

Function and Therapeutic Potential of Non-Coding RNA in Ameloblastoma

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Abstract: Ameloblastoma (AB) is a common odontogenic tumor that develops in the mouth. Despite its benign nature, AB exhibits significant invasiveness leading to tumor metastasis and high postoperative recurrence rates. Studies have shown a relationship between the occurrence and development of various tumors and non-coding RNA (ncRNA). ncRNA, transcribed from the genomes of mammals and other complex organisms, are often products of alternative splicing and processing into smaller products. MicroRNA (miRNA), circular RNA (circRNA), and long non-coding RNA (lncRNA) are the main types of ncRNA. ncRNA play increasingly significant roles in the pathogenesis of human cancers, regulating their occurrence and progression as oncogenes or tumor suppressors. They are involved in tumor development and progression through alternative splicing of pre-mRNA, transcriptional regulation, mRNA stability, protein translation, and chromatin remodeling and modification. The importance of ncRNA in AB has received significant attention in recent years. However, the biological functions and mechanisms of ncRNA in AB remain largely unknown. In this review, we not only explore the functions and roles of ncRNA in AB, but also describe and envision their potential functional roles as biomarkers in AB diagnosis. In particular, we highlight the potential of miR-29a as a molecular marker for diagnosis and therapy. As promising novel therapeutic targets, the biological functions of ncRNA need further study, which is indispensable.

Keywords: ameloblastoma, miRNA, biomarker, therapy

Introduction

As a locally aggressive benign odontogenic epithelial tumor, ameloblastoma (AB) usually occurs in the jaw. Despite being classified as benign, the invasive growth pattern of AB can lead to severe destruction of the jaw, tooth loss, and metastasis to local lymph nodes or distant organs, such as the brain, lungs, and skin.^{1,2} AB has an alarming recurrence rate of up to 70%, and malignant transformation is possible.³ Although serious complications include large jaw defects and impaired oral and facial aesthetic issues, the edge of the jaws or segmental resection remains the main treatment for AB.⁴ Despite the discovery and investigation of various risk factors that may be trigger AB progression, such as chronic inflammation, viral infection (human tumor virus), malnutrition, individual genetic polymorphisms, and poor dental health (Figure 1), no substantial progress has been made in finding non-invasive therapies to eliminate or prevent AB.^{5,6} Pivotal molecular events in AB pathogenesis include BRAF p.V600E mutations and the activation of the mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) signaling pathways. BRAF p.V600E is a somatic missense mutation that alters the kinase domain of exon 15 (c.1799), specifically converting thymidine to adenosine (T > A), leading to the substitution of valine (V) in codon 600 with glutamate (E). Despite clinical and histopathological variations, BRAF p.V600E mutations occur in AB with a frequency ranging from 46% to 80%. Its malignant counterpart, ameloblastic carcinoma (AC), exhibits this mutation in 48% of cases. However, especially in BRAF wild-type cases, these factors alone are insufficient to explain the tumor's complex biological behavior.⁷⁻⁹

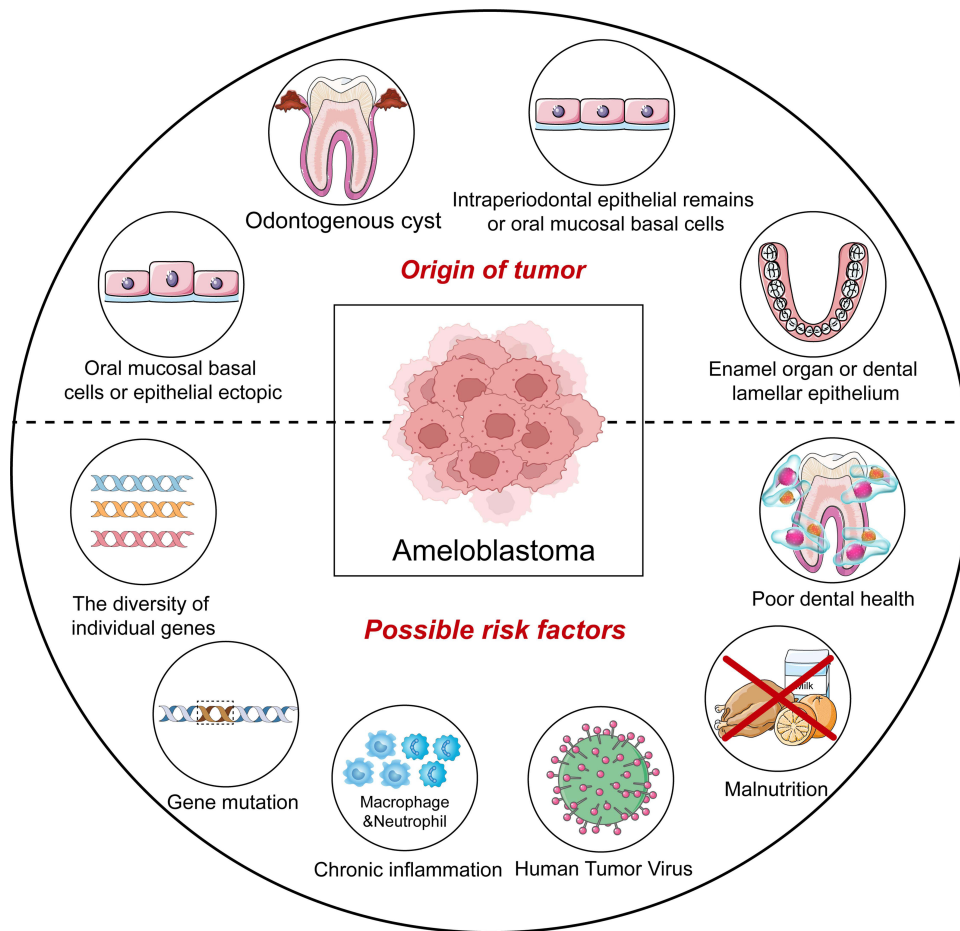


Figure 1 Sources of AB and possible risk factors.

Both mutational variability and tumor suppressor genes such as p53 are closely related to ncRNA, making it essential to study their role in the pathogenesis of AB.^{10,11}

So far, the exploration of markers and genetic variants has been the focus of molecular research in AB for accurate diagnosis and better prognosis prediction. Therefore, further research on the molecular level is now the scientific focus in order to explore the pathogenesis of AB.¹² Moreover, the role of ncRNA in AB has also attracted extensive attention.

The majority (98%) of the transcribed genome is composed of ncRNA, which are endogenous RNAs. Previously referred to as “dark matter” due to their lack of protein-coding ability, ncRNA are now recognized as important signaling molecules that regulate key cellular pathways.¹³ They are numerous, diverse, and stable in structure, mainly including miRNA, circRNA, and lncRNA. Differences in lncRNA expression between AB and normal tissues were first reported in 2017 by Davanian et al, who also proposed that lncRNA expression may affect AB tumor size. This provides new ideas and possibilities for the diagnosis and treatment of AB.¹⁴ Some findings have shown that changes in the tumor microenvironment of AB are related to the expression of miRNA.¹² Subsequently, scholars have proposed that miR-29a-3p may promote the invasion and metastasis of AB by targeting CTNNBIP1, thereby activating the catenin Wnt/ β -catenin pathway.¹⁵ In contrast to protein biomarkers, which require biopsy staining and antibody capture, ncRNA have characteristics that are conducive to the development of more sensitive PCR screening in puncture biopsies and liquid biopsies. This enables accurate and rapid diagnosis, as well as the ability to monitor tumor growth and control pathology to improve the quality of life of patients affected by such tumors. Therefore, the role of ncRNA as diagnostic and prognostic biomarkers cannot be overlooked due to their involvement in and influence on the pathogenesis of AB.

We conducted a search on AB and ncRNA in the PubMed database using keywords such as “ameloblastoma”, “AB”, “ncRNA”, and “miRNA”. The Boolean operators “AND” and “OR” were included to combine different search words.

Our selection criteria focused on validated results from fresh tissue, sampled tissue, or human fluids. Our search found that while some previous works had partially explored the role of ncRNA in AB, the scope of research was too broad and mechanisms were unclear. Therefore, in this study, we focused on typical ncRNA frequently reported in search results and elaborated on their mechanisms of action in AB.

However, the clear etiology of AB, the mutation of coding genes, and the signaling molecular pathways involved in these changes have not been clearly established, requiring further exploration by researchers. Therefore, this article reviews the role of ncRNA in AB, summarizes the mechanisms and functions of ncRNA and discusses the future development direction of ncRNA in diagnostic and therapeutic research.

Overview of ncRNA

Over the past few decades, a whole class of molecules called ncRNA has been characterized as the key regulatory factor for almost all cell processes.

Biogenesis of ncRNA

NcRNA are similar to mRNA in biological occurrence, depending on their features. Understanding the biogenesis of ncRNA is important, not only for distinguishing it from the other RNAs, but also for evaluating its functional correlations, which has profound significance.¹⁶ Nucleosomal maturation, transcription, production of functional RNA, and exportation towards the cytoplasm for processing are all essential parts of the biogenesis process. RNA polymerase II/III transcribes polycistrons to produce large progenitors (pri-miRNA) with a hairpin loop structure, 5' capping, and 3' polyadenylation (Figure 2).¹⁷ Pri-miRNA pass through two processing steps: the microprocessor complex, DGCR8, by Drosha fracture identification and control pre-miRNAs. This leads to the formation of pre-miRNAs, which are then transported from the nucleus to the cytoplasm by the RAN-GTP and Exportin-5 (XPO5) proteins. Furthermore, in the cytoplasm, the RNase III endonuclease Dicer processes the progenitor molecule, enabling it to interact with the Argonaute protein (AGO-2) within the miRNA-induced silencing complex (RISC).^{18,19} In contrast, the biogenesis of lncRNA is controlled by cell type and stage-specific stimuli.²⁰ A variety of DNA components in eukaryotic genomes, including promoters, enhancers, and intergenic regions, control the transcription of different kinds of lncRNA.²¹ The main biological processes involved include cleavage by RNase P to produce mature ends, formation of small nucleolar RNA (snoRNA) and small nucleolar ribonucleoprotein (snoRNP) complexes, and the addition of an end cap and circular structure.²² In the process of synthesizing specific lncRNA, unique subnuclear structures called “paracolecules” have

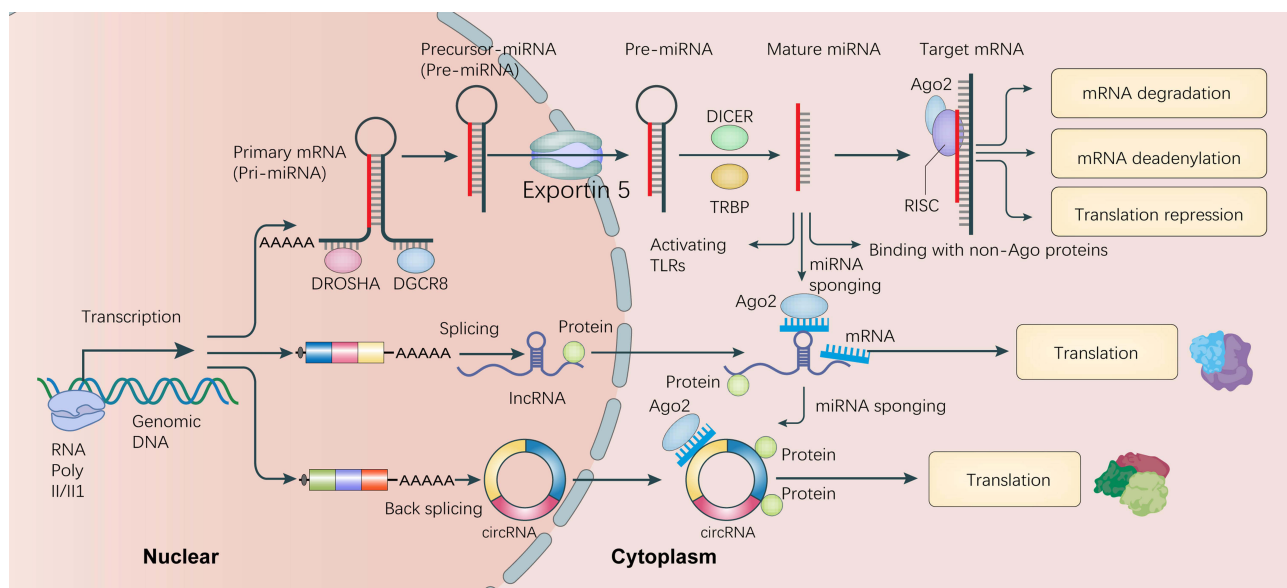


Figure 2 Overview biogenesis and function of ncRNA in AB cells. MicroRNA (miRNA), long non-coding RNA (lncRNA), and circular RNA (circRNA) are presented along with their fundamental biogenesis and main functional mechanisms. The details are described in the text.

recently been discovered.²³ In general, the biosynthesis pathways and unique regulation of ncRNA are not yet fully understood. However, in the coming years, the use of various techniques, such as RNA structure mapping, chromatin separation by RNA purification (ChiRP-Seq), cross-linked immunoprecipitation (CLIP), CRISPR-Cas9 for targeted genome engineering, advanced ribosome analysis, phylogenetic lineage tracing, and genetic testing will likely enhance our understanding of the origins and applications of ncRNA.²⁴

The role of ncRNA in disease

Accumulating evidence supports the critical role played by ncRNA in regulating glucose homeostasis and lipid metabolism. The importance of ncRNA in the development of cardiovascular diseases and metabolic diseases such as diabetes, non-alcoholic fatty liver disease, abdominal aneurysms, atherosclerosis, and obesity has been repeatedly highlighted.²⁵ Sarkar et al found that miR-34a expression activates synaptic connections, unveiling the formation mechanism of polygenic Alzheimer's disease (AD).²⁶ Gui et al found that cerebrospinal fluid (CSF) secretions are rich in ncRNA, with significant differences between normal and neurodegenerative diseases, suggesting that CSF ncRNA can be used as early biomarkers.²⁷ This is particularly significant for neurodegenerative diseases like Parkinson's disease and AD. A recent study found that in an epileptic rat model, after miRNA sequencing validation, the levels of miR-346 and miR-331-3p were significantly reduced. The identification of signaling pathways and targets through enrichment analysis provides a new research direction for identifying the potential mechanisms of epilepsy.²⁸ Studies have shown that some ncRNAs promote fatty acid oxidation by targeting heterogeneous ribonucleoproteins through high expression in skeletal muscle, thus playing a role in metabolic diseases such as insulin sensitivity, diabetes, and obesity.²⁹ In psoriasis, ncRNA regulate keratinocyte proliferation, differentiation, inflammation, and immune cell function.³⁰ Autoimmune skin diseases, including lichen vulgaris, pemphigus, bullous pemphigoid, and psoriasis, are closely associated with ncRNAs, which play an important role in activating T cells, stimulating keratinocyte proliferation, triggering inflammatory cascades, inhibiting cell apoptosis, modulating innate immune responses, and regulating the differentiation and function of Th17 cells.³¹ In addition, the analysis of 21 different ncRNA involved in the malignant transformation of oral leukoplakia suggests that four of them play a potential role through epithelial–mesenchymal transition (EMT), invasion, and migration, thereby serving as potential markers for malignant transformation of oral leukoplakia.³²

Functional Role of ncRNA in Ameloblastoma

This review discusses the role of ncRNA in AB, validated by in vitro or in vivo studies (Table 1).

Table 1 NcRNA in Ameloblastoma

NcRNA	Targets	Expression	Function	(Refs)
miR-29a-3p	CTNNB1P1	+	MiR-29a-3p promotes the invasion and migration of AB cells by targeting CTNNB1P1 and Wnt/ β -catenin signaling pathway.	[15]
miR-608	EGFR/P53	+	MiR-608 may further regulate the cell cycle process, differentiation, proliferation and apoptosis of AB cells through MAPK signaling pathway.	[33]
miR-141-3p	NCAM1	-	NCAM1 was found to be highly expressed in AB regulated by miR-141-3p, which inhibited the migration of AB cells, suggesting that it may be valuable as a therapeutic target for AB.	[34]
miR-524-5p	IL-33/ST2	-	MiR-524-5p, which is down-regulated in AB, participates in the tumor microenvironment of AB by targeting the IL-33/ST2 axis.	[12]
miR-489		+	MiR-489 suggests a distinction between solid and unicystic AB.	[35]
KIAA0125		+	LncRNA KIAA0125 may participate in the pathological biology of AB.	[35]
HOXC-AS5	HOXC13	-	LncRNA HOXC-AS5 can prolong the cell division cycle and reduce the proliferation and invasion of AB cells by inhibiting the target gene HOXC13.	[36]
ENST00000512916	HOXC13	+	Promotes cell cycle progression, proliferation and migration of AB cells.	[37]
Circ-0089153	EGFR and p53	+	Regulates cell cycle processes, differentiation, proliferation, and apoptosis of AB cells.	[33]

Note: CTNNB1P1: catenin beta interacting protein I EGFR: epidermal growth factor receptor NCAM1: neural cell adhesion molecule I. IL-33: interleukin 33 HOXC13: Homeobox C13 MAPK: mitogen-activated protein kinase AB: ameloblastoma +: represents high expression in ameloblastoma -: represents high expression in ameloblastoma.

MiR-29a

The miR-29 family is one of the more common miRNA families, consisting of miR-29a, miR-29c, and miR-29b (including b-1 and b-2). These miRNAs are generated from two main transcripts: the pri-miR-29a/b1 cluster on human chromosome 7q32.3 and the pri-miR-29b2/c cluster on human chromosome 1q32.2.³⁸ Several studies indicate that miR-29a may serve as a vital biomarker for predicting cancer recurrence and progression, and is closely related to the aggressiveness and prognosis of malignant tumors.³⁹ For example, it has been reported that c-Myc down-regulates miR-29a, leading to overexpression of TRAF4, which could be a mechanism promoting prostate cancer progression and bone metastasis. TRAF4 activates NF- κ B through glucocorticoid-induced TNF-R (GITR). Considering the inhibitory effect of NF- κ B on miR-29a transcription, there may be a positive feedback loop involving NF- κ B, miR-29a, and TRAF4, leading to the progression of prostate cancer.⁴⁰ In addition, some scholars believe that miR-29a/miR-29b may promote the anti-apoptotic effect of myeloid leukemia cells by binding to the 5'-UTR of Bcl-2 and Mcl-1 genes, indicating potential future applications for regulating miR-29a/29b expression in the treatment of myeloid leukemia.⁴¹ Some research results showed that miR-29a affected the cell response to BPDE-induced DNA damage by targeting Cdc7, suggesting that downregulation of miR-29a in lung cancer cells may contribute to BPDE-induced mutagenesis and lesion accumulation.⁴² In the oral cavity, miR-29a is down-regulated in oral squamous cell carcinoma (OSCC) and promotes cancer invasion and anti-apoptosis by up-regulating matrix metalloproteinase 2 (MMP2).⁴³ Furthermore, a near-term study investigated the expression of miR-29a during the proliferation and apoptosis of oral cancer cells. SNHG20 can up-regulate the expression of DIX domain containing 1 (DIXDC1) through sponge miR-29a, thus promoting tumor progression in OSCC.⁴⁴ One study showed that miR-29a-3p directly targeted catenin beta interacting protein 1 (CTNBP1). In the nucleus, CTNBP1 inhibits the activity of the beta-catenin/TCF complex, suggesting that CTNBP1 may act as a tumor suppressor by inhibiting Wnt/ β -catenin signaling, thereby blocking oncogenic phenotypes.⁴⁵ These results suggest that miR-29a-3p may promote the invasion and metastasis of AB by silencing and binding to the Wnt/ β -catenin regulator CTNBP1, thereby activating the Wnt/ β -catenin pathway.¹⁵ Therefore, miR-29a-3p may serve as a potential biomarker or therapeutic target for AB.

MiR-141

As an important member of the miR-200 family, miR-141 is located on chromosome 12 in humans and chromosome 6 in mice.⁴⁶ MiR-141 is aberrantly expressed in many malignancies, and affects various tumor biological behaviors including EMT, proliferation, invasion, metastasis, migration, and drug resistance.⁴⁷ Numerous studies have reported that miR-141-3p can be a silent downstream target to regulate cancer cell migration and invasion. For example, low miR-141-3p expression, through activation of NF- κ B, induces bone metastasis of prostate cancer.⁴⁸ MiR-141-3p also inhibits colorectal cancer cell invasion by targeting TNF receptor-associated factor 5 (TRAF5).⁴⁹ Furthermore, studies show that miR-141 can be inhibited by cirx-0032822 to reduce the inhibition of its target E2F transcription factor 3 (E2F3) and promote cell proliferation in head and neck squamous cell carcinoma.⁵⁰ In OSCC, miR-141 inhibits tumor progression by targeting PBX homeobox 1 (PBX1) through the JAK2/STAT3 pathway.⁵¹ A study speculated that miR-141-3p influences AB cell metastasis and invasion by targeting neural cell adhesion molecule 1 (NCAM1), confirmed through dual-luciferase reporter gene testing. As a member of the immunoglobulin superfamily of adhesion molecules, NCAM1 plays an important role in regulating neurogenesis, neurite growth, proliferation, and cell migration.⁵² In addition, the expression of NCAM1 in AM-1 cells was significantly inhibited by the overexpression of miR-141-3p. These findings indicate that miR-141 is involved in the development and progression of AB by suppressing NCAM1, making NCAM1 a promising therapeutic target for the treatment of AB.³⁴

MiR-524

MiR-524 is located on human chromosome 19q13.42 and is reported to act as a tumor suppressor gene in multiple types of cancers. For instance, one study found that miR-524-5p reduces breast cancer cell migration, invasion, and EMT by down-regulating FSTL1 expression.⁵³ Another study showed that by targeting lysine-free kinase 1 (WNK1), miR-524-5p could suppress angiogenesis in colon cancer cells.⁵⁴ In gastric cancer (GC), miR-524-5p is down-regulated, and its overexpression inhibits the development of GC, providing new prospects and ideas for the diagnosis and treatment of

GC.⁵⁵ In OSCC, miR-524 expression is significantly decreased compared to adjacent tissue and is closely related to tumor size, lymph node metastasis, and clinical stage. MiR-524 expression also inhibits MTDH, suppressing activation of the NF- κ B signaling pathway, thus inhibiting oral squamous cell migration, proliferation, and invasion.⁵⁶ In the tumor microenvironment, inflammatory mediators affect the tumor immune response. A recent study showed that down-regulation of miR-524-5p can influence the tumor microenvironment of AB by targeting the IL-33/ST2 axis. It was also found that miR-524-5p is down-regulated in AB tissues compared to normal tissues, providing neoteric insights into the mechanisms of AB.¹² Therefore, understanding the role of miR-524 is crucial in studying the pathogenesis of AB.

KIAA0125

KIAA0125 (also known as FAM30A) is a lncRNA located on chromosome 14 within the heavy chain region of immunoglobulins.⁵⁷ Studies have found that KIAA0125 is aberrantly expressed in different cancers and diseases, functioning as a tumor suppressor. For example, it regulates the growth and metastasis of colorectal cancer through the Wnt/ β -catenin pathway.⁵⁸ Multiple lncRNA may interact with particular miRNA clusters in a collaborative manner. In breast cancer, lncRNA KIAA0125 and MEG3 antagonize miR-150 and miR-379, respectively, to regulate the miRNA-mediated sponging interactions of almost all mRNA expressions in the cancer network.⁵⁹ In cervical cancer, network analysis indicated that KIAA0125 interacts with C-C motif chemokine ligand 21 (CCL21).⁶⁰ KIAA0125 is highly expressed in AB, potentially due to increased copy number of the KIAA0125 gene located on chromosome 14q32.33. This increased copy number has been detected in AB samples, including AM2 and AM4 sample.⁶¹ In a recent study, lncRNA KIAA0125 was predicted to interact with miRNAs (miR-150-5p, miR-205-5p, miR-204-5p, and miR-135a5p) that were previously reported to be dysregulated in AB.³⁵ However, whether KIAA0125 exerts a regulatory role on these miRNAs and the role of miRNAs in AB cells remain to be elucidated.⁶² In this context, given the strong potential of lncRNA as therapeutic targets, conducting functional experiments on KIAA0125 could advance the use of personalized treatments for recurrent lesions.

HOXC-AS5

Recent studies have found that lncRNA HOXC-AS5 is involved in transcriptional regulation, epigenetic regulation, and post-transcriptional regulation, thereby influencing processes such as stem cell maintenance, differentiation, cell proliferation, apoptosis, cell cycle regulation, metabolism, and immune modulation. Through relevant studies, Jaafari discovered how lncRNA HOXC-AS5 intervenes in tumor cell behavior, suggesting high potential for successful lncRNA HOXC-AS5 therapy research.⁶³ Timothée found that Homeobox C13 (HOXC13), which is abnormally expressed in a variety of cancers including odontogenic tumors like AB, plays a vital role in the regulation of tumor migration and proliferation.⁶⁴ Reducing the high expression level of HOXC13 can significantly prolong the cell cycle and suppress AB cell division.⁶⁵ In addition, a recent study showed that HOXC-AS5 overexpression reduces the invasion and migration ability of AB cells, suggesting that HOXC-AS5 can suppress the target gene HOXC13.³⁶ Therefore, HOXC-AS5 is a vital factor in advancing the current understanding of AB pathogenesis.

Circ_0089153

circ_0089153 is an exon which located on chromosome 9. Guan found that circRNA circ_0089153 competes with miR-198 to modulate sentrin/SUMO-specific peptidase 1 (SENP1), impacting colorectal cancer development.⁶⁶ Gao indicated that circ_0089153 enhanced the metastasis and proliferation of breast cancer cells through sponge miR-2467-3p/E2F6.⁶⁷ Coincidentally, a recent study characterized for the first time a novel circRNA in AB, circ_0089153. Screening and validation of six circRNA using high-throughput genomic technology revealed a further circRNA-miRNA-mRNA axis, namely circ_0089153/miR-608/EGFR and p53. They concluded that circ_0089153/miR-608 combined with a sponge structure down-regulates EGFR and p53, potentially influencing MAPK signaling pathways to regulate processes such as the cell cycle, cell differentiation, proliferation, and apoptosis.³³ These results indicate the great significance of understanding circ_0089153 in the early pathogenesis of AB and further optimizing treatment strategies.

Other ncRNA in AB may play important roles that should not be overlooked. In one study, Davanian et al found a positive correlation between lncRNA LINC340 expression and tumor lesion size.¹⁴ In addition, miR-489 has been

implicated in distinguishing between solid and unicystic AB.³⁵ According to another study, ENST00000512916 plays a promoting role in the cell migration, proliferation, and cell cycle progression of AM-1 cells, as well as increasing tumor growth in vivo. Interestingly, ENST00000512916 was found to mediate expression of HOXC13 in AM-1 cells, highlighting its potential as a therapeutic target against AB.³⁷

Among the above ncRNA, miR-29a-3p is most closely associated with AB. MiR-29a-3p can promote the invasion and migration of AB cells by targeting CTNNBIP1 and activating the Wnt/ β -catenin signaling pathway, increasing the expression of miR-29a-3p in AB. This is of great significance for both the diagnosis and treatment of AB. Moving forward, the high expression of miR-29a-3p can be utilized for auxiliary diagnosis and provide a clear therapeutic target for targeted therapy, providing a direction for subsequent treatment strategies.

Future Expectations

Computed tomography (CT) imaging and biopsy are routine methods for the diagnosis of AB. However, tissue biopsy is an invasive assessment and requires considerable time to obtain test results. If not managed properly, the suffering of AB patients may be exacerbated. The high recurrence rate and significant tissue defects present unresolved challenges for doctors in the treatment of AB. Hence, there is an urgent need for a non-invasive and accurate detection tool to assist clinical diagnosis.

Cancer metastasis is the leading cause of cancer-related deaths. Current cancer treatments face challenges due to the lack of specificity and low bioavailability of drugs, affecting therapeutic efficacy. Despite its benign classification, AB is aggressive in nature, making tumor metastasis common, such as to local lymph nodes or distant organs including the brain, lung, and skin. Tumor-derived exosomes are involved in tumor progression and metastasis by communicating with the tumor microenvironment and are critical in establishing the pre-metastatic niche (PMN).⁶⁸ A recent study showed that the release of exosomes can be induced by cisplatin, while miR-29a-3p inhibits lung tumor metastasis through tumor exosomes or liposome-based nanovesicles, thereby reducing type I collagen expression in lung fibroblasts and inhibiting metastasis by disrupting the establishment of a viable PMN.⁶⁹ Although upregulated miR-29a-3p can promote AB invasion and metastasis by targeting genes through signaling pathways, this finding provides us with a new therapeutic concept. Another recent study revealed that miR-141, an ovarian cancer-derived exosomal miRNA, mediates tumor-stroma interactions and promotes the formation of the tumor stroma microenvironment by activating the YAP1/GRO α /CXCRs signaling cascade. This provides a new approach for the treatment of ovarian cancer patients with peritoneal metastasis.⁷⁰ MiRNA can be used within tumor exosomes to further mediate tumor-stroma interactions by activating certain signaling cascades and promoting the formation of a matrix niche that supports tumor growth. They can also be delivered via exosomes or liposome-based nanovesicles delivery to inhibit tumor metastasis, providing new research directions and insights for the treatment of AB.

The identification of precise RNA transcripts or clusters of differentially expressed transcripts has led to insights into tumor biology and improvements in the molecular diagnosis of cancer. Prognostic and therapeutic cancer markers based on RNA have great value, because the RNA landscape of tumors determines their initiation, form, and proliferation. Technologies such as RNA sequencing and global transcriptome microarrays have provided tremendous support in expanding our view of the tumor RNA landscape. In the genome of living cells, protein-coding transcripts, which account for less than 2% of the entire genome, are the most well-defined, while up to 75% of the genome is actively transcribed into ncRNA. Emerging research suggests that ncRNA are new participants in cancer paradigms, playing a role in tumorigenesis and showing potential as biomarkers. For biomarkers used in diagnosis, prediction of disease prognosis, and treatment, durability and sensitivity are vital characteristics for effective functionality. Biomarkers offer a relatively painless method of assessment compared to invasive methods like biopsies. Recently, the feasibility of miRNA as biomarkers was demonstrated in the diagnosis of certain diseases and as therapeutic targets. Therefore, we hypothesize that they could serve as valuable biomarkers in the diagnosis of AB. However, it is important to recognize that most of the studies have been single-center retrospective studies, with many being cohort studies with poor confidence. As a result, non-overlapping and even contradictory reports are common in the literature.⁷¹ Many tumor-associated ncRNA were found to be associated with the survival outcomes of multiple cancer types, including gastric cancer, breast cancer, and non-small cell lung cancer. Recent studies have shown that some AB cases contain SMO and

BRAF mutations, which may sensitize them to novel small molecule therapies. The incidence of BRAF-V600E mutant AB may be as high as 40%, and BRAF-targeted therapies have shown promising results in patients with malignant BRAF-V600E mutant AB.⁷²

Defining the tumor-associated RNA landscape has a profound role for isolating RNA in tumorigenesis, enabling the identification of diagnostic and therapeutic targets to improve current AB therapy. In the context of AB, a small array studies have demonstrated that the spectrum of protein-encoding transcription contributes to the occurrence and progression of this tumor.⁷³ Traditionally, markers known to participate in cell proliferation, such as minichromosome maintenance complex component 2 (MCM2), MCM3, p16 protein, Ki-67, and CD138 have been used in immunohistochemical analyses to clarify histopathological characteristics of AB and clinical data. Protein biomarkers were not significantly associated with clinical features of AB, except for Ki-67, which showed a positively correlation with growth rate and shorter disease-free survival.^{74,75} Compared to ncRNA, protein biomarkers require biopsy slice staining and antibody capture. The characteristics of ncRNA, such as the applicability of molecular assays and bioavailability in biological fluids, thus favor the development of more sensitive PCR screening in needle biopsy and liquid biopsy. Therefore, the predictive capabilities of ncRNA surpass the currently available protein markers, enabling the monitoring and management of tumor growth to improve the quality of life of patients affected by AB.

Cytokine therapy has recently become a prominent research focus, with preliminary studies proving its efficacy. Molecular targeted therapy for AB can be used as a new auxiliary therapy. Increasing evidence suggests that dysregulated ncRNA may contribute to or be associated with AB carcinogenesis. Therefore, ncRNA holds promise as potential biomarkers for AB. By building the competitive endogenous RNA networks mediated by lncRNA, some researchers found that lncRNA can modulate miRNA expression and influence the pathogenesis of human diseases.⁷⁶ Diniz et al found, through the use of high-density genome-wide microarray analysis, raised levels of KIAA0125 lncRNA in AB. They predicted that this lncRNA interacts with a family of 41 miRNAs, with three miRNAs, including miR-204-5p, miR-205-5p, and miR-135a-5p, being overexpressed and miR-150-5p underexpressed in AB. In the future, KIAA0125-lncRNA may be used as a therapeutic target in the treatment of extensive and recurrent cases of AB.⁶² CircRNA are widespread in eukaryotic transcription groups due to their resistance to ribonuclease degradation. They play important roles in several signaling pathways and regulating downstream molecules, influencing tumor occurrence, development, and other pathological processes. Hence, circRNA hold potential as biomarkers for tumor diagnosis and as therapeutic targets. Although there have been numerous preclinical studies over the years involving miRNA therapy, so far only a few miRNAs have progressed to clinical development. One of the most significant challenges in developing miRNA-based therapies is identifying the optimal miRNA candidates or targets. Other challenges include designing miRNA delivery carriers, enhancing stability of drug candidates for treatment, achieving targeted tissue specificity, and avoiding potential toxicity and off-target effects.⁷⁷ Many unanswered questions remain about the pathogenesis of AB. Gaining deeper insights into the role of the ncRNA-miRNA-cytokine pathway in the pathogenesis of AB will be valuable in guiding future directions for the treatment of AB. Furthermore, these findings may also be useful for advancing single-gene therapy approaches.

Conclusion

AB is a relatively common oral tumor that, despite being clinically classified as benign, exhibits high aggressiveness, with most AB cases experiencing metastases and recurrence after treatment. The current clinically effective treatment is surgery, requiring an extended excision of the patient's jaw, which can lead to severe complications and dysfunction for patients. Many cytokines are involved in the occurrence of AB, and ncRNA may play a significant role in regulating processes such as tumor cell proliferation, differentiation, invasion, migration, and apoptosis. The regulatory pathways of ncRNA-miRNA in AB are not well understood, necessitating further research into their molecular mechanisms. We reviewed several important ncRNA studies and examined their role in various signaling pathways. This review can lay a foundation for future studies, provide potential biomarkers for the diagnosis of AB, and provide possible therapeutic targets for non-invasive therapies for AB, including drug therapy. In addition, further exploration of ncRNA therapy in *in vitro* and animal model studies of AB is crucial in gaining deeper insights into the pathogenesis of AB and therapeutic approaches.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas. All authors have agreed on the journals to which their articles will be submitted and agree to be responsible for all aspects of their work.

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Disclosure

The authors declare no conflicts of interest in this work.

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