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REVIEW ARTICLE

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CircRNAs: a family number of miRNA regulatory transcriptome in laryngeal carcinoma

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Abstract

Laryngeal carcinoma (LC) is a common head and neck cancer, which is the result of mutational changes due to gene dysregulation and etiological factors such as tobacco and smoking. A large number of patients received a poor prognosis due to diagnosis at an advanced stage. This highlights the need for definitive, early, and efficient diagnoses. With rapid development of high-throughput sequencing, circular RNA (circRNA) has been reported to play a pivotal role in cancer. CircRNA functions as a microRNA (miRNA) sponge in the regulation of mRNA expression, forming circRNA-miRNA regulatory axis. In this review, we described the axis in LC. The result indicated that CDR1as, hsa_circ_0042823, hsa_circ_0023028, circPARD3, hsa_circ_103862, hsa_circ_0000218, circMYLK, circCORO1C, hsa_circ_100290, circ-CCND1, hsa_circ_0057481, circFLAN, and circRASSF2 expressed higher in LC, whereas, hsa_circ_0036722 and hsa_circ_0042666 expressed lower. The circRNAs regulated the target genes by sponging miRNAs and contributed to the pathogenesis of LC.

KEYWORDS
circRNA, circRNA-miRNA axis, laryngeal carcinoma, miRNA sponge, regulation

1 | INTRODUCTION

In 2021, an estimated 12,620 laryngeal carcinoma (LC) cases, the most common type is laryngeal squamous cell carcinoma (LSCC), will be diagnosed, including 9940 males and 2680 females in the United States. Approximately 3770 patients will die from the disease, including 3020 males and 750 females. Despite the reduction of overall incidence, the 5-year survival rate has decreased from 66% to 63%.[1] Several risk factors contributed to the pathogenesis of laryngeal cancer including tobacco and alcohol consumption, asbestos, polycyclic aromatic hydrocarbons, textile dust, and HPV infection.[2] The most significant of these are tobacco and alcohol consumption. A linear association between tobacco and alcohol use with the development of laryngeal cancer has been reported. A large number of patients were diagnosed at advanced stage due to lack of early efficient diagnostic methods. Patients diagnosed at early stage benefit from the success of organ preservation-based surgical approaches, which preserves the basic function of the larynx, breathing and speech.[3] Therefore, it is particularly important to explore new biomarkers for the early diagnosis to prolong the 5-year survival rate and improve the quality of life for LC patients.

Circular RNA (circRNA), containing highly conserved loop structure and without 5′-cap and 3′-poly (A) structures, enable their resistance to exonuclease degradation.[4] In recent years, with the development of high-throughput RNA sequencing (RNA-seq) and circRNA-specific bioinformatics algorithms, thousands of circRNAs with tissue-specific expression pattern have been identified in eukaryotes.[5,6] Recent study found that circRNAs control mRNA stability and transcription by forming a regulatory axis with microRNA (miRNA),[7] raising the possibility of their potential as biomarkers in cancer. This review discusses the prospects of the circRNA-miRNA axis as a potential biomarker for LC.

2 | circRNA BIOGENESIS AND miRNA SPONGING

The three main ways of biogenesis of CircRNAs are described below. First,back-splicing mechanism, looping of the intron sequences flanking the downstream splice-donor site, and the upstream splice-acceptor site bring these sites into close proximity (Figure 1). This looping can be mediated by base pairing between inverted repeat elements such as *Alu* elements,[8,9] or by the dimerization of RNA-binding proteins (RBPs)[10] or RNA binding protein that bind to specific motifs in the flanking introns.[11] Double-stranded RNA (dsRNA)-specific adenosine deaminase (ADAR) enzymes, and ATP-dependent RNA helicase A (also known as DHX9) were reported to suppress the biogenesis circRNAs by preventing base pairing between inverted repeats.[12] NF90/ NF110, products of interleukin enhancer-binding factor 3 (*ILF3*) promote the production of circRNA by stabilizing intronic RNA pairs.[13]

Additionally, alternative splicing (exon skipping) is another circRNA biogenesis method. Exons were removed from mRNA and contained in the lariats, which form circRNA by internal splicing.[8,14] Finally, intronic lariats, when escaping from debranching, can lead to the formation of ciRNAs.[15] According to their structures, circRNAs are classified into three types: exonic circRNAs (ecircRNAs), circular intronic RNAs (ciRNAs), and exon-intronic circRNAs (EIciRNAs).

CircRNAs have been identified to act as sponges of miRNAs, which are 25 nucleotides long and play a role in the stability of mRNA. CircRNAs have the potential to act as oncogenes or tumor suppressors by sponging different miRNAs.[16,17] This review discusses the prospects of the miRNA-circRNA axis as a potential biomarker for LC.

3 | THE miRNA-circRNA AXIS REPORTED IN LC

This review will describe only circRNAs that form the circRNA-miRNA regulatory axis in LC and their roles in other cancers. Table 1 briefly describes the regulatory network and expression levels in LC tissues.

3.1 | CDR1as

CDR1as (also known as ciRS-7), one of the earliest and best characterized circRNAs, containing about 70 binding sites for miR-7 per molecule and can affect the activity of miR-7 markedly.[4,18] Several studies have analyzed the expression of CDR1as in Hepatocellular Carcinoma and Cholangiocarcinoma (HCC). The result showed that CDR1as promoted the proliferation and invasion of HCC cells by inhibiting the expression of miR-7 and its downstream target genes CCNE1, PIK3CD, KLF4, and p70S6K.[19-22] Su et al.[23] demonstrated that CDR1as was upregulated in nonsmall cell lung cancer (NSCLC) and increased the proliferation, metastasis, and invasion ability of NSCLC cells by the CDR1as/miR-7/NF-kB axis. It is reported that CDR1as is highly expressed in LSCC patients with high TNM stage, poor tumor differentiation, lymph node metastasis and poor prognosis, while the expression level of miR-7 is low. In vitro study demonstrated that CDR1as molecules could upregulate the key targets of miR-7, CCNE1, and PIK3CD in LSCC cells by acting as a sponge of miR-7.[24]

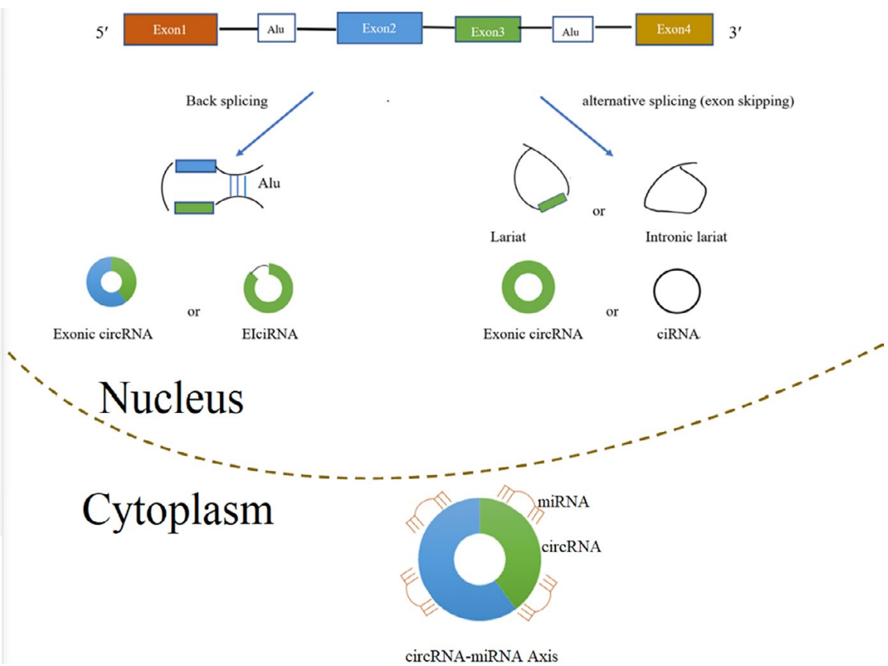

FIGURE 1 The biogenesis of circRNAs. Base repairing inverted repeat elements (such as Alu elements) bring a downstream splice-donor site into close proximity with an upstream splice-acceptor site, and this association may lead to back-splicing. circRNAs can also be generated from splicing intermediates known as lariat precursors that are created by an exon-skipping event during linear splicing or from intronic lariat precursors that escape from the debranching step of canonical linear splicing. miRNA sponged by circRNA in the cytoplasm

TABLE 1 A brief summarization circRNA-miRNA pathway regulatory axis in Laryngeal carcinoma

CircRNA	Expression in LC	Sponged MiRNA	Regulatory axis	Reference
CDR1as	Up	miR-7	CDR1as /miR-7/ CCNE1/PIK3CD	26
hsa_circ_0042823	Up	miR-877-5p	hsa_circ_0042823/ miR-877-5p/ FOXM1	31
circABCB10	/	miR-588	circABCB10/miR-588/ CXCR4	36
hsa_circ_0023028	Up	miR-486-3p	circ_0023028/miR-486-3p/LASP1	41
circPARD3	Up	miR-145-5p	circPARD3/miR-145-5p/PRKCI-Akt-mTOR	44
hsa_circ_103862	Up	miR-493-5p	circ-103862/ miR-493-5p/GOLM1	45
hsa_circ_0000218	Up	miR-139-3p	Circ_0000218/ miR-139-3p/Smad3	49
hsa_circ_0036722	Down	miR-1248	circ_0036722/ miR-1248/RHCG	54
circMYLK	Up	miR-195	circMYLK/ miR-195/cyclinD1	58
	Up	miR-145-5p	circMYLK/miR-145-5p/MEK/ERK and NF-κB	59
circCORO1C	Up	let-7c-5p	CircCORO1C /let-7c-5p/PBX3	60
hsa_circ_100290	Up	miR-136-5p	circRNA_100290/ miR-136-5p /RAP2C	65
circ-CCND1	Up	miR-646	Circ-CCND1/ miR-646 and HuR/ CCND1	70
hsa_circ_0057481	Up	miR-200c	Hsa_circ_0057481/ miR-200c/ZEB1	72
hsa_circ_0042666	Down	miR-223	Hsa_circ_0042666/ miR-223/TGFBR3	73
circFLAN	Up	miR-486-3p	CircFLAN/ miR-486-3p/ FLNA	78
circRASSF2	Up	miR-302b-3p	CircRASSF2/ miR-302b-3p/IGF-1R	86

3.2 | hsa_circ_0042823

MiR-877-5p was reported to implicated in various cancers such as colorectal cancer (CRC)[25] and HCC.[26] Another study found miR-877 could combine with the specific fork-head box protein M1(FOXM1) mRNA 3′UTR-binding sites and play a role in inhibiting the expression of FOXM1 gene,[27] which is associated with cellular proliferation, cell cycle progression, tissue repair, and carcinogenesis.[28] Recently, hsa_circ_0042823 was found expressed high in the LSCC cell lines (AMC-HN-8 and TU686), and could promote proliferation, migration, and invasion of AMC-HN-8 cells by upregulating the expression of FOXM1 via sponging miR-877-5p.[29]

3.3 | circABCB10

CircABCB10 was increased in NSCLC and promoted proliferation and invasion of NSCLC cell lines by forming circABCB10/miR-584-5p/E2F5 axis.[30] Sun et al.[31] observed high expression of circ-ABCB10 and fatty acid binding protein 5 (FABP5) in glioma tissues, whereas lower expression of miR-620. Further assays demonstrated silencing of circ-ABCB10 significantly inhibited the proliferation, migration, and invasion of glioma cells by sponging toward miR-620 whose target gene was FABP5, which could upregulate vascular endothelial growth factor (VEGF) and matrix metalloproteinases (MMPs) that related to angiogenesis and metastasis.[32,33] Zhao et al.[34] found deletion or knockdown of circABCB10 significantly reduce the proliferation, invasion, and migration of LSCC cells. The mechanism was circABCB10 down-regulated chemokine receptor 4 (CXCR4) that play a vital role in human cancers[35] by severing as a sponge for miR-588. Nevertheless, the author did not describe the expression level of circABCB10 in LSCC tissues or cells, the expression of circABCB10 in LSCC tissues needs to be further explored.

3.4 | has_circ_0023028

Chen et al. first observed has_circ_0023028 up-regulated in LC, that inhibiting the proliferation, migration, and invasion, and could act as miR-194-5p sponge.[36] MiR-194-5p has been reported to promote the growth of HCC by miR-194-5p/fork-head box A1(FOXA1) axis[37] and inhibit cell migration and invasion in bladder cancer by targeting E2F3.[38] Zheng et al.[39] found has_circ_0023028 expressed high in LSCC tissues and cells could promote cell proliferation, metastasis, and cell cycle process. Mechanism analysis showed circ_0023028 could sponge miR-486-3p, that suppressed LSCC cell progression via binding to Lin-Isl-Mec (LIM) and SH3 domain protein1 (LASP1), which was found implicated in several human cancers and could be targeted by miRNAs.[40,41]

3.5 | circPARD3

Gao et al. observed circPARD3 expressed high in LSCC tissues and was associated with LSCC progression. Functional analysis demonstrated that circPARD3 inhibited autophagy and promoted LSCC cell proliferation, migration, invasion, and chemoresistance. Further study revealed that circPARD3 inhibited autophagy by PRKCI-Akt-mTOR pathway through sponging miR-145-5p.[42] The role of circPARD3 played in other cancers has not been reported.

3.6 | has_circ_103862

Researchers found that has_circ_103862 was upregulated in LSCC tissues and was related to metastasis and prognosis of LSCC patients. Knock down of circ_103862 reduce proliferation, migration, and invasion ability of LSCC cells. Mechanically, exploration showed that miR-493-5p, sponged by has_circ_103862, could target Golgi membrane protein 1 (GOLM1). Thus, has_circ_103862/ miR-493-5p/ GOLM1 regulatory axis was formed.[43] GOLM1, a type II transmembrane protein of the Golgi cisternae, highly expressed in tumor cells and is regarded as a potential cancer cell marker.[44] Zhang et al. reported GOLM1 act as an oncogene in NSCLC and promoted the proliferation and invasion.[45]

3.7 | has_circ_0000218

Pei et al.[46] found that has_circ_0000218 was upregulated in CRC tissues and cell lines, which significantly related to clinical stage and overexpression promoted the proliferation and metastasis of CRC cells by forming has_circ_0000218/miR-139-3p/RAB1A axis. Bai et al.[47] reported that circ_0000218 silencing inhibited the LSCC cell viability, growth and promoted apoptosis by regulating miR-139−3p which can bind to smad family member3 (Smad3). Smad3, could regulate canonical transforming growth factor-β(TGF-β) which plays a key role in angiogenesis and has been demonstrated to related to several cancers including colon cancer,[48] CRC,[49] bladder cancer,[50] and prostate cancer.[51]

3.8 | has_circ_0036722

Has_circ_0036722 was observed decreased in LSCC tissues, and the expression level was associated with poor differentiation. ROC curve analysis indicated that hsa_circ_0036722 could act as a diagnostic biomarker for LSCC with AUC of 0.838. Luciferase reporter assays showed that hsa_circ_0036722 regulate the expression of RHCG in LSCC by sponging miR-1248.[52] RHCG, the parental gene of has_circ_0036722, were downregulated in LSCC tissues and has been proved as a cancer suppressor gene in several cancers including tongue squamous cell carcinoma (TSCC)[53] and esophageal squamous cell carcinoma (ESCC).[54]

3.9 | circMYLK

Chen et al. found circMYLK was upregulated in bladder cancer, which could promote the progression of bladder cancer in mechanism that circMYLK could relieve the suppression on VEGFA by binding to miR-29a. When knockdown, circMYLK inhibited cell proliferation and induced apoptosis. The progression of bladder cancer xenografts was promoted by circMYLK high expression.[55] Duan et al.[56] found that the circMYLK promoted LSCC cell proliferation may partly by accelerating cell cycle progression by sponging to miR-195 which can target cyclin D1, a regulator of the G1/S transition. Another study found that circMYLK was highly expressed in laryngeal cancer and could sponge miR-145-5p, thereby blocking MEK/ERK and NF-κB pathway.[57]

3.10 | circCORO1C

CircCORO1C, composed of exons 7 and 8 of CORO1C, has been demonstrated as highly expressed in LSCC tissues and cells. Suppression of circCORO1C inhibited the activity LSCC cells. Mechanism research found that circCORO1C could competitively bind to let-7c-5p and relieve the repression of Pre-B-cell leukemia homeobox transcription factor 3 (PBX3), which promoted the EMT and finally the malignant progression of LSCC.[58] PBX3 was reported to express high in cancer tissues such as prostate cancer[59] and cervical cancer.[60]

3.11 | circRNA_100290

Chen et al. reported that circRNA_100290 was upregulated in oral squamous cell carcinoma (OSCC) and promoted the cancer progression by relieving the repression on Glucose transporter 1(GLUT1) via acting as a ceRNA of miR-378a.[61] Fang et al.[62] found circRNA_100290 taking part in the progression of CRC by circRNA_100290/miR-516b/FZD4/Wnt/b-catenin axis. CircRNA_100290 was found expressed remarkably high in LSCC tissues and cell lines compared with the normal controls and positively related to advanced TNM stage and lymph node metastasis in LSCC patients. Functional analysis demonstrated upregulated circRNA_100290 promoted LSCC cell proliferation, migration, and invasion, while the effect on cell apoptosis was opposite. CircRNA_100290 display sponge activity to miR-136-5p, whose target gene was RAP2C, a family member of RAS,[63] which was validated to function as an oncogene in various cancers.[64,65]

3.12 | circ-CCND1 (hsa_circ_0023303)

Circ-CCND1 is derived from Cyclin D1 (CCND1), which is one number of highly conserved cyclin family protein and has been demonstrated to be necessary for the transition of cell cycle from G1 phase into S phase[66] and the dysregulation can lead to uncontrolled cell proliferation and malignancy.[67] Circ-CCND1 was found significantly up-regulated in LSCC and correlated to aggressive clinical features and prognosis of LSCC patients. It interacts with human antigen R (HuR) protein and acts as the sponge for miR-646, thereby enhances CCND1 mRNA stability and increases CCND1 expression, and finally facilitates LSCC growth. [68]

3.13 | hsa_circ_0057481

Gao et al. reported that hsa_circ_0057481 was significantly upregulated in LC tissues, silencing of which restrained the cell activity, and caused cell apoptosis in LC cells. Hsa_circ_0057481 showed sponging activity toward miR-200c, which targeted ZEB1, forming hsa_circ_0057481/ miR-200c/ ZEB1.[69] ZEB1/ miR-200 feedback loop was demonstrated to play a role in human cancers via Notch pathway.[70]

3.14 | hsa_circ_0042666

Fan et al. reported that hsa_circ_0042666 expression was significantly decreased in LSCC tissues, which associated with advanced tumor stage, lymph-node metastasis, and poor prognosis of LSCC patients and cloud reduce the proliferation and invasion abilities in LSCC cells by sponging to miR-223, whose target gene was TGFBR3[71] that was a common tumor suppressor gene[72-74] and the inhibition of miR-223/TGFBR3 axis on lung cancer progression has been demonstrated.[75]

3.15 | circFLAN

Shan et al. reported high expression of circFLAN in LSCC, that was correlated with lymph node metastasis and showed sponge activity to miR-486-3p in LSCC cells, relieved miR-486-3p-induced repression of flamin A(FLNA) which promotes LSCC cell migration.[76] FLNA has the ability of actin-binding properties,[77] which is involved in multiple cell functions, such as migration and adhesion.[78] FLNA was demonstrated to be a tumor-promoting protein and involved in several human cancers, including bladder cancer,[79] lung cancer,[80] and breast cancer.[81] CircFLAN has also been observed to promote progression of gastric cancer (GC) by targeting 6-phosphofructo-2-kinase (PFKFB2) through showing sponging activity to miR-646.[82] Lately, another study demonstrated that circFLNA acted as a sponge of miR-486-3p to promote the proliferation, migration, and invasion of lung cancer cells via regulating XRCC1 and CYP1A1.[83]

3.16 | circRASSF2

circRASSF2 was upregulated in LSCC and higher expression of circRASSF2 was positively correlated with LSCC metastasis. circRASSF2, when knockdown, inhibited cell proliferation and markedly decreased cell colony formation, whereas circRASSF2 overexpression has the opposite effect. Further study declared that circRASSF2 displayed sponge activity toward miR-302b-3p, which targets insulin-like growth factor 1 receptor (IGF-1R).[84] CircRASSF2/ miR-1178/TLR4 axis was reported to regulate papillary thyroid carcinoma progression and may be a promising therapeutic target for therapy.[85] Zhong et al.[86] revealed that CircRASSF2 promoted breast cancer progression through regulating Homeobox gene A1(HOXA1) by sponging to miR-1205.

4 | CONCLUSIONS AND PERSPECTIVES

The discovery of circRNAs has opened a new chapter of cancer progression. The unique features of circRNAs including high conservative, stability, expression abundance, and tissue and disease expression-specificity enable them to act as biomarkers for cancer diagnosis and progression. With the development of sequencing technologies, the exploration of circRNAs has made a big step forward. Increasing evidences have revealed the important role of circRNAs in the development of LC. They can act as biomarkers for LC diagnosis and prognosis. Most circRNAs implicated in LC are reported to function by sponging miRNAs to cause a substantial change in the downstream miRNA activity via circRNAs-miRNAs-mRNAs axis. CircRNAs have been demonstrated to affect cancer-related signaling pathways in LC, such as PI3K/Akt/mTOR axis, and might play a role in the chemo-sensitivity and radio-sensitivity of LC.

The field of studying circRNAs still faced lots of challenges. First, the present studies focus predominantly on the ceRNA function of circRNAs. Research on their protein sponges' or protein scaffolds' capabilities is blank; this review does not cover it either. Additionally, the study of circRNAs is limited to function as potential biomarkers. The application on clinical is lacking, and present conclusions are based on a small part of LC patients, which need further verification that is necessary for use in clinical use. Finally, circRNAs are reported to participate in intercellular communication and tumor micro-environment, whereas the study of circRNAs exomes lacks LC, and future research in this field will be of great significance to the diagnosis and pathogenesis of LSCC.

Nevertheless, inspiring findings are emerging. Hg19_circ_0005033 was demonstrated to affect LSCC stem cells and promote tumor occurrence and chemotherapy resistance, which may help clinician make therapy design.[87] CircRNA was constructed to treat cardiac hypertrophy in vitro and cardiac function was preserved in treated mice.[88] All these findings are inspiring and clarify the significance of further study of circRNA, which will contribute to a better understanding of cancer pathology and personalized treatment.

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CONFLICT OF INTEREST

The authors report no conflicts of interest in this work.

AUTHOR CONTRIBUTIONS

Hua Yuan designed the study. Limin Miao drafted the manuscript. Guanying Feng revised the manuscript.

DATA AVAILABILITY STATEMENT

The data sets analyzed during the current study are available from the first author on reasonable request.

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