biomarker and therapeutic target	Zhang et al. (2020)
7	miR-7111-5p miR-6870-5p	30 OSCC *Tissue*	miR-7111-5p: Down miR-6870-5p: Down	Associated with tumor stages, family history	Not determined	↑ *SRF*	Down regulation of miRs and up regulation of SRF may serve as biomarkers for diagnosis and monitoring	Prognostic marker	Saraei (2021)
8	miR-487a-3p	20 OSCC *Tissue*	Down		Under expression of miR-487a-3p leads to increased cell growth and invasion.	↑ *PPM1A* Increases cell growth and invasion	miR-487a-3p binds to the PPM1A 3′ UTR and regulates its expression at the mRNA and protein level. Exogenous delivery of miR-487a-3p inhibits the expression of PPM1A, thus reduces growth and invasion	Therapeutic target	L. Wang, Ge, and Zhou (2021)

Abbreviations: ↑, increased; ↓ decreased; EMT, epithelial–mesenchymal transition; LINCRNA, long intergenic noncoding ribonucleic acid; miR, microribonucleic acid; OC, oral cancer; OSCC, oral squamous cell carcinoma; OTSCC, oral tongue squamous cell carcinoma; *PCNA*, proliferating cell nuclear antigen; *PPM1A*, protein phosphatase, Mg^{2+}/Mn^{2+} dependent 1A; *PRXL2A*, peroxiredoxin like 2A; PTEN, phosphatase and tensin homolog; RCAN1, regulator of calcineurin 1; ROS, reactive oxygen species; SRF, serum response factor; SRY-box 4, sex determining region-box 4.

on microRNA delivery methods are warranted to further strengthen the utilization of microRNAs as therapeutic targets.

Concurrently, to support the potential of microRNAs in OC, Guo et al., have developed a mechanistic Chinese hamster oral buccal mucosal squamous cell carcinoma model and induced OC by treating the hamsters with DMBA/acetone. Based on RNA sequencing of treatment and control hamster OC tissue sample, they screened 11 known (crg-miR-130b-3p, crg-miR-142-5p, crg-miR-21-3p, crg-miR-21-5p, crg-miR-542-3p, crg-miR-486-3p, crg-miR-499-5p, crg-miR-504, crg-miR-34c-5p, crg-miR-34b-5p, and crg-miR-34c-3p) and three novel (Novel-117, Novel-118, and Novel-135) differentially expressed miRNAs. The results were validated by qRT-PCR. Based on gene ontology analysis miR-21 was selected for biological and pathway studies. PTEN was selected as it is the common target of miR-21. miR-21 regulated apoptotic protein expression through the PI3K/Akt signal pathway. A total of 3 novel miRNAs (Novel-117, Novel-118, and Novel-135) and 11 known miRNAs (crg-miR-130b-3p, crg-miR-142-5p, crg-miR-21-3p, crg-miR-21-5p, crg-miR-542-3p, crg-miR-486-3p, crg-miR-499-5p, crg-miR-504, crg-miR-34c-5p, crg-miR-34b-5p, and crg-miR-34c-3p) were identified. The study concluded that, crg-miR-504 and crg-miR-34c-5p will be further studied for functional mechanistic studies (Xu et al., 2019).

In summary, miRNAs show great potential in the diagnosis, prognosis and treatment of OC. However, further studies are warranted in developing human models including organoids, tumoroids, and spheroid models that would accelerate the translation of the utility of microRNAs in OC. Furthermore, the identified miRNAs needs to be validated in large cohorts, especially in regions with high incidence of OC.

6.2 | Long noncoding RNA

The lncRNAs are a unique class of ncRNAs that are greater than 200 nucleotides in length. According to Gencode there are more than 18,000 lncRNA genes and more than 50,000 lncRNA loci transcripts. They usually have little or no protein-coding ability. Most lncRNAs are transcribed by RNA polymerase II and are capped at the 5′ end mostly by 7-methyl guanosine (m7G) and more than 60% of the lncRNAs are polyadenylated at the 3′ end and spliced similar to mRNA (Statello et al., 2020). Based on the chromosomal position, lncRNAs can be sub-divided into long intergenic RNA, antisense RNA, enhancer RNA, long intronic RNA, promoter-associated lncRNA, and bidirectional lncRNA. Even though they do not encode proteins, they have the potential to regulate the transcription of target genes at epigenetic, transcriptional, and post-transcriptional levels (Fang & Fullwood, 2016; Gao et al., 2020). The level of regulation depends on the site where lncRNA is localized. As an example, if lncRNA is located in the nucleus, this results in affecting chromatin and transcription level and cytoplasmic localization results in post-transcriptional regulation. Ultimately, they play a key role in fine-tuning of the translation process and regulating the critical functions of other ncRNAs namely, miRNAs, snoRNAs, and so on. This regulation is achieved either directly or by affecting the expression of a gene upstream or downstream.

In addition, lncRNAs have been shown to act through a wide range of mechanisms, including miRNA sponging, interfere with cellular signaling pathways, mRNA stability/degradation, translocation, alternative splicing, transcription, epigenetic imprinting, and enhancing DNA synthesis. Several functions of lncRNAs are reported to be involved in carcinogenesis. Aberrant expression of numerous lncRNAs are reported in specific cancer types and involve in complex cellular mechanisms by interacting with proteins, DNA, and RNA. Many lncRNAs are reported to be functionally associated with several cancers including, leukemia, hepatocellular carcinoma, colorectal cancer, and more importantly OC (Bao et al., 2019; D. Liu, Zhan, et al., 2020; Yu et al., 2017; C. Zhang, Bao, et al., 2019).

6.2.1 | Biogenesis of long noncoding RNA

The different elements of genomic DNA such as enhancers, promoters, and intergenic regions act as transcriptomic sites for the different classes of lncRNAs. The majority of the lncRNAs are transcribed by RNA polymerase II. Complex mechanisms are involved in the biogenesis of lncRNAs including generation of mature ends by ribonuclease P cleavage, capping of their ends by small nucleolar–RNA–protein complex, and circularization (Dahariya et al., 2019; Wu et al., 2017). Figure 3 shows an overview of the sources of different classes of lncRNAs.

LncRNAs acts as signal, decoy, guide and scaffold, enhancer RNAs and short peptides. A signal lncRNA is responsible for the regulation of transcription in response to various stimuli by serving as a molecular signal thus indicating the

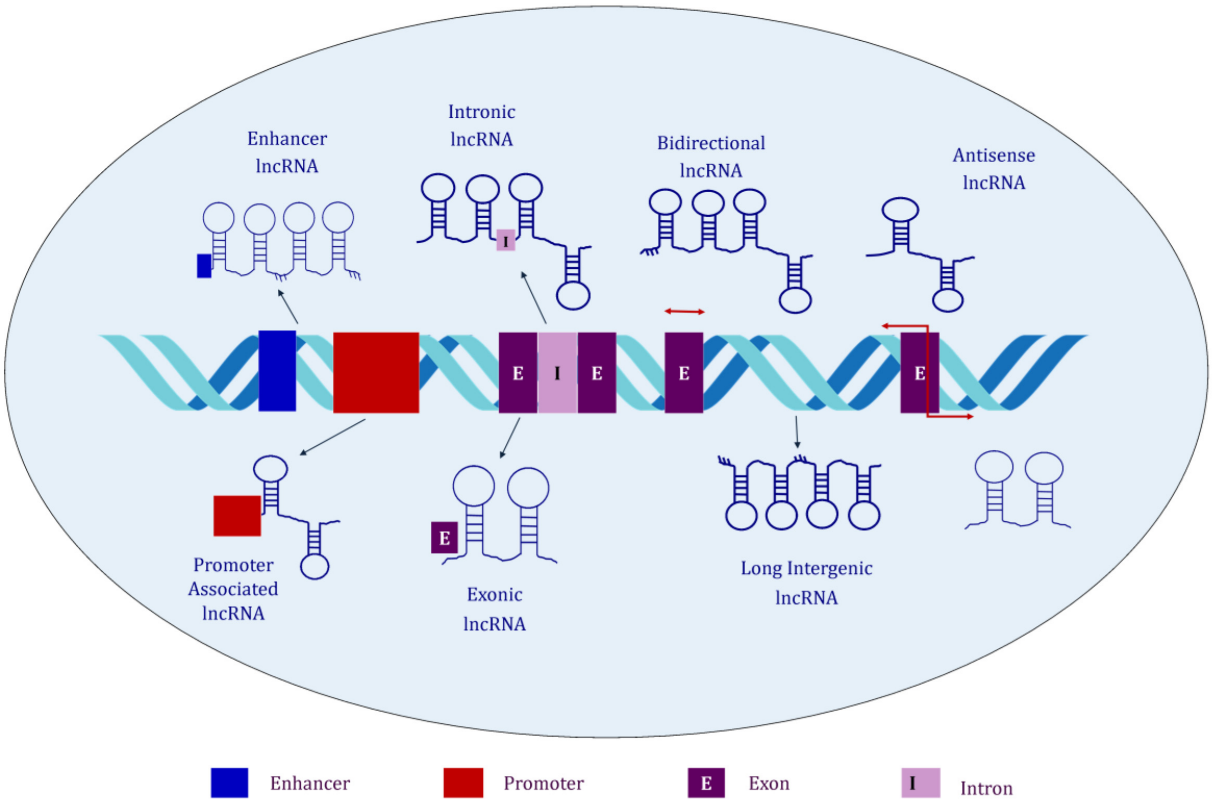

FIGURE 3 Overview of sources of different classes of long-noncoding RNAs. The majority of lncRNAs are transcribed by RNA polymerase II. Different classes of lncRNAs are transcribed from different DNA elements such as promoters, enhancers, exons, and intergenic regions. The classes of lncRNAs are enhancer, intronic, bidirectional, antisense, promoter associated, exonic, and long intergenic lncRNAs.

activity of transcription. Decoy lncRNAs regulate transcription by blocking the regulatory factors such as transcription factors, subunits of large chromatin producing complexes, catalytic proteins, and more importantly miRNAs which itself regulate gene expressions by employing "decoy" binding sites. Guide lncRNAs direct the RNPs to their specific target genes ensuring the proper localization of RNPs. Enhancer lncRNAs involve in chromatin interactions. Finally, lncRNAs are capable of encoding short peptides (Gao et al., 2020; Statello et al., 2020).

6.2.2 | Role of lncRNA in OC

Recent literature reports potential clinical utility of lncRNA in diagnosis, prognosis and treatment of OC. The majority of lncRNAs are overexpressed in OC, thus functioning as oncogenes, while other lncRNAs are underexpressed and act as tumor suppressor genes. A large number of studies have reported lncRNAs as potential therapeutic targets for OC, while some studies have reported lncRNA-UCA1 as a diagnostic marker (Yang et al., 2016). Fan et al., reported that lncRNA-LOC284454 was upregulated in serum from OC patients and can be used as a diagnostic marker with an AUC of 0.698 (Fan et al., 2020). Lie et al., reported overexpression of lncRNA-RBM5-AS1 in OC and was found to regulate the expression of miR-1285-3p by acting as a competitive endogenous RNA, leading to the regulation of *YAP1* gene. This gene is a transcriptional regulator of the Hippo signaling pathway, suggesting that indirect downregulation of *YAP1* by lncRNA-RBM5-AS1 may lead to carcinogenesis (C. Li, Ye, et al., 2020). This phenomenon could be used to identify potential biomarkers for diagnosis and treatment.

Expression levels of many lncRNAs are significantly correlated associated with tumor nodes metastasis (TNM) staging, lymph node metastasis and especially with poor overall patient survival. Upregulated lncRNAs can enhance cell proliferation, migration, invasion, and reduce apoptosis. Furthermore, lncRNAs also play a role in inducing chemoresistance, As an example, lncRNAs such as UCA1 and CILA1 are overexpressed and reported to be positively

associated with cisplatin resistance (Fang et al., 2017). lncRNAs also enhance the epithelial to mesenchymal transition (EMT) of normal oral keratinocytes.

EMT is the process of acquiring mesenchymal traits by epithelial cells. Mesenchymal cells are more migratory than epithelial cells. EMT is a vital process in normal embryogenesis and organogenesis. In contrast, EMT has been implicated in the pathophysiology of some diseases, especially in OC cells, enhancing migration and invasion, leading to increased risk of recurrence, metastasis, and poor overall survival (Jayanthi et al., 2020). Downregulation of E-cadherin and upregulation of mesenchymal type N-cadherin cause loss of cell–cell adhesion and increase cell motility. This is a hallmark of EMT, which is known as "cadherin switching." The functional loss of E-cadherin can be caused by germline or somatic mutations, DNA hypermethylation, proteolytic cleavage, and transcriptional suppression. Epigenetic modification, including DNA hypermethylation in the promoter region of the E-cadherin gene is the most common cause. lncRNAs such as H19 (Hong et al., 2018), 00958 (F. Chen, Liu, et al., 2019), NEAT1 (Huang et al., 2018), CILA1 (Lin et al., 2018), HNF1A-AS1 (Liu et al., 2019), HOXA11-AS (Niu et al., 2020), KRT16P3 (Yang et al., 2021), SNHG12 (Yin et al., 2020), and MIAT (Zhong et al., 2019) have been shown to promote EMT in OC cells. Knockdown of overexpressed lncRNAs showed an increase in E-cadherin and α-catenin levels and a decrease in Vimentin and N-cadherin levels, indicating the reversal of EMT. Furthermore, the activation of EMT-transcription factors (EMT-TFs) that suppress E-cadherin gene expression is an important event in EMT. There are five types of EMT-TFs namely, SNAIL1, SNAIL2, ZEB1, ZEB2, and TWIST1. Knockdown of lnc-PRKG1-AS1 resulted in a decrease in SNAIL1 levels, indicating the ability of lncRNA to activate EMT-TFs (T. Wu, Zhang, et al., 2020).

Furthermore, lncRNAs are reported to be involved in various signaling pathways that are aberrant in OC. Signal transduction is defined as a series of events that convert an external stimulus into a cellular response. The ability of cells to receive and respond to an external signal is a fundamental requirement for tissue development, repair, immunity and homeostasis. A range of pathways are involved in the regulation of carcinogenesis. The hippo pathway is one such highly conserved pathway that regulates the expression of genes that control key biological processes including cellular proliferation, survival, differentiation, organ size, and tissue homeostasis (Calses et al., 2019). The *LATS1* gene is one of the upstream regulators of the hippo pathway. lncRNA-LEFT1 inhibits the hippo pathway by directly binding to the *LATS1* gene, which is a negative regulator of *YAP1* in the hippo pathway. It acts as a tumor suppressor by restricting proliferation and promoting apoptosis. Therefore, upregulation of lncRNA-LEFT1 decreases the expression of *LATS1*, thereby enhancing proliferation and inhibiting apoptosis (C. Zhang, Bao, et al., 2019). Similarly, this pathway regulates other normal biological processes, such as cell differentiation, organ development, tissue regeneration, and prevention of tumorigenesis (Jung & Park, 2020). In human cancers, this pathway is highly activated. More importantly, lncRNAs such as UCA1, TUG1, CILA1, CCAT2, AFAP1-AS1, MIAT1, and CCAT1 are associated with the regulation of this pathway and are aberrantly expressed in OC. Increased activation of this pathway leads to uncontrolled proliferation and carcinogenesis. Therefore, this pathway can be considered as a therapeutic target in OC patients. Similarly, other studies have associated aberrant expression of dozens of other lncRNAs in the development of OC, as summarized in Table 3.

In summary, evidences show that lncRNAs can regulate oral carcinogenesis, thus could be used for the management of OC. However, the there are several aspects that needs to be uncovered to enhance the utility of lncRNAs in OC. For instance, further studies investigating the role of lncRNAs in OPMDs, oral tumor microenvironment would enhance the understanding of the mechanism of OC from progression to distant metastasis. Furthermore, as majority of the studies were focused on the treatment of OC using lncRNAs, effective drug delivery methods needs to be established for better outcome.

6.3 | Small nucleolar RNA

Small nucleolar RNAs (snoRNAs) are another type of ncRNAs that belongs to the subclass of lncRNAs with 60–300 nucleotides (Bachellerie et al., 2002; Maxwell & Fournier, 1995). snoRNAs are primarily found in the cell nucleoli and are significantly involved in pre-rRNA processing by endonucleolytic cleavage, post-transcriptional modification and maturation of ribosomal RNAs, small nuclear RNAs, and other cellular RNAs. snoRNAs can be divided into two classes, namely, C/D box snoRNAs and H/ACA box snoRNAs in which the former guide *O*-ribose methylation and the latter direct pseudo uridylation of nucleotides (Bachellerie et al., 2002; Maxwell & Fournier, 1995). It is estimated that each human cell consists of 150 different snoRNAs (Terns & Terns, 2002). More importantly, snoRNAs are capable of regulating gene expressions through mRNA splicing and editing (Stepanov et al., 2015).

TABLE 3 lncRNAs involved in the development of OC

No.	Long noncoding RNA	Sample	Up regulation/ down regulation	Clinical association	Functional regulation	Target gene	Pathway affected/ investigated	Interactor miRNA	Function	Clinical application	References
1	LEF1-AS1	88 OSCC tissue	Up	High expression levels associated with unsatisfied overall survival, tumor stage, N stage	↑ Cell survival, Proliferation, Migration ↓ Cell apoptosis	LATS1	Inhibits Hippo pathway	ND	Interaction decoy, act as oncogene	Biomarker for prognosis, treatment	C. Zhang, Bao, et al. (2019)
2	01234	88 OSCC tissue	Up	High expression levels associated with short overall survival, T stage, N stage, pathological stage	↑ Proliferation by enhancing DNA synthesis, metastasis, invasion	PAK4	ND	miR-433-3p	miR-433-3p sponging, act as oncogene	Diagnostic biomarker and therapeutic target	D. Liu, Jian, et al. (2020)
3	KCNQ1OT1	60 OSCC tissue	Up	High expression levels associated with poor overall survival	↑ Invasion, migration ↓ apoptosis	Rab14, MMP2, MMP9, Bcl-2 ↑ Caspase-3	ND	miR-185-5p	miR-185-5p sponging, act as oncogene	Therapeutic target	Bao et al. (2019)
4	00673	Set 1–15 TSCC tissue Set 2: 202 paraffin embedded tissue	Up	High expression levels associated with poor overall survival, poor relapse free survival, tumor size, invasion of tongue muscles, TNM stage, relapse	↑ invasion, migration	ND	ND	ND	ND	Early detection, Prognosis predictor of overall survival	Yu et al. (2017)
5	UCA1	124 TSCC tissue	Up	High expression levels associated with lymph node metastasis and TNM stage	↑ Invasion, Migration Proliferation ↓ Apoptosis	ND	Activation of WNT/β-catenin pathway	ND	ND	Diagnostic and therapeutic	Yang et al. (2016)
6	UCA1	30 OSCC tissue	Up	High expression levels associated with Cisplatin resistance (high expression) and progression	↑ Proliferation, Cisplatin resistance ↓ Cisplatin induced apoptosis	SF1	ND	miR-184	miR-184 sponging	Therapeutic target	Fang et al. (2017)
7	AC007271.3	82 OSCC tissue	Up	High expression levels associated with poor overall survival, TNM classification, lymph node metastasis	↑Proliferation, migration, invasion	Slug ↓ E-cadherin	Canonical NF-κB pathway	miR-125b-2-3p	Destabilized pri-miR-125b-2 and sponged with miR-125b-2-3p. miR-125b-2-3p inhibit the translation of Slug mRNA	Therapeutic target	Zheng et al. (2020)
8	CCAT1	15 OSCC tissue	Up	Not determined	↑ Proliferation Invasion, migration ↓ Apoptosis	↑Cyclin D1, CDK4 ↓Bax, Cleaved Caspase3, Cleaved Caspase9	WNT/ β-catenin pathway	miR-181a	miR-181a sponging, act as oncogene	Therapeutic target	G. H. Li, Ma, and Wang (2019)

TABLE 3 (Continued)

No.	Long noncoding RNA	Sample	Up regulation/ down regulation	Clinical association	Functional regulation	Target gene	Pathway affected/ investigated	Interactor miRNA	Function	Clinical application	References
9	FALEC	17 TSCC tissue	Down	Low expression levels associated with positive prognosis and T classification	↑ Proliferation, colony formation, migration ↓ Apoptosis	ECM1 ↑, EZH2	ND	ECM1 expression	FALEC binds with EZH2 to epigenetically silence ECM1 by methylation, inhibiting cell proliferation, and migration in TSCC cell lines	Therapeutic target	B. Jia, Xie, et al. (2019)
10	H19	42 OSCC tissue	Up	High expression levels associated with poor overall survival, TNM stage and nodal invasion	↑ proliferation, migration, invasion, Epithelial–mesenchymal transition ↓ Apoptosis, sub cutaneous tumor growth	EZH2 ↓ Bax, Cleaved Caspase3, Cleaved PARP ↑ Vimentin, N-cadherin ↓ ZEB1, E-cadherin	ND	miR-138	Enhance EMT, function as ceRNAs or molecular sponges by sponging miR-138	Therapeutic target	Hong et al. (2018)
11	Linc RoR	60 OSCC tissue	Up	High expression levels associated with poor response to treatment regimen, high recurrence, tobacco usage, and cellular differentiation	ND	↓ *p53* ↑ *Klf4*	ND	miR-145-5p	Act as molecular sponge, by sponging miR-145-5p	Predictor of therapeutic response	Arunkumar et al. (2017)
12	00958	70 OSCC tissue	Up	High expression levels associated with poor prognosis	↑ Proliferation, migration, invasion, epithelial–mesenchymal transition ↓ Apoptosis	↑ YBX2	ND	miR-627-5p	miR-627-5p sponging LINC00958 regulated cell growth, motility, and EMT through YBX2 in OSCC.	Prognostic marker and therapeutic target	F. Chen, Liu, et al. (2019)
13	LOC284454	167 OC 121 Healthy serum	Up	No association	ND	ND	ND	ND	Sensitivity 65% Specificity 95.87% AUC = 0.698	Diagnostic biomarker	Fan et al. (2020)
14	CEBPA-AS1	60 OSCC tissue	Up	High expression levels associated with poor overall survival, differentiation stage, lymph node metastasis, and clinical stage	↑ Proliferation, migration, invasion ↓ Apoptosis	↑ CEBPA ↑ Bcl2 (Target of CEBPA)	ND	ND	Might play a role in nuclear membrane and cytoplasm trafficking, promotes the tumorigenesis via CEBPA/Bcl2 in OSCC	Prognostic marker	Guo et al. (2018)
15	NEAT1	30 OSCC tissue	Up	High expression levels associated with poor prognosis, aggressive cancer phenotypes, and TNM stage, lymph node metastasis, clinical stage	↑ Proliferation, migration, invasion Epithelial–mesenchymal transition ↓ Apoptosis	↑ RGS20 cyclin D1, N-cadherin and vimentin ↓ E-cadherin	ND	miR-365	NEAT1 sponges miR-365, thereby suppressing the tumor-suppressive function of miR-365	Therapeutic target	Huang et al. (2018)

(Continues)

TABLE 3 (Continued)

No.	Long noncoding RNA	Sample	Up regulation/ down regulation	Clinical association	Functional regulation	Target gene	Pathway affected/ investigated	Interactor miRNA	Function	Clinical application	References
16	NKILA	10 TSCC tissue	Down	Low expression levels associated with poor overall survival, tumor size, advanced clinical staging, lymph node metastasis, relapse	↑ Migration, invasion	ND	NF-κB signaling pathway	ND	Controls tumor cell migration and invasion by blocking the phosphorylation of IκB, NF-κB activation, and the following EMT process	Potential predictor of overall survival and therapeutic target	Huang et al. (2016)
17	RBM5-AS1	80 OSCC tissue	Up	High expression levels associated with primary tumor size, lymph node metastasis, TNM staging, pathological grade, differentiation	↑ Proliferation, migration, invasion	YAP1	ND	miR-1285-3p	Regulates the level of miR-1285-3p as a competitive endogenous RNA (ceRNA) YY1 binds to the promoter of RBM5-AS1 and it promoted the proliferation, migration, and invasion of the cells, while miR-1285-3p mimic partially rescued these phenotypes	Diagnosis, treatment	C. Li, Ye, et al. (2020)
18	TUG1	96 OSCC tissue	Up	High expression levels associated with TNM stage, lymph node metastasis and tumor grade	↑ Cell growth, Proliferation, colony formation, migration, invasion ↓ Apoptosis	TUG1 siRNA transfection significantly increased the protein expression levels of cleaved caspase-3, cleaved caspase-9, and Bax, ↓ Bcl2	Wnt/β-catenin signaling	ND	TUG1 promotes the cell growth, proliferation and invasion of OSCC possibly via suppressing the level of Wnt/β-catenin signaling	Therapeutic target	Liang et al. (2017)
19	PRNCR1	57 TSCC tissue	Up	High expression levels associated with shorter overall survival, clinical stage, lymph node metastasis	↑ Cell proliferation, migration and invasion, tumor growth ↓ Apoptosis	HOXB5	ND	miR-944	PRNCR1 acted as a competing endogenous RNA on microRNA-944 Targeting of HOXB5 mRNA by miR-944 and the resultant downregulation of HOXB5	Therapeutic target	Lin et al. (2020)
20	CILA1	Cisplatin resistant TSCC tissue	Up	High expression levels associated with chemoresistance and EMT, poor survival	↑ Migration and invasion, EMT ↓ Cisplatin induced apoptosis	Wnt5A ↑ Vimentin ↑ E cadherin ↓	Activates the Wnt/b-catenin signaling pathway	ND	CILA1 promotes EMT, invasiveness, and chemoresistance in TSCC cells	Biomarker of chemo sensitivity, therapeutic target	Lin et al. (2018)

TABLE 3 (Continued)

No.	Long noncoding RNA	Sample	Up regulation/ down regulation	Clinical association	Functional regulation	Target gene	Pathway affected/ investigated	Interactor miRNA	Function	Clinical application	References
									CILA1 regulates EMT and chemo-resistance in TSCC cells via the Wnt/b-catenin signaling		
21	FGD5-AS1	30 OSCC tissue	Up	High expression levels associated with smoking, clinical stage, tumor size	↑ Cell growth, Proliferation, migration, invasion ↓ Apoptosis	USP21 ↑	ND	miR-520b (Tumor suppressor)	miR sponging of miR-520b Tumor stimulator in OSCC carcinogenesis and development	FGD5-AS1 functions as ceRNA in regulating the expression of USP21 by sponging miR-520b in OSCC cells.	L. Liu, Zhan, et al. (2020)
22	HNFAS1	62 OSCC tissue	Up	High expression levels associated with poor overall survival, nodal invasion, T stage and differentiation	↑ Cell proliferation, migration, EMT ↓ Apoptosis	STAT3↑ pSTAT3 ↑ Notch1 ↑ Hes1 ↑	Notch signaling	ND	STAT3 upregulated HNF1A-AS1 by promoting the transcription activity of HNF1A-AS1	Not reported	Liu et al. (2019)
23	CCAT2	62 OSCC tissue	Up	High expression levels associated with, poor overall survival. Poor differentiation grade, higher T stage and clinical stage	↑ Cell growth, invasion	GSK-3β ↓ β-catenin ↑ CCND1 ↑ MYC ↑	Activates the Wnt/b-catenin signaling pathway	ND	Wnt/β-catenin signaling pathway could partly restore the CCAT2-mediated malignant biological behaviors of OSCC cells	Prognostic marker	Ma et al. (2017)
24	HOXA11-AS	50 OSCC tissue	Up	High expression levels associated with lower survival rate	↑ Proliferation, migration, invasion and EMT ↓ apoptosis	YBX2 ↑	ND	miR-98-5p (Oncogene)	HOXA11-AS regulated YBX2 level through sponging miR-98-5p in OSCC	Therapeutic target	Niu et al. (2020)
25	RP11-284F21.9	50 OSCC tissue	Up	High expression levels associated with poor survival, nodal invasion, T stage, differentiation	↑ Proliferation, migration, and invasion	MAL2 ↑	ND	miR-383-5p	RP11-284F21.9 acted as a competing endogenous RNA (ceRNA) of miR-383-5p, leading to MAL2 upregulation promote OSCC cell growth and metastasis by sequestering miR-383-5p	Therapeutic target	Shao et al. (2020)
26	HULC	30 OC tissue	Up	ND	↑ Proliferation, migration, and invasion, EMT ↓ Apoptosis	ND	ND	ND	CDDP inhibits cell viability HULC increases drug tolerance	Therapeutic target	Su, Tang, et al. (2019)
27	CCAT1	OSCC cell lines	Up	ND	↑ Proliferation, migration, and invasion, cell cycle progression	DDR2 ↑	Activates ERK/AKT signaling	ND	CAT1 regulates TCA-8113 cells through mediating the ERK/AKT axis via modulating DDR2	Biological marker and therapeutic target	Sun and Shen (2020)

(Continues)

TABLE 3 (Continued)

No.	Long noncoding RNA	Sample	Up regulation/ down regulation	Clinical association	Functional regulation	Target gene	Pathway affected/ investigated	Interactor miRNA	Function	Clinical application	References
28	ELDR	20 OSCC tissue	Up	ND	↑ cell proliferation, colony formation, PCNA expression	EGFR	ND	miR-7		Therapeutic	Sur et al. (2020)
29	AFAP1-AS1	103 TSCC tissue	Up	High expression levels of AFAP1-AS1 is associated with short overall survival, T classification, clinical stage (TNM), depth of invasion, relapse	↑ Cell proliferation, migration, invasion Enhance cell cycle	↑ EMT related genes (SLUG, SNAIL1, VIM, CADN, ZEB1, ZEB2, SMAD2 and TWIST1)	Activates the Wnt/b-catenin signaling pathway	ND		Biomarker and therapeutic target	Z. Y. Wang, Hu, et al. (2018)
30	PRKG1-AS1	340 OSCC tissue	Up	High expression levels of PRKG1-AS1 is associated with worse overall survival, age, gender, and pathologic stage, lymph node metastasis	↑ Cell growth, invasion, and migration	↓ E-cadherin ↑ N-cadherin, Vimentin, Snail	ND	ND	PRKG1-AS1 modulated OSCC cell motility partially through EMT	Not reported	T. Wu, Zhang, et al. (2020)
31	KRT16P3	103 TSCC tissue	Up	High expression levels of KRT16P3 is associated with poor overall survival, T, N stage, treatment type	↑ proliferation, migration, invasion, EMT ↓ apoptosis	↓ E-cadherin, α-catenin ↑ Vimentin, N-cadherin	Activating JAK2/ STAT3 signaling pathway	ND	KRT16P3 can modulate the malignant progression, EMT process, and the JAK2/STAT3 signaling pathway of TSCC in vitro	Prognostic biomarker and therapeutic target	Yang et al. (2021)
32	BANCR	50 OSCC tissue	Up	High expression levels of BANCR is associated with poor prognosis, lymph node metastasis	↑ Proliferation, migration, and invasion ↓ Apoptosis	ND	MAPK signaling pathway	ND	BANCR might promote OSCC proliferation by regulating the MAPK signaling pathway	Prognostic and therapeutic target	Yao et al. (2021)
33	SNHG12	32 OSCC tissue	Up	ND	↑ Proliferation, migration, invasion, and EMT ↓ Apoptosis	↑ E2F1 ↓ E-cadherin ↑ Vimentin, N-cadherin	ND	miR-326	SNHG12/miR-326/ E2F1 feedback loop facilitated OSCC progression Sponging miR-326	Therapeutic biomarker	Yin et al. (2020)
34	LINC00668	50 OSCC tissue	Up	High expression levels of LINC00668 is associated with shorter overall survival	↑ Proliferation	VEGFA	ND	miR-297	ceRNA for miR-297 in OSCC. LINC00668 facilitates cell proliferation partially via sponging miR-297, and then activating VEGFA. oncogenic role of LINC00668 is mediated by miR-297-VEGFA axis in OSCC	Diagnosis and Therapeutic target	Zhang (2017a)

TABLE 3 (Continued)

No.	Long noncoding RNA	Sample	Up regulation/ down regulation	Clinical association	Functional regulation	Target gene	Pathway affected/ investigated	Interactor miRNA	Function	Clinical application	References
35	FTH1P3	70 OSCC tissue	Up	High expression levels of FTH1P3 is associated with poor overall survival	↑ Cell growth	Fizzled 5	ND	miR-224-5p	Molecular sponge of miR-224-5p to modulate fizzled 5 expression oncogenic effects	Therapeutic target	Zhang (2017b)
36	MALAT1	30 tongue cancer tissue	Up	ND	↑ Proliferation, invasion, metastasis	JAG1	ND	miR-124	MALAT1/miR-124/ JAG1 interaction plays a key role in tongue cancer growth	Therapeutic target	Zhang et al. (2017)
37	MIAT	116 TSCC tissue serum	Up	High expression levels of MIAT is associated with poor overall survival, high mortality, cervical lymph node metastasis, and histological grading,	↑ Invasion, EMT	↑ vimentin, β-catenin, N-cadherin, and SNAI1 ↓ E-cadherin	Activation of Wnt/β-catenin signaling pathway.	ND	promoted EMT of TSCC cells through activation of Wnt/β-catenin signaling pathway	Prognostic marker	Zhong et al. (2019)
38	FOXD2-AS1	41 TSCC tissue	Up	High expression levels of FOXD2-AS1 is associated with lymphatic metastasis and poor TNM stages. Poor prognosis	↑ migration, invasion	↑ p-p65 and p-p44	NF-kB and ERK MAPK signaling pathways	ND	FOXD2-AS1 exerted influences on TSCC through modulating NF-kB and ERK MAPK signaling pathways.	Therapeutic and prognostic marker	Zhou et al. (2020)

Abbreviations: ↑, increased; ↓ decreased; ceRNA, competitive endogenous ribonucleic acid; ND, not determined; OSCC, oral squamous cell carcinoma.

6.3.1 | Biogenesis

The majority of the snoRNAs are encoded in introns of coding or noncoding genes and the remaining are anonymously transcribed by RNA polymerase II (Liang et al., 2019; Reichow et al., 2007). The steps include co-transcription, splicing, and debranching. Maturation of nascent intronic snoRNAs requires the recruitment of ribonucleoproteins that provide stability and nucleolar localization (Reichow et al., 2007). Consequently, snRNPs are transported to Cajal bodies where they undergo processing and maturation and are finally delivered to the nucleolus (Liang et al., 2019).

6.3.2 | Role of snoRNAs in OC

The snoRNAs have been reported to be involved in many physiological and as well as pathological processes. To date, a number of studies have demonstrated that snoRNAs are involved during carcinogenesis by regulating cell proliferation, migration and invasion, cell apoptosis. More importantly, several studies have demonstrated that snoRNAs are also involved during OC tumorigenesis (Gao et al., 2019; X. Liu, Zhang, et al., 2020; Liu & Tao, 2020; Qiao et al., 2022; T. Wang, Liang, & Yang, 2021; Yin et al., 2020). Liu and Tao reported that SNHG3 was upregulated in OSCC cell lines and it promoted cell proliferation and migration by up-regulating *NFYC* and Wnt/β-catenin pathway by recruiting ELAVL1 which stabilizes *NFYC* mRNA (Liu & Tao, 2020). Similarly, SNHG20, SNHG3, SNHG15, SNHG17, SNHG12, and SNHG16 were reported to be up regulated in OSCC cell lines and OSCC tumor tissue (Gao et al., 2019; X. Liu, Zhang, et al., 2020; Lu et al., 2021; Qiao et al., 2022; T. Wang, Liang, & Yang, 2021; Yin et al., 2020). It was reported that these snoRNAs are capable of regulating cell proliferation, migration and invasion, cell apoptosis. These studies have concluded that snoRNAs and their related pathways can be used as a therapeutic targets. However, compared with the other ncRNAs, the understanding of the role of snoRNAs in OC is still in its infancy. Therefore, extensive research is required to translate the role of snoRNAs into clinical practice. As an example, SNHG3, SNHG17, and SNHG20 were reported to be involved in the regulation of Wnt/β-catenin pathway, thus selective down regulation of particular snoRNAs might be useful in the treatment of OC (Gao et al., 2019; Lu et al., 2021; Qiao et al., 2022) (Table 4**)**. Also, expressions of NFYC, DIXDC1, HOXB8, DAAM1, E2F1, c-Myc, and ELF1 were positively regulated by SNHG3, SNGH20, SNHG3, SNHG15, SNHG17, SNHG20, SNHG12, SNHG16, and SNHG17, respectively. It is also worth noting here that SNGH17, SNHG20 were correlating with the TNM stage and lymph node metastasis showing poor overall survival in OC patients (X. Liu, Zhang, et al., 2020). Therefore, they can be used as an independent prognostic marker for the prediction of overall survival of OC patients.

EMT is one of the key steps involved during carcinogenesis, especially, invasion and metastasis. SNHG3, SNHG12 are reported to be overexpressed during EMT, thus playing a key role in invasion and metastasis in OC (Chen et al., 2018). Moreover, some snoRNAs functioning as competitive endogenous RNA by blocking the action of microRNAs leading to the regulation of the relevant gene expressions.

It is evident that aberrant expressions of different snoRNAs have been reported in cancers including OC. Some of these expression patterns are tumor specific. Furthermore, the expressions are stable in tissue and as well as plasma, urine of cancer patients. Therefore, the expression patterns can be used for the diagnosis and prognosis of OC. Furthermore, utilizing the regulatory functions of snoRNAs, they can be used as a therapeutic target. However, compared with the other ncRNAs the understanding of the role of snoRNAs in OC is in the infancy stage. Therefore, extensive research is required to translate the role of snoRNAs into clinical practice in the context of OC.

6.4 | PIWI-interacting RNAs

PIWI interacting RNAs (piRNAs) are a novel class of small noncoding RNAs with 24–31 nucleotides in length that usually bind to the Piwi protein (a subclade of the Argonaute family). piRNAs are unique as they differ from miRNAs as they contain 2′-*O*-methyl-modification site at 3′ end (Ohara et al., 2007). PiRNAs use the PIWI-clade Argonautes, unlike miRNA that uses AGO-clade proteins. Furthermore, piRNAs are synthesized from single stranded precursor transcripts from piRNA clusters which does not follow a dicer dependent mechanism (S. Chen, Ben, et al., 2021; Iwasaki et al., 2015; Ozata et al., 2018). Historically, they were identified as key players in the maintenance of germline stem cells and self-renewal (Aravin et al., 2007). However, growing number of literature suggests that piRNAs are involved in epigenetic regulation, transposon silencing and genomic rearrangements (Ozata et al., 2018). Although these piRNAs

TABLE 4 Aberrant expression of small nucleolar RNAs that are associated with OC development

No.	miRNA	Population/*sample*	Up/down	Clinical association	Functional regulation	Target gene	Function	Clinical application	References
1	SNHG3	OSCC cell lines	Up	Not determined	↑ Cell proliferation, migration	↑ NFYC	SNHG3 Recruits ELAVL1 (RBP) to stabilize NFYC mRNA, SNHG3-promoted OSCC cell proliferation and migration by upregulating NFYC and Wnt/β-catenin pathway	Therapeutic target for OSCC	Liu and Tao (2020)
2	SNHG20	20 OSCC tissue, adjacent normal tissue, OSCC cell lines	Up	High expression levels associated with low survival rate	↑ Migration and Invasion	↑ DIXDC1	SNHG20 promoted OSCC progression via the miR-29a/DIXDC1/Wnt signaling pathway SNHG is a oncogene	Therapeutic target	Gao et al. (2019)
3	SNHG3	30 OSCC, adjacent normal control tissue	Up	Not determined	↑ Cell proliferation, migration, EMT	↑ HOXB8	SNHG3 acted as a ceRNA to elevate HOXB8 expression via binding to miR-2682-5p. SNHG3/miR-2682-5p/HOXB8 axis promotes cell proliferation and migration in OSCC	Therapeutic target	Lu et al. (2021)
4	SNHG15	OSCC cell lines	Up	Not determined	↑ Proliferation, migration, invasion ↓ Apoptosis	DAAM1	SNHG15 could exert oncogenic function in OSCC cells by targeting miR-188-5p/DAAM1 axis	Therapeutic biomarker	T. Wang, Liang, and Yang (2021)
5	SNHG17	56 TSCC tissue, adjacent tumor	Up	High expression levels associated with shorter overall survival, tumor size, TNM stage, lymph node metastasis	↑ Proliferation, migration, and invasion	SP1	SNHG17 serves as a sponge of miR-876 in TSCC thereby weakening the inhibitory action of miR-876 on SP1	Therapeutic target	X. Liu, Zhang, et al. (2020)

(Continues)

TABLE 4 (Continued)

No.	miRNA	Population/*sample*	Up/down	Clinical association	Functional regulation	Target gene	Function	Clinical application	References
							expression and driving aggressive TSCC progression		
6	SNHG12	32 OSCC tissue, NAT	Up		↑ Cell proliferation, migration, invasion, and EMT	E2F1	SNHG12 aggravated the progression of OSCC	Therapeutic	Yin et al. (2020)
7	SNHG16	29 OSCC, NAT OSCC cell lines	Up	Not determined	↑ Cell proliferation, cell migration and invasion, apoptosis	c-Myc	Upregulation of c-Myc increased the expression of SNHG16 in a dose-dependent manner	Therapeutic target	S. Li, Zhang, and Chen (2019)
8	SNHG17	OSCC cell lines	Up	Not determined	↑ Cell proliferation, ↓ cell apoptosis	ELF1	SNHG17 regulated ELF1 to affect CTNNB1 transcription in OSCC. SNHG17 aggravated OSCC cell growth by regulating miR-384-targeted ELF1	Therapeutic target	Qiao et al. (2022)

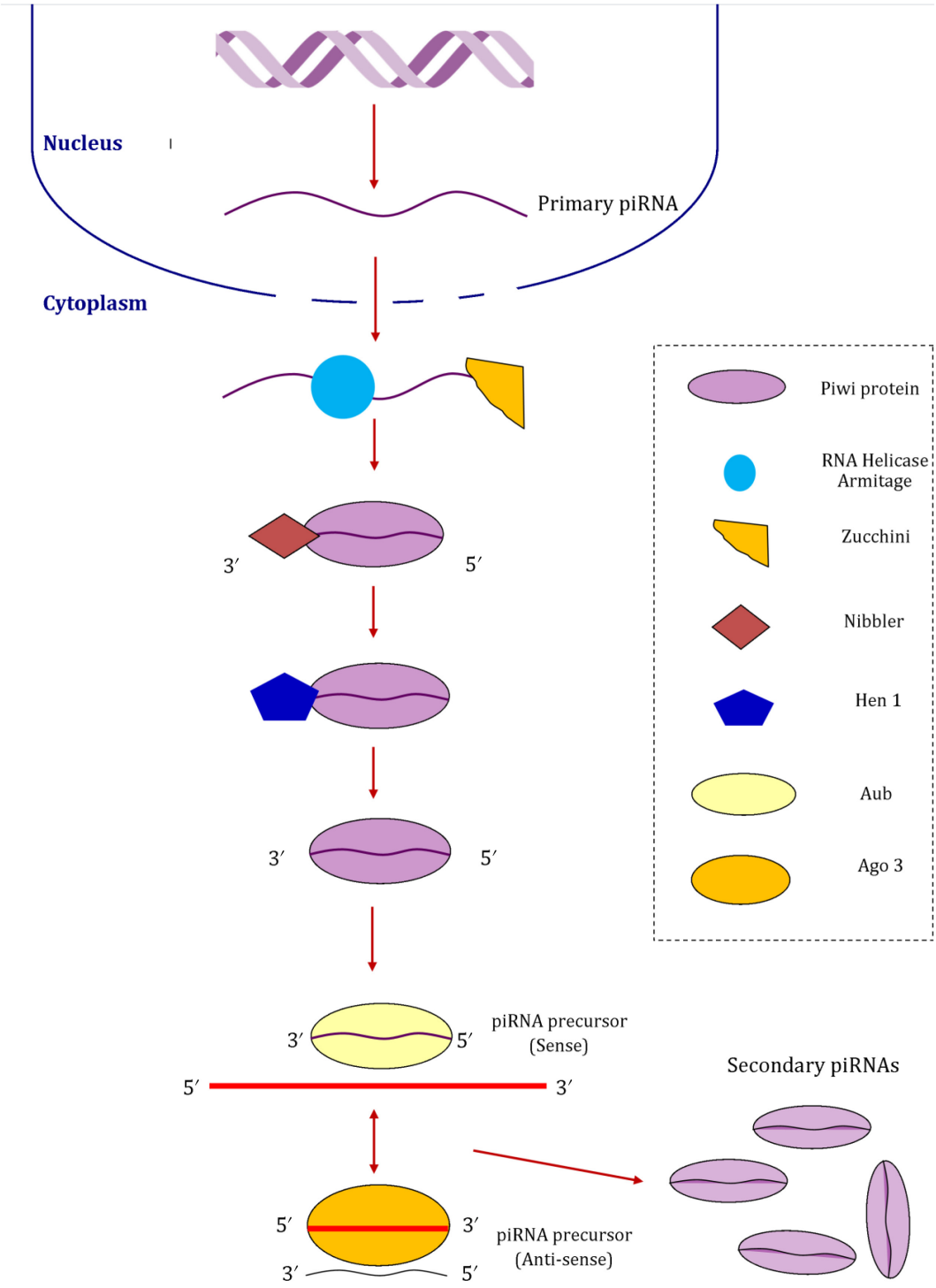

FIGURE 4 Overview of the biogenesis of piRNA. Primary piRNAs are produced from piRNA clusters in the nucleus and transported to the cytoplasm. RNA Helicase Armitage resolves the secondary structures of primary piRNA followed by despiralization, conversion to pre-piRNAs by the endonuclease Zucchini, loading onto piwi proteins and trimming by the 3′–5′ exonuclease Nibbler. The newly formed 3′ termini are methylated by small RNA 2′-*O*-methyltransferase Hen1. This process is called primary piRNA biogenesis. Alternatively, piRNAs can be produced by secondary biogenesis (ping–pong cycle). The Aub protein binds to the antisense piRNA strand and cleaves sense piRNA, leading to sense piRNAs loaded onto Ago3. The Ago3/piRNA complex then cleaves antisense piRNA precursors. This produces antisense piRNAs loaded onto Aub. This cleavage and trimming cycle is repeated many times to produce piRNAs.

do not participate in protein synthesis, they have a regulatory function and are identified to be tissue-specific in health and disease (Martinez et al., 2015). The expression levels of piRNAs and Piwi proteins have been reported in many studies. Furthermore, the latest literature reports that piRNAs and Piwi proteins are detected at various stages of tumor

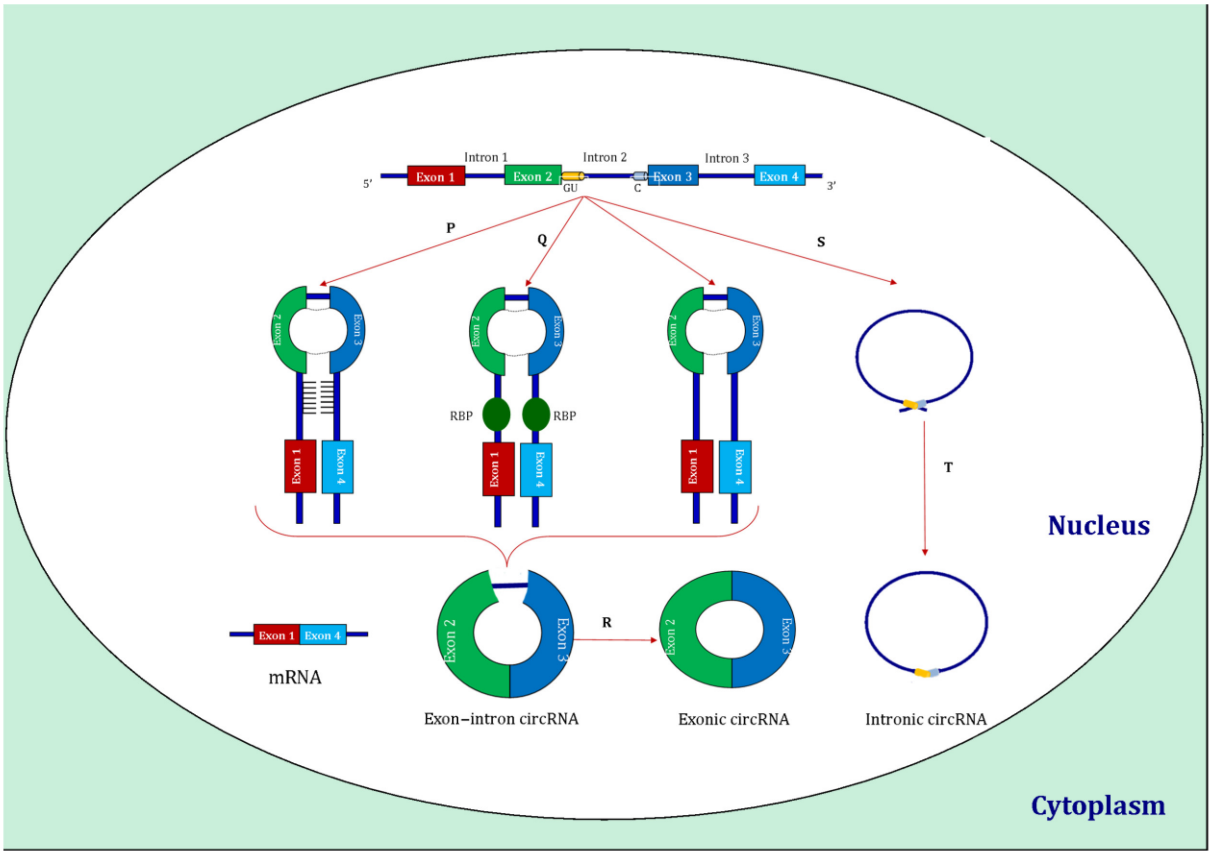

FIGURE 5 Overview of biogenesis of circular RNA. The biogenesis of circRNAs occur in nucleus. Different classes of circRNAs can be produced from pre-mRNA splicing catalyzed by debranching enzymes such as by spliceosome machinery or group I and II ribozyme. Exon–intron circRNA is produced as a result of pre-mRNA splicing resulting in merging of exons with an intron placed in between on the other side. Subsequent removal of intron results in the formation of exonic circRNA. Circularization can be promoted by RNA binding proteins. Intronic circRNAs are produced from lariat portions of introns that are resistant to spliceosomic enzymes. The GU rich and C rich portions are merged together and subsequent trimming of the tail results in the formation of intronic circRNAs. C, cytosine-rich region; GU, guanine, uracil rich region; P, circularization driven by intron pairing; Q, RBP-mediated circularization; R, intron removal; RBP, RNA binding protein; S, circularization driven by lariat structures; T, tail trimming.

development. As such this provides a great opportunity to utilize levels in cancers. This raises the opportunities of using them as biomarkers for early detection and as therapeutic targets.

6.4.1 | Biogenesis of piRNAs

The biogenesis of piRNAs in humans is not well understood and most of the present understanding is derived from *Drosophila* germline cells (Figure 4). The primary pathway that produces primary piRNAs and the ping–pong cycle that produces secondary piRNAs are the two major pathways for the biogenesis of piRNAs (Iwasaki et al., 2015; Ozata et al., 2018). A similar pathway with the involvement of different Piwi proteins has been observed in mice. Furthermore, preliminary evidence suggests that these mechanisms are conserved between *Drosophila* and humans (Xi Wu, Pan, et al., 2020). The majority of the piRNA precursors are derived from genetic regions of either uni-strand or dual-strand piRNA clusters. Transcription from these clusters result in the formation of relevant piRNA precursors. Some precursors can be produced from 3′ UTR of protein-coding genes or transposons as well. Dicer ribonuclease processes the precursor piRNA giving rise to primary piRNA. Consequently, primary piRNAs are cleaved into small RNAs which form complexes with PIWI proteins. The piRNA/PIWI protein complex migrates into the nucleus and targets its specific gene for regulation. In contrast,

TABLE 5 Circular RNAs whose expression is associated with OC development

No.	Circular RNA	Sample	Up/down	Clinical association	Functional regulation	Interacting miRNA	Gene	Function	References
1	circPVT1	50 OSCC tissue	Up	ROC = 0.787 Sensitivity 68.6% Specificity 86.0% High expression levels associated with tumor size, tumor node, and metastasis	↑ Proliferation	miR-125b	STAT3	Prognostic circPVT1 serves as a ceRNA via sponging miR-125b in OSCC. circPVT1 may promote cell growth by sponging mir-125b and therefore increasing STAT3 expression	He et al. (2019)
2	hsa_circ_0086414	55 OSCC tissue	Down	Low expression levels associated with TNM, size of tumor, lymph node metastasis. ROC = 0.749 Sensitivity = 65.5% Specificity = 87.3%	↑ Growth and metastasis	ND	ND	Diagnosis	Li and Zhang (2020)
3	hsa_circ_0055538	44 OSCC Tissue	Down	Low expression levels associated with tumor differentiation	↑ Proliferation, migration, invasion ↓ Apoptosis	ND	↓ p53, Bax, Apaf1, caspase-3, cleaved caspase-3, and p21 ↑ Bcl-2	Diagnostic and prognostic hsa_circ_0055538 regulates tumor growth via the p53/Bcl-2/caspase signaling pathway	Su, Sun, et al. (2019)
4	CircDOCK1	Cell lines	Up	ND	↓ Apoptosis	miR-196a-5p	BIRC3	Diagnostic, therapeutic target	L. Wang, Wei, et al. (2018)
5	circRNA-081069	14 OSCC tissue samples	Up	ND	↑ Migration, proliferation Apoptosis no change	miR-665	ND	Diagnostic, therapeutic target	Wei et al. (2020)

Abbreviations: ↑, increased; ↓ decreased; ND, not determined; OSCC, oral squamous cell carcinoma.

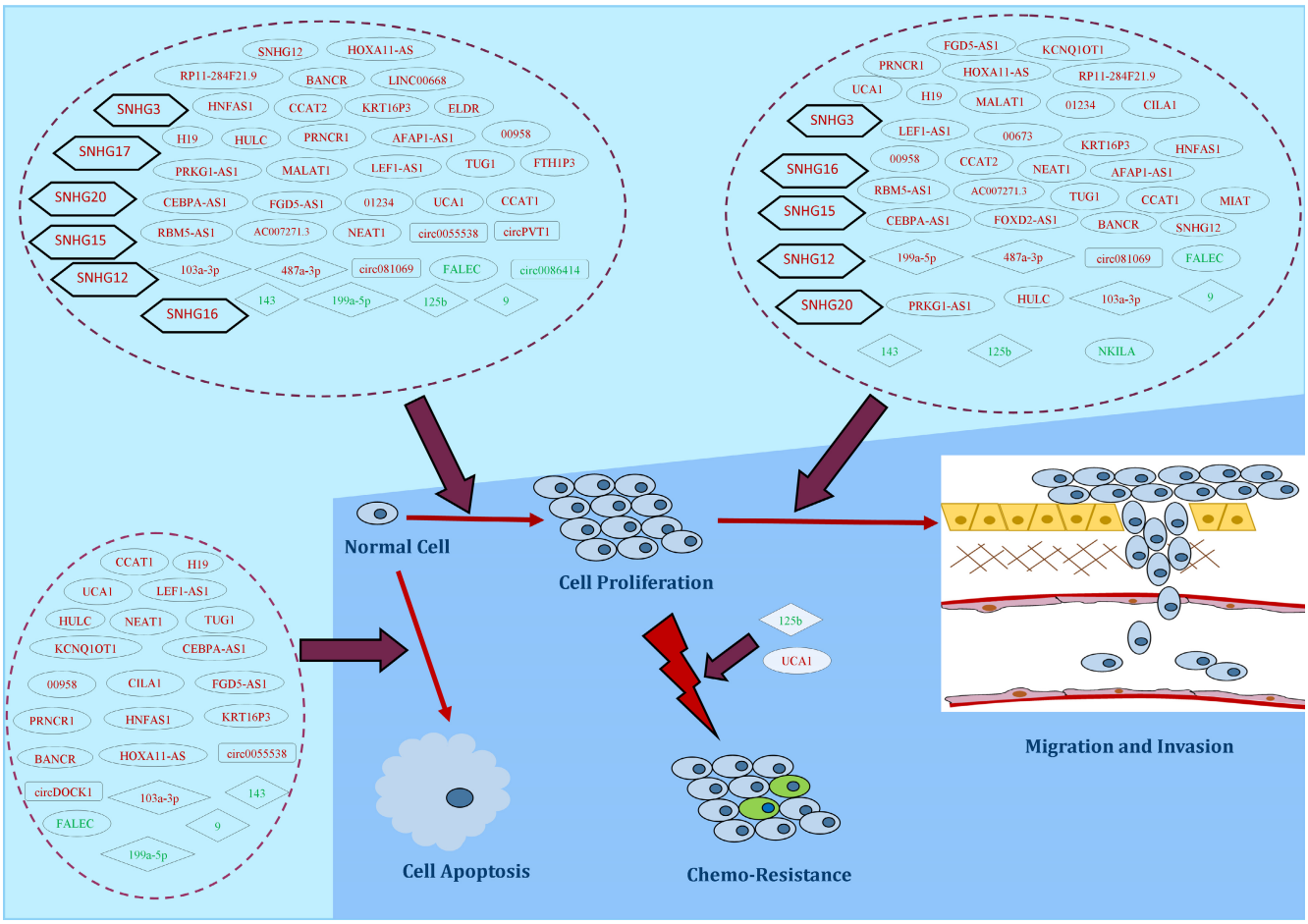

FIGURE 6 Summary of the role of ncRNAs in oral carcinogenesis. Noncoding RNAs can regulate cell proliferation, migration and invasion, cell apoptosis, and chemoresistance. The figure shows the different ncRNAs involving at different levels regulating OC. Red colored: Over-expressed ncRNAs, Green colored: Under-expressed ncRNAs. ⬡, snoRNAs; ⬭, lncRNAs; ▭, circular RNAs; ◇, microRNAs.

the ping pong mechanism amplifies the production of piRNAs which produces a large number of piRNAs within a short time. It is achieved by the binding of Aub protein to antisense-strand piRNA and subsequent cleavage of sense piRNA precursors leading to the production of sense piRNAs bound by Ago 3 protein. Ago 3 protein binds to sense-strand and subsequent cleavage of antisense-piRNAs. The cleavage step is repeated for many cycles and a large number of piRNAs are produced. These piRNAs bind with PIWI proteins and enter the nucleus. The production of secondary piRNA is through ping pong mechanism and accumulated in the cytoplasm. piRNAs form complexes with Ago proteins to produce new primary piRNAs (S. Chen, Ben, et al., 2021; Iwasaki et al., 2015).

In addition, piRNAs function as transposons that can produce unfavorable effects on the stability of genes, due to exon insertion and or intron insertion in which the former alters the coding sequence and the latter may alter the splicing patterns. This may lead to potentially deleterious fusion proteins. Furthermore, piRNAs and PIWI proteins modify the chromatin structure and histone proteins in the nucleus. At post-transcriptional level, piRNAs are capable of degrading mRNA through deadenylation (X. Wu, Pan, et al., 2020).

6.4.2 | Role of piRNAs in OC

Data from several studies suggest that piRNAs are potential regulators of gene expression in physiological and pathological processes at both transcriptional and post-transcriptional stages. Importantly, researchers have attempted to evaluate the role of piRNAs in OC. piRNA-1037 was reported to be significantly upregulated in OC cell lines in a dose-

TABLE 6 ncRNAs detected in liquid biopsies

No.	miRNA	Study cohort	Sample	Gene target/ protein	Over- or under expressed	Results	Clinical application/s	References
1	miR-139-5p	25 OSCC patients and 25 Healthy controls	Saliva	ND	↓	Discrimination of pre-operative TSCC from healthy controls: AUC = 0.805 Discrimination of pre-operative TSCC from post-operative TSCC: AUC = 0.713	Early diagnostic marker	Duz et al. (2015)
2	miR-146-5p	18 OSCC	Whole blood Saliva	*TRAF6*	↑	Blood: AUC = 0.8 Saliva = 0.9	Diagnostic marker	Min et al. (2017)
3	miR-9,	47 HPV negative HNSCC	Saliva	ND	miR-9 ↑	AUC = 0.82	Diagnostic marker	Wan et al. (2017)
	miR-127	113 healthy			miR-127 ↓	Sensitivity = 60%		
	miR-134				miR-134 ↓	Specificity = 94%		
	miR-191				miR-191 ↓			
	miR-222				miR-222 ↑			
	miR-455				miR-455 ↑			
4	miR-21	30 OLP	Saliva	ND	miR-21—↑ OLP, Dysplastic OLP	Increased miR-21 with decreased miR-125a in OLP	Diagnosis and prognosis	Mehdipour et al. (2018)
	miR-125a	15 OSCC			OSCC	Poor prognosis		
	miR-31	15 healthy controls			miR-125a—↓ OLP, dysplastic OLP	Normal levels of miR-31 and miR-200a—Absence		
	miR-200a				OSCC	of malignant transformation		
					miR-31—↑ dysplastic OLP, OSCC; not in OLP			
					miR-200—↓ OSCC			
5	miR-24-3p	30 OSCC	Oral swirl	ND	ND	High risk dysregulation score	Diagnosis	Yap et al. (2018)
	miR-21-5p	30 healthy control				Sensitivity 86.5%		
	let-7c-5p					Specificity 81.5%		

(Continues)

TABLE 6 (Continued)

	miR-99a-5p miR-100-5p					AUC = 0.8676		
6	miR-24-3p	45 OSCC 15 healthy controls	Salivary exosome	*PER1*	↑	AUC 0.738 Sensitivity = 64.4% Specificity = 80%	Diagnostic marker	He et al. (2020)
7	miR-31	19 OSCC 2 Healthy	Saliva	ND	↑	Overexpression: pre-operative > post-operative (6 weeks)	Monitor surgery outcomes during postoperative follow-up	Kumari et al. (2021)
8	miR-196b	30 Oral pre cancer 52 Healthy	Saliva	ND	Overexpressed	AUC = 0.979 Sensitivity 90% Specificity 98.1%	Diagnostic biomarker for OPC	Cheng et al. (2021)
9	miR-106b-5p miR-423-5p miR-193b-3p	89 OC 58 Healthy	Saliva	ND	miR-106b-5p—↓ miR-423-5p—↑ miR-193b-3p—↑	AUC = 0.98	Diagnostic biomarker	Romani et al. (2021)
10	miR-423-5p	15 Pre-operative and 15 post-operative OC	Saliva	ND	Pre-operative—↑ Post-operative—↓	ND	Prognostic biomarker	Romani et al. (2021)
11	miR-9-5p	7 OCC 15 Healthy	Saliva	Galetin-3	↓	ND	Predictive biomarker	Wan et al. (2021)
12	LOC284454	167 OC 121 Healthy	Serum	ND	↑	Sensitivity 65% Specificity 95.87% AUC = 0.698	Diagnostic biomarker	Fan et al. (2020)

Abbreviations: ↑, increased; ↓ decreased; ND, not determined; OC, oral cancer; OSCC, oral squamous cell carcinoma.

TABLE 7 Clinical trials using ncRNAs in OC

No.	Primary contributor; country; year	Study design	Aim	Population	Sample	Primary outcome measures	Time frame	Results
1	Shin-Jung; Cheng; Taiwan; 2014	Observational	To evaluate the prognostic role of microRNA-29b in OC	OC patients	Tissue—At the time of surgery Blood before and after 3 months of surgery Saliva—Before surgery and after for once 3 consecutive days of surgery	miR-29b	3 years	Not yet reported
2	Catherine Poh; Canada; 2011	Observational	To assess the clinical utility of a miRNA expression signature derived from serum collected from patients with OC and OPLs	OC and OPL (pathology-proven oral pre-cancers)	FFPE Blood Saliva Tissue Exfoliated cells	Cancer progression	10 years	Not yet reported
3	Ghareeb; Egypt; 2019	Observational	To evaluate the use of miRNA-412 and 512 to detect the malignant transformation in potentially malignant lesions	Healthy Oral pre-malignant lesions OC	Tissue Saliva	Measuring sensitivity and specificity of using the salivary miRNA-412 and 512	2 years	Not yet reported

dependent manner when treating with cisplatin. The chemoresistant cells showed an upregulation of piRNA-1037 and when inhibiting its expression using cisplatin showed a reduction in the cell viability and enhanced apoptosis. Interestingly, epithelial markers, such as E-cadherin, were upregulated and mesenchymal markers, such as N-cadherin, were downregulated, suggesting the reversal of EMT. One of the mechanisms whereby piRNA-1037 induces chemoresistance is by interacting with the apoptosis-inhibiting protein XIAP and regulating the motility of cancer cells by controlling EMT pathways (G. Li, Wang, et al., 2019).

Another study has investigated the effects of alcohol consumption on the expression of piRNAs in HNC. Expressions of piRNAs were analyzed by RNA sequencing data obtained from TCGA. OC cell lines were treated with 0.1% (social drinker), 0.3% (moderate drinker), and 1% ethanol (heavy) daily for 4 weeks. The differentially expressed piRNAs were validated using cell culture and qRT-PCR. It was found that in people who consume alcohol (both smoking and nonsmoking), piR-58510, -43219, -38034, -34946 were upregulated and piR-70732 was identified to be downregulated in people who consume alcohol (both smoking and nonsmoking). Upregulation of piR-258904, -35373, -266308, and -34946 was found in the alcohol-drinking, nonsmoking cohort, demonstrating the only cause of upregulation is alcohol consumption. Ethanol causes upregulation of piR-35373, -266308, -58510, and -38034, which was in concordance with the results obtained in the analysis of the RNA-seq data. In addition, the expression level of PIWIL4 was dysregulated in cells exposed to both ethanol and acetaldehyde treatments. Low expression of piR-58510 and piR-35373 significantly correlated with improved patient survival. Therefore, alcohol consumption causes dysregulation of piRNA expression in HNC samples and in vitro data report that these piRNAs may serve as therapeutic targets or biomarkers for early detection of HNC (Saad et al., 2019).

Overall, piRNAs have shown promising roles in cancers including OC. However, when compared with other ncRNAs the understanding of the role of piRNAs in OC is in its' infancy. Therefore, in upcoming years we could expect more studies focusing on the role of piRNAs in OC and OPMD as well.

6.5 | Circular RNAs

Circular RNAs (circRNAs) are another unique type of ncRNAs that form continuous covalent loops. The 3′ and 5′ ends of these RNAs are joined together forming circular molecules (Greene et al., 2017). They are produced by noncanonical back splicing. The existence of circRNAs in eukaryotes was revealed in 1979 with the aid of an electron microscope (Hsu & Coca-Prados, 1979). Historically, circRNAs were considered "junk RNA" produced during aberrant splicing events. However, with recent advancements in RNA sequencing and bioinformatics, the expression patterns of circRNAs are reported to be tissue-specific and they are well-known for their ability to regulate gene expression, synchronize alternative splicing, sponging miRNAs, RBPs, and scaffolds, It is also evident from literature that circRNA could be translated into proteins and are capable of producing pseudogenes (Greene et al., 2017). More importantly, it also has significant function in regulating parental gene expression, circRNAs can be categorized into exonic, exon–intron, or intronic circRNAs in which exonic circRNA is the most abundant type (Chen & Yang, 2015; Geng et al., 2020).

6.5.1 | Biogenesis of circRNA

Biogenesis of circRNAs is a complex, multistep process. circRNAs are generated from back splicing of exons or introns to form exonic or intronic circRNAs (Figure 5). Exonic circRNAs are located in the cytoplasm, whereas the remaining are located in the nucleus. There are three models that are widely accepted for circRNA biogenesis namely, direct back-splicing, circularization mediated by RNA-binding proteins, and circularization driven by lariat structures (Chen & Yang, 2015; Kristensen et al., 2019; Vicens & Westhof, 2014). Direct back splicing involves in the merging of a downstream splice donor with an upstream splice acceptor. The splice sites are brought together by complementary base pairing of introns containing repeated elements (Alu elements) that are found in the upstream and downstream introns or by dimerization of RBPs that binds to special motifs in the flanking introns. RBPs regulate the biogenesis of circRNAs by regulating the adjacent splicing sites (Ebbesen et al., 2017; Vicens & Westhof, 2014).

Lariat driven circularization is facilitated when skipping of exons occurs during pre-mRNA transcription. Removal of flanking exon is facilitated by internal splicing leading to the production of ecircRNAs. The generation of ciRNA is also facilitated by this process, in the presence of a ciRNA-specific consensus motif containing a 7 nucleotide Guanine

Uracil rich element at the 5′ splice site and a 11 nucleotide Cytosine rich element at the branch point (Chen & Yang, 2015; Ebbesen et al., 2017; Kristensen et al., 2019; Preiss et al., 2012; Vicens & Westhof, 2014).

6.5.2 | Role of circular RNAs in OC

Studies have shown that circRNAs can be used as diagnostic, prognostic and as therapeutic targets in OC, as the circRNAs are expressed in a tissue-specific manner (L. Wang, Wei, et al., 2018). Preiss et al., reported that the expression of a circular RNA isoform derived from the ncRNA ANRIL correlated with INK4/ARF expression, as well as with atherosclerosis risk, suggesting a role of this circRNA in the development of these disease conditions (Preiss et al., 2012). Recently, researchers have investigated the effects of circRNAs in cancer, including in OC. Expression patterns of circRNAs have been reported in discriminating OC from healthy controls and some of them possess good clinical association in OC patients. Furthermore, the same group has demonstrated that the reported circRNAs regulated cell proliferation, migration and invasion, cell apoptosis in OC. He et al., have reported that circPVT1 was upregulated in OSCC tissue samples ($n = 50$) and overexpression resulted in increased cell proliferation. Furthermore, circPVT1 was reported to discriminate OSCC from healthy controls with an AUC of 0.787 with a sensitivity and specificity of 68.6% and 86.0%, respectively (He et al., 2019). The expression level of circPVT1 was associated with tumor size, tumor node and metastasis. In addition, circPVT1 was shown to regulate the expression of *STAT3* gene through functioning as a competitive endogenous RNA via sponging miR-125b, thereby increasing the expression of *STAT3*. Similarly, hsa_circ_0086414 was also found to be downregulated in OSCC tissue samples ($n = 55$) with an AUC of 0.749 and sensitivity and specificity of 65.5% and 87.3%, respectively. Downregulation of hsa_circ_0086414 resulted in increase in growth and metastasis. These results suggest the possibility of using circRNAs as biomarkers for the diagnosis, prognosis and as a therapeutic target. Similar studies that associate circRNAs with OC development are summarized in Table 5. However, in depth understanding of the role of circRNAs in OC is warranted to utilize them as biomarkers for the management of OC.

It is now evident that ncRNAs are involved in the development of OC. Figure 6 shows the summary of all ncRNAs and their role in hallmarks of OC.

7 | NONCODING RNAs IN BODY FLUIDS

"Liquid biopsy" is a term that is frequently used in the clinical oncology field. It refers to capturing tumor-derived biomarkers that are present in body fluids such as blood, saliva, cerebrospinal fluid, and urine. Detection of genetic, epigenetic, transcriptomic, and proteomic biomarkers in liquid biopsies provide opportunity to discern tumor activity in real-time (Punyadeera et al., 2011; Punyadeera & Slowey, 2019; Sun et al., 2017). ncRNAs are widely detected in liquid biopsies, such as blood, saliva, and urine. Studies have shown strong correlation between biomarkers present in tumor tissue that of liquid biopsies (Lim et al., 2016; Ovchinnikov et al., 2014; Wan et al., 2017). In tumor tissues, the expression of ncRNAs were shown to correlate with expression levels in plasma and saliva. Moreover, studies have reported that liquid biopsy-based biomarkers may be used for the early detection of cancer. There is a growing body of literature demonstrating that detection of miRNAs in liquid biopsies is advantageous in early cancer detection, monitoring tumor dynamics, predicting malignant transformation, prognosis, and chemoresistance in cancer patients (Komatsu et al., 2018). Table 6 shows a summary of ncRNAs that have been investigated in liquid biopsies.

8 | THE USE OF NONCODING RNAs IN CANCER CLINICAL TRIALS

Clinicians have registered clinical trials evaluating the use of ncRNAs, especially miRNAs as therapeutic targets for OC. According to the global clinical trial registry (www.clinicaltrials.gov), three clinical trials have been registered to evaluate the clinical utility of miRNAs as biomarkers in diagnosis and prognosis of OC (Table 7). However, results of all these trials have not yet been reported. This is a huge drawback for the development of liquid biopsy biomarkers using ncRNAs. Furthermore, trials including multi-center, multi-institutional trials from various geographic regions could assist in establishing a microRNA signature panel to be used for early detection and prognosis of OC (Table 7).

9 | CONCLUSION AND FUTURE PERSPECTIVES

ncRNAs play a major role in tumorigenesis. Moreover, they can be extracted from body fluids, tissues, and cells. As such, given both their central importance in cancer development and their ready accessibility, they are ideally placed to act as biomarkers in diagnostic, prognostic, and therapeutic applications for patients with cancer. Depending on their size and function, ncRNAs can be divided into several categories including miRNA, lncRNA, snoRNA, piRNA, and circular RNA. Arguably, the most investigated ncRNAs in both biomedical research and therapeutics are miRNAs and lncRNAs. Although, other ncRNA such as snoRNAs, and more recently circRNAs have also found to be involved during the pathogenesis of OC.

Studies have shown that specific expression changes of ncRNA are associated with poor outcomes for patients with cancer. However, these findings are yet to be translated into clinical practice for OC patients. This may be due to a paucity of biological and technical validation studies, an absence of multicenter clinical trials, insufficient standardization of workflow to isolate and amplify ncRNA and a lack of normalization targets. As OC is closely associated with both lifestyle risk factors and genetic predisposition, studies need to consider population-level variations, and therefore, large-scale studies involving patient cohorts from different geographic regions need to be conducted to validate these targets. In addition, limitations to human in vitro model systems (tumoroids and organoids) hamper in-depth characterization of cancer causing ncRNAs. To address these limitations, researchers are now developing panels of ncRNAs combining different types of ncRNAs to increase clinical utility. This is further enabled by the interrelated actions of some ncRNAs. Multiple studies across the world have reported miR-21-5p, miR-24-3p, lncRNA-UCA1, and lncRNA-CCAT1 as biomarkers in OC. Additionally, expression changes of miR-146-5p, miR-196b, and lncRNA-LOC284454 were reported to be detectable in body fluids collected from patients with OC. This shows promise in revolutionizing the management of OC patients by using liquid biopsies.

Many ncRNAs have proven to be reliable, noninvasive biomarkers for OC. Furthermore, many of them have also been shown to possess functional qualities at the molecular level. As such, targeting these ncRNAs could expand the currently limited treatment choices for OC. The small size of ncRNAs make them ideal drug targets, with treatments such as antisense oligonucleotides and small interfering RNAs, easily packed into nanoparticles for more effective targeted delivery. Indeed, in 2019, the first ever small ncRNA drug patisiran (Onpattro, Alnylam Pharmaceuticals) was approved by the Food and Drug Administration (FDA) for the treatment of peripheral nerve disease (polyneuropathy) with many more drugs set to follow. In conclusion, there is promise that ncRNA based biomarkers will become a reality for managing patients with OC, thereby reducing the high rates of morbidity and mortality associated with this disease.

AUTHOR CONTRIBUTIONS

Jaikrishna Balakittnen: Conceptualization (equal); data curation (lead); writing – original draft (lead); writing – review and editing (equal). **Chameera Ekanayake Weeramange:** Conceptualization (equal); supervision (equal); writing – review and editing (equal). **Daniel Wallace:** Conceptualization (equal); supervision (equal); writing – review and editing (equal). **Pascal Duijf:** Conceptualization (equal); supervision (equal); writing – review and editing (equal). **Alexandre Cristino:** Supervision (equal); writing – review and editing (equal). **Liz Kenny:** Conceptualization (supporting); supervision (equal). **Sarju Vasani:** Supervision (equal); writing – review and editing (equal). **Chamindie Punyadeera:** Conceptualization (lead); methodology (equal); project administration (equal); supervision (lead); writing – review and editing (equal).

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CONFLICT OF INTEREST

The authors have declared no conflicts of interest for this article.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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