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REVIEW

Biogenesis, Functions, and Role of CircRNAs in Lung Cancer

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Abstract: CircRNAs, a class of endogenous non-coding RNAs with closed-loop structures, have attracted increasing attention because of their good stability, high specificity of tissue expression, long half-life, and highly conserved sequence. CircRNAs have multiple biological functions, including miRNA sponge, transcription regulator, protein translation, interaction with protein, RNA maturation, and so on. These functions indicate the important role of circRNAs in tumorigenesis and malignant progression and their potential as potent diagnostic biomarkers and therapeutic molecules. In recent years, an increasing body of evidence suggests that circRNAs play a crucial role in proliferation, migration, invasion, and apoptosis of lung cancer cells. Therefore, circRNAs have gradually become a research focus in the diagnosis and treatment of lung cancer patients. This review summarizes the classification, biogenesis, and function of circRNAs, and discusses the role of circRNAs in the diagnosis, prognosis, and treatment of lung cancer patients.

Keywords: circRNA, lung cancer, diagnosis, prognosis, treatment

Introduction

According to data reported by a cancer journal, approximately 2.2 million new lung cancer (LC) cases worldwide make it the second cancer (11.4% of all cancers), and approximately 1.8 million deaths place lung cancer at the top of the list of cancer-related deaths (18.0% of all cancer deaths, much more than other cancers).[1] Lung cancers are generally divided into two pathological types: 85% of the total cases are non-small cell lung cancer (NSCLC), and 15% of the total cases is small cell lung cancer (SCLC).[2] NSCLC can be mainly classified into three types: lung adenocarcinoma (LUAD; 40%), lung squamous cell carcinoma (LUSC; 25%), and large cell lung carcinoma (LCLC; 10%).[1] Although advances in diagnosis and treatment have improved the survival rates of lung cancer patients, the 5-year survival rate of advanced lung cancer patients is only 17.7%.[3] Moreover, the survival rate of patients with early stage LC is significantly higher than that of patients with advanced LC. Therefore, more effective biomarkers are crucial for early diagnosis and prediction of prognosis.

Circular RNAs (circRNAs), a class of endogenous non-coding RNAs, were first discovered in RNA viruses via electron microscopy in 1976.[4] In contrast to linear RNAs, circRNAs have no 5′ to 3′ polarity and a polyadenylated tail but form a highly stable covalent closed-loop structure, which makes them more stable in tissues and plasma.[5] Many studies have confirmed the crucial role of circRNAs in the development and progression of various cancers.[6] Furthermore, an increasing body of research

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shows that abnormal expression of circRNAs plays an important role in the development and progression of LC.[7] This suggests that circRNAs can function as potential targets for the diagnosis and prognosis of LC. The current review introduces the classification and biogenesis of circRNAs, and summarizes the roles and corresponding mechanisms of many discovered circRNAs in lung cancer, and discusses the potential value of circRNAs as diagnostic and prognostic biomarkers for lung cancer.

Classification and Biogenesis of circRNAs

Based on their origins and compositions, circRNA can be mainly classified into six categories (Table 1).

Exonic circRNAs (ecircRNAs)

EcircRNA consists of one or multiple exons, which is the most common type (more than three-fourths of the whole).[8] There are two types of ecircRNA formation, namely, direct back-splicing, and exon skipping.[9] The direct back-splicing model includes two mechanisms, intron-pairing-driven, and RNA-binding proteins (RBPs)-driven circularization, while lariat-driven circularization is the main mechanism in the exon-skipping model.[10]

Intronic circRNA (ciRNAs)

CiRNAs are only composed of introns that have failed to be debranched and abundantly distributed in the nucleus. Furthermore, the processing of ciRNAs mainly depends on consensus sequence motif that might be essential for escaping from de-branching.[11]

Exonic-Intronic circRNAs (ElciRNAs)

EIciRNAs consist of exons and introns that are retained between the exons.[12] That is to say, in circular RNA containing several exons and introns, introns were not removed.

Table 1 Classification of circRNAs

Type	Example	References
Exonic circRNAs	HIPK2/3	[8]
Intronic circRNA	ci-ankrd52	[11]
Exonic-intronic circRNAs	cSMARCA5	[16]
Intergenic circRNAs	chr5: 10,213,603|10,224,173	[13]
tRNA intronic circRNAs	tric31905	[14]
Antisense circRNAs	circANRIL	[17]

Intergenic circRNAs

The two intronic RNA fragments with GT-AG splicing signal act as splicing donor and acceptor to form the entire circRNA.[13]

tRNA Intronic circRNAs (tricRNAs)

Pre-tRNAs, which containing introns, are cut by endonuclease complex and forming a special type of intronic circRNAs and mature tRNAs.[14]

Antisense circRNAs

Mechanically speaking, they are also a type of ecircRNAs, but are formed from antisense non-coding RNAs.[15]

Schematic of circRNAs biogenesis is shown in Figure 1.

Functions of circRNAs

miRNA Sponge

MiRNA is an important negative regulator of protein expression, which inhibits the translation of target gene mRNA or promotes the degradation of mRNA by binding to mRNA.[18] Many studies have demonstrated that circRNAs can act as competitive endogenous RNAs (ceRNAs), namely miRNA sponges, which bind to miRNAs by means of microRNA response elements (MREs) to inhibit the function of mRNAs.[19,20] For example, CDR1As were observed to act as miRNA sponges, with more than 70 conserved binding sites of miRNA-7, and overexpression of ciRS-7 competitive binding to miR-7 and facilitated malignant progression in esophageal squamous cell carcinoma (ESCC).[21] Moreover, circRNA-FOXO3 inhibits proliferation, migration, and invasion of NSCLC cells through specifically sponging miR-155 and abrogating the inhibition of FOXO3 gene.[22] In addition, circ-HIPK3 can both facilitate tumor progression by regulating miR-421/ZIC5 axis in glioma and promote epithelial–mesenchymal transition (EMT) of cervical cancer through sponging miR-338-3p to release HIF-1α gene.[23,24] It can also inhibit tumorigenesis of hepatocellular carcinoma via the miR-582-3p/DLX2 axis.[25] Therefore, one circRNA can sponge multiple miRNAs to play a role in promoting or inhibiting tumorigenesis in different cancers.

Translation Regulator

Further evidence has suggested that circRNAs can be involved in regulating gene transcription. Compared with

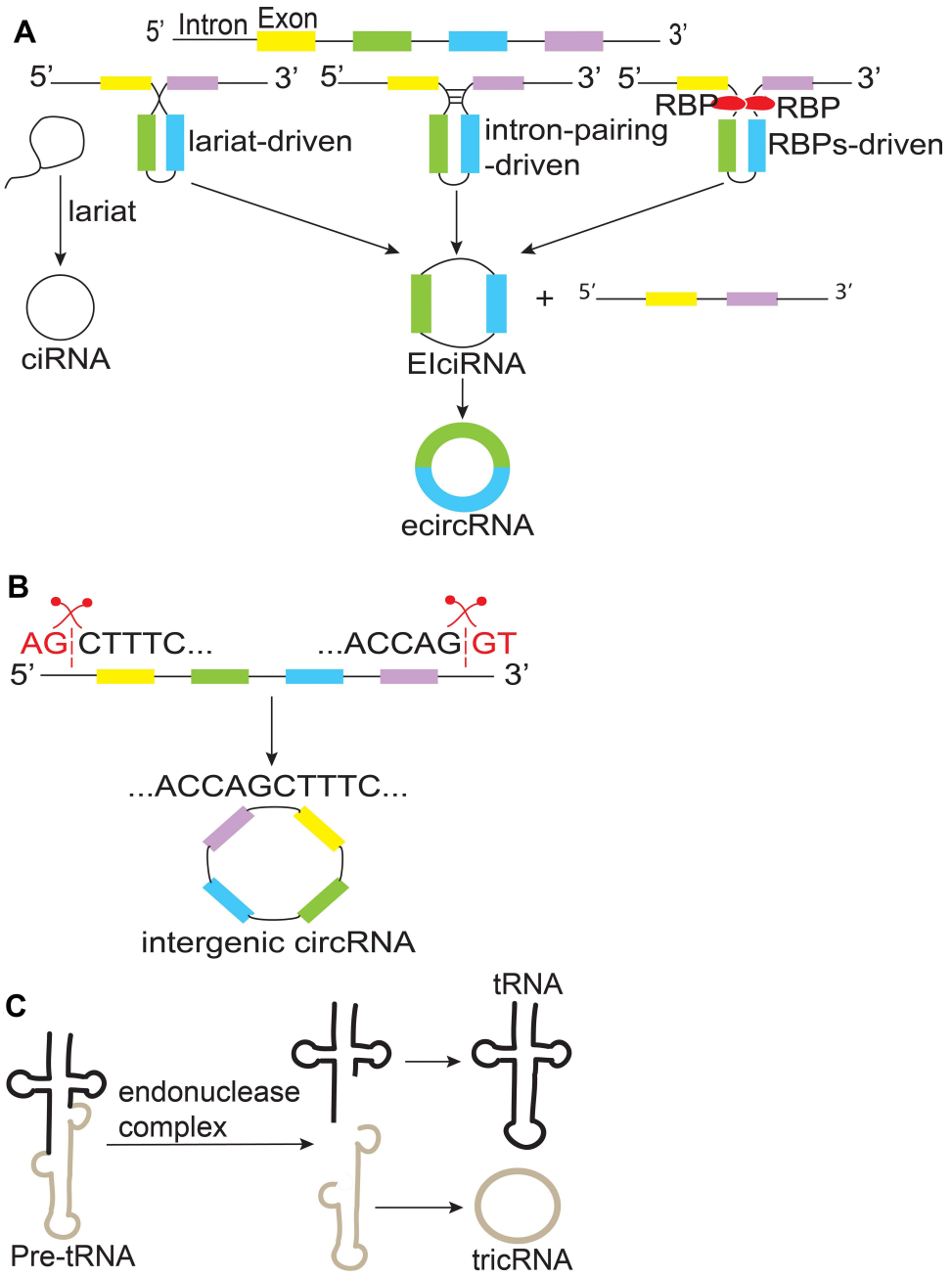

Figure 1 Biogenesis of circRNAs. (**A**) CircRNAs are mainly produced by three mechanisms: lariat-driven, intron-pairing-driven, RNA-binding proteins (RBPs)-driven circularization. (**B**) Inter-genic circRNAs are spliced by two intronic circRNA fragments containing GT-AG splicing signals. (**C**) TricRNAs are produced from pre-tRNAs that containing introns.

ecircRNAs, which are mainly located in the cytoplasm, EIciRNAs and ciRNAs are predominantly located in the nucleus and do not sponge miRNA, so they are normally involved in regulating gene expression levels. ElciRNAs may form ElciRNA-U1 snRNA complexes through specific RNA–RNA interactions with U1 snRNA, and then interact with the promoters of the Pol II transcription complex to promote gene expression.[12] Similar to EIciRNAs, cirRNAs also can interact with polymerase II complex, such as c-siRT7, which down-regulates the expression of the corresponding genes ANKRD52 and SIRT7 by interacting with the polymerase II complex.[11] Thus, circRNA plays a crucial role in the regulation of gene expression.

Protein Translation

CircRNAs were initially considered to be non-coding RNAs, but more and more evidence has emerged that

some circRNAs can also encode proteins. As long as circRNA has a complete and sufficiently long open reading framework, and with the help of some necessary regulatory elements, such as N6-methyladenosine (m^6A) modifications and the internal ribosome entry site (IRES) element, it can be translated into proteins, but the translation efficiency may be slightly lower than that of linear RNA.[26–28] As early as 1986, it was found that the circRNA of the hepatitis δ virus can generate a kind of protein with 122 amino acids.[29] Then, circ-ZnF609 was found to translate proteins into mouse myoblasts when driven by IRES.[30] In addition, other studies have indicated that circular RNA molecules can be translated into protein even without any IRES sequence, poly A, or cap structure.[31] All the above findings prove that circRNAs do have the ability to encode proteins.

Interaction with Protein

CircRNAs can bind to and interact with RNA-binding proteins (RBPs) through conserved protein-binding sites. For instance, CDR1as and circSry can bind with the miRNA effector AGO to cleave it and eventually promote its degradation.[15] CDK2 is essential for G1-S phase transition, the formation of circ-Foxo3–p21–CDK2 complex would inhibit the function of CDK2; then, cell cycle progression would be arrested in G1 phase.[32] In addition, circ-Foxo3 could bind to senescence-related proteins ID1 and E2F1 and stress-related proteins HIF1α and FAK to decrease levels of these proteins in the nucleus, block the anti-senescent function of these proteins and promote cellular senescence.[33] In summary, the interaction between circRNAs and proteins can alter the biological activity of proteins to affect their biological function or change the subcellular localization of proteins.

RNA Maturation

A variety of circRNA–protein interactions can be used to control ribosomal RNA maturation. For example, circANRIL binding to the C-terminal lysine-rich domain of PES1 hinders pre-rRNA binding and exonuclease-mediated rRNA maturation, thereby circANRIL impairs ribosome biogenesis, leading to activation of p53, promoting cell apoptosis and decreasing cell proliferation.[17] Consequently, circRNAs can be involved in regulating rRNA maturation.

Inhibit RNA Polymerase II Elongation

Acting as endogenous small regulatory RNAs, circRNAs can interfere with gene expression in the nucleus. The complex formed by circRNAs with NRDE-3 associates with NRDE-2 and recruits it into the nucleus, where it inhibits RNAP II during the elongation phase of transcription.[34] These nuclear-localized circRNAs direct an NRDE-2-dependent silencing of pre-mRNAs 3′ to sites of RNAi, thus inhibiting gene expression during the elongation phase of transcription. This is also a part of the regulation of gene expression.

Modulate Linear Splicing

CircRNAs are generally produced by pre-mRNA spliceosome.[35] CircRNAs production competes with linear splicing of flanking exons, and they can mutually regulate each other by competing for splice sites. Splicing factor-mediated exon circularization replaces linear splicing, thereby reducing the production of its mRNA. In brief, these competition effects might regulate the levels of both circRNAs and mRNAs.

The functions of circRNA are shown in Figure 2

CircRNAs in Lung Cancer

Advanced studies suggest that circRNAs may play an important role in the progression and development of lung cancer. CircRNAs can be involved in regulating the proliferation, migration, invasion, and apoptosis of tumor cells, and play a crucial role in the diagnosis, prognosis, and treatment of lung cancer.

CircRNAs as Potential Diagnostic Biomarkers in Lung Cancer

Compared with other non-coding RNAs, circRNAs have higher tolerance to RNA exonuclease due to their covalently closed structure.[36] Therefore, circRNAs can function as potential diagnostic biomarkers for lung cancer by virtue of their stable structure, high abundance, and tissue-specific expression (Table 2).

circ-ITCH

Circ-ITCH can sponge of miR-7 and miR-214 and inhibit the activation of the Wnt/β-catenin pathway in lung cancer, and thus regulate lung cancer cell proliferation.[37] Circ-ITCH serves as epigenetic miRNA sponges to competitively inhibit the binding between miRNA and ITCH, thereby increasing ITCH expression. ITCH can promote proteasome

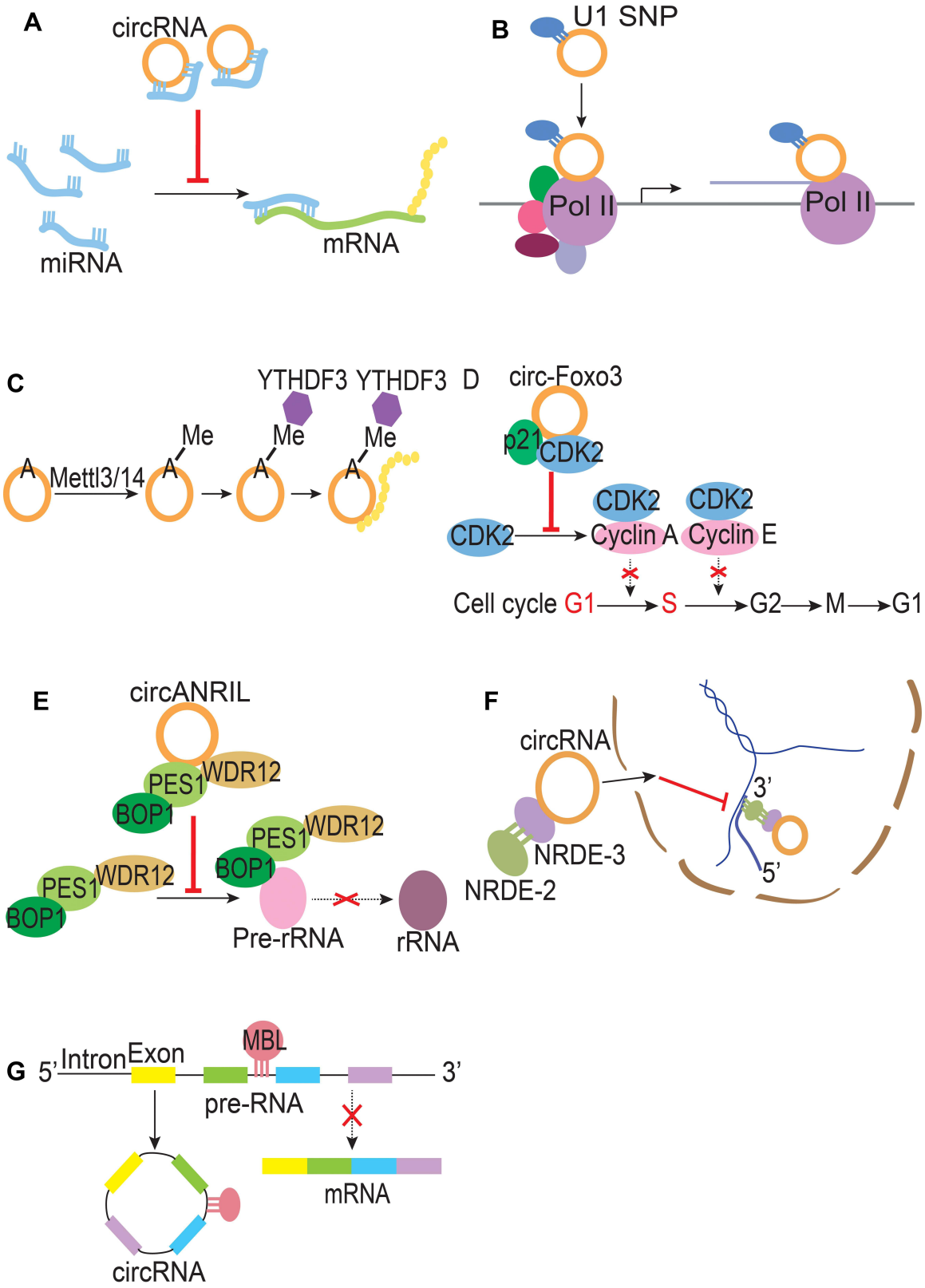

Figure 2 Function of circRNAs. (**A**) miRNA sponge (**B**) Translation regulator (**C**) Protein translation (**D**) Protein sponge (**E**) RNA maturation (**F**) Inhibit RNA polymerase II elongation (**G**) Modulate linear splicing.

Table 2 CircRNAs as Potential Diagnostic Biomarkers in Lung Cancer

circRNA	Function	Mechanism	Expression Pattern	Cell Characteristics	Clinical Characteristics	References
circ-ITCH	miRNA sponge	circ-ITCH↓- miR-7↑/ miR-214↑-Wnt/β-catenin↑	Down	Proliferation↓	Age (≥60), TNM	[37]
circPVT1	miRNA sponge	circPVT1↑-miR-125b↓-E2F2 pathway↑	Up	Proliferation↑, migration↑, invasion↑, apoptosis↓	Distant metastasis	[38]
circMET	miRNA sponge	circMET↑-miR-145-5p↓-CXCL3↑	Up	Proliferation↑, migration↑, invasion↑	TNM, LNM, tumor differentiation, OS	[39]
circGFRA1	miRNA sponge	circGFRA1↑-miR-188-3p↓-PI3K/AKT↑	Up	Proliferation↑	Unknown	[40]
hsa_circ_0013958	miRNA sponge	hsa_circ_0013958↑-miR-134↓-cyclin D1↑	Up	Proliferation↑, migration↑, invasion↑, apoptosis↓	TNM, LNM	[41]
circ_0005280	Unknown	Unknown -	Down	Unknown	Age (≥60), tumor size	[62]
circRNA100146	miRNA sponge	circRNA100146↑- miR-361-3p ↓/miR-615-5p↓-SF3B3↑	Up	Proliferation↑, migration↑, invasion↑, apoptosis↓	Unknown	[66]
hsa_circ_0001946	miRNA sponge	hsa_circ_0001946↓-NER signaling pathway↑	Down	Proliferation↓, migration↓, invasion↓, apoptosis↑, cisplatin sensitivity↑	Unknown	[70]
hsa_circ_0030998	miRNA sponge	hsa_circ_0030998↓-miR-558↑-MMP1/MMP17↓	Down	Proliferation↓, migration↓, invasion↓, Taxol resistance↓	TNM, distal metastasis	[72]
circFARSA	miRNA sponge	circFARSA↑-miR-330-5p↓/ miR-326↓-FASN↑	Up	Migration↑, invasion↑	Gender	[73]
circ-CCS	miRNA sponge	circ-CCS↑-miR-383↓-E2F7↑	Up	Proliferation↑, migration↑, apoptosis↓	TNM, LNM, tumor size	[77]
circ-IGF1R	miRNA sponge	circ-IGF1R↓–miR-1270↑–VANGL2↓	Down	Migration↓, invasion↓	LNM, tumor size	[82]
circRNA_102179	miRNA sponge	circRNA_102179↑-miR-330-5p↓-HMGB3↑	Up	Proliferation↑, migration↑, invasion↑	Unknown	[95]
circSATB2	miRNA sponge	circSATB2↑-miR-326↓-FSCN1↑	Up	Proliferation↑, migration↑, invasion↑	LNM	[96]
circ-ZKSCAN1	miRNA sponge	circ-ZKSCAN1↑-miR-330-5p↓-FAM83A↑	Up	Proliferation↑, migration↑	OS, tumor size, clinical stage	[97]
hsa_circ_0007059	miRNA sponge	hsa_circ_0007059↓-miR-378↑-Wnt/β-catenin↑ /ERK1/2↑	Down	Proliferation↓, EMT↓, apoptosis↑	TNM, LNM	[99]
circ-PITX1	miRNA sponge	circ-PITX1↑-miR-1248↓-CCND2↑	Up	Proliferation↑, migration↑, invasion↑, glycolysis↑, glutamine metabolism↑, apoptosis↓	Unknown	[126]

(*Continued*)

Table 2 (Continued).

circRNA	Function	Mechanism	Expression Pattern	Cell Characteristics	Clinical Characteristics	References
circ_0000429	miRNA sponge	circ_0000429↑-miR-1197↓-MADD↑	Up	Proliferation↑, migration↑, invasion↑, apoptosis↓	Unknown	[132]
circ_0001287	miRNA sponge	circ_0001287↓-miR-21↑-PTEN↓	Down	Proliferation↓, migration↓, invasion↓, radio-resistance↓	N status, histological grade	[136]
hsa_circ_0000064	Unknown	hsa_circ_0000064↑-caspase-3/9↑/ bax↑/p21↑/ CDK6↑/cyclin D1↑/bcl-2↓/ MMP-2/9↑	Up	Proliferation↑, migration↑, invasion↑, apoptosis↓	TNM, LNM, T stage	[147]

Notes: ↑, up-regulated; ↓, down-regulated.
Abbreviations:TNM, the high stage of tumor node metastasis; LNM, lymph node metastasis; OS, overall survival.

degradation and inhibit Wnt/β-catenin pathway. Thus, it can be concluded that circ-ITCH can act as a tumor suppressor gene in lung cancer by controlling miRNA activity, which increases the concentration of ITCH and results in suppression of the canonical Wnt/β-catenin pathway. Consequently, the related research of circ-ITCH is important for the diagnosis and treatment of cancer.

circPVT1

CircPVT1 can sponge miR-125b and promote E2F2 expression in NSCLC.[38] C-Fos upregulated circPVT1 in NSCLC and decreased the Ago2-based activity of miR-125b, which increased the E2F2 and the downstream effector expression. Overexpressed E2F2 is crucial for cell cycle regulation in NSCLC and is significantly associated with poor prognosis. In summary, c-Fos-activated circPVT1 acts as a ceRNA and may be considered as a diagnostic biomarker and therapeutic target for NSCLC patients.

circMET

CircMET primarily sponge miR-145-5p to regulate CXCL3 expression in NSCLC cells[39] and is significantly upregulated in NSCLC tissues. Thus, circMET promotes the expression level of CXCL3. CXCL3 is a well-known oncogene, which has been confirmed to promote cancer progression. Taken together, circMET might be considered a novel diagnostic biomarker and potential therapeutic target for NSCLC treatment.

circGFRA1

The expression of circGFRA1 in NSCLC tissues increased, consistent with the previous data in breast cancer and ovarian cancer, and was negatively correlated with the expression of miR-188-3p.[40] CircGFRA1 acts as a ceRNA to sponge miR-188-3p, and the circGFRA1/miR-188-3p axis may regulate the proliferation of NSCLC cells through the PI3K/AKT signaling pathway, which is a classical oncogenic signaling pathway. Consequently, circGFRA1 plays a crucial role in NSCLC, and might be a potential diagnostic biomarker and therapeutic target for NSCLC.

hsa_circ_0013958

hsa_circ_0013958 could act as a sponge of miR-134 and inhibit miR-134 activity.[41] Studies have shown that miR-134 could inhibit the expression of CCND1. It promotes G1-S progression by sequentially phosphorylating retinoblastoma proteins, thereby promoting the initiation and progression of tumor cells. In conclusion, the up-regulated expression of hsa_circ_0013958 is closely related to the tumorigenesis of NSCLC and could be used as a potential diagnostic biomarker for NSCLC, especially for early lung adenocarcinoma.

CircRNAs as Potential Prognostic Biomarkers in Lung Cancer

Prognostic assessment plays a momentous role in the treatment of lung cancer, which can help prolong the survival of lung cancer patients. Hence, circRNAs have gradually gained some value as potential prognostic biomarkers for lung cancer[42] (Table 3).

circFGFR3

The high expression of circFGFR3 promotes the invasion and proliferation by sponging miR-22-3p to upregulate the Gal-1, p-AKT, and p-ERK1/2 expressions in NSCLC cells.[43] miR-22-3p acts as a tumor suppressor gene in multiple cancers, including NSCLC. Gal-1, p-AKT, and

Table 3 CircRNAs as Potential Prognostic Biomarkers in Lung Cancer

circRNA	Function	Mechanism	Expression Pattern	Cell Characteristics	Clinical Characteristics	References
circFGFR3	miRNA sponge	circFGFR3↑-miR-22-3p↓-Gal-1↑/p-AKT↑/p-ERK1/2↑	Up	Proliferation↑, invasion↑	TNM, LNM, tumor size, tumor differentiation, OS	[43]
circ_0003645	miRNA sponge	circ_0003645↑-miR-1179↓-TMEM14A↑	Up	Proliferation↑, migration↑, invasion↑, apoptosis↓	TNM, LNM, OS	[46]
CDR1as	miRNA sponge	CDR1as↑-miR-7↓-EGFR↑/CCNE1↑/PIK3CD↑	Up	Proliferation↑, apoptosis↓	TNM, LNM, OS, tumor size	[47,59]
circ_POLA2	miRNA sponge	circ_POLA2↑-miR-326↓-GNB1↑	Up	Unknown	Distant metastasis, TNM, OS	[48]
circ-FOXM1	miRNA sponge	circ-FOXM1↑-miR-1304-5p↓-PPDPF↑/MACC1↑	Up	Proliferation↑, migration↑, invasion↑, apoptosis↓	TNM, LNM	[49]
circPIP5K1A	miRNA sponge	circPIP5K1A↑-miR-600↓-HIF-1α↑ circPIP5K1A↑-miR-101↓-ABCC1↑	Up	Proliferation↑, migration↑, invasion↑, apoptosis↓, EMT↑, cisplatin sensitivity↓	Unknown	[86,87]
circRNA_010763	miRNA sponge	circRNA_010763↑-miR-715↓-c-Myc↑	Up	Proliferation↑, migration↑, invasion↑	Unknown	[93]
circRNA_100876	Unknown	Unknown	Up	Unknown	LNM, tumor staging, OS	[101]
circ-ANXA7	miRNA sponge	circ-ANXA7↑- miR-331↓-LAD1↑	Up	Proliferation↑, migration↑, invasion↑	TNM, LNM, tumor size, recurrence status, OS	[119]
circ-PTEN	miRNA sponge	circ-PTEN↓-miR-155↑/miR-330-3p↑-PTEN↓	Down	Proliferation↓	TNM, tumor size, OS	[140]
hsa_circ_0008003	miRNA sponge	hsa_circ_0008003↑-miR-488↓-ZNF281↑	Up	Proliferation↑, migration↑, invasion↑	TNM, LNM	[142]
circ-MTHFD2	Unknown	Unknown	Up	Unknown	TNM, LNM, tumor size, recurrence, smoking history, OS	[157]

Notes: ↑, up-regulated; ↓, down-regulated.
Abbreviations: TNM, the high stage of tumor node metastasis; LNM, lymph node metastasis; OS, overall survival.

p-ERK1/2 are downstream regulators of miR-22-3p in NSCLC cells. The AKT and ERK1/2 pathways activated abnormally by forced expression of Gal-1 are closely related to tumor proliferation and invasion.[44,45] Therefore, circFGFR3 may upregulate the Gal-1 expression and activate the AKT and ERK1/2 pathways to promote NSCLC cell invasion and proliferation, and it may be a novel biomarker for the prognosis of lung cancer.

circ_0003645

Circ_0003645 was both increased in the NSCLC cells and tissues, and functions as an oncogene in NSCLC.[46] Circ_0003645 could upregulate TMEM14A expression by acting as a ceRNA to sponge miR-1179. Circ_0003645 affects cell growth, apoptosis, and metastatic properties, and thus participates in the initiation and progression of NSCLC. Elevated circ_0003645 expression in NSCLC

tissues was related to advanced TNM stages and positive lymph node invasion. Additionally, a high expression of circ_0003645 results in a worse overall survival. Therefore, circ_0003645 may possess significant potential as a prognostic predictor and therapeutic target for patients with NSCLC.

CDR1as

Plenty of research evidence has suggested that circRNA CDR1as could function as an oncogene through sponge of tumor suppressor miR-7.[21] Tumor suppressor miR-7 can induce apoptosis and G1/S arrest, while CDR1AS can negatively regulate the antitumor effects of miR-7.[47] The cell growth-related target gene expression of miR-7, EGFR, CCNE1, and PIK3CD can be remarkably elevated by the overexpression of CDR1as. That is to say, CDR1as could promote cell growth via the miR-7/EGFR/CCNE1/PIK3CD signaling pathway in NSCLC. Consequently, CDR1as may serve as a novel prognostic marker for NSCLC.

circ_POLA2

Circ_POLA2 is significantly upregulated in lung cancer cells and tissues, and promotes lung cancer progression via miR-326/GNB1 axis.[48] GNB1 is a direct target of miR-326 and necessary for the miR-326-mediated suppression on the stemness of lung cancer cells. In conclusion, circ_POLA2 plays a potential regulatory role via regulating the miR-326/GNB1 axis in lung cancer cell stemness. Meanwhile, lung cancer patients with a high expression of circ_POLA2 exhibited a worse overall survival. Thus, circ_POLA2 may act as a potential prognostic biomarker and therapeutic target for lung cancer treatment.

circ-FOXM1 (hsa_circ_0025033)

The expression of circ-FOXM1 is remarkably increased in NSCLC tissues and cell lines and promotes NSCLC cell progression.[49] Circ-FOXM1 can upregulate PPDPF and MACC1 expression via acting as a sponge of miR-1304-5p to facilitate cell growth and invasion. Previously, studies indicated that PPDPF and MACC1 were elevated and involved in tumor invasion and metastasis in different types of malignancies.[50,51] In addition, the high expression of circ-FOXM1 was tightly connected to advanced TNM stages, lymph node invasion, and poor prognosis. To sum up, circ-FOXM1 may play a crucial role in the progression of NSCLC, which could function as a novel potential prognostic marker and therapeutic target for NSCLC.

CircRNAs as Potential Therapeutic Target in Lung Cancer

With further research on circRNAs, many circRNAs have been proven to be involved in the initiation and progression of lung cancer, and their potential targets and mechanisms in the treatment of lung cancer have also been gradually known to the public. The correlational research of circRNAs may contribute to further breakthroughs in the treatment of lung cancer (Table 4).

circ_0003998

The expression of circ_0003998 has been verified to be associated with NSCLC resistance to docetaxel (DTX).[52] The expression level of circ_0003998 was originally significantly increased in DTX-resistant NSCLC tissues and cells, while knockdown of circ_0003998 inhibited cell colony formation and enhanced apoptosis and DTX sensitivity of DTX-resistant NSCLC cells in vitro and in vivo. Meanwhile, circ_0003998 directly sponged miR-136-5p, and CORO1C was a functionally crucial target of miR-136-5p in regulating DTX-resistant NSCLC cell colony formation, apoptosis, and DTX sensitivity. In summary, circ_0003998 modulated CORO1C expression by acting as a ceRNA of miR-136-5p to regulate DTX-resistant NSCLC cell colony formation, apoptosis, and DTX sensitivity at least partially, revealing the potential of circ_0003998 as a therapeutic target for chemoresistant NSCLC.

circRNA_103762

CircRNA_103762 was remarkably highly expressed in NSCLC tissues and cell lines and circRNA_103762 acts as an oncogene in NSCLC.[53] A series of cell experiments in vitro determined that the upregulation of circRNA_103762 was associated with multidrug resistance (MDR). The circRNA_103762 was upregulated in NSCLC patients after cisplatin chemotherapy, and downregulation of circRNA_103762 expression can reduce IC50 values of different drugs. Furthermore, circRNA_103762 enhanced MDR by inhibiting CHOP expression in NSCLC cells, which has been pointed out to be related to tumor in early reports, and its expression can be induced by chemotherapeutic drugs and is associated with MDR.[54,55] Based on the above results, the correlation between circRNA_103762 and MDR of NSCLC provides new ideas and strategies for the therapy of NSCLC.

Table 4 CircRNAs as Potential Therapeutic Target in Lung Cancer

circRNA	Function	Mechanism	Expression Pattern	Cell Characteristics	Clinical Characteristics	References
circ_0003998	miRNA sponge	circ_0003998↑- miR-136-5p↓-CORO1C↑	Up	Proliferation↑, migration↑, invasion↑, apoptosis↓, dtx sensitivity↓	TNM, LNM, tumor metastasis	[52]
circRNA_103762	Unknown	circRNA_103762↑-CHOP↓	Up	Proliferation↑, migration↑, invasion↑, mdr↑	OS	[53]
hsa_circ_0020123	miRNA sponge	hsa_circ_0020123↑-miR-144↓-ZEB1↑ /EZH2↑	Up	Proliferation↑, migration↑, invasion↑, apoptosis↓	TNM, LNM, tumor differentiation, OS	[56]
circSEC31A	miRNA sponge	circSEC31A↑-miR -376a↓-SEC31A↑	Up	Migration↑, invasion↑, glycolysis↑, apoptosis↓	TNM, LNM, tumor size	[57]
circCDYL	miRNA sponge	circCDYL↓-miR-185-5p↑/TNRC6A↓-ERK1 /2↑	Down	Proliferation↓, apoptosis↑	Unknown	[58]
circRNA-FOXO3	miRNA sponge	circRNA-FOXO3↓-miR -155↑-FOXO3↓	Down	Proliferation↓, migration↓, invasion↓, apoptosis↑	Unknown	[22]
circFADS2	miRNA sponge	circFADS2↑-miR-498↓-HMGA2↑	Up	Proliferation↑, migration↑, invasion↑, apoptosis↓	TNM, LNM, tumor differentiation, OS	[60,61]
hsa_circ_100395	miRNA sponge	hsa_circ_100395↓-miR -1228↑- TCF21↓	Down	Proliferation↓, migration↓, invasion↓	TNM, LNM, OS	[63]
circRNA_102231	Unknown	Unknown	Up	Proliferation↑, migration↑, proliferation↑,	TNM, LNM	[64]
circUBAP2	miRNA sponge	circUBAP2↑-miR -3182↓- KLF4↑	Up	Proliferation↑, migration↑, invasion↑, chemo-resistance↑	LNM, disease stage	[65]
hsa_circ_0008305 (circPTK2)	miRNA sponge	circPTK2↓-miR-429↑/ miR-200b-3p↑-TIF1γ↓	Down	Invasion↓, migration↓, emt↓	Unknown	[67]
circFGFR1	miRNA sponge	circFGFR1↑- miR-381-3p↓-CXCR4↑	Up	Proliferation↑, migration↑, invasion↑	Tumor size	[68]
circ-ENO1	miRNA sponge	circ-ENO1↑-miR-22-3p↓-ENO1↑	Up	Proliferation↑, migration↑, apoptosis↓, glycolysis↑, emt↑	Unknown	[69]
hsa_circRNA_103809	miRNA sponge	hsa_circRNA_103809↑-miR-4302↓-ZNF121↑ /MYC↑ hsa_circRNA_103809↑-miR-377-3p↓-GOT1↑	Up	Proliferation↑, invasion↑, apoptosis↓, cisplatin resistance↑	Unknown	[71,158]
circ_0026134	miRNA sponge	circ_0026134↑-miR -1256↓/miR-1287↓-TCTN1↑/GAGE1↑	Up	Proliferation↑, migration↑, invasion↑	Unknown	[74]

(*Continued*)

Table 4 (Continued).

circRNA	Function	Mechanism	Expression Pattern	Cell Characteristics	Clinical Characteristics	References
circ0001320	miRNA sponge	circ0001320↓- miR-558↑-TNFAIP1↓/ TPM1↓	Down	Proliferation↓, invasion↓, apoptosis↑	Unknown	[75]
circ-BANP	miRNA sponge	circ-BANP↑- miR-503↓-LARP1↑	Up	Proliferation↑, migration↑, invasion↑, apoptosis↓	Clinical stages, LNM, OS	[76]
circHIPK3	miRNA sponge	circHIPK3↑-miR124 -3p↓-STAT3↓-PRKAA↑ (STK11 mutant) circHIPK3↑-miR-107↓-BDNF↑ circHIPK3↑-miR-381-3p↓-AKT/mTOR↑ circHIPK3↑- miR-149↓-FOXM1↑	Up	Proliferation↑, migration↑, invasion↑, glycolysis↑, apoptosis↓	TNM, LNM, tumor size	[78–81]
circMAN2B2	miRNA sponge	circMAN2B2↑-miR -1275↓-FOXK1↑	Up	Proliferation↑, invasion↑	Unknown	[83]
circNDUFB2	Protein scaffold	circNDUFB2↓-IGF2BPs↑(m6A-dependent)	Down	Proliferation↓, migration↓, invasion↓, immune responses↑	LNM, tumor size	[84]
circ-PAX2	miRNA sponge	circ-PAX2↑- miR-186↓	Up	Proliferation↑, migration↑, apoptosis↓	TNM	[85]
circPTPRA	miRNA sponge	circPTPRA↓-miR-96-5p↑-RASSF8↓ /E-cadherin↓	Down	Migration↓, invasion↓, emt↓	OS	[88]
circBIRC6	miRNA sponge	circBIRC6↑-miR-145↓-FSCN1↑/S6K1↑	Up	Proliferation↑, migration↑, invasion↑	Unknown	[89]
circCDR1as	miRNA sponge	circCDR1as↑-miR -219a-5p↓-SOX5↑ circCDR1as↑-miR -641↓-HOXA9↑	Up	Proliferation↑, migration↑, invasion↑, apoptosis↓, stemness↑, cisplatin resistance↑	Unknown	[90,91]
circRNA_001010	miRNA sponge	circRNA_001010↑-miR -5112↓-CDK4↑	Up	Proliferation↑, migration↑, invasion↑, apoptosis↓	Unknown	[92]
hsa_circRNA_101237	miRNA sponge	hsa_circRNA_101237↑-miR-490-3p↓-MAPK1↑	Up	Proliferation↑, migration↑, invasion↑	TNM, LNM, OS, tumor size	[94]
circ_0002483	miRNA sponge	circ_0002483↓- miR-182-5p↑-GRB2↓ /FOXO1↓/FOXO3↓	Down	Proliferation↓, invasion↓, taxol sensitivity↑	OS	[98]
hsa_circ_0012673	miRNA sponge	hsa_circ_0012673↑-miR-320a↓-LIMK18521↑	Up	Proliferation↑, migration↑, invasion↑, apoptosis↓, emt↑	Unknown	[100]

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Table 4 (Continued).

circRNA	Function	Mechanism	Expression Pattern	Cell Characteristics	Clinical Characteristics	References
circTADA2A	miRNA sponge	propofol↑-circTADA2A↓-miR-455-3p↑-FOXM1↓	Down	Proliferation↑, migration↑, invasion↑, aerobic glycolysis↑	Unknown	[102]
hsa_circ_0002130	miRNA sponge	hsa_circ_0002130↑-miR-498↓- GLUT1↑/HK2↑/LDHA↑	Up	Proliferation↑, glycolysis↑, apoptosis↓, osimertinib-resistant↑	Unknown	[103]
circ_0000376	miRNA sponge	circ_0000376↑-miR-1182↓-NOVA2↑	Up	Migration↑, invasion↑, glycolysis↑	TNM, LNM, tumor size	[104]
circ_0000735	miRNA sponge	circ_0000735↑-miR-635↓-FAM83F↑ circ_0000735↑-miR-940↓-BMPER↑	Up	Proliferation↑, migration↑, invasion↑, glycolysis↑, apoptosis↓	TNM, LNM, OS	[105,106]
circ_0014130	miRNA sponge	circ_0014130↑-miR-142-5p↓- IGF-1↑ circ_0014130↑- miR-136-5p↓- BCL2↑	Up	Proliferation↑, apoptosis↓	Tumor size, distant metastasis	[107,108]
circ_0016760	miRNA sponge	circ_0016760↑-miR-4295↓-E2F3↑ circ_0016760↑-miR-1287↓-GAGE1↑	Up	Proliferation↑, migration↑, invasion↑, glycolysis↑, apoptosis↓	TNM, LNM, OS	[109,110]
circ_0020123	miRNA sponge	circ_0020123↑-miR-142-3p↓-ZFX↑ circ_0020123↑- miR-488-3p↓- ADAM9↑ circ_0020123↑-miR-590-5p↓-THBS2↑	Up	Proliferation↑, migration↑, invasion↑, apoptosis↓	TNM, LNM	[56,111,112]
circ_100565	miRNA sponge	circ_100565↑- miR-506-3p↓- HMGA2↑ circRNA_100565↑-miR-337↓-3p-ADAM28↑	Up	Proliferation↑, migration↑, invasion↑, autophagy↑, apoptosis↓, cisplatin resistance↑	TNM, LNM, OS	[113,133]
circ_ZFR	miRNA sponge	circ_ZFR↑-miR-195-5p↓-KPNA4↑ circ_ZFR↑-miR-101-3p↓-CUL4B↑	Up	Proliferation↑, migration↑, invasion↑, apoptosis↓, ptx resistance↑	Unknown	[114,115]
circABCB10	miRNA sponge	circABCB10↑-miR-1252↓-FOXR2↑ circABCB10↑-miR-584-5p↓- E2F5↑	Up	Proliferation↑, migration↑, invasion↑	OS	[116,117]
circAGFG1	miRNA sponge	circAGFG1↑-miR-203↓-ZNF281↑	Up	Proliferation↑, migration↑, invasion↑	Unknown	[118]
circDCUN1D4	RBPs	circDCUN1D4↓-TXNIP↓/HuR↓	Down	Migration↓, invasion↓, glycolysis↓	LNM, OS	[120]

(*Continued*)

Table 4 (Continued).

circRNA	Function	Mechanism	Expression Pattern	Cell Characteristics	Clinical Characteristics	References
circDENND2A	miRNA sponge	circDENND2A↑-miR-34a↓-CCNE1	Up	Proliferation↑, migration↑, invasion↑, apoptosis↓	Unknown	[121]
circEPSTI1	miRNA sponge	circEPSTI1↑-miR-145↓-HMGB3↑ circEPSTI1↑- miR-1248↓- TRIM24↑	Up	Proliferation↑, migration↑, invasion↑	Unknown	[122,123]
circFOXP1	miRNA sponge	circFOXP1↑-miR-185-5p↓- WNT1↑	Up	Proliferation↑, apoptosis↓	Unknown	[124]
circNFIX	miRNA sponge	circNFIX↑-miR-212-3p↓-ADAM10↑	Up	Proliferation↑, migration↑, invasion↑, glycolysis↑	TNM, distant metastasis	[125]
circ_EPB41L2	miRNA sponge	circ_EPB41L2↓-miR-211-5p↑-CDH4↓	Down	Proliferation↓, migration↓, invasion↓	Unknown	[127]
hsa_circ_0018414	miRNA sponge	hsa_circ_0018414↓-miR-6807↑-3p-DKK1↓	Down	Proliferation↓, stemness↓, apoptosis↑	Unknown	[128]
hsa_circ_0087862	miRNA sponge	hsa_circ_0087862↑-miR-1253↓-RAB3D↑	Up	Proliferation↑, migration↑, invasion↑, apoptosis↓	TNM, LNM, tumor size, OS	[129]
circZNF609	miRNA sponge	circZNF609↑-miR-623↓-FOXM1↑ circZNF609↑-miR-142-3p↓-GNB2↑	Up	Proliferation↑, migration↑, invasion↑, apoptosis↓	TNM, LNM, OS	[130,131]
circ-SOX4	miRNA sponge	circ-SOX4↑-miR-1270↓-PLAGL2↑ /WNT↑	Up	Proliferation↑, migration↑, invasion↑	Unknown	[134]
circ_0000284	miRNA sponge	circ_0000284↑-miR-377-3p↓-PD-L1↑	Up	Proliferation↑, migration↑, invasion↑	LNM, OS, tumor stage	[135]
circ_0074027	miRNA sponge	circ_0074027↑- miR-185-3p↓-BRD4↑ /MADD↑	Up	Proliferation↑, migration↑, invasion↑, apoptosis↓	TNM, tumor differentiation, OS	[137]
circMAGI3	miRNA sponge	circMAGI3↑-miR-515-5p↓-HDGF↑	Up	Proliferation↑, glycolysis↑	TNM, OS	[138]
circ-PRMT5	miRNA sponge	circ-PRMT5↑-miR-377/382/498↓- EZH2↑	Up	Proliferation↑	TNM, LNM, tumor size, OS	[139]
hsa_circ_0006571	miRNA sponge	hsa_circ_0006571↑-miR-138↓-Sirt1↑	Up	Proliferation↑, migration↑, invasion↑, apoptosis↓, emt↑	spinal metastasis	[141]
circSMARCA5	miRNA sponge	circSMARCA5↓-miR-19b-3p↑-HOXA9↓	Down	Proliferation↓, migration↓, invasion↓	Unknown	[143]
circTUBA1C	miRNA sponge	circTUBA1C↑- miR-143-3p↓	Up	Proliferation↑, apoptosis↓	Unknown	[144]
hsa_circ_0007580	miRNA sponge	hsa_circ_0007580↑-miR-545-3p↓-PRKCA↑	Up	Invasion↑, apoptosis↓	OS	[145]

(*Continued*)

Table 4 (Continued).

circRNA	Function	Mechanism	Expression Pattern	Cell Characteristics	Clinical Characteristics	References
circRNA_103993	miRNA sponge	circRNA_103993↑-miR-1271↓- ERG↑	Up	Proliferation↑, apoptosis↓	Unknown	[146]
hsa_circ_0001073	miRNA sponge	hsa_circ_0001073↓-miR-626↑-LIFR↓	Down	Proliferation↓, invasion↓, apoptosis↑	Unknown	[148]
hsa_circ_0010235	miRNA sponge	hsa_circ_0010235↑-miR-433-3p↓-TIPRL↑	Up	Proliferation↑, migration↑, invasion↑, autophagy↑, apoptosis↓	TNM, LNM, tumor size, OS, recurrence, smoking history	[149]
hsa_circ_0038646	miRNA sponge	hsa_circ_0038646↑-miR-331-3p↓-GRIK3↑	Up	Proliferation↑, migration↑	Unknown	[150]
hsa_circ_11780	miRNA sponge	hsa_circ_11780↓-miR-544a↑-FBXW7↓	Down	Proliferation↓, migration↓, invasion↓	Tumor size, distant metastasis, OS	[151]
hsa_circ_0002874	miRNA sponge	hsa_circ_0002874↑-miR-1273f↓-MDM2/P53↑	Up	Apoptosis↓, paclitaxel resistance↑	TNM, histology	[152]
circCCDC66	miRNA sponge	circCCDC66↑-miR-33a-5p↓-KPNA4↑	Up	Proliferation↑, migration↑, invasion↑, apoptosis↓	Unknown	[153]
circP4HB	miRNA sponge	circP4HB↑-miR-133a-5p↓- vimentin↑	Up	Migration↑, invasion↑, emt↑	OS	[154]
circARHGAP10	miRNA sponge	circARHGAP10↑-miR-150-5p↓-GLUT1↑	Up	Proliferation↑, migration↑, invasion↑, emt↑	Unknown	[155]
circVANGL1	miRNA sponge	circVANGL1↑-miR-195↓-Bcl-2↑	Up	Proliferation↑, migration↑, invasion↑, apoptosis↓	TNM, tumor size, OS	[156]

Notes: ↑, up-regulated; ↓, down-regulated.
Abbreviations: TNM, the high stage of tumor node metastasis; LNM, lymph node metastasis; OS, overall survival; MDR, multidrug resistance; EMT, epithelial–mesenchymal transition.

hsa_circ_0020123

The expression level of hsa_circ_0020123 in NSCLC tissues was significantly higher than that in normal tissues, and higher hsa_circ_0020123 expression level was associated with a poorer differentiation degree, lymph node metastasis, a higher TNM stage, and a shorter overall survival.[56] hsa_circ_0020123 facilitates the growth and metastasis of NSCLC cells through sponging miR-144 to suppress their functions. Thence, the well-known oncogenes EZH2 and ZEB1, which were targeted by miR-144, were upregulated by high-level hsa_circ_0020123. It is worth noting that knockdown hsa_circ_0020123 could dramatically inhibit NSCLC growth and metastasis in nude mice test. Therefore, it can be concluded that hsa_circ_0020123 might serve as a promising prognostic predictor and therapeutic target for NSCLC treatment.

circSEC31A

CircSEC31A and SEC31A were significantly highly expressed in NSCLC cells and tissues, and circSEC31A expression levels were closely associated with tumor size, TNM stage, and lymphatic metastasis.[57] CircSEC31A could promote NSCLC cell migration, invasion, glycolysis, and apoptosis by sponging miR-376a, and SEC31A was directly targeted and inhibited by miR-376a in NSCLC Cells. That is to say, circSEC31A promoted NSCLC malignant progression through modulating SEC31A expression by acting as a miR-376a sponge. Conversely, knockdown of circSEC31A weakened tumor growth and thus suppressed NSCLC malignant progression. Based on the above results, we draw the conclusion that circSEC31A may serve as a novel molecular target for NSCLC therapy.

circCDYL

CircCDYL was decreased in NSCLC patients' tissues and plasma, also downregulated in NSCLC cell lines.[58] However, the overexpression of circCDYL can inhibit proliferation and induce apoptosis in NSCLC cells. The downregulated circCDYL binds to miR-185-5p, and miR-185-5p was upregulated in NSCLC. After that, TNRC6A is a downstream target of miR-185-5p and mRNA and protein levels were downregulated in NSCLC. Further, circCDYL repressed the phosphorylation of ERK1/2, which was induced by miR-185-5p or si-TNRC6A. Taken together, circCDYL inhibits ERK1/2 signaling pathway by targeting miR-185-5p/TNRC6A to block NSCLC malignant progression. Therefore, circCDYL possesses the potential to be a promising therapeutic target for NSCLC treatment.

CircRNAs Associated with Chemotherapy and Radiotherapy

At present, chemotherapy plays an indispensable role in the treatment of lung cancer, especially preoperative neoadjuvant chemotherapy to shrink tumor or reduce tumor stage and postoperative adjuvant chemotherapy to prevent recurrence and metastasis, but chemotherapy resistance in cancer cells becomes a fundamental challenge. Our common chemotherapy drugs for lung cancer include cisplatin, Taxol, 5-Fu, MIT, and so on. Cisplatin, a kind of heavy metal drug, is one of the most commonly used chemotherapy drugs at present, hsa_circRNA_103809,[158] circ_PIP5K1A,[87] circRNA CDR1as,[91] circRNA_100565[133] can promote cisplatin resistance. While hsa_circ_0001946[70] can enhance cisplatin sensitivity. Taxol, which is extracted from the bark of the Pacific Yew tree, is also one of the most commonly used chemotherapy drugs. Circ_0003998,[52] circ_ZFR[115] can reduce Taxol sensitivity. While hsa_circ_0030998,[72] circ_0002483[98] can actually reduce Taxol resistance. Other common resistant chemotherapy drugs, such as osimertinib, an effective EGFR-tyrosine kinase inhibitor for advanced NSCLC patients, have also been found to promote resistance by hsa_circ_0002130.[103] In addition, other studies have found that circRNA_103762 can even promote multidrug resistance (MDR).[53] Consequently, circRNAs are one of the important breakthroughs in solving chemotherapy resistance.

Radiotherapy is a relatively common and effective treatment method, especially for patients with advanced lung cancer, radiotherapy can effectively control the further growth of tumor, relieve a series of symptoms caused by lung cancer, and control bone metastasis and brain metastasis. For patients with early lung cancer, radiotherapy can be considered in the case of inoperable, and it works very well. Studies have shown that circRNAs can modulate radiotherapy resistance. For example, circ_0001287 can reduce radiotherapy resistance, thus providing new clues for the treatment of lung cancer.[136] Therefore, circRNAs are closely related to the solution of radiotherapy resistance.

Conclusion and Perspective

Lung cancer, the second most common cancer and the leading cause of cancer-related deaths, still has so many difficult problems to solve in its diagnosis and treatment. Appearance of circRNAs points out a new direction for the study of lung cancer. Because of its unique structure, circRNAs have advantages in the diagnosis, prognosis, and treatment of lung cancer.

Compared with other protein or non-coding RNA biomarkers, circRNAs have higher sensitivity via their stable structure and high abundance, and higher specificity via their tissue-specific expression. Moreover, some abundant expression has been found in blood, which is conducive to Clinical Blood Testing of circRNA, making circRNA an ideal biomarker.

At the same time, the application of circRNAs in lung cancer still has plenty of limitations. Firstly, although many reports have mentioned that the abnormal expression of circRNAs may be related to lung cancer TNM stage, a relatively accurate diagnostic standard value has not been established to measure the relationship between abnormal expression level of circRNAs and TNM stage. This is still a shortcoming in the early diagnosis of lung cancer. Therefore, a large amount of experimental data are needed to support the staging or early diagnosis of lung cancer. Secondly, a certain amount of circRNAs are still unstable and have a short half-life in the blood, and can only be maintained in a relatively stable content in lung cancer tissues or cells, which has formed a certain obstacle to the non-invasive assisted diagnosis of lung cancer. Finally, as a novel diagnostic marker that has not been widely recognized, the technology, cost, and efficiency of the detection and identification of circRNAs remain to be solved, which increases the difficulty in the clinical application and popularization of circRNAs.

In addition, lung cancer is a kind of tumor with extremely high malignancy, and effective prognostic analysis can help prolong the survival rate of lung cancer patients. It is of concern that the abnormal expression of many circRNAs can affect the prognosis of lung cancer. Based on the comparison of preoperative and postoperative expression, or the change of expression during treatment, the expression level of circRNAs may be able to assess the therapeutic effect and determine tumor growth to some extent.

Target therapy is the frontier of lung cancer treatment. The regulatory mechanism of circRNAs related to lung cancer, especially miRNA sponge, which has been studied extensively, provides effective targets for target therapy of lung cancer. In terms of high-expression circRNAs, exogenous fully complementary siRNA can be introduced to bind to specific back-splice junction of targeted circRNAs and degrade the circRNAs. Additionally, antisense oligonucleotide binding to specific splicing signals of targeted circRNAs can also be introduced into pre-mRNA to interfere with the circRNAs production. In clinical applications of circRNA therapeutics, circRNAs have not been used as a single tumor therapeutic target, more as an adjuvant therapy. However, with the continuous exploration of the molecular mechanism of circRNA, circRNA may play a unique role in lung cancer treatment in the future. In the case of chemotherapy, there are various chemotherapy drugs for lung cancer, and evidences have suggested that diverse circRNAs can enhance or reduce chemotherapy resistance in lung cancer. Even in radiotherapy, a few circRNAs can affect the radiotherapy effect of lung cancer.

In conclusion, although there have been many research achievements on circRNAs, the research on circRNAs is still in its infancy, and their functional role in tumorigenesis is still largely unknown. The evidence that has been found so far makes circRNAs not only as valuable diagnostic and prognostic biomarkers but also as promising therapeutic targets in lung cancer treatment.

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Disclosure

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