Landscape of circular RNAs in different types of lung cancer and an emerging role in therapeutic resistance (Review)

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Abstract. Lung cancer is one of the most common malignant tumor types and the leading cause of cancer-associated death worldwide. Different types of lung cancer exhibit differences in terms of pathophysiology and pathogenesis, and also treatment and prognosis. Accumulating evidence has indicated that circular RNAs (circRNAs) are abnormally expressed among different types of lung cancer and confer important biological functions in progression and prognosis. However, studies comparing different circRNAs in lung cancer subtypes are scarce. Furthermore, circRNAs have an important role in drug resistance and are related to clinicopathological features in lung cancer. Summaries of the association of circRNAs with drug resistance are also scarce in the literature. The present study outlined the biological functions of circRNAs and focused on discriminating differential circRNA patterns and mechanisms in three different types of lung cancer. The emerging roles of circRNAs in the resistance to chemotherapy, targeted therapy, radiotherapy and immunotherapy were also highlighted. Understanding these aspects of circRNAs sheds light on novel physiological and pathophysiological processes of lung cancer and suggests the application of circRNAs as biomarkers for diagnosis and prognosis, as well as therapeutic resistance.

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Contents

1. Introduction

Circular RNA (circRNA) is a novel and important class of endogenous noncoding RNAs (ncRNAs) in addition to long ncRNA and microRNA (miRNA) and was first discovered several decades ago (1,2). Unlike linear RNAs, circRNAs are covalently closed-loop molecules formed by back-splicing without 5' to 3' polarity or the poly(A) tail, which makes circRNAs difficult to degrade by RNase and more stable in plasma and tissues than most other ncRNAs (3,4). With the development of high-throughput sequencing technologies and bioinformatic methods, abundant circRNAs have been identified and demonstrated to have high stability, sequence conservation and specific localization in subcellular compartments (5). Multiple studies have indicated that circRNAs have different expression patterns and biological functions in different types of cancer (6-8). Research on the mechanisms of circRNAs in tumor development, as well as the diagnosis, treatment and prognosis of cancer, has become a hotspot in recent years.

Lung cancer is one of the most common cancer types worldwide. Although treatments are improving, the prognosis of lung cancer remains poor and the five-year survival rate is still <20% (9). Histologically, lung cancer is usually divided into two categories: Non-small cell lung cancer (NSCLC) and SCLC (10). NSCLC, which includes lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC), accounts for >85% of lung cancers (11). Clinically, the survival rate of patients with early lung cancer is significantly higher than that of patients with late-stage lung cancer (12). However, due to the occult symptoms of early lung cancer, a large number of patients are not diagnosed until reaching the intermediate

and late stages. After diagnosis, the treatments and prognosis vary for the different types of lung cancer (13). Therefore, it is necessary to improve the understanding of the molecular mechanisms of different types of lung cancer to develop efficient and accurate diagnostic and prognostic biomarkers and to identify different therapeutic targets.

In recent studies, a variety of circRNAs have been discovered in tumor tissues and blood samples and they have important roles in the development and progression of lung cancer (14). In the present review, the expression of different circRNAs and their function in different types of lung cancer were systematically summarized to understand circRNAs as potential biomarkers for the diagnosis and prognostication of different types of lung cancer. The emerging roles of circRNAs and their biological functions in resistance to clinical chemotherapy, targeted therapy, radiotherapy and immunotherapy are also discussed in detail.

2. Biogenesis of circRNA

circRNAs are a class of noncoding RNA molecules that form a loop structure via covalent bonds after back-splicing and have no 5' caps or 3' poly(A) tails (15). Depending on their source, circRNAs may be divided into exonic circRNAs (EcircRNAs), intronic circRNAs (ciRNAs), and exon-intron circRNAs (EIciRNAs) (16) (Fig. 1). EcircRNAs consist of one or multiple exons and mainly reside in the cytoplasm after biogenesis (17). EIciRNAs and ciRNAs mainly reside in the nucleus. CiRNAs are composed of only introns, and EIciRNAs are composed of exons and the introns located between the exons (18). Among them, EcirRNAs are the most common and account for ~80% of the total circRNAs (19). EcircRNAs are transferred into the cytoplasm after being synthesized in the nucleus and do not only serve as miRNA sponges or interact with proteins to perform various functions but may also be contained in exosomes together with a large number of other nucleic acids, proteins and lipids (20). A large number of studies have indicated that circRNAs are stable and enriched in exosomes (21-25), and the composition of circRNAs in exosomes may be regulated by changes in the levels of related miRNAs in donor cells, after which the molecular information is transferred to recipient cells (26). Therefore, the predominant studies are related to cytoplasmic EcircRNAs.

circRNAs are generated through different mechanisms, including intron-pairing-driven circularization, RNA binding protein (RBP)-driven circularization, exon-skipping lariat-driven circularization and intron lariat-driven circularization (27). Intron pairing means that two flanking introns located on both sides of the pre-mRNA exon/exons have a connectable structure and are sufficiently close to each other to form a secondary conformation via base pairing, which enables the splicing site to conduct back-splicing and produce EcirRNA or EIciRNA (19,28). RBPs are trans-acting factors that are able to bind to specific motifs of pre-mRNAs and close the flanking introns (29). RBP protein dimerization promotes the formation of an RNA loop. Muscleblind (MBL), heterogeneous nuclear ribonucleoprotein L and quaking are common RBPs that have crucial roles in circRNA biogenesis (29-31). Exon skipping means that one or more exons of pre-mRNA are missing, which enables lariat structure-driven circularization of circRNA (32). During circularization, the spliceosome removes the introns in the lariat. If all intron sequences are removed, EcircRNAs are formed, and if the introns are not completely removed, EIciRNAs are generated. The intron lariat model mainly drives the formation of ciRNAs, which mainly depends on a 7-nt GU-rich sequence near the 5' end splice site and an 11-nt C-rich sequence near the branching point (4,33). These two sequences combine with each other during the back-splicing process and the branch point of the 3' downstream region is trimmed to form a stable ciRNA (34).

3. Function of circRNA

circRNAs are widely present in diverse cells and have stable structures, conserved sequences and cell-tissue expression specificity that determine their functions (35). The main functions of circRNAs include miRNA sponging, interaction with proteins, gene transcription regulation and translation templates (Fig. 1). Most circRNAs, particularly EcircRNAs, have been proposed to exert their function as miRNA sponges. These circRNAs contain miRNA response elements and may competitively bind miRNAs, similar to 'sponge' effects, which may prevent miRNA from interacting with mRNA in the 3' untranslated region and indirectly regulate downstream mRNA targets of miRNA (36).

Certain circRNAs with introns that are found in the nucleus, mainly ciRNAs and ElcircRNAs, may directly regulate host gene transcription. ElcircRNAs or ciRNAs are able to bind to RNA polymerase II (Pol II) in the nucleus and regulate gene transcription (18). The ciRNA ci-ankyrin repeat domain 52 (ANKRD52), which is derived from the second intron region of the ANKRD52 gene and accumulates in the nucleus, binds to elongation Pol II machinery and promotes the transcriptional activity of Pol II, thus serving a cis regulatory role for the parent gene (34). In addition, EIciRNAs, e.g., circ-eukaryotic translation initiation factor 3 subunit J (EIF3J) and circ-poly(A)-binding protein-interacting protein 2 (PAIP2), are able to interact with U1 small nuclear ribonucleoprotein to form a complex, which binds to the promoter of the parent gene along Pol II, promoting the transcription of the parent genes EIF3J and PAIP2 and having a positive regulatory role (19,37). circRNAs may also change splicing patterns or mRNA stability by binding to RBPs to form RNA-protein complexes (38).

Although circRNAs are noncoding RNAs, certain studies have indicated that certain circRNAs have the potential to encode functional polypeptides (39). One way to realize the translation of circRNAs is to promote the direct binding of initiation factors or ribosomes with translatable circRNAs through internal ribosome entry site elements, such as circ-ZNF609 and circMBL (40,41). In addition, N6-methyladenosine (m6A) may also drive the translation of circRNAs into polypeptides and a study strongly suggested that m6A-containing RRACH sequences (R=G or A; H=A, C or U) may be involved in the translation initiation of circRNAs (42). A few specific circRNAs, including circ-ZNF609 (40), circNlgn (43), circMBL (44), circ-FBXW7 (45), circ-E-Cad (46), circRNA Rho GTPase activating protein 35 (circARHGAP35) (47), circMAPK1 (48), circPINTexon2 (49) and circRNA SNF2 histone linker PHD RING helicase (50), have been reported

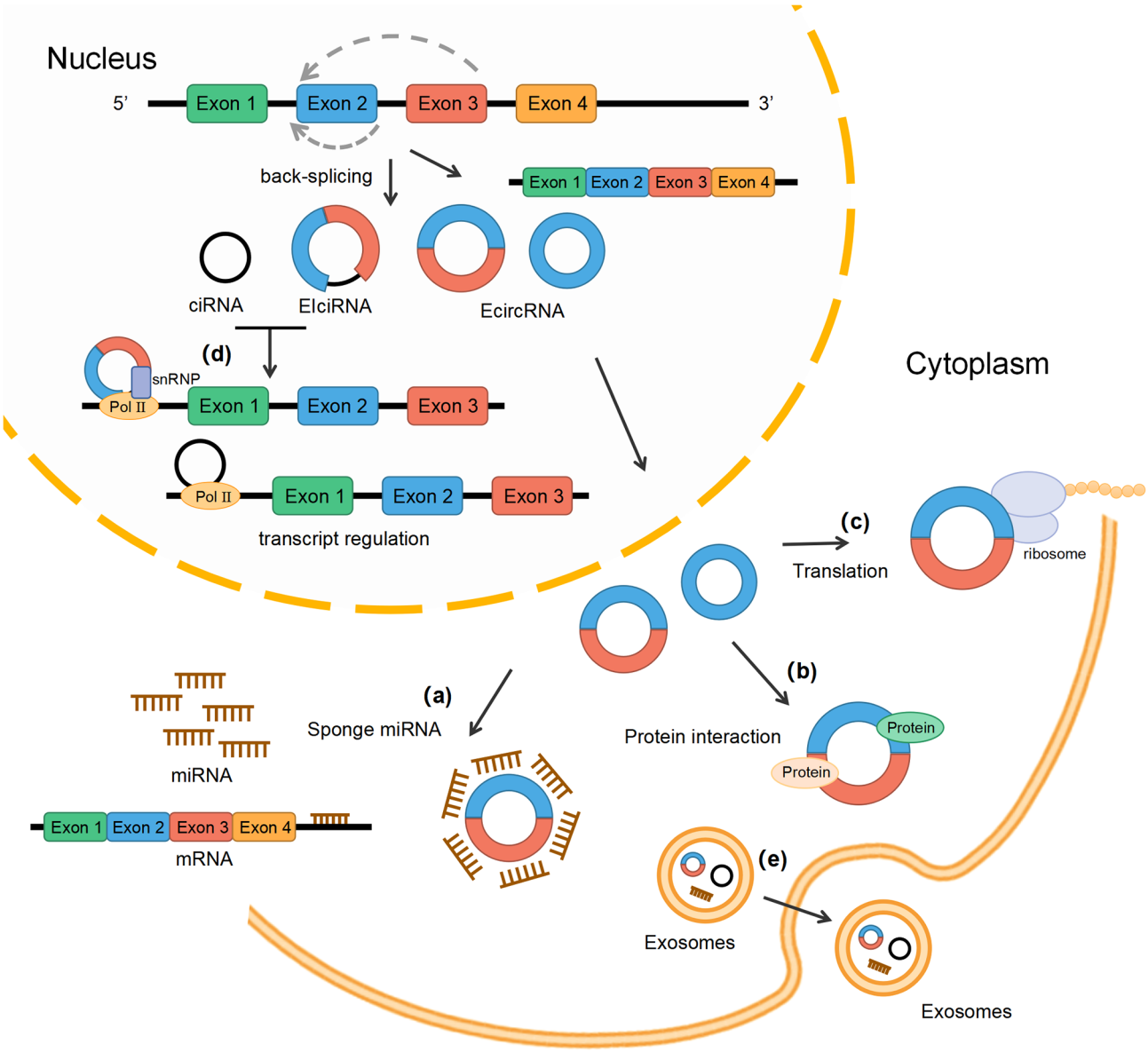

Figure 1. circRNA biogenesis and functional mechanisms. circRNAs are a class of non-coding RNA molecules that form a loop structure via covalent bonds after back-splicing. According to their source, they may be divided into EcircRNAs, ciRNAs and EIciRNAs. circRNAs may (a) serve as miRNA sponges, (b) interact with the proteins such as RNA binding protein, and (c) encode peptides and proteins. (d) In addition, EcircRNAs and ciRNAs are able to directly interact with transcription complexes in the nucleus and regulate the expression of their parental gene. (e) Furthermore, circRNAs may be contained in exosomes and take their effect on distant cells. circRNA, circular RNA; EcircRNAs, exonic circRNAs; ciRNAs, intronic circRNAs; EIciRNAs, exon-intron circRNAs; miRNA, microRNA; snRNP, small nuclear ribonucleoprotein; Pol II, RNA polymerase II.

to act as protein templates. circPINTexon2, the circular form of the long intergenic nonprotein-coding RNA p53-induced transcript, may encode an 87-amino-acid peptide that is able to suppress glioblastoma cell proliferation *in vitro* and *in vivo* (49). However, most of the functional proteins/peptides encoded by circRNAs remain to be elucidated.

4. Characteristic circRNAs in the progression of different types of lung cancer

Different types of lung cancer have different molecular mechanisms, therapeutic targets and prognoses. Contemporary emerging evidence has indicated that circRNAs are abnormally expressed and have pivotal roles in different lung cancers (51). However, the expression patterns and clinical significance of different circRNAs in different types of lung cancer remain to be fully elucidated. circRNAs confer a great diversity of important biological functions by acting as miRNA sponges or interacting with proteins. Considering the possible discriminative roles of circRNAs in different types of lung cancer, their differential expression and possible mechanisms in LUAD, LUSC and SCLC are summarized below and are outlined in Fig. 2.

circRNAs in NSCLC. NSCLC is the leading cause of cancer-related death and the major pathological type of lung cancer in China (52). Recent studies have focused on investigating the roles of circRNAs in lung cancer and have demonstrated the prospects of circRNAs as significant contributors to tumor progression.

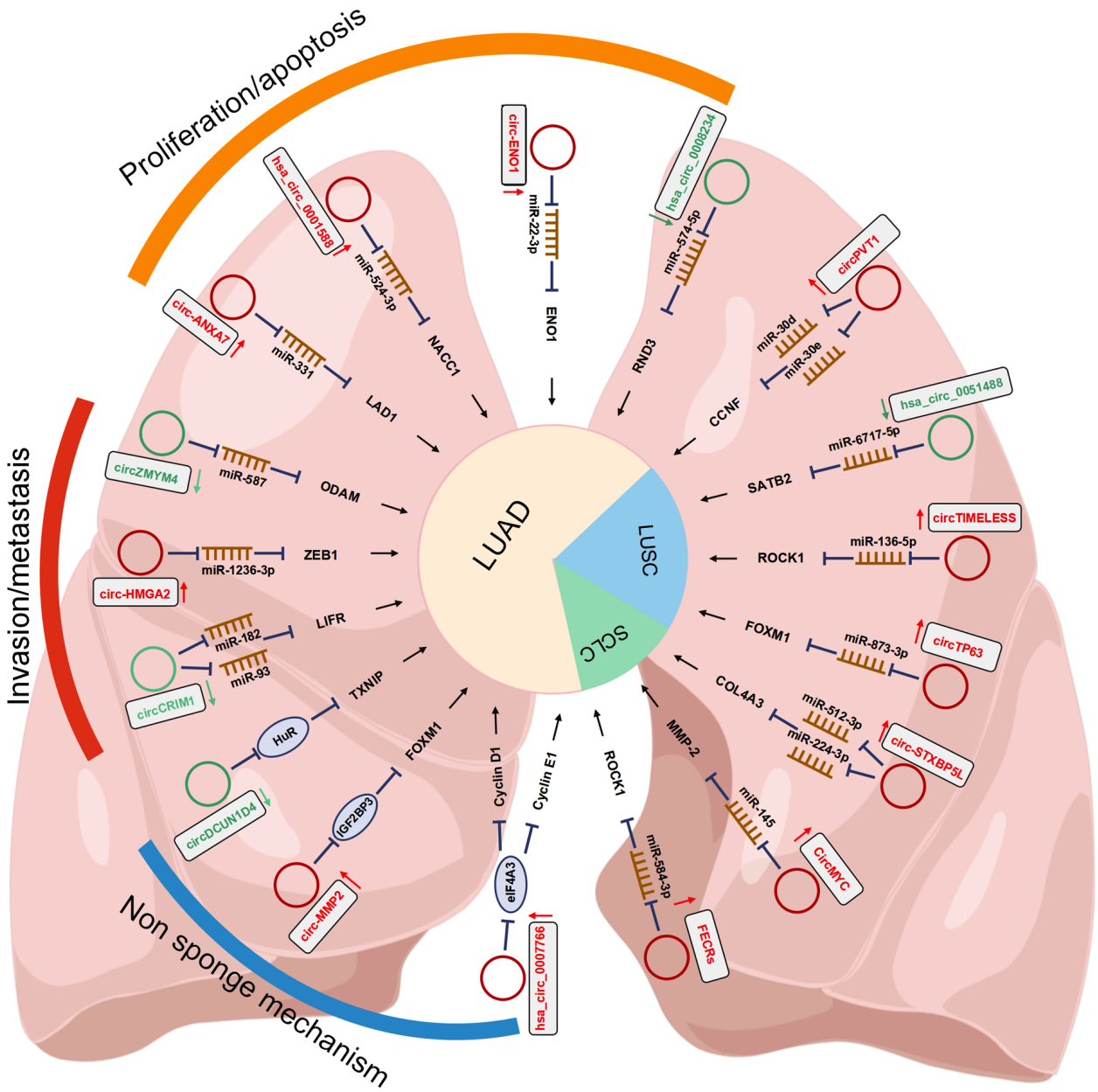

Figure 2. Regulation of cellular properties and pathways of lung cancer-related circRNAs. The schematic diagram illustrates representative circRNAs and their mechanisms in LUAD, LUSC and SCLC. Particularly in LUAD, circRNAs were able to affect tumor proliferation/apoptosis and invasion/metastasis by sponge and non-sponge mechanisms. circRNA, circular RNA; miR, microRNA; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; SCLC, small-cell lung cancer; LIFR, leukemia inhibitory factor receptor; ODAM, odontogenic ameloblast-associated; LAD1, ladinin-1; NACC1, nucleus accumbens associated 1; ENO1, enolase 1; RND3, Rho family GTPase 3; PAX2, paired box 2; SATB2, special AT-rich sequence-binding protein 2; ROCK1, Rho associated coiled-coil containing protein kinase 1; FOXM1, forkhead box M1; COL4A3, collagen type IV α3; MMP-2, matrix metallopeptidase 2; TXNIP, thioredoxin-interacting protein. ZEB1, zinc finger E-box binding homeobox 1.

Numerous circRNAs were reported to be abnormally expressed in NSCLC. Fluorescence *in situ* hybridization assays indicated that circARHGAP10 was highly expressed in human NSCLC samples compared to adjacent normal tissues and poor survival was associated with high circARHGAP10 (circRNA Rho GTPase activating protein 10) expression in NSCLC (53). Knockdown of circARHGAP10 suppressed the proliferation and metastasis of NSCLC cells through a miRNA sponge mechanism via the miR-159-5p/glucose transporter 1 axis. Subsequently, circPTPRA (circRNA protein tyrosine phosphatase receptor-type A) overexpression was found to cause an invasive phenotype in NSCLC cell lines (54). A higher level of circPTPRA is correlated with lower E-cadherin together with higher N-cadherin and vimentin protein levels, indicating that circPTPRA may accelerate invasion by promoting epithelial-mesenchymal transition (EMT). Furthermore, circPTPRA was found to sponge miR-96-5p to suppress EMT in NSCLC cells. By circRNA microarray, hsa_circRNA_012515 expression was found to be significantly upregulated in NSCLC tissues and cells (55), particularly in gefitinib-resistant NSCLC cells.

These findings of recent studies demonstrated that circRNA may have a promising role in NSCLC and highlighted their novel biological functions and possible uses as diagnostic and

therapeutic targets. NSCLC primarily comprises LUAD and LUSC, which exhibit nonidentical circRNA expression signatures (8). Thus, in the chapters below, characteristic circRNAs in LUAD and LUSC were discussed.

circRNAs in LUAD. Up- or downregulated circRNAs in LUAD are summarized and listed in detail in Table I. For instance, the expression levels of circRNA enolase 1 (circ-ENO1) (56), circRNA-002178 (57) and hsa_circ_0072088 (58) in LUAD were all elevated, whereas hsa_circ_0006427 (59) and circRNA cysteine-rich motor neuron protein 1 (circCRIM1) (60) were downregulated. Although the functions of these circRNAs are not entirely clear, emerging studies have confirmed that circRNAs may have the ability to regulate the progression of LUAD through multiple mechanisms.

Increased cell proliferation and blockage of apoptosis are the main hallmarks of cancer; therefore, circRNAs usually have roles in regulating the proliferation and apoptosis of cancer cells (61,62). Several circRNAs were demonstrated to be upregulated in LUAD and to regulate LUAD progression and apoptosis. For instance, circ-ENO1 may promote proliferation and EMT in LUAD via the miR-22-3p/ENO1 axis and inhibit apoptosis in LUAD cells (56). Furthermore, the silencing of circ-ENO1 prohibits the expression of ENO1 and downregulates glycolysis in LUAD cells (56). Ladinin-1 (LAD1), a collagenous anchoring filament protein, has been reported to be a marker of aggressive malignancy in multiple cancers (63,64). circRNA Annexin A7 (circ-ANXA7) is highly expressed in LUAD. It may act as a sponge for miR-331 and indirectly upregulate LAD1 to facilitate proliferation and suppress apoptosis in LUAD cells (65). Furthermore, hsa_circ_0001588 functions as a miR-524-3p sponge to increase nucleus accumbens associated 1 expression and promote the malignant progression of LUAD (66). circ_0007766 mainly affects the malignant proliferation of LUAD and significantly activates the cell cycle in the G0/G1 phase by upregulating the expression of the cell cycle-related proteins cyclin D1/cyclin E1/cyclin-dependent kinase 4 (67). No significant difference in the percentage of apoptosis was found between LUAD with high and low circ_0007766 expression (67). circ_104640 and circFOXP1 were also demonstrated to promote LUAD progression and decrease apoptosis. Jiang *et al* (68) found that circ_104640 affected the expression of C-C motif chemokine ligand 20 by combining with miR-145-5p and it had a tumor-promoting role. circ_104640 also inhibited apoptosis in early-stage LUAD. Wnt family member 1 (WNT1), a member of the WNT family, is implicated in oncogenesis and developmental processes and may inhibit cell apoptosis (69,70). Downregulation of circFOXP1 inhibited cell proliferation and increased cell apoptosis in LUAD cells via the circFOXP1/miR-185-5p/WNT1 axis (71).

Of note, several circRNAs were reported to be downregulated in LUAD. Rho family GTPase 3 (RND3), a member of the Rho GTPase family (72), is associated with unfavorable prognosis of patients and participates in functions such as cell proliferation and differentiation (73). Jiang *et al* (74) demonstrated that circ_0008234 was downregulated in LUAD cells and exerted a protective role in LUAD, since it may decelerate proliferation and accelerate apoptosis of LUAD cells by sponging miR-574-5p and subsequently inhibiting RND3. circRNA cMras was also decreased in LUAD and suppressed cell proliferation by modulating the miR-567/protein tyrosine phosphatase receptor type G (PTPRG) axis. Transwell migration and invasion assays further suggested that overexpression of circRNA cMras suppressed the migration and invasion ability of LUAD cells by sponging miR-567 to upregulate PTPRG (75). Dong *et al* (76) found that circFBXW7 affects patient prognosis and attenuates malignant progression in LUAD via the miR-942-5p/BarH-like homeobox 2 axis. Further downregulated circRNAs in LUAD are listed in detail in Table I.

The development of cancer invasion and metastases is a leading cause of cancer-related death; therefore, it is essential to prevent such malignant behaviors (77). Several studies have indicated that certain circRNAs in LUAD promote metastasis and malignant progression. For instance, circZMYM4 (circRNA zinc finger MYM type 4) inhibited growth and metastasis in LUAD by sponging miR-587 to upregulate odontogenic ameloblast-associated (ODAM) expression (78). Knockdown of ODAM reversed the suppressive effect caused by circZMYM4 on cell proliferation, migration and invasion abilities. Wang *et al* (60) found that circCRIM1 is associated with favorable survival in LUAD and inhibits LUAD cell migration and invasion. circCRIM1 functions as a ceRNA of miR-93 to promote leukemia inhibitory factor receptor expression, which suppresses PI3K/AKT signaling and functions as a suppressor of LUAD metastasis (79,80). In addition, circ-HMGA2 (hsa_circ_0027446), circRNA high mobility group AT-hook 2 was upregulated in LUAD cells, promoting metastasis and EMT via the miR-1236-3p/zinc finger E-box binding homeobox 1 axis (81).

In addition, it is worth noting that circRNA may also function via other distinct non-sponge mechanisms in LUAD cells. Liang *et al* (82) reported the suppression of LUAD cell metastasis *in vitro* and *in vivo*. circDCUN1D4 (circRNA defective in cullin neddylation 1 domain containing 4) interacts with thioredoxin-interacting protein (TXNIP) mRNA directly through base complementation to suppress metastasis and glycolysis in LUAD cells in a TXNIP-dependent manner. Mechanistically, circDCUN1D4 enhances the stability of TXNIP mRNA by facilitating the interaction between the thioredoxin interacting protein protein and TXNIP as a scaffold. In addition, circXPO1 (circRNA exportin 1) was upregulated in LUAD tissues and was associated with unfavorable overall survival (83). High expression of circXPO1 may promote LUAD progression by binding with insulin-like growth factor (IGF) 2 mRNA binding protein (IGF2BP)1 and enhancing catenin β1 mRNA stability. In addition, circ-MMP2 (circ-0039411) promotes malignant behaviors of LUAD cells by recruiting IGF2BP3 (insulin-like growth factor II mRNA-binding protein 3) to enhance the stability of forkhead box M1 (FOXM1) mRNA. In addition, FOXM1 may also upregulate circ-0039411 and induce nuclear translocation of β-catenin to form a positive feedback loop (84). These studies suggested that sponge and nonsponge circRNAs both function in regulating the LUAD process.

circRNAs in LUSC. Compared with LUAD, the dysregulated circRNAs and their mechanistic underpinnings in LUSC remain largely elusive (52). A small number of circRNAs have been reported to be dysregulated in LUSC (Table II).

Table I. Dysregulated circRNAs in LUAD.

circRNA (circBase ID)	circRNA (other name)	Gene symbol	Full name	Length (bp)	Expression	Function	Mechanism	Pathways	(Refs.)
hsa_circ_0000013	circ-ENO1	ENO1	Enolase 1	154	Up	Promotes glycolysis and tumor progression in LUAD	miRNA sponge	miR-22-3p/ENO1	(56)
hsa_circ_0000211		SFMBT2	Scm like with four mbt domains 2	434	Up	Promotes LUAD cell migration and invasion	miRNA sponge	miR-622/HIF1-α	(138)
hsa_circ_0000326		TCONS_l2_00004572		96	Up	Promotes proliferation, migration and apoptosis	miRNA sponge	miR-338-3p/RAB14	(139)
hsa_circ_0000519	hsa_circRNA_002178	RPPH1	Ribonuclease P RNA component H1	98	Up	Involved in tumor immune escape	miRNA sponge	miR-34/PDL1/PD1	(57)
hsa_circ_0000567		SETD3	SET domain containing 3, actin histidine methyltransferase	683	Up	Suppresses acquired gefitinib resistance and proliferation	miRNA sponge	miR-377-3p/ZFX	(140)
hsa_circ_0000615	circ-ZNF609	ZNF609	Zinc finger protein 609	874	Up	Promotes LUAD proliferation	miRNA sponge	miR-1224-3p/ETV1	(141)
hsa_circ_0000788	hsa_circRNA_000881	MSI2	Musashi RNA binding protein 2	246	Down	Suppresses the progression of LUAD	miRNA sponge	miR-665/PRICKLE2	(142)
hsa_circ_0001016	circXPO1	XPO1	Exportin 1	175	Up	Promotes LUAD cell proliferation	Interaction with protein	circXPO1/IGF2BP1-CTNNB1	(83)
hsa_circ_0001320	hsa_circ_0001320	FOXP1	Forkhead box P1	692	Down	Inhibits lung cancer cell growth and invasion	miRNA sponge	miR-558/TNFAIP1 and TPM1	(143)
hsa_circ_0001361	hsa_circ_0001361	FNDC3B	Fibronectin type III domain containing 3B	215	Up	Facilitates tumorigenesis and development	miRNA sponge	miR-525-5p/VMA21	(144)
hsa_circ_0001451	circFBXW7	FBXW7	F-box and WD repeat domain containing 7	1227	Down	Inhibits proliferation and migration	miRNA sponge	miR-942-5p/BARX2	(76)
hsa_circ_0001522	circCSNK1G3	CSNK1G3	Casein kinase 1 gamma 3	536	Up	Promotes growth and metastasis	miRNA sponge	miR-143-3p/HOXA10	(145)
hsa_circ_0001588	hsa_circ_0001588	HIST1H4E	H4 clustered histone 5	204	Up	Promotes proliferation, migration and invasion	miRNA sponge	miR-524-3p/NACC1	(66)
hsa_circ_0001681	circRAPGEF5	RAPGEF5	Rap guanine nucleotide exchange factor 5	516	Up	Promote proliferation and metastasis	miRNA sponge	miR-1236-3p/ZEB1	(146)
hsa_circ_0001806	hsa_circRNA_104640	CSPP1	Centrosome and spindle pole associated protein 1	432	Up	Accelerates the proliferation of LUAC cells, while inhibiting LUAC cell apoptosis	miRNA sponge	miR-145-5p/CCL20	(68)

Table I. Continued.

circRNA (circBase ID)	circRNA (other name)	Gene symbol	Full name	Length (bp)	Expression	Function	Mechanism	Pathways	(Refs.)
hsa_circ_0001821	circ-PVT1	TCONS_00015354		410	Up	Promotes progression of LUAD and enhances its sensitivity to DDP	miRNA sponge	miR-429/FOXK1	(147)
hsa_circ_0001946		CDR1	Cerebellar degeneration related 1	1485	Up	Promotes cell growth in LUAD	miRNA sponge	miR-135a-5p/SIRT1	(148)
hsa_circ_0002015	hsa_circMMD_007	MMD	Monocyte to macrophage differentiation associated	172	Up	Promotes oncogenic effects in the progression of LUAD	miRNA sponge	miR-197-3p/protein tyrosine phosphatase non-receptor type 9	(149)
hsa_circ_0002346	circCRIM1	CRIM1	Cysteine rich transmembrane BMP regulator 1	538	Down	Inhibits invasion and metastasis in LUAD	miRNA sponge	miR-93 and miR-182/LIFR	(60)
hsa_circ_0002483		PTK2	Protein tyrosine kinase 2	482	Up	Promotes growth and invasion of LUAD	miRNA sponge	miR-125a-3p/CCL4-CCR5	(150)
hsa_circ_0004287		MALAT1	Metastasis associated lung adenocarcinoma transcript 1	2275	Up	Contributes to malignant progression by repressing ferroptosis of lung cancer	miRNA sponge	miR-520a-5p/SLC7A11	(151)
has_circ_0006427		BCAR3	BCAR3 adaptor protein, NSP family member	325	Down	Suppresses cell proliferation, migration and invasion	miRNA sponge	miR-6783-3p/DKK1	(59)
hsa_circ_0006571		SATB2	Special AT-rich sequence-binding protein 2	842	Up	Promotes tumor cell migration and invasion	miRNA sponge	miR-138/Sirt1	(152)
hsa_circ_0007031	circTUBGCP3	TUBGCP3	Tubulin gamma complex associated protein 3	972	Up	Facilitates growth and invasion of LUAD cells	miRNA sponge	miR-885-3p/Wnt10b	(153)
hsa_circ_0007142		DOCK1	Dedicator of 1 cytokinesis	427	Up	Promotes LUAD progression	miRNA sponge	miR-186/FOXK1	(154)
hsa_circ_0007874	circ-MTO1	MTO1	Mitochondrial tRNA translation optimization 1	318	Down	Inhibits the proliferation of LUAD	miRNA sponge	miR-17/QKI-5	(155)
hsa_circ_0007928	circDCUN1D4	DCUN1D4	Defective in cullin neddylation 1 domain containing 4	389	Down	Suppresses tumor metastasis and glycolysis	Protein scaffold	circDCUN1D4/HuR/TXNIP RNA-protein ternary complex	(82)

Table I. Continued.

circRNA (circBase ID)	circRNA (other name)	Gene symbol	Full name	Length (bp)	Expression	Function	Mechanism	Pathways	(Refs.)
hsa_circ_0008193		FAM120A	Family with sequence similarity 120A	330	Down	Suppresses proliferation, migration, invasion and Warburg effect in LUAD cells	miRNA sponge	miR-1180-3p/TRIM62	(156)
hsa_circ_0008234	circFOXP1	FOXP1	Forkhead box P1	587	Up	Promotes cell proliferation and represses cell apoptosis	miRNA sponge	miR-185-5p/WNT1	(71)
hsa_circ_0008234		FOXP1	Forkhead box P1	587	Down	Inhibits cell growth and increases apoptosis	miRNA sponge	miR-574-5p/RND3	(74)
hsa_circ_0008274		UGGT2	UDP-glucose glycoprotein glucosyltransferase 2	244	Down	Represses proliferation and invasion	miRNA sponge	miR-578/HMGA2	(157)
hsa_circ_0011240	circPUM1	PUM1	Pumilio RNA binding family member 1	1165	Up	Promotes proliferation, migration and invasion ability	miRNA sponge	miR-326/Cyclin D1 and Bcl-2	(158)
hsa_circ_0011536	circZMYM4	ZMYM4	Zinc finger MYM-type containing 4	755	Down	Inhibits the growth and metastasis of LUAD	miRNA sponge	miR-587/ODAM	(78)
hsa_circ_0012673		DHCR24	24-dehydrocholesterol reductase	225	Up	Promotes LUAD proliferation	miRNA sponge	miR-22/ErbB3	(159)
hsa_circ_0013958		ACP6	Acid phosphatase 6, lysophosphatidic	340	Up	Promotes cell proliferation and invasion and inhibits cell apoptosis	miRNA sponge	miR-134/CCND1	(160)
hsa_circ_0014130		PIP5K1A	Phosphatidylinositol-4-phosphate 5-kinase type 1 alpha	724	Up	Promotes proliferation and invasion of a LUAD cell line	miRNA sponge	hsa-miR-566/TWIST1	(161)
hsa_circ_0018414		DKK1	Dickkopf WNT signaling pathway inhibitor 1	1805	Down	Represses cell proliferation and stemness, while promoting cell apoptosis	miRNA sponge	miR-6807-3p/DKK1	(162)
hsa_circ_0018808	circ-ANXA7	ANXA7	Annexin A7	508	Up	Facilitates proliferation, migration and invasion of LUAD cells	miRNA sponge	miR-331/LAD1	(65)
hsa_circ_0020732	circ-TSPAN4	TSPAN4	Tetraspanin 4	639	Up	Promotes LUAD metastasis	miRNA sponge	miR-665/ZEB1	(163)
hsa_circ_0020850		NUP98	Nucleoporin 98 and 96 precursor	4401	Up	i) Migration, invasion, proliferation and angiogenesis;	miRNA sponge	i) miR-326/BECN1; ii) miR-195-5p/IRS2	i) (164); ii) (165)

Table I. Continued.

circRNA (circBase ID)	circRNA (other name)	Gene symbol	Full name	Length (bp)	Expression	Function	Mechanism	Pathways	(Refs.)
						ii) Knockdown repressed LUAD cell proliferation, migration and invasion and promoted apoptosis			
hsa_circ_0025036		FOXM1	Forkhead box M1	174	Up	Promotes cell proliferation and suppresses apoptosis	miRNA sponge	miR-198/SHMT1& TGF-α	(166)
hsa_circ_0027446	circ-HMGA2	HMGA2	High mobility group AT-hook 2	138	Up	Promotes metastasis and epithelial-mesenchymal transition	miRNA sponge	miR-1236-3p/ZEB1	(81)
hsa_circ_0030605	circABCC4	ABCC4	ATP binding cassette subfamily C member 4	1280	Up	Promotes LUAD cell proliferation and migration	miRNA sponge	miR-3186-3p/ TNRC6B	(167)
hsa_circ_0031968		FERMT2	FERM domain containing kindlin 2	329	Down	Suppresses the progression of LUAD	miRNA sponge	MiR-3611/GCG	(168)
hsa_circ_0039411	circ-MMP2	MMP2	Matrix metallopeptidase 2	2209	Up	Promotes the proliferation and migration of LUAD cells	Interaction with protein	IGF2BP3/FOXM1 mRNA	(84)
hsa_circ_0049271	circKEAP1	KEAP1	Kelch like ECH associated protein 1	686	Down	Represses tumor growth	miRNA sponge	miR-141-3p/KEAP1	(169)
hsa_circ_0067512	cMras	MRAS	Muscle RAS oncogene homolog	211	Down	Inhibits tumour growth and metastasis	miRNA sponge	miR-567/PTPRG	(75)
hsa_circ_0067512	cMras	MRAS	Muscle RAS oncogene homolog	211	Down	Inhibits cell proliferation, migration, invasion and promotes cell apoptosis	Interaction with protein	NF-κB signaling pathway	(170)
hsa_circ_0067934	circPRKCI	PRKCI	Protein kinase C iota	170	Up	Facilitates LUAD cell migration, proliferation and cell cycle	miRNA sponge	miR-219a-5p/ CAMK1D	(171)
hsa_circ_0067934	circPRKCI	PRKCI	Protein kinase C iota	170	Up	Promotes proliferation and tumorigenesis of LUAD	miRNA sponge	miR-545 and miR-589/E2F7	(172)
hsa_circ_0084606	circASPH	ASPH	Aspartate beta-hydroxylase	654	Up	Promotes proliferation, migration and invasion	miRNA sponge	miR-370/HMGA2	(173)
hsa_circ_0126678	circ-AASDH	AASDH	Aminoadipate-semialdehyde dehydrogenase	903	Up	Promotes progression of LUAD	miRNA sponge	miR-140-3p/E2F7	(174)
hsa_circ_0128332	circ-CAMK2A	CAMK2A	Calcium/calmodulin dependent protein kinase IIα	308	Up	Enhances LUAD metastasis	miRNA sponge	miR-615-5p/FN1	(175)

Table I. Continued.

circRNA (circBase ID)	circRNA (other name)	Gene symbol	Full name	Length (bp)	Expression	Function	Mechanism	Pathways	(Refs.)
hsa_circ_0131457	circ-SOX4	SOX4	SRY-box transcription factor 4	143	Up	Drives the tumorigenesis and development of LUAD	miRNA sponge	miR-1270/PLAGL2	(176)

Up, upregulated; Down; downregulated; miRNA, microRNA; circRNA, circular RNA; LUAD, lung adenocarcinoma; ENO1, enolase 1; SFMBT2, Scm like with four mbt domains 2; RPPH1, ribonuclease P RNA component H1; SETD3, SET domain containing 3, actin histidine methyltransferase; ZNF609, zinc finger protein 609; MSI2, Musashi RNA binding protein 2; XPO1, exportin 1; FOXP1, forkhead box P1; FNDC3B, fibronectin type III domain containing 3B; FBXW7, F-box and WD repeat domain containing 7; CSNK1G3, casein kinase 1 γ3; HIST1H4E, H4 clustered histone 5; RAPGEF5, Rap guanine nucleotide exchange factor 5; CSPP1, centrosome and spindle pole associated protein 1; CDR1, cerebellar degeneration related 1; MMD, monocyte to macrophage differentiation associated; CRIM1, cysteine rich transmembrane BMP regulator 1; PTK2, protein tyrosine kinase 2; MALAT1, metastasis associated lung adenocarcinoma transcript 1; BCAR3, BCAR3 adaptor protein, NSP family member; SATB2, special AT-rich sequence-binding protein 2; TUBGCP3, tubulin γ complex associated protein 3; DOCK1, dedicator of cytokinesis 1; MTO1, mitochondrial tRNA translation optimization 1; DCUN1D4, defective in cullin neddylation 1 domain containing 4; FAM120A, family with sequence similarity 120A; FOXP1, forkhead box P1; FOXP1, forkhead box P1; UGGT2, UDP-glucose glycoprotein glucosyltransferase 2; PUM1, Pumilio RNA binding family member 1; ZMYM4, zinc finger MYM-type containing 4; DHCR24, 24-dehydrocholesterol reductase; ACP6, acid phosphatase 6, lysophosphatidic; PIP5K1A, phosphatidylinositol-4-phosphate 5-kinase type 1α; DKK1, dickkopf WNT signaling pathway inhibitor 1; ANXA7, annexin A7; TSPAN4, tetraspanin 4; NUP98, nucleoporin 98 and 96 precursor; FOXM1, forkhead box M1; HMGA2, high mobility group AT-hook 2; ABCC4, ATP binding cassette subfamily C member 4; FERMT2, FERM domain containing kindlin 2; MMP2, matrix metallopeptidase 2; KEAP1, kelch like ECH associated protein 1; MRAS, muscle RAS oncogene homolog; MRAS, muscle RAS oncogene homolog; PRKCI, protein kinase Cι; ASPH, aspartate β-hydroxylase; AASDH, aminoadipate-semialdehyde dehydrogenase; CAMK2A, calcium/calmodulin dependent protein kinase IIα; SOX4, SRY-box transcription factor 4.

Xu *et al* (85) investigated the expression profiles of circRNAs in LUSC and matched adjacent normal tissues, and identified 126 differentially expressed circRNAs, including 135 upregulated and 81 downregulated circRNAs. By constructing a miRNA-circRNA interaction network, 10 key circRNAs were further screened out. Among them, the survival of the hsa_circRNA_000122 high group and hsa_circRNA_103827 high groups was significantly longer than that of the respective low expression groups. Thus, hsa_circRNA_103827 and hsa_circRNA_000122 may be potential biomarkers for clinical prognostication (85). However, their biological effects and mechanisms remain to be elucidated.

Furthermore, circRNA tumor protein p63 (circTP63) was found to be upregulated in LUSC and silencing of circTP63 suppressed cell growth in LUSC (86). circTP63 may function as a miRNA sponge for miR-873-3p and regulate FOXM1 expression. The expression of hsa_circ_0000408 (circTIMELESS) in LUSC was increased and positively correlated with the TNM stage (87). A xenograft tumor growth assay suggested that it acted as a tumor promoter in LUSC and influenced LUSC proliferation and invasion via the miR-136-5p/Rho associated coiled-coil containing protein kinase 1 (ROCK1) axis (87). In addition, hsa_circ_0051488 expression in cancer tissues was inversely correlated with tumor diameter, lymphatic metastasis and TNM stage (88). Further experiments indicated that circ0051488 may promote LUSC progression through the miR6715/special AT-rich sequence-binding protein 2 (SATB2) axis, suggesting that circ0051488/miR6715/SATB2 may be a potential pathway for LUSC therapeutic intervention (88).

circRNA in SCLC. Compared with NSCLC, SCLC is a more aggressive disease (89), which means that it exhibits faster progression and a shorter course. Numerous circRNAs are dysregulated in SCLC (Table III), which may help understand the detailed mechanisms of this subtype of lung cancer. Next-generation sequencing of paired SCLC tumors and adjacent noncancerous tissues indicated that five circRNAs were significantly upregulated and 30 circRNAs were significantly downregulated in SCLC tissues (90). Of note, circRNA syntaxin binding protein 5L (circ-STXBP5 L) was detected only in SCLC samples and was not able to be detected in normal control tissues (90). circ-STXBP5 L is closely related to the regulation of metabolic and developmental processes and it participates in various classic cancer-related pathways. The expression of both miR-224-3p and miR-512-3p was negatively correlated with circ-STXBP5 L and may be responsible for the effect of circ-STXBP5 L (90). Furthermore, circRNA bHLH transcription factor (circMYC) was highly expressed in SCLC cells and knockdown of circMYC indicated that it had an oncogenic effect through the miR-145/matrix metallopeptidase 2 (MMP2) axis, inhibiting proliferation, migration and invasion and inducing apoptosis of SCLC cells (91). circInteractome and luciferase reporter assays demonstrated the binding of circMYC, miR-145 and MMP2 mRNA, establishing a ceRNA axis to explain the functional roles of circMYC in SCLC cells. Friend leukemia integration 1 (FLI1) circular RNAs were also found to be upregulated in SCLC cells and were identified as a new oncogenic driver and to promote tumor metastasis through the miR545/ROCK1 axis (92). However, the circRNAs reported in SCLC are

Table II. Dysregulated circRNAs in LUSC.

circRNA (circBase ID)	circRNA (other name)	Gene symbol	Full names	Length (bp)	Expression	Function	Mechanism	Pathways	(Refs.)
hsa_circ_0000408	circTIMELESS	TIMELESS	Timeless circadian regulator	378	Up	Promotes the proliferation and invasion of LUSC cells	miRNA sponge	miR-136-5p/ ROCK1	(87)
hsa_circ_0001821	circPVT1	PVT1	Pvt1 oncogene	410	Up	Promotes proliferation of LUSC	miRNA sponge	miR-30d and miR-30e/CCNF	(177)
hsa_circ_0051488		ERCC1	ERCC excision repair 1, endonuclease non-catalytic subunit	141	Down	Reduces migration and invasion of tumor cells	miRNA sponge	miR-6717-5p/ SATB2	(88)
hsa_circ_0068515	circTP63	TP63	Tumor protein p63	295	Up	Promotes cell proliferation	miRNA sponge	miR-873-3p/ FOXM1	(86)
hsa_circ_0092400	circ-PAX2	PAX2	Paired box 2	206	Up	Promotes proliferation and metastasis	miRNA sponge	miR-186/ PAX2	(178)
hsa_circ_0026195	hsa_circRNA_026195	RACGAP1	Rac GTPase activating protein 1	852	Up	Unknown	miRNA sponge	Predicted	(85)
hsa_circ_0001383	hsa_circRNA_103565	DLG1	Discs large MAGUK scaffold protein 1	278	Up	Unknown	miRNA sponge	Predicted	(85)
hsa_circ_0008621	hsa_circRNA_103827	HMGCS1	3-hydroxy-3-methylglutaryl-CoA synthase 1	899	Up	Unknown	miRNA sponge	Predicted[a]	(85)
hsa_circ_0072387	hsa_circRNA_103829	HMGCS1	3-hydroxy-3-methylglutaryl-CoA synthase 1	609	Up	Unknown	miRNA sponge	Predicted	(85)
hsa_circ_0072391	hsa_circRNA_103831	HMGCS1	3-hydroxy-3-methylglutaryl-CoA synthase 1	331	Up	Unknown	miRNA sponge	Predicted	(85)
hsa_circ_0006174	hsa_circRNA_104852	RAD23B	RAD23 homolog B, nucleotide excision repair protein	349	Up	Unknown	miRNA sponge	Predicted	(85)
hsa_circ_0000122	hsa_circRNA_000122	TXNIP	Thioredoxin interacting protein	196	Down	Unknown	miRNA sponge	Predicted	(85)

Table II. Continued.

circRNA (circBase ID)	circRNA (other name)	Gene symbol	Full names	Length (bp)	Expression	Function	Mechanism	Pathways	(Refs.)
hsa_circ_0002131	hsa_circRNA_002131	BNIP3L	BCL2 interacting protein 3 like	511	Down	Unknown	miRNA sponge	Predicted	(85)
hsa_circ_0003271	hsa_circRNA_102556	AXL	AXL receptor tyrosine kinase	485	Down	Unknown	miRNA sponge	Predicted	(85)
hsa_circ_0057551	hsa_circRNA_102878	SLC39A10	Solute carrier family 39 member 10	1227	Down	Unknown	miRNA sponge	Predicted	(85)
hsa_circ_0060898	hsa_circATP9A_009	ATP9A	ATPase phospholipid transporting 9A (putative)	1225	Up	Unknown	miRNA sponge	Predicted	(179)
hsa_circ_0027570	hsa_circPTPRR_004	PTPRR	Protein tyrosine phosphatase receptor type R	873	Up	Unknown	miRNA sponge	Predicted	

LUSC, lung squamous cell carcinoma; Up, upregulated; Down, downregulated; circRNA, circular RNA; miRNA, microRNA; TIMELESS, timeless circadian regulator; PVT1, Pvt1 oncogene; ERCC1, ERCC excision repair 1, endonuclease non-catalytic subunit; TP63, tumor protein p63; PAX2, paired box 2; RACGAP1, Rac GTPase activating protein 1; DLG1, discs large MAGUK scaffold protein 1; HMGCS1, 3-hydroxy-3-methylglutaryl-CoA synthase 1; HMGCS1, 3-hydroxy-3-methylglutaryl-CoA synthase 1; HMGCS1, 3-hydroxy-3-methylglutaryl-CoA synthase 1; RAD23B, RAD23 homolog B, nucleotide excision repair protein; TXNIP, thioredoxin interacting protein; BNIP3L, BCL2 interacting protein 3 like; AXL, AXL receptor tyrosine kinase; SLC39A10, solute carrier family 39 member 10; ATP9A, ATPase phospholipid transporting 9A (putative); PTPRR, protein tyrosine phosphatase receptor type R.

Table III. Dysregulated circRNAs in small cell lung cancer.

circRNA (circBase ID)	circRNA (other name)	Gene symbol	Full names	Length (bp)	Expression	Function	Mechanism	Pathways	(Refs.)
hsa_circ_0000368	FLI1 exonic circular RNAs	FLI1	Fli-1 proto-oncogene	367	Up	Promotes cell proliferation and metastasis	miRNA sponge	miR-584-3p/ ROCK1	(92)
hsa_circ_0084927	cESRP1	ESRP1	Epithelial splicing regulatory protein 1	287	Down	Inhibits EMT and cell proliferation and promotes chemosensitivity	miRNA sponge	miR-93-5p/ TGF-β	(180)
hsa_circ_0121597	circ-STXBP5L	STXBP5L	Syntaxin binding protein 5L	307	Up	Unknown	miRNA sponge	Predicted	(90)
hsa_circ_0064558	circ-SATB1	SATB1	SATB homeobox 1	539	Up	Unknown	/	/	(90)
hsa_circ_0001421	circ-SEC31A	SEC31A	SEC31 homolog A	403	Up	Unknown	/	/	(90)
hsa_circ_0011670	circ-THRAP3	THRAP3	Thyroid hormone receptor associated protein 3	2726	Up	Unknown	/	/	(90)
hsa_circ_0046906	circ-VAPA	VAPA	VAMP associated protein A	378	Up	Unknown	/	/	(90)
hsa_circ_0005895	circ-CARD6	CARD6	Caspase recruitment domain family member 6	1923	Down	Unknown	/	/	(90)
hsa_circ_0028544	circ-TBX5	TBX5	T-box transcription factor 5	400	Down	Unknown	/	/	(90)
hsa_circ_0001778	circ-WDR60	WDR60	Dynein 2 intermediate chain 1	558	Down	Unknown	/	/	(90)

[a]According to the prediction analysis with WebGestalt and miRanda and construct the miRNA-mRNA and circRNA-miRNA networks. Up, upregulated; Down, downregulated; circRNA, circular RNA; miRNA, microRNA; EMT epithelial to mesenchymal transition; FLI1, Fli-1 proto-oncogene; ESRP1, epithelial splicing regulatory protein 1; STXBP5L, syntaxin binding protein 5L; SATB1, SATB homeobox 1; SEC31A, SEC31 homolog A; THRAP3, thyroid hormone receptor associated protein 3; VAPA, VAMP associated protein A; CARD6, caspase recruitment domain family member 6; TBX5, T-box transcription factor 5; WDR60, dynein 2 intermediate chain 1.

scarce compared with those in NSCLC, which necessitates further investigation to reveal their biological effects in this subtype of lung cancer.

5. circRNAs in the therapeutic resistance of lung cancer

Recently, chemotherapeutic drugs, targeted therapy and radiation have been commonly employed in lung cancer (93). Furthermore, immunotherapy has recently been utilized more frequently. However, resistance is increasingly obvious throughout the prolonged period of use and limits the efficacy of therapy (94). The development of resistance involves several mechanisms, and circRNA may be a promising target to improve the therapeutic efficacy and act as diagnostic and prognostic markers to improve treatment efficacy. The circRNAs that are highly relevant to the efficacy of therapeutic treatment and their mechanisms of action are presented in Table IV and Fig. 3.

Resistance to chemotherapy. The most commonly used chemotherapeutic agents include platinum drugs [cisplatin (CDDP)], taxol derivatives [paclitaxel (PTX), docetaxel (DTX)] and pemetrexed (95). circRNAs have a role in tumor sensitivity and resistance to chemotherapy and act as potential diagnostic biomarkers to predict the efficiency of chemotherapy (96,97).

CDDP was reported to be the most efficient chemotherapeutic drug for the treatment of NSCLC and SCLC (98). It mainly interacts with DNA and activates signal transduction pathways, including ATR, p53, p73 and MAPK, resulting in the apoptosis of cancer cells (99). Hsa_circ_0008305 (circPTK2) expression was decreased in CDDP-resistant NSCLC tissues and cells, and its overexpression significantly inhibited CDDP resistance in NSCLC through the miR-942/tripartite motif containing 16 axis (100). However, circ_0008928 was highly expressed in CDDP-resistant NSCLC cells (101). Knockdown of circ_0008928 improved CDDP sensitivity and accelerated cell proliferation, migration and invasion via the miR-488/hexokinase 2 signaling pathway. In addition, the expression of circ_0008928 was significantly upregulated in serum exosomes of patients with CDDP-resistant NSCLC, indicating its potential as a biomarker to predict the resistance of NSCLC (101).

PTX resistance was also reported to be related to circRNAs. Hsa_circ_0002483 was downregulated in PTX-resistant NSCLC cells (102). Its overexpression significantly enhanced the sensitivity of NSCLC cells to PTX. circ_0002483 was demonstrated to sponge miR-182-5p and inhibit growth factor receptor bound protein 2, forkhead box protein O1 (FOXO1) and FOXO3 expression, which may lead to increased sensitivity to PTX (102). By contrast, circRNA zinc-finger (circ_ZFR) and hsa_circ_0002874 were demonstrated to promote PTX resistance in NSCLC (103). circ_ZFR was discovered to be highly expressed in PTX-resistant NSCLC tissues and cell lines. Mechanistically, circ_ZFR markedly upregulates the expression of karyopherin subunit α4 by sponging miR-195-5p, leading to PTX resistance, cell cycle progression, proliferation, migration and invasion (103). In addition, high expression of hsa_circ_0002874 regulated the miR1273f/mouse double minute 2 protein/P53 signaling pathway to promote PTX resistance *in vitro* and *in vivo* (104). Knockdown of hsa_circ_0002874 promoted PTX sensitivity and induced apoptosis in PTX-resistant NSCLC cells (104).

DTX is also a useful taxane chemotherapeutic medicine for lung cancer, for which resistance is a common problem (105,106). Hsa_circ_0003998 was found to be upregulated in LUAD tissue and DTX-resistant cell lines. Knockdown of hsa_circ_0003998 significantly reversed DTX resistance in LUAD cells by directly binding with miR-326 (107). In addition, in contrast to DTX-sensitive tissues and cells, the 5-year survival rate of NSCLC DTX-resistant patients was significantly lower and hsa_circ_0074027 (HC0074027) was significantly upregulated in DTX-resistant tissues and cells (108). Mechanistically, HC0074027 enhanced NSCLC DTX resistance *in vitro* and *in vivo* via the miR-379-5p/insulin-like growth factor 1 (IGF1) axis (108).

circRNAs may also modulate resistance to other chemotherapeutics and combined chemotherapy, such as pemetrexed. Mao and Xu (109) reported that cerebellar degeneration-related protein 1 transcript (CDR1-AS) is highly expressed in patients with pemetrexed- and CDDP-insensitive LUAD, and silencing CDR1-AS significantly sensitized LUAD cells to PTX and CDDP via the epidermal growth factor receptor (EGFR)/PI3K signaling pathway. circRNA planning target volume 1 (circPVT1) was highly expressed in CDDP- and pemetrexed-resistant LUAD tissues, while knockdown of circPVT1 resensitized chemoresistant LUAD cells (110). In addition, subsequent experiments revealed that circPVT1 knockdown resulted in decreased ATP binding cassette subfamily C member 1 expression through miR-145-5p and inhibited resistance to drugs including doxorubicin, etoposide and vincristine (110,111). These studies on drug resistance will help elucidate the mechanisms of chemoresistance and may provide a therapeutic target for lung cancer.

Resistance to targeted therapy. Recently, targeted therapies for the management of lung cancer have provided promising results (112). Of note, several circRNAs were reported to cause resistance to targeted drugs. EGFR is currently the most favored target in lung cancer. Gefitinib was the first EGFR inhibitor, approved in 2003. Hsa_circRNA_012515 was particularly highly expressed in peripheral blood samples of patients with gefitinib-resistant NSCLC compared to the sensitive group, demonstrating that upregulation of hsa_circRNA_012515 may be a mechanism leading to gefitinib resistance in patients with NSCLC (55). Furthermore, hsa_circRNA_012515 exhibited high diagnostic accuracy as a biomarker for efficient targeted therapy [area under the receiver operating characteristic (ROC) curve (AUC)=0.89] (55). Similarly, hsa_circ_0004015 expression regulated proliferation and invasion and contributed to gefitinib resistance in NSCLC cells via the miR-1183/3-phosphoinositide dependent protein kinase-1 signaling pathway (96). Of note, exosomal circRNA_102481 was upregulated in NSCLC with EGFR-tyrosine kinase inhibitor (TKI) resistance and it was able to promote EGFR-TKI (gefitinib and erlotinib)-resistant NSCLC cell proliferation and inhibit cell apoptosis by regulating the miR-30a-5p/receptor tyrosine kinase like orphan receptor 1 axis (113). A total of 58 patients treated with gefitinib or erlotinib were collected to validate these results and circRNA_102481 was demonstrated to be significantly upregulated in patients with EGFR-TKI resistance (113).

Table IV. circRNAs that are highly relevant to the treatment of lung cancer and their mechanisms of action.

circRNA	Function	Pathway	(Refs.)
CDR1-AS	Improves PTX and CDDP resistance of LUAD	EGFR/PI3K	(109)
circ_0001287	Inhibits radioresistant of NSCLC	miR-21/PTEN	(116)
circ_0008928	Improves the CDDP-resistance and accelerated cell proliferation, migration, and invasion of NSCLC	miR-488/HK2	(101)
circ_0086720	Inhibits radioresistance and prevents the growth of NSCLC	miR-375/SPIN1	(117)
circ_ZFR	Leads to PTX resistance, cell cycle process, proliferation, migration and invasion of NSCLC	miR-195-5p/KPNA4	(103)
circHMGB2	Drives immunosuppression and anti-PD-1 resistance of LUAD	miR-181a-5p/CARM1	(125)
circIGF2BP3	Promotes the deubiquitination of PD-L1 and improves anti-PD1 immunotherapy resistance of NSCLC	miR-181a/CARM1	(123)
circMTDH.4	Improves chemoresistance and radioresistance of NSCLC	miR-630/AEG-1	(118)
circNEIL3	Inhibits radioresistance of LUAD	miR-1184/PIF1	(119)
circPVT1	Improves cisplatin and pemetrexed resistance of NSCLC	miR-145-5p/circPVT1	(110)
circRNA_102481	Promotes EGFR-TKIs (gefitinib and erlotinib) resistance of NSCLC	miR-30a-5p/ROR1	(113)
circUSP7	Improves anti-PD1 immunotherapy resistance of NSCLC	miR-934/SHP2	(122)
circZNF208	Improves radioresistance to X-rays of NSCLC	miR-7-5p/SNCA	(120)
hsa_circ_0002483	Inhibits the PTX resistance of NSCLC	miR-182-5p/GRB2, FOXO1, FOXO3	(102)
hsa_circ_0002874	Inhibits PTX sensitivity of NSCLC	miR1273f/MDM2/P53	(104)
hsa_circ_0003998	Improves resistance of LUAD	miR-326	(107)
hsa_circ_0004015	Regulates the proliferation and invasion and contributes to gefitinib resistance of NSCLC	miR-1183/PDPK1	(96)
hsa_circ_0005576	Improves osimertinib resistance of LUAD	miR-512-5p/IGF1R	(114)
hsa_circ_0007312	Improves osimertinib resistance of LUAD	miR-764/MAPK1	(115)
hsa_circ_0008305	Inhibits the CDDP-resistance of NSCLC	miR-942/TRIM16	(100)
hsa_circ_0074027	Improves DTX resistance of NSCLC	miR-379-5p/IGF1	(108)
hsa_circRNA_012515	Improves gefitinib resistance of NSCLC	-	(55)

circRNA, circular RNA; miR, microRNA; DTX, docetaxel; PTX, paclitaxel; CDDP, cisplatin; NSCLC, non-small cell lung cancer; LUAD, lung adenocarcinoma; CDR1-AS, cerebellar degeneration-related protein 1 transcript; EGFR, epidermal growth factor receptor; PTEN, phosphatase and tensin homolog; SPIN1, spindling 1; KPNA4, karyopherin subunit α4; CARM1, coactivator associated arginine methyltransferase 1; IGF2BP3, insulin-like growth factor II mRNA-binding protein 3; NEIL3, circRNA Nei endonuclease VIII-like 3; USP7, ubiquitin specific protease 7; SHP2, Src homology-2-containing protein tyrosine phosphatase 2; SNCA, α-synuclein; GRB2, growth factor receptor bound protein 2; FOXO1, forkhead box protein O1; MDM2, mouse double minute 2 protein; PDPK1, 3-phosphoinositide dependent protein kinase-1; IGF1R, insulin-like growth factor 1 receptor; TRIM16, tripartite motif containing 16.

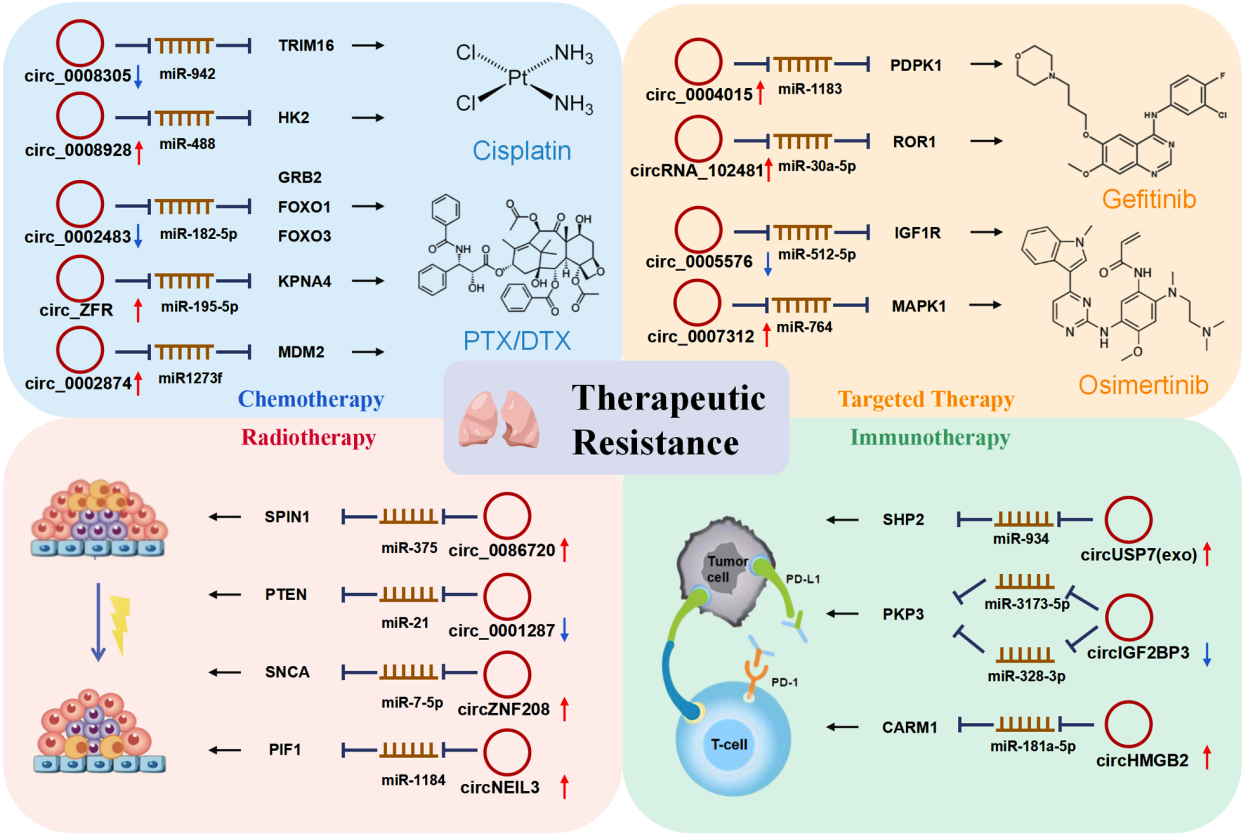

Figure 3. Roles of circRNAs in therapeutic resistance of lung cancer. The examples provided outline the role of circRNAs and related mechanisms in the resistance to therapies, including chemotherapy, targeted therapy, radiotherapy and immunotherapy. Cisplatin, PTX and DTX are typical chemotherapeutic drugs for lung cancer. Gefitinib and osimertinib are EGFR tyrosine kinase inhibitors targeting EGFR-activating mutations. circRNA, circular RNA; miR, microRNA; PTX, paclitaxel; DTX, docetaxel; TRIM16, tripartite motif containing 16; HK2, hexokinase 2; GRB2, growth factor receptor bound protein 2; FOXO1, forkhead box protein O1; FOXO3, forkhead box protein O3; KPNA4, karyopherin subunit α4; MDM2, mouse double minute 2 protein; PDPK1, 3-phosphoinositide dependent protein kinase-1; ROR1, receptor tyrosine kinase like orphan receptor 1; IGF1R, insulin-like growth factor 1 receptor; MAPK1, mitogen-activated protein kinase 1; SPIN1, spindling 1; PTEN, phosphatase and tensin homolog; SNCA, α-synuclein; PIF1, phytochrome-interacting factor1; SHP2, Src homology-2-containing protein tyrosine phosphatase 2; PKP3, plakophilin-3; CARM1, coactivator associated arginine methyltransferase 1.

Osimertinib is a third-generation EGFR inhibitor against the acquired gefitinib-resistant mutation EGFR T790 M. However, resistance to osimertinib has also been observed and circRNAs are also involved. Hsa_circ_0005576 was markedly increased in osimertinib-resistant LUAD cells. Knockdown of hsa_circ_0005576 recovered osimertinib sensitivity via the miR-512-5p/IGF1 receptor pathway (114). In addition, hsa_circ_0007312 (circ7312) was positively correlated with osimertinib IC_{50} values and xenograft experiments indicated that knockdown of circ7312 decreased resistance to osimertinib *in vivo*. Mechanistically, circ7312 caused osimertinib resistance in LUAD cells by sponging miR-764 to upregulate MAPK1 and suppress pyroptosis and apoptosis (115).

Resistance to radiotherapy. Studies have indicated that circRNAs also regulate cancer radiotherapy resistance. Colony-formation experiments indicated that overexpression of circ_0001287 significantly inhibited the survival of NSCLC cells after irradiation at different ionizing radiation (IR) intensities (116), and knockdown of circ_0001287 promoted radioresistance, indicating that circ_0001287 was a vital regulator of radiotherapy resistance. In addition, knockdown of circ_0086720 was observed to enhance radiosensitivity and prevent the growth of NSCLC (117). circ_0086720 expression was upregulated in radioresistant NSCLC tissues and inhibited the radiation sensitivity of NSCLC by regulating the miR-375/spindling 1 axis (117). Astrocyte elevated gene-1 (AEG-1) was indicated to significantly induce the apoptotic rate of NSCLC cells after radiation (118). circMTDH.4 is able to regulate the radioresistance of NSCLC cells to IR by sponging miR-630 to regulate AEG-1 expression (118). Knockdown of circRNA Nei endonuclease VIII-like 3 (circNEIL3) efficiently enhanced the sensitivity to radiation treatment. After irradiation, knockdown of circNEIL3 in LUAD cells led to increased efficacy of pyroptosis through the DNA damage pathway via the miR-1184/phytochrome-interacting factor 1 axis (119). This evidence indicates that circNEIL3 may target pyroptosis in LUAD cells and may have the potential to enhance the efficacy of radiotherapy in lung cancer. Furthermore, knockdown of circZNF208 inhibited DNA synthesis and decreased radioresistance in NSCLC cells with radioresistance to IR. However, circZNF208 knockdown was not able to change the radiosensitivity of NSCLC cells to carbon ions, which provides a new perspective to further explore the mechanisms of circRNAs in association with different types of irradiation (120).

Resistance to immunotherapy. Immunotherapy, particularly immune checkpoint inhibitors, has emerged in recent years as

an important treatment option for numerous different cancers and has been successful for certain types of cancer. However, it was reported that with the use of anti-PD1, the majority of patients inevitably acquire resistance after several cycles of treatment (121), and circRNAs were involved in the resistance to these immunotherapies. In a humanized mouse model, tumors with circRNA ubiquitin specific protease 7 (circUSP7) overexpression exhibited elevated exosomal circUSP7 in the serum and obvious resistance to anti-PD1 immunotherapy. The expression of plasma exosomal circUSP7 in patients with NSCLC was found to be negatively correlated with CD8+ T-cell infiltration in the tumor and increased levels of circUSP7 predicted a poor clinical outcome. circUSP7 was also found to promote CD8+ T-cell dysfunction via the circUSP7/miR-934/Src homology-2-containing protein tyrosine phosphatase 2 axis (122). These results may be helpful for predicting the efficacy of immune checkpoint therapy in patients with NSCLC.

circIGF2BP3 (hsa_circ_0079587) was also observed to be increased in the tumor microenvironment and negatively correlated with CD8+ T-cell infiltration (123). Elevated circIGF2BP3 led to compromised antitumor immunity in an immunocompetent mouse and CD8+ T cells were indispensable in this effect. Further examination indicated that circIGF2BP3 also restricted the efficacy of anti-PD-1 treatment through miR-181a/coactivator associated arginine methyltransferase 1 (CARM1) in patients with NSCLC. CARM1 was reported to promote the type 1 interferon response and the sensitivity of the tumor to T-cell-dependent immune attack (124). Overexpression of circIGF2BP3 elicits high PD-L1 expression via the plakophilin-3/OTU deubiquitinase 1 axis and damages anti-PD-1 treatment-mediated CD8+ T-cell recruitment and tumor regression (123). Furthermore, circHMGB2 was demonstrated to increase the proliferation of LUAD and LUSC cells and regulate anti-PD-1 resistance (125). These studies help elucidate the mechanism of resistance to immunotherapy in lung cancer and may also provide a potential therapeutic target for lung cancer.

6. circRNAs as potential diagnostic and prognostic biomarkers

The analysis of circRNAs enables the construction of a reliable system and demonstrates their potential for providing new diagnostic and prognostic biomarkers (126). Following the rapid development of high-throughput transcriptome analysis techniques, liquid biopsy assays have finally been implemented in clinical practice (127). circRNA molecules have the characteristics of high abundance, stability, sequence conservation, tissue specificity and a long half-life, and distinct differences are exhibited in peripheral blood and tissue from cancer patients (128). Therefore, circRNAs have been increasingly recognized as promising and specific tumor biomarkers. Due to the convenience and low injury risk for patients, combined with the detectability of circRNA in peripheral body fluids (126), the use of circRNA as a significant biomarker for lung cancer is promising.

Diagnosis. To help diagnose lung cancer, circRNAs should be easily detected in the periphery. Compared to normal human bronchial epithelial cells, circSATB2 was highly expressed in NSCLC cells and knockdown of circSATB2 was able to markedly decrease the cell proliferation, migration and invasive capacity of NSCLC cells, signifying that circSATB2 has the potential to predict the presence of NSCLC (129). Furthermore, circSATB2 was also able to be specifically and sensitively detected in serum exosomes from patients with lung cancer, supporting its use as a blood biomarker for convenient clinical diagnosis of NSCLC. In addition, patients with NSCLC exhibited higher serum circRNA_001846 levels than healthy participants (130). circRNAs was also able to predict the level of lymph node metastasis, tumor differentiation and TNM stage. Furthermore, in the ROC analysis, the AUC was 0.678, which revealed the specificity of circRNA_001846 in diagnosing patients with NSCLC.

Tumor-educated platelets have emerged as rich sources of cancer-related RNA profiles in liquid biopsies and are also applicable for cancer detection (131). A total of 411 circRNAs differentially expressed between patients with NSCLC and healthy controls were identified, and circNRIP1 was the most significantly differentially expressed circRNA in platelets between patients with NSCLC and healthy controls. In addition, downregulation of circNRIP1 is associated with an advanced tumor stage. This suggests that circNRIP1 is a potential diagnostic biomarker for NSCLC (132). All of these studies indicated the potential of circRNAs as noninvasive biomarkers for diagnosing lung cancer.

Prognosis. Prognostic evaluation is an important part of formulating an optimal treatment, which is of great significance for improving the medical effects and the quality of life of patients. Studies have confirmed that a variety of circRNAs have high specificity in respiratory diseases and are closely related to the survival of patients with lung cancer, such as circ-ANXA7 (65), circRNA ArfGAP with SH3 domain ankyrin repeats and PH domain 1 (133), and hsa_circ_0001715 (134). These circRNAs may be used as independent prognostic indicators for patients with lung cancer.

Zhang *et al* (135) reported that hsa_circRNA_101237 was highly expressed in NSCLC tissues and was associated with inferior patient outcomes. Elevated hsa_circRNA_101237 levels promoted the proliferation, migration and invasion of NSCLC cells via the miR-490-3p/MAPK1 axis and were correlated with lymph node metastasis, a large tumor size, advanced TNM stage and shorter survival of patients with NSCLC (135). Furthermore, downregulation of circ_0000567 in LUAD cells was an independent prognostic factor (136). Decreased circ_0000567 levels accelerated the migration and invasion of LUAD cells via the miR-421/transmembrane protein 100 axis.

In addition to circRNAs in the tumor tissue, several circRNAs upregulated in the blood of patients with lung cancer may also efficiently predict the progression of the disease. Luo *et al* (137) observed that the plasma level of oncogenic circRNA hsa_circ_0000190 (C190) was highly expressed in patients with NSCLC and the AUC indicated that the diagnostic accuracy of hsa_circ_0000190 was good, particularly in the later stages (III-IV), and it was a potentially valuable blood-based biomarker to assess the prognosis of NSCLC. At the same time, exosomal circRNA FLI1 exonic circular RNA

(FECR), exo-FECR were detected at relatively high levels in the serum of patients with SCLC compared with other cancers, and longer disease remission periods were observed in patients with lower exo-FECR1 compared to patients with higher exo-FECR1. This evidence suggests that exo-FECR1 may serve as a useful clinical indicator to monitor disease progression and predict survival outcomes in SCLC (92).

7. Conclusions and perspective

In recent years, numerous studies have focused on circRNAs, revealing diverse molecular mechanisms and functional roles in lung cancer. As mentioned above, circRNAs exhibit the characteristics of structural specificity and biological stability, which is helpful for diagnosis, drug resistance monitoring, treatment evaluation and prognostication of lung cancer. Liquid biopsy detection technology for circRNAs is of great potential clinical value. At present, although numerous strategies have been used to treat lung cancer, such as chemotherapy, radiotherapy, surgery, immunotherapy and targeted therapy, in most patients with NSCLC, treatment resistance is still an important reason for poor treatment effects or relapse. There is a close relationship between circRNAs and the treatment resistance of NSCLC. In the future, circRNAs may be used to screen and predict treatment efficacy in populations treated with chemotherapy, radiotherapy and immunotherapy, as well as the sensitivity to and tolerance of these treatments, to provide a theoretical basis for the clinical optimization of treatment strategies for NSCLC.

circRNAs function by acting as miRNA molecule sponges, protein decoys, gene transcriptional regulators or translation templates and have important roles in gene expression and signaling pathways involved in a variety of biological processes and diseases. With the advancement of high-throughput sequencing and related research, the functions of circRNAs continue to be revealed. Of note, circRNAs are considered to be conserved, stable and abundant, and frequently exhibit tissue specificity. Based on these findings, circRNAs hold extraordinary promise as diagnostic, prognostic and predictive biomarkers. Due to their stability, circRNAs may be present in exosomes and blood plasma, and their stable presence in exosomes and plasma provides a more convenient way to diagnose cancer compared to tumor tissues.

However, numerous challenges and controversies remain that require to be resolved to move this field forward. The present review indicated that most studies mainly focused on LUAD, while the current understanding of circRNAs in LUSC and SCLC remains limited. SCLC has a rapid development process and a high degree of malignancy, and it requires more thorough research on its mechanisms in the future to improve patient prognosis. In addition, most circRNAs exert their effects as miRNA sponges. Whether the miRNA sponge function is the primary function of circRNAs remains controversial. In addition, current research on circRNAs mainly focuses on lung cancer tissue or cell lines, but there remains a gap in the study of circRNAs in body fluids, which may be more feasible and convenient in the clinic. Furthermore, the current research is mostly aimed at single circRNAs. It is necessary to construct lung cancer-related circRNA networks to obtain a full view of their roles in lung cancer development before these results become clinically applicable.

In conclusion, in addition to the diagnostic and prognostic value of circRNAs in lung cancer, the construction of circRNAs and the continuous development and maturity of circRNA interference technology make it possible to use circRNAs to alter biological regulation. There will be additional breakthroughs in the field of circRNAs in the future, which will offer profound clinical diagnostic and therapeutic applications.

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Authors' contributions

Conceptualization: SX and LC. Compilation of literature: FW and CTY. Article writing and editing: FW and CTY. Figures: FW and CTY. Supervision: SX and LC. All authors have read and approved the final manuscript. Data authentication is not applicable.

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Competing interests

The authors declare that they have no competing interests.

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