


Circular RNAs: Diversity of Functions and a Regulatory Nova in Oral Medicine: A Pilot Review

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Abstract

Oral diseases, such as cancers, inflammation, loss of bone/tooth/soft tissues, are serious threats to human health since some can cause systemic disease and effective treatments are limited. Thus, discovering promising biomarkers for physiological and pathological processes in oral medicine, and identifying novel targets for therapy have become a most critical issue. Recently, circular RNAs (circRNAs), which were once thought to be a class of non-coding RNAs (ncRNAs), are found to be of coding potential. CircRNAs are highly present in the cytoplasm of eukaryotic cells and are key elements in the physiological and biological processes of various pathological conditions, and are also reflected in oral development and progress. Previous studies have indicated that circRNAs are involved in the initiation and development of different types of diseases and tissues (e.g., cancers, cardiovascular diseases, neural development, growth and development, wound healing, liver regeneration). Moreover, growing evidence demonstrates that circRNAs play vital roles in oral cancers and osteogenic differentiation of periodontal ligament stem cells (PDLSCs). Here, we focus on the biological characteristics of circRNAs, beginning with an overview of previous studies on the functional roles of circRNAs as diagnostic biomarkers and therapeutic targets in oral medicine. We hope this will give us a promising new comprehension of the underlying mechanisms occurring during related biological and pathological progress, and contribute to the development of effective diagnostic biomarkers and therapeutic targets for oral diseases.

Keywords

circular RNAs, microRNA sponges, regulatory function, oral medicine

Introduction

Oral diseases, such as cancers, inflammation, loss of bone/tooth/soft tissues, have become a severe public health issue worldwide¹. These conditions not only damage local function, but may also cause other systemic diseases^{2,3}. Therefore, there is an urgent need to explore the relevant molecular mechanisms underlying these oral diseases and to identify valuable diagnostic biomarkers and therapeutic targets.

Non-coding RNAs (ncRNAs) are RNA molecules that are generally not translated into proteins but may participate in many biological processes⁴. Functionally abundant and important types of ncRNAs include linear transfer RNAs (tRNAs), ribosomal RNAs (rRNAs), small ncRNAs such as microRNAs (miRNAs), small interfering RNA (siRNAs), small nuclear RNAs (snRNAs), long ncRNAs (lncRNAs), and circular RNAs (circRNAs)^{4,5}. The differences and similarities of these ncRNAs are listed in Table 1^{6–12}. Among

these different types of ncRNAs, circRNAs are a newly discovered class of functional ncRNAs that exist widely in the cytoplasm of eukaryotic cells^{13,10}. Unlike linear RNAs,

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Table 1. Similarities and Differences of ncRNAs.

Categories of ncRNAs	Similarities	Differences			
		Structure	Function	References	
Small ncRNAs	miRNAs	RNA molecules generally not translated into proteins	Small ncRNA molecule with single-stranded RNA (20-24 bp)	Function in RNA silencing Regulate post-transcriptional gene expression	Bartel et al ⁶
	siRNAs		Short double-stranded RNA with phosphorylated 5' ends and hydroxylated 3' ends (20–25 bp)	Interfere with specific genes Degrade mRNA after transcription Prevent translation	Wittrup et al ⁷
	snRNAs		Transcribed by RNA polymerase II or III within the splicing speckles and Cajal bodies (about 150 bp)	Participate in the processing of pre-messenger RNA Aid in regulation of transcription factors or RNA polymerase II Maintain the telomeres.	Adachi et al ⁸
	tRNAs		An adaptor molecule composed of RNA (76–90 bp)	Physical link between mRNA and amino acid sequence of proteins Necessary component of translation Participate in biological synthesis of new proteins	Suzuki et al ⁹
Long ncRNAs	circRNAs	Covalently closed continuous loop without 5' or 3' ends	Resistant to degradation More stable than most linear RNAs Serve as miRNA or RBP sponges Regulate gene expression Code for proteins Participate in cell signal pathway.	Memczak et al ¹⁰	
	Other lncRNAs				Usually more than 200 nucleotides

ncRNAs: non-coding RNAs; miRNAs: microRNAs; siRNAs: small interfering RNAs; snRNAs: small nuclear RNAs; tRNAs: transfer RNAs; circRNAs: circular RNAs; lncRNAs: long non-coding RNAs.

circRNAs are presumably more stable as they exist in covalently closed continuous RNA loops without 5' or 3' ends, and, therefore, are resistant to exonuclease-mediated degradation¹⁴.

Recent studies of circRNAs have revealed their functions under physiological conditions and in different types of disease^{15,16}. CircRNAs have been demonstrated to play important roles in brain development, neurological disorders, stress handling, and cellular proliferation^{10,16–18}. In addition, circRNAs are shown to be abnormally expressed in multiform types of cancers, including colorectal cancer¹⁹, hepatocellular carcinoma²⁰, pancreatic ductal adenocarcinoma²¹, gastric cancer²², lung cancer²³, osteosarcoma²⁴, bladder cancer²⁵, and breast cancer²⁶. circAmot11, a circRNA derived from angiomin-1-like 1 (circAmot11), which has tumorigenic

capacity²⁷, is reported to be highly expressed in patient tumor samples and cancer cell lines, and can promote tumor formation by induction of c-myc into the nucleus²⁷. In light of these reports, we believe that circRNAs may serve as promising biomarkers, and even provide clues to the discovery of new therapeutic targets to treat cancers and other diseases.

In oral medicine, several studies have suggested that circRNAs play pivotal roles in the progress of oral cancer²⁸ and the osteogenic differentiation of periodontal ligament stem cells (PDLSCs)²⁹. These reports provide us with hints that circRNAs could be important regulatory nova in oral medicine. In this pilot review, we focus primarily on the basic biological characteristics of circRNAs, summarize the roles of circRNAs in oral medicine, and provide insights into the mechanisms underlying the related biological and pathological progresses.

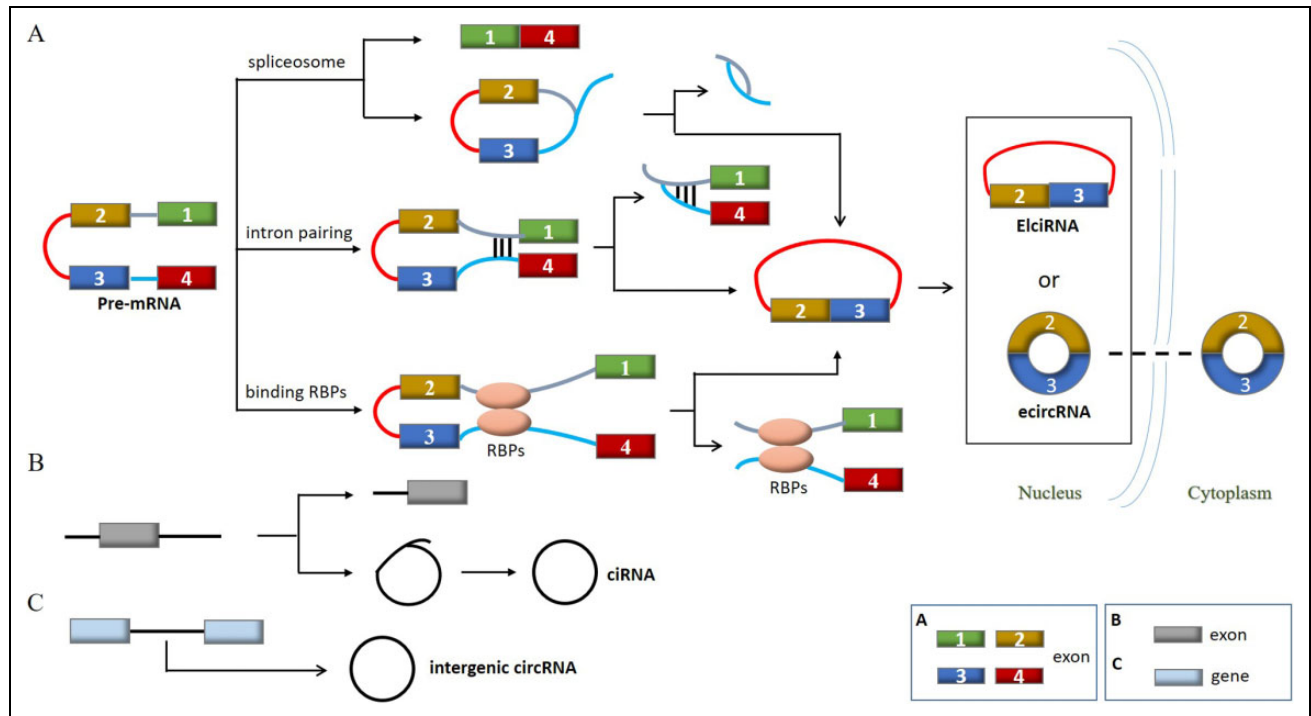


Fig 1. Biosynthesis of circRNAs. (A) The biogenesis of ecircRNAs and ElciRNAs. (B) The biogenesis of ciRNAs. (C) The biogenesis of intergenic circRNAs. circRNAs: circular RNAs; ecircRNAs: exonic circRNAs; ElciRNAs: exon-intron circRNAs; ciRNAs: circular intronic RNAs; RBPs: RNA-binding proteins.

Biogenesis and Categories of CircRNAs

Much effort has been focused on understanding the mechanisms of circRNA formation. Thousands of circRNAs are transcribed from diverse genomic locations in a tissue-, cell-type-, or developmental-stage-specific manner¹⁰. CircRNAs formed from coding and non-coding exons, introns, intergenic regions, and transcripts antisense to 5' and 3' UTRs have been reported¹⁰. Notably, unlike linear RNAs, many circRNAs are formed by head-to-tail splicing of exons, suggesting a previously unrecognized regulatory potential of coding sequences^{10,30}.

According to the different biogenesis patterns from genomic regions, circRNAs can be divided into four subtypes: exonic circRNAs (ecircRNAs), circular intronic RNAs (ciRNAs), exon-intron circRNAs (ElciRNAs), and intergenic circRNAs¹⁵. Each subtype is produced from a different circularizing mechanism (Fig 1, Table 2).

EcircRNAs. It has been reported that ecircRNAs are generated predominantly from back-splice exons, where downstream 3' splice donors are covalently linked to upstream 5' splice acceptors in a reverse order³¹. EcircRNAs account for the majority of identified circRNAs. Their biogenesis process requires RNA-binding proteins (RBPs) to act as trans-factors to promote ecircRNAs formation³². Given that ecircRNAs are alternative splicing isoforms, it is suggested

Table 2. Differences of Four Categories of circRNAs.

	Difference	
circRNAs	Origin	Function
ecircRNAs	Exons	miRNA or RBP sponges Regulate parental gene transcription
ciRNAs	Introns	Positive regulators of RNA Pol II transcription Regulate transcription of parental genes
ElciRNAs	Exons and introns	Enhance transcription of the parental genes
intergenic circRNAs	Intronic circRNA fragments	Contain two intronic fragments

circRNAs: circular RNAs; ecircRNAs: exonic circRNAs; ciRNAs: circular intronic RNAs; ElciRNAs: exon-intron circRNAs.

that they could function as miRNA or RBP sponges, and regulate transcription of their parental genes³³.

CiRNAs. CiRNAs are generated from lariat introns that fail in debranching. GU-rich sequences near the 5' splice site and C-rich sequences near the branch point are sufficient for an intron to escape debranching and become a stable circRNA³⁴. CiRNAs are located predominantly in the nucleus and are widely expressed in human cells with little

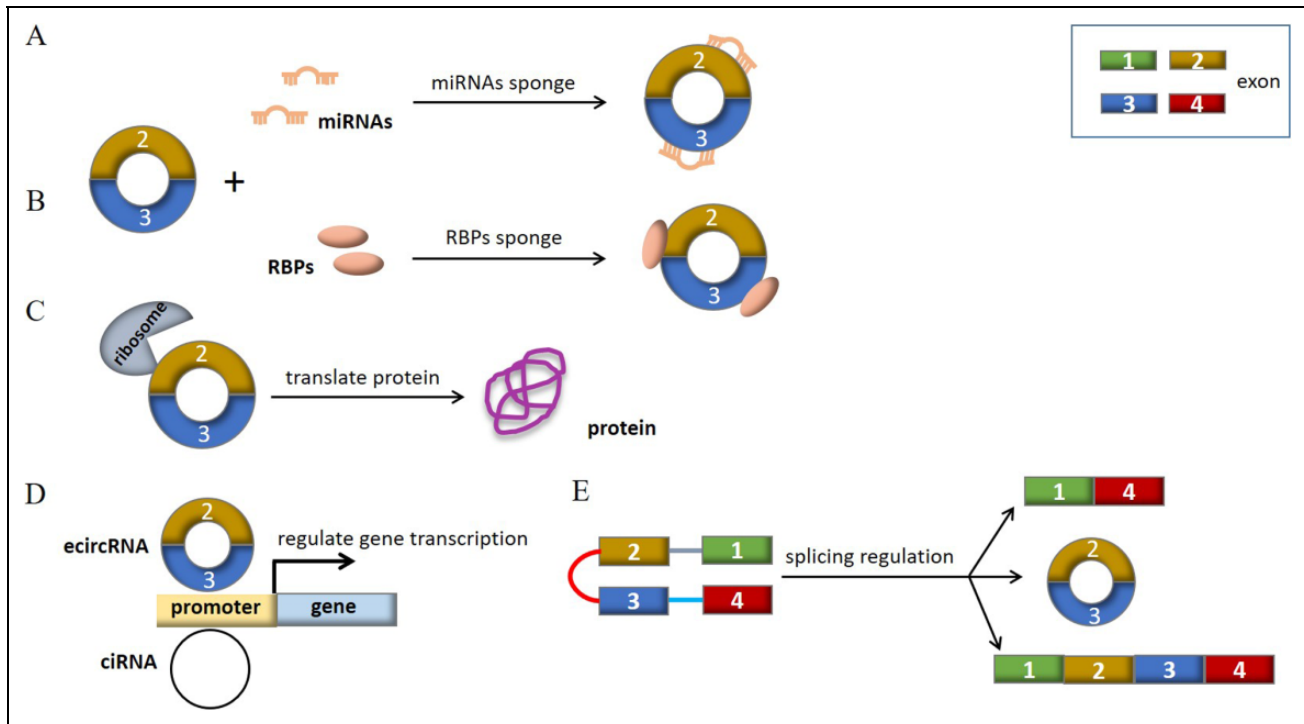


Fig 2. Main functions of circRNAs. (A) miRNAs sponge. (B) RBPs sponge. (C) Translate protein. (D) Regulate gene transcription. (E) Splicing regulation. circRNAs: circular RNAs; ecircRNAs: exonic circRNAs; ElicRNAs: exon-intron circRNAs; ciRNAs: circular intronic RNAs; RBPs: RNA-binding proteins.

enrichment of miRNA targeting sites. Some ciRNAs have been found to function as positive regulators of RNA Pol II transcriptase to regulate the transcription of their parental genes³⁴.

ElicRNAs. ElicRNAs are circRNAs that are circularized with both exons and introns. Internal repeat sequences may play important roles in their generation, and they might be similar to ecircRNAs³⁵. ElicRNAs are relatively abundant in the nucleus and can enhance the transcription of their parental genes by interacting with small nuclear ribonucleoproteins³⁵.

Intergenic circRNAs. An intergenic circRNA contains two intronic circRNA fragments flanked by GT-AC splicing signals acting as the splice donor and acceptor of the circular junction while forming an integrated circRNA³⁶. They were discovered using the CIRI (CircRNA Identifier, a circRNA identification tool) in human transcriptomes by Gao et al³⁶. However, at the moment, little is known about the functions of circRNAs.

Functions and Roles of CircRNAs

CircRNAs, as a special type of RNA molecules, have an array of functions according to their different origins and structures. Further studies are needed to precisely define the specific roles of circRNAs and to understand how they are

regulated. Up to now, circRNAs have been found to function as miRNA and RBP sponges, regulators of protein translation and gene transcription, and competing products during pre-mRNA splicing (Fig 2). Here, we summarize recent studies on the functions of circRNAs and further discuss their regulatory roles under physiological and disease conditions.

CircRNAs Can Serve as Efficient miRNA Sponges. Up to now, the most important and most widely studied function of circRNAs is in their role as miRNA sponges. Abundant endogenous circRNA molecules, with multiple complementary binding sites for miRNAs, are inherently resistant to exonucleolytic RNA degradation. Therefore, they form a large class of post-transcriptional regulators acting as potent miRNA sponges carrying out important biological functions³⁷. For example, cerebellar degeneration-related protein 1 antisense (CDR1as), is massively bound by miR-7 and miR-671 in human and mouse brains³⁸. When the CDR1as locus is removed from the mouse genome, the expression of both miR-7 and miR-671 are mis-regulated in all brain regions. In addition, miR-671 directs cleavage of the circular antisense transcript, the cerebellar degeneration-related protein 1(CDR1), which could produce a highly abundant and circularized species³⁹. These results indicate that the interactions between circRNAs and miRNAs are important for normal brain function.

Another study shows that circHIPK2 takes part in regulating astrocyte activation via cooperation of autophagy and endoplasmic reticulum (ER) stress by functioning as an endogenous miR124-2HG sponge to sequester miR124-2HG and inhibit its activity, which in turn results in increased expression of sigma non-opioid intracellular receptor 1. Knocking-down of circHIPK2 expression could significantly inhibit astrocyte activation via the regulation of autophagy and ER stress through the targeting of miR124-2HG and SIGMAR1⁴⁰.

Another circRNA, circITCH, is aligned in a sense orientation to the known protein-coding gene, ITCH—a member of the E3 ubiquitin ligases²³. circITCH acts as a sponge of miR-7, miR-17, miR-214, and promotes the expression of its parental gene ITCH^{23,41}. Interestingly, the upregulation of ITCH could inhibit the Wnt/ β -catenin signaling pathway. In light of these reports, it is suggested that circITCH is able to suppress cancer progression by indirectly inhibiting the activation of the Wnt/ β -catenin signaling pathway^{23,41}.

Furthermore, Huang et al⁴² have identified that circHIPK3 binds to multiple miRNAs (9 miRNAs with 18 binding sites), indicating that one circRNA can be associated with a variety of miRNAs. Taken together, circRNAs have been repeatedly demonstrated to function as efficient miRNA sponges to regulate their parental genes and therefore affect their biological functions in health and disease.

CircRNAs Can Act as RBP Sponges. In addition to miRNA sponges, the function of “sponging” other factors, such as RBPs and ribonucleoprotein complexes, has also been proposed for circRNAs¹⁶. HuR is an RBP that regulates protein expression by interacting with lots of RNAs⁴³. circPABPN1, which originates from poly(A)-binding protein nuclear 1 (PABPN1) pre-mRNA, is one of the HuR targeted circRNAs⁴³. Besides, it is reported that circPABPN1 inhibits HuR binding to PABPN1 mRNA and reduces PABPN1 production⁴³. Furthermore, circAmot1 is capable of binding to c-myc and STAT3 to contribute to their translocation into the nucleus, thus regulating the expression of their target genes^{27,44}.

Production of circRNAs Can Regulate Gene Transcription and Translation. Several studies have shown that circRNAs can function as transcriptional and translational regulators. For instance, EICiRNAs, which retain the intronic sequences from their parental genes, could interact with the transcription machinery⁴⁵. As a result, EICiRNAs can regulate the expression of their parental genes in *cis* via specific RNA-RNA interaction between U1 snRNAs and EICiRNAs³⁵.

In addition, ciRNAs, another subclass of circRNAs, are abundant in the nucleus. They play regulatory roles in the Pol II transcription of their parental coding genes, which adds to the growing evidence of circRNAs' regulatory functions in gene expression³⁴.

As an important class of post-transcriptional regulators, circRNAs could directly target (m)RNAs by partial base pairing^{10,46}. For example, CDR1 serves as a component in the sense of mRNAs stabilization and plays an important role in regulating RBPs³⁹. In addition, the binding of circPABPN1 to HuR can suppress PABPN1 translation⁴³. Therefore, circRNAs may take part in the regulation of gene expression.

Certain circRNAs Have Protein-Coding Potential. CircRNAs can serve as translational templates *in vitro* and *in vivo*. Two endogenous circRNAs, circMbl and circZNF609, are reported to be translatable^{47,48}, suggesting that the peptides and proteins produced by circRNAs could be biologically functional molecules in cells³⁰. Recently, Zhang et al. verified that circRNA circFBXW7 encodes a functional protein FBXW7-185aa⁴⁹, which has a negative regulatory role in glioma carcinogenesis, further supporting the coding ability of circRNAs. FBXW7-185aa has a synergistic effect with the parental gene coding protein FBXW7 on inhibiting the expression of c-myc in human cells, which, in turn, decreases glioma cell proliferation and inhibits cell cycle acceleration *in vitro* and *in vivo*⁴⁹. In addition, circRNAs can be driven translationally by N6-methyladenosine^{50,51}. Some studies indicate that eukaryotic ribosomes can initiate translation of circRNAs with internal ribosome entry site (IRES) elements^{52,53}, while other reports show that circRNAs could translate into proteins through a mechanism similar to rolling circle amplification without IRES⁵⁴. Further investigations are needed to determine the mechanisms of how these translatable circRNAs are translated into proteins.

CircRNAs Compete with pre-mRNA Splicing. As the splicing pattern of any pre-mRNA is dictated by competition between alternative pairing of 5' and 3' splice sites, the production of circRNAs may play a role in the regulation of pre-mRNA splicing^{16,45}. For example, the second exon of the splicing factor muscleblind (MBL) is circularized, which generates a circRNA (circMbl). CircMbl contains conserved MBL binding sites, which are bound by MBL. As a result, modulation of MBL levels can strongly affect circMbl biosynthesis⁵⁵. Taken together, the formation of circRNAs influences the splicing of pre-mRNA to alter gene expression.

Other Possible Functions of circRNAs. Studies have shown that circRNAs can regulate certain cell signaling pathways. For instance, circZNF292 is found to be induced under hypoxic conditions and in gliomas cell lines⁵⁶. The latter report shows that circZNF292 silencing could suppress tumor tube formation through regulating cell cycle by the Wnt/ β -catenin signaling pathway⁵⁶.

In addition, circular antisense ncRNAs in the INK4 locus (circANRIL) can regulate rRNA maturation⁵⁷. CircANRIL binds to the C-terminal lysine-rich domain of pescadillo homologue 1, an essential 60S-preribosomal assembly

factor, and prevents pre-rRNA binding and exonuclease-mediated rRNA maturation^{57,58}. In vascular smooth muscle cells and macrophages, circANRIL impairs ribosome biogenesis, which leads to activation of p53 and a subsequent increase in apoptosis and decrease in proliferation rate⁵⁷.

Moreover, other studies^{19,59} have indicated that circRNAs also exist in secreted extracellular vesicles (EV), suggesting that extracellular expulsion is one way that cells can eliminate accumulated circRNAs. Intriguingly, it may also be a way for cells to transfer functional circRNAs as a way of communication, which needs more in-depth investigation.

Relationship of circRNAs with Diseases. According to the functions of circRNAs, it is recognized that circRNAs are essential for the development process of eukaryotes and can influence the pathogenesis and physiology of disease.

For example, in a mouse model of lead-induced neurotoxicity, circRar1 induces the upregulation of apoptosis-associated factors caspase8 and p38 via modulation of their common target miR-671⁶⁰. For another, in tumor cells circFoxo3 can promote MDM2-induced p53 ubiquitination and subsequent degradation, resulting in an overall decrease of p53, which, in turn, prevents MDM2 from inducing Foxo3 ubiquitination and degradation, and results in increased levels of Foxo3 protein⁶¹. Thereby, according to the previous studies we can conclude that cell apoptosis can be induced by circRNAs directly or indirectly.

On the other hand, circFoxo3 is generated from a member of the forkhead family of transcription factors Foxo3. It is highly expressed in hearts and is correlated with extensive cellular senescence⁶². CircFoxo3 is distributed mainly in the cytoplasm, where it interacts with the anti-senescent protein ID-1 and the transcription factor E2F1, as well as the anti-stress proteins FAK and HIF1a, which results in increased cardiac senescence⁶². Among the differentially expressed senescence-associated circRNAs, circPVT1, which is generated by circularization of an exon of PVT1 gene, is identified as a circRNA displaying markedly reduced levels in senescent fibroblasts⁶³. CircPVT1 might selectively inhibit let-7 activity and hence the expression of let-7-regulated mRNA⁶³. Silencing circPVT1 can promote cell senescence and reverse the proliferative phenotype after let-7 function is impaired⁶³.

CircRNAs are also largely enriched in platelets compared with nucleated cell types, which is a signature of transcriptome degradation⁶⁴. Fusion circRNAs (f-circRNAs) are produced from transcribed exons of distinct genes affected by the chromosomal translocations⁶⁵. During leukemia progression, f-circRNAs could contribute to cellular transformation, promote cell viability and resistance upon therapy, and have tumor-promoting properties in *in vivo* models⁶⁵.

Beyond that, during the priming phase of rat liver regeneration (LR), the comprehensive circRNAs expression profile has been analyzed by high-throughput RNA sequencing, which revealed their potential roles in rat LR⁶⁶. Gene

ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) biological pathway analysis indicates that, during the early phase of rat LR, circRNAs contribute critically to the process of energy metabolism, substance metabolism, and hepatocyte proliferation⁶⁶.

Recently, Yang et al. discovered that circAmotl1 could accelerate healing processes in a mouse excisional wound model⁴⁴. They found that circAmotl1 can increase protein levels of Stat3 and Dnmt3a. The increased Dnmt3a then inhibits the expression of miR-17-5p, which stimulates the expression of fibronectin, Dnmt3a, and Stat3, and leads to increased cell adhesion, migration, proliferation, survival, and wound repair⁴⁴.

Moreover, the investigation of the transcriptomic landscape of human pre-implantation development has identified abundant circRNAs⁶⁷. Quaking (QKI), which functions in the formation of circRNAs, is strongly expressed by Müller glial cells in both the developing and adult retina⁶⁸. It is well accepted that many circRNAs are expressed in tissue- and developmental-stage-specific manners, which reveals a striking regulation of circRNAs during neuronal development. It is plausible that some circRNAs can act as local regulators of gene expression at distal neuronal sites, such as growth cones and synapses, and contribute to aspects of neural development⁶⁹. In addition, emerging evidence also indicates that circRNAs are involved in the development and progression of various neurological disorders⁷⁰.

Taken together, current studies focus mainly on the interactions between RNAs and proteins, while much is unknown about their diverse and complex functions. The use of circRNAs for diagnosis and therapy still needs extensive investigation.

CircRNAs in Oral Medicine

To date, there have been few studies on the roles of circRNAs in oral medicine. However, it is realized that circRNAs are involved in the initiation and development of different types of diseases and tissues, which indicates that circRNAs might be a regulatory nova in this field. In this pilot review, we describe the primary landscape of the correlatively existing literatures on circRNAs in oral medicine (Table 3).

CircRNAs and Oral Cancers. Oral cancer is a multifactorial pathological disease thought to be the result of genetic modifications (including activation of oncogenes and silence of tumor suppressor genes). However, there is a lack of accurate diagnosis and efficient treatment⁶⁴. Therefore, reliable biomarkers for the timely detection of the disease and patient stratification are required.

So far, miRNAs are the most well studied ncRNAs in the physiological and pathological processes of all types of oral cancers⁷⁹. A great number of miRNAs have been discovered as key participants in tumorigenesis, acting either as tumor suppressors or as oncogenes (oncomiRs)^{80,81}. Moreover,

Table 3. Recently Published Studies for Detecting circRNAs in Oral Medicine.

Investigated models	circRNAs	Expression	Potential functions	References
OSCC	circRNAs expression pattern	1921 existing circRNAs and 10021 novel circRNAs	circRNA expression profiling Biomarker miRNA sponges	Wang et al ⁷¹
	circRNAs expression pattern hsa_circ_0008309	16 circRNAs significantly up- or downregulated Down	circRNA expression profiling Biomarker Therapeutic target miRNA sponges	Li et al ⁷²
	circRNA100290	Up	Biomarker Therapeutic target miR-29 sponge	Chen et al ²⁸
	circDOCK1	Down	Biomarker Therapeutic target miR-196a-5p sponge	Wang et al ⁷³
PDLSCs osteogenic differentiation	circRNA expression pattern	1456 circRNAs differentially expressed	circRNA expression profiling Biomarker miRNA sponges	Gu et al ⁷⁴
	circRNA expression pattern	12693 circRNAs detected	circRNA expression profiling Biomarker miRNA sponges	Zheng et al ²⁹
	CDR1as	Up	Biomarker Therapeutic target miRNA sponges	Li et al ⁷⁵
Saliva	circRNA expression pattern	More than 400 circRNAs detected	circRNA expression profiling Biomarker	Bahn et al ⁷⁶ Jafari et al ⁷⁷
OMM	circRNA expression pattern	90 circRNAs significantly up- or downregulated	circRNA expression profiling Biomarker miRNA sponges	Ju et al ⁷⁸

OSCC: oral squamous cell carcinomas; OMM: oral mucosal melanoma; PDLSCs: periodontal ligament stem cells.

emerging lines of evidence predict that circRNAs, as sponges of miRNAs, are associated with the progression and induction of oral cancers⁸².

There have been studies on circRNAs in oral squamous cell carcinoma (OSCC)^{28,71–73}. Using circRNA and mRNA microarrays, Chen et al. identified circRNAs that are differentially expressed between OSCC tissue and paired non-cancerous matched tissue²⁸. They discovered that circRNA100290 is upregulated in OSCC tissues, and its knock-down decreases the expression of CDK6—a direct target of miR-29b—and inhibits proliferation of OSCC cells in vitro and in vivo²⁸. Their results reveal that circRNA100290 may function as a competing endogenous RNAs (ceRNAs) to regulate CDK6 expression by sponging of miR-29b family members in OSCC²⁸. Meanwhile, it is reported that circDOCK1 can suppress cell apoptosis via inhibition of miR-196a-5p by targeting BIRC3 in OSCC⁷³.

In addition, Ju et al. found that the expression pattern of circRNAs is altered in oral mucosal melanoma (OMM), suggesting that circRNAs might play vital roles in metastasis of OMM and in regulating OMM progression⁷⁸.

In conclusion, these reports indicate that circRNAs exert regulatory functions and might be potential biomarkers in oral medicine. Based on the functions of circRNAs in various cancers, we believe that they have tremendous potential to serve as biomarkers for the diagnosis and treatment of oral tumors, even as new therapeutic targets for the treatment of oral cancers.

CircRNAs and Oral Inflammation. Although there is still no study on the roles of circRNAs in common inflammation of oral diseases such as periodontitis, there have been studies of circRNAs involved in rheumatoid arthritis (RA)⁸³ and osteoarthritis⁸⁴. It is reported that circRNAs are expressed differentially in RA patients compared with healthy controls, indicating that circRNAs play crucial roles in the regulation of expression of symbol genes that control the occurrence and development of RA⁸³. Interestingly, periodontitis shares a similar occurrence and developmental process with RA⁸⁵, which suggests that circRNAs may play certain roles in oral inflammation.

It is known that inflammation in oral medicine is manifested mainly via periodontal diseases—the most common form of oral disease⁷⁶. Intriguingly, it is reported that more than 400 putative circRNAs that may function in intercellular signaling and inflammatory response exist in human cell-free saliva⁷⁶. Consequently, salivary circRNAs, as endogenous RNAs, may be novel clues for detecting a wide range of local or systemic diseases, including inflammation and be used routinely in personalized medicine^{76,77}.

CircRNAs and Cell Differentiation and Tissue Regeneration. Some reports have clearly established the participation of circRNAs in the maintenance of pluripotency. For example, circBIRC6 acts as a sponge for miR-34a and miR-145 to regulate the molecular circuitry in human embryonic stem cells⁸⁶. And during human epidermal stem cell differentiation, circRNAs are abundantly expressed and upregulated in a coordinated manner⁸⁷, further suggesting that they may play important roles during the process.

Recent findings also demonstrate that expression profiles of circRNAs are significantly altered during osteogenic differentiation of PDLSCs, which provides clues leading to further insight into the roles of circRNAs in osteoblast differentiation in an oral setting²⁹. Moreover, Gu et al. found a total of 1456 circRNAs differently expressed during PDLSCs osteogenic differentiation⁷⁴. What's more, it is suggested that specific circRNAs could serve as ceRNAs to promote PDLSCs osteogenic differentiation and periodontal regeneration. For instance, CDR1as was proved to promote osteoblastic differentiation of PDLSCs via the miR-7/GDF5/SMAD and p38 MAPK signaling pathway⁷⁵.

However, up to now, there have been only a few reports about circRNAs' functions during orthodontic tooth movement (OTM), which involves alveolar bone remodeling. It is recognized that PDLSCs are key seed cells in OTM and alveolar bone remodeling^{88,89}. Previous studies by our research team have found that circRNAs expression changed in mechanical force-induced PDLSCs⁹⁰. Besides, it is known that circRNAs can serve as regulators of cellular stress both positively and negatively: to maintain homeostasis, combat acute infection, and regulate cell growth and death, or dysregulation of others to enhance stress response to adapt chronic stress⁹¹. All this evidence indicates that circRNAs may participate in the regulation of OTM and bone remodeling.

Although there is currently not enough understanding of tissue regeneration and bone remodeling in oral medicine, we believe that there will be more reports on the functions of circRNAs in this field in the near future.

Conclusions

Current research in oral medicine usually focus on tissue regeneration, tooth development, oral cancer, tooth movement, and inflammatory disease. To explore the relevant

potential mechanisms of each of these processes has extreme clinical significance.

CircRNAs are shown to play important roles in various physiological and pathological processes. It is generally accepted that circRNAs are involved in regulating cell proliferation, apoptosis, and multiple signaling pathways. Currently, circRNAs have been found to play pivotal roles in different types of diseases and tissues. We have also learnt that circRNAs play a vital part in OSCC^{28,71–73}, metastatic OMM⁷⁸, saliva^{76,77} and the osteogenic differentiation of PDLSCs^{29,74,75}. Based on these studies, we suggest that circRNAs participate in the regulation of oral biological processes, and might be a regulatory nova in the development and outcome of oral medicine. There is no doubt that a great number of studies will be carried out to further explore the functions of circRNAs and the associated mechanisms.

Undeniably, findings on the roles of circRNAs in oral medicine are also confronted by many challenges. On the one hand, strategies and technical limitations might affect the detection of circRNAs in experiments⁹². For example, some smaller circRNAs may be missed in length selection, and the use of some artificial primers may affect the enrichment of circRNAs⁹². On the other hand, there is still no uniform verdict on the predictions of the detection algorithms of different circRNAs^{33,93}. In addition, low expressed-circRNAs also tend to be overlooked by bioinformatics analysis^{94,95}. All these limitations restrict functional studies of circRNAs in oral medicine and other fields. Therefore, establishing a gold standard with which to assess the accuracy of predictions from algorithms and choose appropriate thresholds are needed to overcome these challenges, in addition to reducing operational errors during experiments^{92,94}. The continued development of such a standard will provide a statistical test that could be used to evaluate the false discovery rate, and defining appropriate thresholds will be beneficial for the detection of high-confidence circRNAs⁹². Besides, normalization procedures to assess the enrichment or depletion of circRNAs are necessary to improve the accuracy of the results during the experiments⁹².

Motivated mainly by the finding that they function as miRNA sponges, circRNAs are stepping forward into the light of broader comprehension and clinical application of their physiological and pathological phenomena in oral medicine. We hope that this pilot review can help us tap into this new field and lay the groundwork for a more in-depth understanding of the diagnosis, prognosis, and treatment in oral diseases, and offer a primary glimpse into the functions of circRNAs involved in oral health.

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