OncoTargets and Therapy

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REVIEW

CircRNAs: A New Chapter in Oral Squamous Cell Carcinoma Biology

This article was published in the following Dove Press journal:
OncoTargets and Therapy

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Abstract: With the rapid development of bioinformatics and gene sequencing technologies, understanding of circular RNAs (circRNAs) has been extended, and numerous studies have identified the key regulator role of circRNAs in a variety of diseases, especially in cancer. Recently, accumulated studies of oral squamous cell carcinoma (OSCC) have discovered the great potential of circRNAs, which can serve as prognostic or diagnostic biomarkers and affect the development and therapy of OSCC. In this review, we detail the new progress of circRNA research for OSCC in order to provide new strategies for clinical diagnosis and treatment.

Keywords: circular RNA, oral squamous cell carcinoma, miRNA sponge, biomarker

Introduction

Oral squamous cell carcinoma (OSCC) includes cancers that occur in the mouth and oropharynx, accounting for about 90% of all oral malignancies.[1] Worldwide, the incidence of OSCC is approximately 4/100,000, more common in men and the elderly.[2] In some Asia-Pacific countries, its incidence ranks among the top three of all cancers.[3] Moreover, they are usually diagnosed at an advanced stage, and environmental risk factors, viral infections, as well as genetic changes all augment the incidence of OSCC. Currently, the 5-year overall survival rate of OSCC patients is estimated to be 50% to 60%.[4] Therefore, it is necessary to clarify the molecular mechanisms of OSCC pathogenesis, which will help to develop more effective diagnostic methods and treatment strategies.

Circular RNA (circRNA) is a subclass of non-coding RNA (ncRNA). After long non-coding RNA (lncRNA) and microRNA (miRNA), it has developed into a new research hotspot in the field of cancer.[5] CircRNAs are produced by reverse splicing and are characterized by a closed single-stranded structure and lack of 5 'cap and 3′ polyadenylation (poly(A)) tail, which makes them more stable than lncRNA and miRNA.[6] And circRNAs are highly conserved in eukaryotes, and their expression exhibits tissue- and developmental stage-specific. Numerous studies have revealed that circRNAs have an important effect on the progression and treatment of cancer and play a regulatory role in the tumor microenvironment (TME). Therefore, it suggests that circRNAs may serve as new cancer biomarkers as well as potential therapy targets.[7–9]

At present, plenty of studies have been devoted to exploring the function of circRNAs in OSCC and found that copious abnormally expressed circRNAs are closely related to the clinical characteristics of OSCC, indicating that circRNAs can

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http://doi.org/10.2147/OTT.S263655

be used as biomarkers for OSCC. In addition, aberrantly expressed circRNAs can act as miRNA sponges or participate in several cancer-related signaling pathways, thereby altering the progression of OSCC and affecting drug resistance and radiotherapy in OSCC patients. In this review, we comprehensively discuss the research progress of circRNAs in OSCC and outline their functions.

Characterization and Main Functions of CircRNA

CircRNAs are produced by a non-canonical splicing event named back-splicing, during such event the downstream splice-donor site is covalently linked to upstream splice-acceptor site.[10] The formed closed-loop structure of circRNAs makes them much more stable than linear RNAs, and their half-life is about 4 times longer than linear RNAs.[11] In addition, back-splicing makes circRNAs lack 5' cap and 3′ tail, which enables them resistant to ribonuclease RNase R. This feature is usually used in experiments to distinguish circRNAs from linear counterparts.[12] According to the sequences it contains, circRNA can be divided into three main different types: exon circRNA (EcRNA), intron circRNA (CiRNA) and exon-intron circRNA (EIcRNA).[13] Among them, EcRNA is the most common and is mainly distributed in the cytoplasm, while circRNAs containing introns are distributed in the nucleus.[14] CircRNAs exhibit widespread expression in different species and abundant expression in human tissues, especially in brain.[15] And their sequences are highly conserved, and many studies have detected about 15,000 human circRNAs sequences in mice.[15,16] Moreover, their expression exhibits in tissue-, cell- and developmental stage-specific manner, and partially dysregulated circRNAs have a close relationship with tumor pathological differentiation, TNM stage and Lei et al, indicating that they may be suitable candidates for cancer biomarkers.[17–19]

CircRNAs have shown multiple functions in a variety of cancers. Currently, the most established function of circRNAs is that circRNAs can act as miRNA sponges, competitively inhibit gene translation and regulate relevant signaling pathways, thereby affecting the progression of cancer.[20] Some circRNAs containing RNA binding proteins (RBPs) motifs can serve as protein sponges to indirectly regulate the function of RBPs.[21] And a few circRNAs can directly interact with proteins and enzymes to regulate various physiological processes, which is called protein scaffolds.[22] Intriguingly, as non-coding RNAs, a handful of circRNAs have been confirmed with protein-coding ability, and currently, the widely accepted mechanism is internal ribosome entry site (IRES)-mediated translation, which is a cap-independent translation mechanism. IRES is a sequence located in the 5′ untranslated region (UTR) and can recruit ribosomes to initiate translation, and plenty of IRES sequences have been identified in circRNAs. Several circRNAs have been found to code proteins in human cancers, such as glioma and glioblastoma.[23,24] However, the current research is still in the initial stage, and the function of proteins encoded by circRNAs needs further exploration, especially in OSCC (Figure 1).[25,26]

The fast development of bioinformatics has accelerated the exploration of circRNAs. At present, high-throughput RNA-sequencing and microarray analysis are the most popular detection methods. With the help of find-circ, CIRI2 and other computer algorithms, the unique back-splice junction (BSJ) of each circRNA can be determined, which greatly improves the reliability of detection. And the experimental validation methods are more mature. The combination of RNase R digestion, qRT-PCR based on divergent primers and Northern blotting can accurately verify circRNAs. Furthermore, we can better predict the function of circRNAs based on the establishment of the circRNA databases and sequencing results. Whether they have miRNAs sponges, protein sponges, translation ability or other potentials can be well predicted.

Currently, lncRNAs, which are defined as ncRNAs of more than 200 nucleotides, have been systematically discussed in the OSCC, and they can act as miRNA sponges and participate in cancer-related signaling pathways.[27] LncRNAs can also be used as biomarkers, but their stability and conservation are poor. MiRNAs refer to a class of short ncRNAs with a length of about 20 nucleotides, and they played an important role in the development and treatment of OSCC.[28] And miRNAs are identified as key molecules in various signaling pathways through miRNA sponge function. Like lncRNAs and miRNAs, circRNAs are also abundantly expressed in body fluids (such as blood and saliva) and tumor tissues in a cancer-specific manner. These ncRNAs are stable in body fluids and their levels are often related to the clinical and pathological features of cancer. They all are inspiring for the early diagnosis of OSCC in a non-invasive way. Moreover, circRNAs with a covalent closed loop structure have higher stability and longer half-life than lncRNAs and

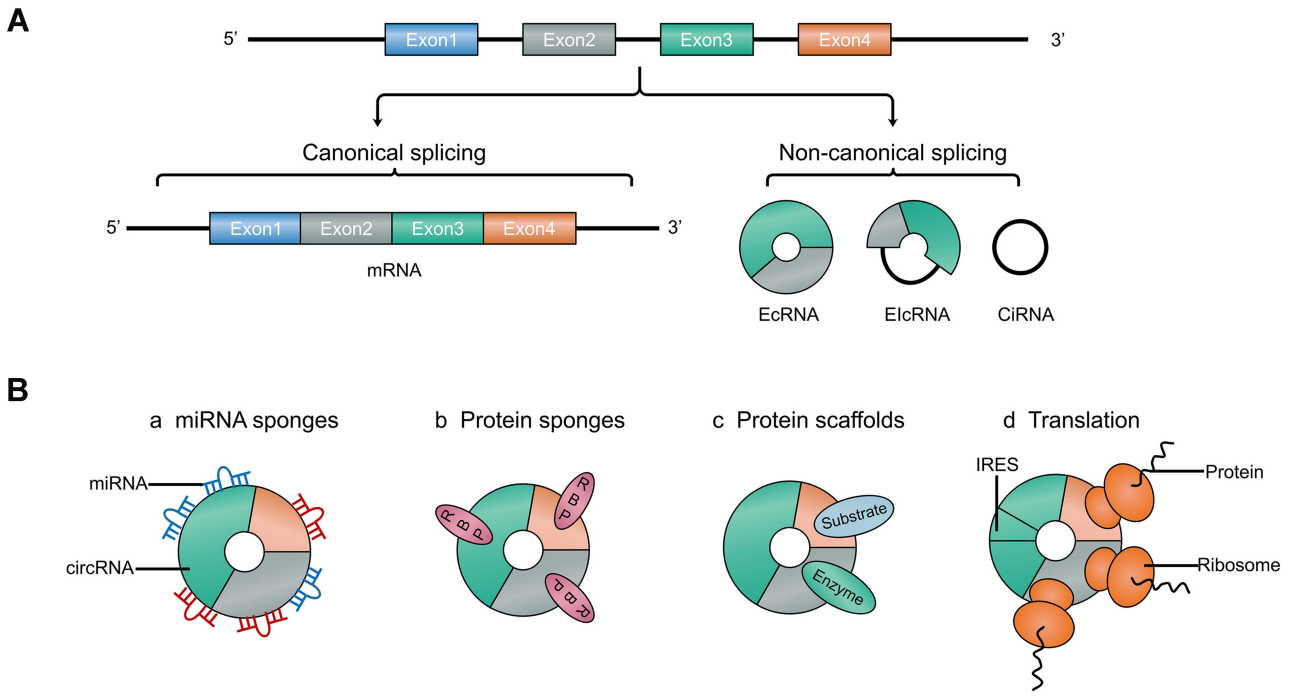

Figure 1 Schematics of the biogenesis and main functions of circRNAs. (**A**) CircRNAs are produces by non-canonical splicing events and can be divided into three subclasses: EcRNA, EIcRNA and CiRNA. (**B**) The main functions of circRNAs include miRNA sponges, protein sponges, protein sponges, and coding proteins.

miRNAs. And circRNAs exhibited high conservation across different species. Extensive research on the association of lncRNAs-miRNAs and circRNAs-miRNAs may help to elucidate the complex pathological mechanism of OSCC.

CircRNAs in OSCC

The function of circRNAs in the development of various cancers has been extensively studied. In recent years, research on circRNA in the field of OSCC has been increasing, and it was found that circRNAs have an important impact on the progression, treatment and prognosis of OSCC (Supplementary Figure 1).

Expression of CircRNAs in OSCC

Ascending evidence reveals that the abnormal expression of circRNAs is related to the development and prognosis of OSCC. CircPVT1 was overexpressed in OSCC patients and its expression was related to mutant *p53* protein status in OSCC patients.[29] In vitro experiments confirmed that *p53* protein depletion can downregulate the expression of circPVT1, but there was no inverse regulation between *p53* and circPVT1. In addition, RNA immunoprecipitation (RIP) and chromatin immunoprecipitation (ChIP) experiments showed that circPVT1 did not directly bind to *p53* but was regulated by the mut-*p53*/YAP (Yes-Associated Protein)/TEAD complex. Particularly, circPVT1 can control and enhance its expression in the nucleus. Through high-throughput sequencing and microarray analysis, Wang et al analyzed the expression of circRNAs in 8 pairs of OSCC tissues and controls, with a total of 1921 existing circRNAs and 10,021 new circRNAs.[30] Most circRNAs were derived from exons and were distributed on chromosomes 1 and 2. There were 16 circRNAs with significantly different expressions in OSCC and adjacent tissues, with fold changed ≥2.0. Among them, 8 circRNAs were upregulated and 8 circRNAs were downregulated. Deng et al performed high-throughput circRNA microarray analysis on 3 pairs of OSCC and matched normal tissues and filtered them with volcanic maps.[31] A total of 213 circRNAs with ≥1.5-fold changes were screened out, of which 124 were upregulated and 89 were downregulated. Under GO and Functional categories analysis, 20 differentially expressed circRNAs were involved in MAPK and PI3K signaling pathways. Moreover, Qiu et al analyzed the expression of circRNAs in tongue squamous cell carcinoma (TSCC).[32] High-throughput sequencing and RT-PCR were performed, and 12,156 circRNAs were identified in TSCC. The results showed that 314 circRNAs were significantly upregulated, while 8

circRNAs were remarkably reduced by more than 2 times compared with adjacent tissues. Under KEGG pathway analysis, copious circRNAs were associated with tumor signaling pathway protiens such as MAPK.

In particular, circRNAs in saliva of OSCC patients also exhibited aberrant expression. Through microarray screening and qRT-PCR verification, Zhao et al detected 32 abnormally expressed circRNAs in the saliva of OSCC patients, including 12 overexpressed circRNAs and 20 under-expressed circRNAs.[33] A large number of experiments have identified the function of these dysregulated circRNAs, showing that the abnormal expression of circRNAs has multiple biological effects. However, it is not clear which circRNAs play a more important role and what is the relation between these circRNAs in the development of OSCC.

Biological Functions of CircRNAs in OSCC

Potential Novel Biomarkers

Dysregulated non-coding (ncRNAs) RNAs in OSCC, including miRNAs and lncRNAs, have been identified as ideal biomarkers.[27,34] Similarly, numerous studies have found that circRNAs have great potential as OSCC biomarkers (Table 1).

In OSCC patients with mutant *p53* protein, circPVT1 was significantly upregulated.[29] And patients with overexpressed circPVT1 usually had a poor survival, suggesting that circPVT1 could be a prognostic biomarker for OSCC. Aberrant circRNAs in OSCC patients were also related to their pathological differentiation and might act as diagnostic biomarkers. For example, hsa_circ_0008309,[35] hsa_circ_009755,[36] circRNA_000334 and circRNA_006740[30] were downregulated in OSCC tissues, and their expression was closely connected with the pathological differentiation of OSCC. Receiver operating characteristic (ROC) curve analysis was performed in hsa_circ_0008309 and hsa_circ_009755, and the area under the curve (AUC) values of hsa_circ_0008309 and hsa_circ_009755 were 0.764 and 0.782, respectively. These results indicated that hsa_circ_0008309, hsa_circ_009755, circRNA_000334, and circRNA_006740 can be used as potential diagnostic biomarkers for OSCC.

Furthermore, circRNAs were also found to be related to TNM stage and tumor size of OSCC. Hsa_circ_001242[37] and hsa_circ_0072387[38] were downregulated in OSCC. The expression of hsa_circ_001242 was significantly connected to tumor size and T stage of OSCC and the expression of hsa_circ_0072387 was correlated to the TNM stage. The AUC values of hsa_circ_001242 and hsa_circ_0072387 were 0.784 and 0.746, respectively. Meanwhile, hsa_circ_0109291[39] was overexpressed (approximately 4-times) in OSCC patients and was positively associated with their TNM stage. And the prognosis of OSCC patients with upregulated hsa_circ_0109291 was poor. The results indicated that hsa_circ_001242, hsa_circ_0072387 and hsa_circ_0109291 may be biomarkers in OSCC diagnosis and treatment targets. Hsa_circ_0086414,[40] hsa_circ_0092125[41] and circ_0000140[42] were greatly downregulated in OSCC, and they were notably associated with TNM stage as well as lymph node metastasis. The area below the ROC curve of hsa_circ_0086414 was 0.749. Deng et al screened two circRNAs with the highest and lowest expression in OSCC, hsa_circ_043621 and hsa_circ_102459, respectively.[31] These two circRNAs were closely associated with TNM stage, tumor differentiation and lymph node metastasis, suggesting that they can be used as diagnostic biomarkers. Hsa_circ_0001742 was upregulated in TSCC and showed positive correlation with advanced clinical stage and lymph node metastasis.[43] Li et al found that another circRNA which was also correlated to lymph node metastasis of OSCC, hsa_circ_0004491, which was greatly reduced in OSCC tissues, and ROC analysis showed its diagnostic value (AUC=0.751) for OSCC.[44]

CircRNAs differentially expressed in saliva could also serve as biomarkers. Salivary hsa_circ_0001874 and hsa_circ_0001971 were upregulated in OSCC patients.[33] It was demonstrated that both hsa_circ_0001874 and hsa_circ_0001971 were correlated to TNM stage, and circ_0001874 was also related to tumor grade. In addition, the AUC of hsa_circ_0001874 and hsa_circ_0001971 of OSCC were 0.863 and 0.845, respectively, and reached 0.922 with their combination. The AUC of their combination for distinguishing OSCC and oral leukoplakia (OLK) was 0.895. After surgery, hsa_circ_0001874 and hsa_circ_0001971 reduced to a level with no significant difference. Therefore, the authors believed that those two circRNAs in saliva might be highly effective biomarkers for early diagnosis of OSCC.

Acting as miRNA Sponges

MicroRNA (miRNA) plays an important role in regulating relevant signaling pathway proteins by base-pairing with mRNA. As one of the competitive endogenous RNA

Table 1 The Potential CircRNA Biomarkers for OSCC

CircRNAs	Expression	Host Gene	Clinical Characteristics	Clinical Value	Models	Ref
circPVT1	Up	*PVT1*	Mut-p53 status	Prognostic biomarker	115 pairs of OSCC tissues and adjacent normal tissues	29
hsa_circ_0008309	Down	*CUL3*	Pathological differentiation	Diagnostic biomarker (AUC = 0.764)	45 pairs of OSCC tissues and adjacent normal tissues	35
hsa_circ_009755	Down	*IBTK*	Pathological differentiation	Diagnostic biomarker (AUC = 0.782)	27 pairs of OSCC tissues and adjacent normal tissues	36
circRNA_000334	Down	*SPATA6*	Pathological differentiation	Diagnostic biomarker	42 pairs of OSCC tissues and adjacent normal tissues	30
circRNA_006740	Down	*CUL3*	Pathological differentiation	Diagnostic biomarker	42 pairs of OSCC tissues and adjacent normal tissues	30
hsa_circ_001242	Down	*TRDMT1*	Tumor size and T stage	Diagnostic biomarker (AUC = 0.784)	40 pairs of OSCC tissues and adjacent normal tissues	37
hsa_circ_0072387	Down	*HMGCS1*	TNM stage (P=0.050 between I and II+III)	Diagnostic biomarker (AUC = 0.746)	63 pairs of OSCC tissues and adjacent normal tissues	38
hsa_circ_0109291	Up	*ZNF714*	TNM stage (P<0.05 between I+II and III+IV)	Prognostic biomarker	51 pairs of OSCC tissues and adjacent normal tissues	39
hsa_circ_0086414	Down	-	TNM stage (P=0.047 between I+II and III +IV), tumor size and lymph node metastasis	Diagnostic biomarker (AUC = 0.749)	55 pairs of OSCC tissues and adjacent normal tissues	40
hsa_circ_0092125	Down	-	TNM stage (P<0.001 between I+II and III +IV), tumor size and lymph node metastasis	Prognostic biomarker	84 pairs of OSCC tissues and adjacent normal tissues	41
hsa_circ_0000140	Down	*KIAA0907*	TNM stage (P=0.031 between I+II and III +IV) and lymph node metastasis	Prognostic biomarker	56 pairs of OSCC tissues and adjacent normal tissues	42
hsa_circ_043621	Up	*KRT14*	TNM stage (P=0.029 between I+II and III +IV), pathological differentiation and lymph node metastasis	Diagnostic biomarker	20 pairs of OSCC tissues and adjacent normal tissues	31
hsa_circ_102459	Down	*MAST1*	TNM stage (P=0.017 between I+II and III +IV), pathological differentiation and lymph node metastasis	Diagnostic biomarker	20 pairs of OSCC tissues and adjacent normal tissues	31
hsa_circ_0004491	Down	*ORC4*	Lymph node metastasis	Diagnostic biomarker (AUC = 0.751)	40 pairs of OSCC tissues and adjacent normal tissues	44

(*Continued*)

Table 1 (Continued).

CircRNAs	Expression	Host Gene	Clinical Characteristics	Clinical Value	Models	Ref
hsa_circ_0001874	Up	*BICD2*	TNM stage (P=0.006 between I+II and III +IV) and tumor grade	Diagnostic biomarker (AUC = 0.863)	saliva from 3 pairs of OSCC patients and healthy controls	33
hsa_circ_0001971	Up	*FAM126A*	TNM stage (P=0.019 between I+II and III +IV)	Diagnostic biomarker (AUC = 0.845)	saliva from 3 pairs of OSCC patients and healthy controls	33

Note: - Means not mentioned in the paper.

(ceRNA), circRNAs contain miRNA response elements (MREs), which enable circRNAs to interact with target miRNAs and inhibit their activity, thereby affecting mRNA expression. At present, a large number of circRNA-miRNA-mRNA networks have been found to be closely associated with the process of OSCC (Table 2 and Figure 2).

Verduci et al confirmed that circPVT1 could act as a sponge of miR-497-5p, which had anti-tumor effects in a variety of cancers including OSCC.[29] The potential downstream carcinogenic effects of circPVT1 was to elevate the expression of *aurka*, *mki67* and *bub1* genes, thereby promoting the proliferation of tumor cell. In another study, He et al found that circPVT1 could also effectively sponge miR-

Table 2 CircRNA-miRNA-mRNA Networks and Their Functions in OSCC

CircRNAs	Expression	Host Gene	Sponge Target	Target Gene	Biological Functions in OSCC	Ref
circPVT1	Up	*PVT1*	miR-497-5p	*Aurka/ mki67/bub1*	Oncogenic functions, increased cisplatin resistance	29
circPVT1	Up	*PVT1*	miR-125b	*STAT3*	Promote proliferation	45
circ-PKD2	Down	*PKD2*	miR-204-3p	*APC2*	Suppress proliferation, migration and invasion, induce apoptosis and cell cycle arrest	46
circDOCK1	Up	*DOCK1*	miR-196a-5p	*BIRC3*	Inhibit OSCC cells apoptosis	48
hsa_circ_100533	Down	-	miR-933	*GNAS*	Suppress proliferation, migration and colony formation, induce apoptosis	49
circ-MMP9	Up	*MMP9*	miR-149	*AUF1*	Promote migration and invasion	52
circUHRF1	Up	*UHRF1*	miR-526b-5p	*c-Myc/TGF-β1/ESRP1*	Promote proliferation, migration, invasion and EMT	53
hsa_circ_100290	Up	*SLC30A7*	miR-378a	*GLUT1*	Promote proliferation and glycolysis	54
hsa_circ_0000140	Down	*KIAA0907*	miR-31	*LATS2*	Suppress proliferation, migration, invasion and EMT	42
hsa_circ_0001742	Up	-	miR-634	*RAB1A*	Promote proliferation and invasion	43
hsa_circ_0008309	Down	*CUL3*	miR-136-5p/ miR-382-5p	*ATXN1*	-	35
hsa_circ_0004491	Down	*ORC4*	has-miR-155-5p	*SIRT1**	Suppress migration and invasion	44
hsa_circ_0072387	Down	*HMGCS1*	miR-29-29p/ miR-141-3p	*MMP2/ BCL2/PTEN*	Only based on bioinformatics analysis	38

Notes: - Means not mentioned in the paper, *Means only based on bioinformatics analysis without experimentally proof.

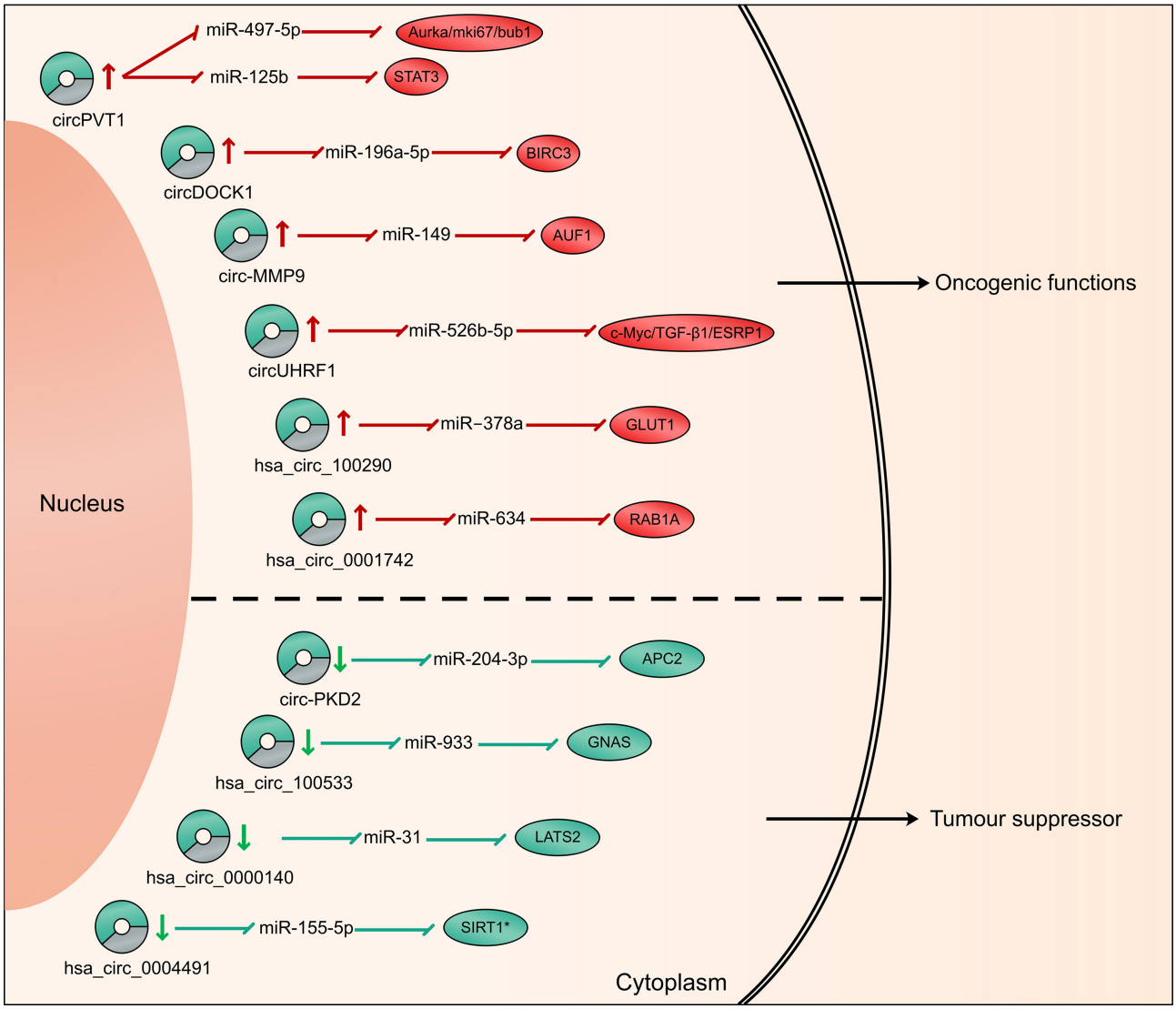

Figure 2 Schematic diagram of the circRNA-miRNA networks in OSCC.

125b.[45] The circPVT1/miR-125b axis promoted OSCC cell proliferation by increasing the expression of the downstream target *STAT3*. Circ-PKD2 was downregulated in OSCC patients and it might sponge to miR-204-3p.[46] Dual-Luciferase Reporter analysis confirmed the direct interaction between circ-PKD2 and miR-204-3p. By overexpressing circ-PKD2, the carcinogenic ability of miR-204-3p was significantly reduced, resulting in inhibition of OSCC cell proliferation, migration as well as invasion, and induction of cell cycle arrest and apoptosis. In vivo study also showed that overexpression of circ-PKD2 can significantly reduce the size and weight of OSCC xenografted tumor. The downstream signaling pathway was studied, and luciferase reporter gene analysis confirmed that *APC2* was the target of miR-204-3p. Circ-PKD2 reduced the inhibitory effect of miR-204-3p and upregulated the expression of *APC2*, causing the inactivation of β-catenin, protein kinase B and extracellular signal-regulated kinase 1/2 pathway. CircDOCK1 was highly expressed in OSCC cells, and miR-196a-5p was identified as the target of circDOCK1. In addition, *BIRC3* was a target of miR-196a-5p, which might cause glioblastoma to escape apoptosis and drug resistance.[47] The authors suggested that the circDOCK1/miR-196a-5p/*BIRC3* axis played an important role in promoting OSCC cell apoptosis.[48] Zhu et al identified hsa_circRNA_100533 as a miRNA sponge of miR-933 by luciferase reporter assays and RIP, which was downregulated in OSCC and exerted its antitumor function through hsa_circRNA_100533/miR-933 pathway.[49] They also found that *GNAS* was downregulated in OSCC, which had been identified as a carcinogenic molecule in colorectal

cancers and hepatocellular carcinoma.[50,51] The luciferase reporter assay confirmed that *GNAS* was closely related to hsa_circ_100533 and miR-933, and its expression was also regulated by hsa_circ_100533 and miR-933. After silencing *GNAS*, the inhibitory effect of the hsa_circRNA_100533-miR-933 axis on OSCC was reversed, indicating that the hsa_circ_100533/miR-933/*GNAS* pathway may play a key role in the process of OSCC. In addition, Xia et al identified a metastasis-associated circRNA in OSCC, hsa_circ_0001162 (circ-MMP9), which was upregulated in OSCC.[52] Circ-MMP9 can act as a miR-149 sponge and target *AUF1* and has a positive correlation with *MMP9* expression. Knocking down circ-MMP can decrease the expression of *MMP9*, thereby inhibiting the invasion and metastasis of OSCC, which was confirmed in vitro and in vivo. CircUHRF1 was significantly overexpressed in OSCC and could serve as a miR-526b-5p sponge to further up-regulate *c-Myc*, which can promote the transcription of TGF-β1 and *ESRP1*. In addition, it was revealed that *ESRP1* can assist circUHRF1 circularization and biogenesis, thereby forming a circUHRF1/miR-526b-5p/*c-Myc*/TGF-β1/*ESRP1* feedback loop to promote OSCC tumorigenesis and EMT.[53] In vitro experiments, silencing circUHRF1 can repress the proliferation, migration, invasion, as well as EMT abilities of OSCC cells. And in vivo function experiments also revealed that suppression of circUHRF1 can effectively inhibit the growth of OSCC tumors. Chen et al identified that hsa_circ_100290 was significantly upregulated in OSCC and could serve as a sponge for miR-378a to regulate OSCC cell growth via *GLUT1*,[54] which was the major glucose transporter involved in the glycolysis and was upregulated in OSCC.[55] Silencing hsa_circ_100290 significantly increased miR-378a expression and inhibited OSCC cell proliferation and glycolysis, and overexpressing *GLUT1* could rescue this effect. Moreover, miR-378a can simultaneously bind to hsa_circ_100290 as well as *GLUT1*and regulate their expression.

CircRNAs in OSCC can function as both biomarkers and miRNA sponges. Peng et al revealed that hsa_circ_0000140 can target and deactivate miR-31, subsequently upregulating *LATS2*.[42] Their study uncovered the role of hsa_circ_0000140/miR-31/*LATS2* network in inhibiting OSCC cell tumorigenesis and EMT. In vivo studies, upregulating hsa_circ_0000140 reduced the xenografted tumor growth and lung metastatic by more than 2-fold. In addition, Shao et al proved that hsa_circ_0001742 was a sponge of miR-634, and miR-634 targeted *RAB1A*. Overexpression of hsa_circ_0001742 could induce TSCC proliferation and invasion via the miR-634/*RAB1A* axis.[43] In another study, hsa_circ_0008309 overexpression downregulated miR-136-5p as well as miR-382-5p and upregulated *ATXN1*, which was a part of the Notch signaling pathway and was involved in mediating hypoxia-induced migration and invasion. However, more experiments were demanded to prove the role of *ATXN1* in OSCC. The author believed that hsa_circ_0008309-miR-136-5P/hsa-miR-382-5P-*ATXN* might have a regulatory effect on the process of OSCC.[35] Li et al demonstrated that hsa_circ_0004491 was decreased in OSCC, and its overexpression can suppress OSCC cell migration and invasion and regulate the expression of EMT-related proteins.[44] Based on bioinformatics analysis, they found 3 potential target miRNAs, including hsa-miR-136-5p, hsa-miR-149-5p and hsa-miR-155-5p. After silencing hsa_circRNA_0004491, only the level of has-miR-155-5p changed. *SIRT1* was the target of has-miR-155-5p and was involved in the regulation of OSCC proliferation and invasion.[56,57] Therefore, the authors predicted that hsa_circ_0004491/miR-155-5p/*SIRT1* may affect the procession of OSCC. Moreover, based on bioinformatics analysis, Dou et al found that hsa_circ_0072387 might affect the progression of OSCC through the hsa_circ_0072387/miR-29-29p/miR-141-3p-*MMP2*/*BCL2*/*PTEN* axis but lacked more experimental evidence.[38] Similarly, Qiu and his colleagues predicted the miRNA sponge effect of circRNAs and found that each abnormally expressed circRNA in TSCC was associated with 10 tumor-related miRNAs.[32]

Currently, a large number of circRNAs have been identified as miRNA sponges and exert their important influence in the development of different cancers.[58] However, compared with the number of circRNAs that have been identified by sequencing technology, only a handful of circRNAs have been confirmed with biological functions. Therefore, although miRNA sponges are currently the most important biological function of circRNAs, this field is still at an early stage. Moreover, by interacting with miRNA, circRNA can not only act as a sponge to reduce its activity, but also act as a "reservoir" to stabilize and activate miRNA. CiRS-7, the most famous circRNA by far, has more than 70 MREs and can interact with different miRNAs, such as miR-7 and miR-671. CiRS-7 can sponge to miR-7,[59] but when ciRS-7 interacts with miR-671 it serves as a miRNA "reservoir" and activates miR-671.[60] All above, the research on the miRNA sponge function of circRNA in OSCC has just begun. Their impact on OSCC is still lacking experimental validations, and only few studies have been verified both in vivo and in vitro.

Table 3 CircRNA-Related Signaling Pathways in OSCC

CircRNAs	Expression	Host Gene	Signaling Pathway	Biological Functions in OSCC	Ref
hsa_circ_043621	Up	*KRT14*	MAPK, PI3K/Akt and Bcl-2/Bax	Promote proliferation; inhibit G0/G1 cell cycle arrest and apoptosis	31
hsa_circ_102459	Down	*MAST1*	MAPK, PI3K/Akt and Bcl-2/Bax	Suppress proliferation; induce G0/G1 cell cycle arrest and apoptosis	31
hsa_circ_0005379	Down	-	EGFR, Bcl-2/Bax and EMT	Suppress proliferation, migration and invasion	61
hsa_circ_0007059	Down	*ZNF720*	AKT/mTOR	Suppress proliferation, migration and invasion; induce apoptosis	62
hsa_circ_0055538	Down	*RMND5A*	p53/Bcl-2/caspase	Suppress proliferation, migration and invasion; induce apoptosis	44

Note: - Means not mentioned in the paper.

Involved in Multiple Cancer-Associated Signaling Pathways

CircRNA has become an important regulator of carcinogenesis and is involved in various signaling pathways related to the initiation and development of cancer. Dysregulated circRNA in OSCC also affects the proliferation, invasion and metastasis of OSCC by regulating cancer-related signaling pathways, such as MAPK, PI3K/Akt/mTOR, Notch signaling pathways (Table 3).

Deng et al screened out 2 circRNAs with the highest and lowest expression from 213 dysregulated circRNAs in OSCC, hsa_circ_043621 and hsa_circ_102459, respectively.[31] Through GO enrichment and functional category analysis, they had the greatest potential to participate in MAPK and PI3K signaling pathways. It was found that overexpression of hsa_circ_102459 or silence of hsa_circ_043621 can inhibit the proliferation of TSCC1 cells and promote G0/G1 cell cycle arrest and apoptosis. Further research confirmed that hsa_circ_102459 overexpression and circ_043621 knockdown both inhibited MAPK, PI3K/Akt and Bcl-2/BAX axes, thereby inhibiting the progression of OSCC and increasing OSCC cell apoptosis. Hsa_circ_0005379 was significantly reduced in OSCC and showed a negative relation to tumor size and differentiation grades of OSCC. Overexpression of hsa_circ_0005379 could significantly reduce the proliferation, migration and invasion of OSCC cells, and upregulate BAX, while Bcl-2, MMP-9, and decrease cyclin D1. In addition, vimentin and N-cadherin decreased, while E-cadherin and β-catenin increased, indicating that hsa_circ_0005379 participated in the EMT process. Furthermore, the authors found that hsa_circ_0005379 may regulate the expression of epidermal growth factor receptor (EGFR) and act as an upstream molecule of the EGFR pathway. This conclusion was based on the fact that hsa_circ_0005379 can negatively regulate the expression of EGFR, but EGFR pathway agonists and inhibitors had no regulatory effect on hsa_circ_0005379.[61] In another study, it was found that downregulated hsa_circ_0007059 in OSCC had similar features. Its overexpression showed a tumor-suppressive effect on OSCC and also regulated Bcl-2 family and EMT-related protein changes. But, the mechanism by which downregulated hsa_circ_0007059 promoted the growth of OSCC cells was by influencing the downstream protein levels of the AKT/mTOR signaling pathway.[62] Similarly, hsa_circ_0055538 was reduced in OSCC and its overexpression could reduce the proliferation, migration and invasion of OSCC and induce OSCC cell apoptosis. After silencing hsa_circ_0055538, it was found that the levels of p53, Bax, caspase-3, etc. decreased in OSCC cells, while Bcl-2 increased. And upregulating p53 levels in OSCC cells would reverse the effect of knocking down hsa_circ_0055538 on OSCC. Therefore, the authors suggested that hsa_circ_0055538 may regulate the progression of OSCC through the p53/Bcl-2/caspase signaling pathway.[63]

All above, most studies have focused on detecting the expression of cell apoptosis-related proteins (BAX/Bcl-2) and EMT-related proteins (such as vimentin and N-cadherin). It suggests that circRNAs play a key role in the development of OSCC, but the specific regulatory mechanism between circRNAs and these proteins is still unclear. Some studies have revealed the protein sponge and protein scaffold capabilities of circRNAs. For instance, circMBNL1 contains multiple MBNL1 binding sites and

can be specifically bound by MBNL1. Excess MBNL1 can promote circMBNL1 biogenesis, thereby reducing its mRNA level. And circMBNL1 can act as a sponge of MBNL1 to promote linear splicing of genes, thereby forming an autoregulatory loop.[64] Moreover, circ-Amotl1 can act as a protein scaffold and promote PDK1-dependent phosphorylation of AKT1 by binding to PDK1 and AKT1.[65] However, it has not been studied whether circRNAs in OSCC can serve as protein sponges or protein scaffolds, and further exploration will help to better understand the molecular mechanism of OSCC pathogenesis.

Therapy-Associated circRNAs

Cetuximab is an anticancer drug that specifically inhibits the cell cycle process by specifically binding to the EGFR domain of cells, thereby inducing tumor cell apoptosis. And EGFR is abundantly expressed in OSCC cells, which could promote the EMT process of OSCC, and cetuximab significantly inhibits the effect by binding to EGFR.[64] Su et al found that after adding cetuximab, the early apoptosis rates of OSCC cells with overexpression of hsa_circ_0005379 increased to 2-fold compared with the control group, indicating that overexpression of hsa_circ_0005379 could increase the sensitivity of cetuximab to OSCC.[61] Fucoidan is a sulfated polysaccharide isolated from various brown algae and brown algae, and has many biological effects including anti-cancer effects.[66,67] Zhang et al found that fucoidan could inhibit OSCC growth, migration and invasion.[68] In addition, bioinformatics database prediction and qPCR experiments confirmed that fucoidan can increase the expression of circFLNA in OSCC cell lines. Overexpression of circFLNA also inhibited the proliferation, migration and invasion of OSCC and induced apoptosis. After silencing circFLNA in OSCC cells, the antitumor effect of fucoidan was reversed, suggesting that the fucoidan-circFLNA axis may regulate the process of OSCC. Chen et al identified that circATRNL1 was significantly downregulated in OSCC and its overexpression could increase the radiosensitivity of OSCC cells by inhibiting cell survival and inducing apoptosis.[69] Further experiments revealed that circATRNL1 was a sponge of miR-23a-3p, which can enhance the expression of its downstream target *PTEN*. In addition, knocking down *PTEN* increased the colony-forming ability and proliferation of OSCC cells, and inhibited cell viability, apoptosis as well as cell-cycle arrest, while circATRNL1 overexpression caused the opposite effect. Therefore, they believed that circATRNL1/miR-23a-3p/*PTEN* axis may play an important role in regulating the radiosensitivity of OSCC. However, it is not clear whether all of the above circRNAs are beneficial to clinical treatment, and a large number of experiments are still required to verify their effects before entering the clinic. Especially when used in humans, safety research is particularly important, and current research still lacks relevant experiments.

Conclusions and Perspectives

Extensive exploration in the field of circRNA research has brought us many new insights into cancer pathobiology. Advanced sequencing technologies can also help researchers better explore circRNAs and predict their functions, thus greatly promoting the development of this field. In addition, with the maturation of experimental verification, the functional research of circRNAs on cancer biological behavior has been greatly promoted. Mounting evidence have revealed the important role of circRNAs in the development of OSCC. They have great potential as biomarkers and may be used to diagnose and predict the prognosis of OSCC patients. And circRNAs can act as miRNA sponges to regulate the expression of downstream oncogenic molecules via circRNAs-miRNAs-mRNAs axis, suggesting that circRNAs play a key role in regulating the progression of OSCC. CircRNAs can also affect cancer-related signaling pathways in OSCC, such as MAPK and PI3K/Akt/mTOR axis, and might have an impact on the chemosensitivity and radiosensitivity of OSCC.

However, the study of circRNAs in OSCC is still in its infancy. First, circRNAs, like other ncRNAs as potential biomarkers, have more complicated design and identification methods in experiments, and these technologies need to be standardized. Second, there is still a lack of clinical applications on circRNAs, and the current research conclusions are only based on the results of a few OSCC patients. Hence, their accuracy and replicability as biomarkers should be validated, and this is crucial for their clinical application in the future. Importantly, current circRNAs exhibit different correlations with the early or advanced stages of OSCC. The underlying differences are interesting and seem worth of further exploration. Third, most existing research on circRNAs in OSCC focuses on circRNAs located in the cytoplasm and their function as miRNA sponges. Nevertheless, there is currently no research on their protein sponges or protein scaffolds capabilities, and these functions have been widely explored in other fields.[70–72] Fourth, circRNA can also be a template for translation, and Chen et al have developed the first protein-coding circRNA database.[73] Circ_ FBXW7[74] can encode a novel protein, which is named FBXW7-185aa, and can inhibit the

proliferation and cell cycle of glioma cells. CircRNA_FECR1[75] located in the nucleus could control the growth of breast cancer by regulating DNA methylase and demethylase. After screening out the most differentially expressed circRNAs, through comprehensive analyzing the characteristic sequences they contain (such as MREs, RBPs motifs, ORF and IRES) and the analysis of existing databases, the function of circRNAs can be well predicted. However, more should be done in OSCC in the future.

In addition, circRNAs can be released through extracellular vesicles and may play a role in intercellular communication and TME.[76] Hsa_circRNA_002178 is highly expressed in lung adenocarcinoma and can be detected in plasma exosomes, showing potential as a diagnostic biomarker.[77] But the study of circRNAs in extracellular vesicles is still blank in OSCC, and future research in this field will be of great significance to the diagnosis and pathogenesis of OSCC. Interestingly, artificial circRNAs have also been found to function in eukaryotic cells. For example, engineered circRNA is designed to treat cardiac hypertrophy by sponging to target miRNA, and shows exciting potential as future therapeutics.[78] Besides, it can enhance PDL1 expression through sponging miR-34 and may be used as a target for immunotherapy. And increased evidence has uncovered the vital role of circRNAs in the sensitivity of radiotherapy and chemotherapy.[79] In conclusion, the results of these studies on circRNAs are inspiring, and fully clarifying the role of circRNAs will hope to accelerate circRNAs from bench to bed, especially in OSCC.

Funding

This work was supported by National Natural Science Foundation of China grants (Nos. 81972542, 81902779 and 21838002) and National Science Foundation of Sichuan Province (No. 2018JY0196, 2020JDRC0018 and 2020YFS0171).

Disclosure

The authors report no conflicts of interest in this work.

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