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Review article

CircRNAs and lung cancer: Biomarkers and master regulators

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ABSTRACT

CircRNAs are a class of competitive, endogenous, non-coding RNAs with closed-loop structures. High-throughput sequencing indicates that circRNAs are ubiquitously expressed in many eukaryotes. Biological functions of circRNAs include interaction with proteins and regulation of gene transcription, translation, and miRNA sponge activity. These functions suggest that circRNAs may be useful as novel biomarkers for disease diagnosis and prognosis. Lung cancer is known worldwide as the most common malignant tumor. It is also the main cause of cancer-related death. In recent years, it has become increasingly evident that circRNAs are involved in the proliferation, migration, and invasion of lung cancer cells. Differentially expressed circRNAs may be used as non-invasive diagnostic and prognostic markers for lung cancer. Therefore, they are considered a research hotspot for lung cancer studies. This article is a systematic review of mechanisms underlying the action, diagnosis, clinical aspects, and drug resistance of circRNAs in lung cancer.

1. Introduction

According to data reported in 2018 by the International Agency for Research on Cancer, lung cancer is the most common cancer worldwide (11.6% of total cases) and the leading cause of cancer-related deaths (18.4% of total cancer deaths) [1]. In 85% of patients, the histological subtype is non-small cell lung cancer (NSCLC), of which lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC) are the most common subtypes [2]. Over the past 20 years, immunotherapy and the use of small molecule tyrosine kinase inhibitors have enabled NSCLC patients to achieve unprecedented survival rates. However, overall cure and survival rates for NSCLC remain very low, especially for those in metastatic stages of the disease [3]. Compared with that for NSCLC, there is a lack of early detection methods for small cell lung cancer (SCLC), which exhibits rapid doubling time and early extensive metastasis [4]. The 5-year survival rate is generally less than 7%, and most patients survive only 1 year or less following diagnosis [5]. Active exploration of lung cancer pathogenesis indicates that identification of new lung cancer-associated biomarkers may be critical for improving treatment and prognosis of lung cancer patients, and thus, it is important to identify molecular mechanisms and signaling pathways that are related to lung cancer.

Circular RNAs (circRNAs), a class of non-coding RNAs, were first discovered in RNA viruses via electron microscopy in 1976 [6]. However, subsequent studies on this class were sporadic. In recent years, the development of high-throughput RNA sequencing, extra-nuclear enrichment tools, and bioinformatics analyses has resulted in reports of widespread expression of circRNAs in many eukaryotes [7]. Memczak et al. identified 1950 human circRNAs, 1903 mouse circRNAs, and 724 nematode circRNAs via RNA sequencing [8]. A number of studies have confirmed the important role played by circRNAs in the development and progression of many human diseases such as cancer [9], heart disease [10], nervous system diseases [11], diabetes [12], and immune system diseases [13]. In addition, a growing body of research indicates that circRNAs may be closely associated with tumor proliferation, apoptosis, invasion, and metastasis. This suggests the potential of circRNAs as novel biomarkers and therapeutic targets. In particular, regulation of circRNAs may be an indispensable factor in the mechanisms underlying lung cancer as well as its diagnosis and treatment [14].

The current review discusses the expression of circRNAs in lung cancer; their regulation of lung cancer proliferation, apoptosis, and invasion mechanisms; their role in lung cancer diagnosis and as prognostic biomarkers; and their therapeutic potential. Although some reviews have introduced the results of circRNAs classification and biogenesis, and summarized the role of many discovered circRNAs in lung cancer and the corresponding mechanisms [15,16], the innovations of this article are that the key aspects of the diagnosis, treatment, drug

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resistance and SCLC are discussed in detail.

2. CircRNAs

2.1. Discovery of circRNAs

CircRNAs, a class of endogenous non-coding RNAs that differ from linear RNAs, which are closed circRNA molecules formed by reverse splicing. CircRNAs do not have a 5′ end cap and a 3′ end poly(A) tail structure and are present in a stable form in various types of eukaryotic cells [17]. In 1976, Sanger et al. found that the viroid genome consisted of single-stranded, closed RNA molecules that could infect plants and cause their death, wherein viroids RNAs were found in the dead plants [6]. Subsequently, circRNA transcripts were found in the cytoplasm of eukaryotic cells, mouse sperm, and *Drosophila* [18–20]. In 2012, Salzman et al. first reported 80 circRNAs, detected via the RNA-Seq method [7]. Following the subsequent development of high-throughput sequencing technology, a large number of cyclic RNA molecules have been discovered.

2.2. Classification of circRNAs

Traditional methods, based on RNA composition, classify circRNAs into 3 categories: exonic circRNAs (ecRNAs), intronic circRNAs (ciRNAs), and exon-intron circRNA (exon). -intron circRNA, (EIciRNAs). Exonic circRNAs produced through spliceosomal splicing, are the most common circRNAs [21]. Intronic circRNAs are composed of non-coding RNAs derived from 2 or more introns and are mainly found in the nucleus [22,23]. Exon-intron circRNAs are composed of two adjacent exons and RNA formed by the transcription of the intron between the two exons and are mainly present in the nucleus [24]. The latest classification method which explains the relationship between circRNAs and parental genes, is based on the positional relationship between circRNAs and adjacent coding RNAs. This method group circRNAs into 5 categories: exon circRNAs, intron circRNAs and justice overlap, sense overlapping circRNAs, antisense circRNAs, and intergenic circRNAs [22].

2.3. Functions of circRNAs

2.3.1. As ceRNAs or miRNA sponges

EcRNAs, consisting of exons, have a stable circular structure, and most of them contain miRNA response elements (MREs). Therefore, ecRNAs may act as highly efficient endogenous RNAs, effectively adsorbing miRNAs and preventing them from interacting with target mRNA [25].

2.3.2. Modulate alternative splicing or transcription

EIciRNAs and ciRNAs are mainly located in the nucleus and have been shown to regulate the transcription of parental genes [26]. Exon-intron circRNAs such as circEIF3J and circPAIP2 could bind to RNA polymerase II (Pol II) and regulate the expression level of their host genes [27]. In the process of precursor RNA splicing, reverse splicing produces circRNAs that can competitively regulate alternative splicing [28,29].

2.3.3. Interact with RNA binding proteins (RBPs)

CircRNAs can bind to RBPs to exert biological functions [8]. When CircRNAs bind to RBPs and ribonucleoprotein complexes, they act as an RNA-binding protein sponge and “storage” [29].

2.3.4. Translate proteins

The function of circRNA-encoded proteins has been demonstrated only in the hepatitis D virus [30], where studies demonstrated that in eukaryotes, circRNAs with an internal ribosome entry site (IRES) are capable of efficient translation [31–33]. Legnini et al. found that circZNF609 has an open reading frame (ORF) with a start codon and a stop codon at both ends to generate a protein by polyribosome translation [34]. In addition, studies have confirmed that natural eukaryotic endogenous circRNAs drive protein translation by methylation of adenosine N6 (m6A) [35].

2.3.5. Enable derivation of pseudogenes

Studies have shown that stable circRNA molecules can be reverse transcribed and integrated into the genome to form circRNA-derived pseudogenes [22].

3. CircRNAs and lung cancer

Studies have shown that circRNAs are differentially expressed in various tissues with tumors [36,37]. High-throughput sequencing demonstrated the presence of a large number of different circRNAs in lung cancer tissues, compared to that in normal tissues, suggesting the involvement of circRNAs in the occurrence and developmental process of lung cancer.

3.1. Expression of circRNAs in lung cancer

Evidence indicates that there are many differentially expressed circRNAs in tissues and plasma of lung cancer patients. Jiang et al. reported that a circRNA microarray in NSCLC tissues exhibited a total of 957 abnormal circRNA expressions, compared to that in adjacent normal tissues [38]. Zhao et al. selected tumor specimens from 4 early lung adenocarcinoma patients and paired adjacent normal tissues. The expression profile of circRNAs, detected via high-throughput circRNA microarray analysis, enabled the identification of 356 circRNA expressions in tumor specimens. In the tumor sample, 204 and 152 circRNAs were up-regulated and down-regulated, respectively, most of which were exon cyclic RNAs [39]. In another study, Ding et al. used RNA sequencing technology to detect 9 cases of lung adenocarcinoma (LUAD) and nontumor tissues in a group of 3 mixed samples. The circRNA prediction algorithm identified 5750 circRNAs, including 3590 new circRNA transcripts, which are less abundant than mRNA and lncRNA. Most circRNAs are less than 1000 nt in length and have a median length of approximately 530 nt [40]. Xu et al. used circRNA microarray analysis to show that, compared with the adjacent normal group, there were 216 circRNA expression profiles in 3 LSCC groups, where 135 were up-regulated and 81 were down-regulated. In another 40 pairs of LSCC tissues, Kaplan-Meier survival analysis indicated that the overall survival time of LSCC patients with high hsa_circRNA_103827 expression and low hsa_circRNA_000122 expression, was significantly shortened [41]. This finding suggested that circRNAs may be a potential marker for the diagnosis and prognosis of lung cancer. As more circRNAs are found in association with lung cancer, the role of circRNAs will continue to receive more attention (See Fig. 1).

3.2. CircRNA and the proliferation and progression of lung cancer

3.2.1. circRNA regulates the proliferation and progression of lung cancer via serving as microRNA sponges

Increasing evidence indicates that miRNAs regulate gene expression in most biological processes, including in carcinogenesis. In-depth studies have found that some circRNAs may act as miRNA sponges to regulate tumor proliferation, metastasis, and invasion.

Studies have demonstrated that circRNF13 is downregulated close to 2.98 times in LUAD tumor tissues and that the expression level is significantly negatively correlated with the tumor nodes and metastases (TNM) stage and lymph node metastasis [42]. Subsequent cytological analyses revealed that circRNF13, which is located in the cytoplasm, interacts with the RNA binding protein Ago2 as a sponge for miR-93-5p.

Similarly, hsa_circ_0007385 was significantly upregulated in NSCLC tissues and lung cancer cells. In vitro experiments have confirmed that

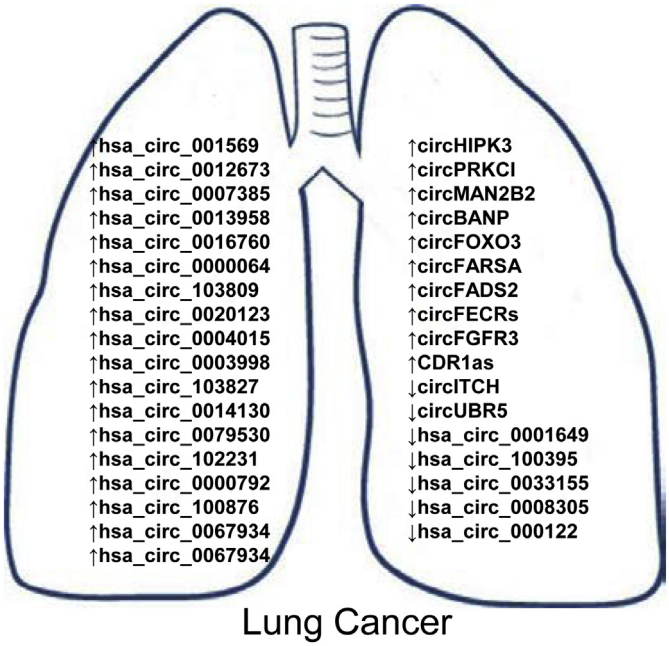

Fig. 1. Deregulated circRNAs in lung cancer.

hsa_circ_0007385 significantly inhibits proliferation, migration, and invasion of NSCLC cells by adsorbing miR-181, and significantly reduces the growth of gene knockout xenograft tumors [38]. Furthermore, hsa_circ_0012673 expression was upregulated in LUAD tissue circRNA microarrays, where the expression level was correlated with tumor size. CircRNAs target erb-b2 receptor tyrosine kinase 3 (ErbB3) via their sponge action on miR-22 to promote the proliferation of LAC cells [43]. Further, circMAN2B2, which promotes FOXK1 expression by sponge action on miR-1275, plays a carcinogenic role in lung cancer [44]. The circ-BANP-mediated miR-503/LARP1 signaling pathway promotes the growth, migration, and invasion of lung cancer [45].

The above stated studies indicate that circRNAs may participate in the processes of proliferation, differentiation, migration, and carcinogenesis through adsorption-related miRNAs, and provide a new direction for the regulation of cancer progression.

3.2.2. CircRNA regulates the proliferation and progression of lung cancer via cancer-associated signaling pathways

Numerous studies have shown that a variety of signaling pathways are involved in abnormal biological processes such as tumor proliferation, apoptosis, and invasion. Increasing data indicate that circRNAs may directly regulate target genes or miRNAs, which are closely associated with cancer-related signaling pathways by acting on the occurrence, proliferation, metastasis, and invasion of lung cancer.

Previous studies have shown that abnormal activation of the Wnt/β-catenin catenin pathway plays a key role in the tumorigenesis, progression, and metastasis of lung cancer [46–48]. The E3 ubiquitin (Ub) protein ligase (ITCH) inhibits Wnt/β-catenin in tumors. Signaling is primarily processed through the promotion of disheveled 2 (Dvl2) ubiquitination and inhibition of its phosphorylation. CircRNA-ITCH (cir-ITCH) has multiple miRNA binding sites that increase ITCH levels and inhibit Wnt/β-catenin cell pathways by adsorbing miR-7, miR-17 and miR-214. Wan et al. found that cir-ITCH expression was significantly reduced in lung tissue. It was also found that cir-ITCH may significantly up-regulate the expression of the parental cancer-suppressive gene, ITCH, thereby inhibiting the proliferation of lung cancer cells. Functional analysis indicated that cir-ITCH adsorption of miR-7, and miR-214 enhanced ITCH levels [49]. Tian et al. also found that hsa_circ_0043256 was up-regulated in NSCLC cells following cinnamaldehyde (CA) treatment [50]. Moreover, hsa_circ_0043256 may inhibit cell proliferation and induce apoptosis, and may be used as a miR-1252 sponge to target ITCH in order to exert its anti-cancer effect.

CircHIPK3 is a rich circRNA derived from Exon2 of the HIPK3 gene with 18 potential miRNA-binding sites [51]. A study reported that circHIPK3 may bind multiple miRNAs, including miR-124 and miR-379, and initiate proliferative activity in lung cancer cell lines and that miR-379 regulates the expression of insulin-like growth factor 1 (IGF1) via sponge action [52]. CircHIPK3 was discovered as a sponge of miRNA-124 and regulates the expression of miR-124-mRNA target genes, SphK1, CDK4, and STAT3, in lung cancer cells [53]. In NSCLC, miR-379 increases the sensitivity of tumor cells to cisplatin and enhances the killing ability of cisplatin [54]. These results suggest that circHIPK3 is involved in the regulation of lung cancer and may represent a new target for NSCLC treatments.

Previous studies have shown that TGF-β may promote epithelial-mesenchymal transition (EMT) and NSCLC cell invasion [55,56]. Recently, we provided evidence that transcriptional intermediary factor 1 γ (TIF1γ) enhances TGF-β-induced EMT in NSCLC cells via the TGF-β/Smad signaling pathway [57–59]. Wang et al. reported that circPTK2 expression was significantly decreased in metastatic NSCLC tissues. Further functional studies found that sponge adsorption of miR- 429/miR- 200 b - 3 p and subsequent targeting of TIF1γ promoted TGF-β-induced EMT in NSCLC metastasis, providing a new strategy for the diagnosis and treatment of NSCLC [60].

These findings suggest that circRNAs may induce lung cancer proliferation and progression via cancer-associated signaling pathways.

3.2.3. Participation in RNA splicing

Qin et al. found that the expression of the circRNA, circ-UBR5, which has no apparent functional phenotype in NSCLC cells, was significantly down-regulated in NSCLC tissues and was associated with poor tumor differentiation, suggesting that circ-UBR5 may be an indicator of NSCLC differentiation [61]. Surprisingly, the researchers found that circ-UBR5 may bind to the splicing regulatory factor (QKI), which contains RNA binding domain and NOVA alternative splicing regulator 1 (NOVA1), and to the U1 small nuclear RNA (snRNA), suggesting that circ-UBR5 may be a novel snRNA involved in RNA splicing that modulates the regulation process. The study first proposed an efficient strategy for identifying specific circRNA-binding proteins using human protein microarrays (Huprot Protoarray), thus providing a fresh objective for subsequent research.

Expression and mechanism of circRNAs in lung cancer are shown in Table 1.

3.3. CircRNA as potential diagnostic biomarkers in lung cancer

In human saliva and peripheral blood, hundreds of circRNAs are more highly expressed than homologous linear mRNAs, and are easier to detect, indicating that circRNAs may be satisfactory biomarkers in non-invasive examinations [62,63].

Early diagnosis of most cancers can significantly improve treatment. In view of the high cost and invasiveness of CT, MRI, histopathology, and other related examinations, a minimally invasive and inexpensive method is urgently needed. According to current research, circRNAs exhibit the following characteristics: (1) CircRNAs are protected from ribonuclease and exonuclease degradation, and have a longer half-life and greater stability than linear RNAs [21]; (2) CircRNAs are different in that they have a high degree of evolutionary conservation between species [64]; (3) circRNAs are distributed in both the cytoplasm and the nucleus. Most circRNAs are enriched in the cytoplasm and sometimes their abundance is over 10 times higher than that of corresponding linear mRNAs, probably due to the higher stability of circRNAs compared to that of linear RNAs [65]; (4) circRNAs are tissue-specific in disease research. The tissue specificity of circRNAs can make them a diagnostic factor for specific tissue diseases [66]; (5) circRNAs are highly abundant and rich in variety [51]. The above characteristics

Table 1
Expression and mechanism of circRNAs in lung cancer.

Name	Dysregulation	Function	Sponge target	Genes/proteins affected	Ref
hsa_circ_001569	UP	Proliferation(+);	–	→Wnt1,TCF4,β-catenin	81
hsa_circ_0012673	UP	Proliferation(+);	miR-22	→ErbB3	43
circHIPK3	UP	Proliferation(+);	miR-379	→IGF1	52
circHIPK3	UP	Proliferation(+);apoptosis(−)	miR-124	→SphK1,STAT3,CDK4	51
hsa_circ_0007385	UP	Proliferation(+);apoptosis(−);invasion and metastasis(+)	miR-181	–	38
hsa_circ_0013958	UP	Proliferation(+);apoptosis(−);invasion and metastasis(+)	miR-134	→cyclin D1,	67
hsa_circ_0016760	UP	Proliferation(+);apoptosis(−);invasion and metastasis(+)	miR-1287	→GAGE1	83
hsa_circ_0000064	UP	Proliferation(+);cell cycles(+);apoptosis(−);invasion and metastasis(+)	–	→caspase-3,caspase- 9, bax,p21,CDK6,cyclin D1; →MMP-2,MMP-9	89
CDR1as	UP	Proliferation(+);cell cycles(+);apoptosis(−)	–	→EGFR,CCNE1,PIK3CD	94
circPRKCI	UP	Proliferation(+);cell cycles(+);invasion and metastasis(+)	miR-545,miR-589	→E2F7	90
circMAN2B2	UP	Proliferation(+);invasion and metastasis(+)	miR-1275	→FOXK1	44
circBANP	UP	Proliferation(+);invasion and metastasis(+)	miR-503	→LARP1	45
circFOXO3	UP	Proliferation(+);invasion and metastasis(+)	miR-155	→FOXO3	78
hsa_circ_103809	UP	Proliferation(+);invasion and metastasis(+)	miR-4302	→MYC	82
hsa_circ_0020123	UP	Proliferation(+);invasion and metastasis(+)	miR-144	→ZEB1,EZH2	86
circFADS2	UP	Proliferation(+);invasion and metastasis(+)	miR-498	–	87
hsa_circ_0004015	UP	Proliferation(+);invasion and metastasis(+)	miR-1183	→PDPK1	105
hsa_circ_0003998	UP	Proliferation(+);invasion and metastasis(+)	miR-326	→Notch1	80
circFECRs	UP	invasion and metastasis(+)	miR584-3p	→ROCK1	110
circFARSA	UP	invasion and metastasis(+)	miR-330-5p,miR-326	→FASN	73
circFGFR3	UP	Proliferation(+);	miR-22-3p	→Gal-1, p-AKT, p-ERK1/2	88
circITCH	Down	Proliferation(−);	miR-7,miR-214	→ITCH	49
hsa_circ_100395	Down	Proliferation(−);cell cycles(−);invasion and metastasis(−)	miR-1228	→TCF21	93
hsa_circ_0001649	Down	Proliferation(−);invasion and metastasis(−)	miR-331-3p,miR-338-5p	–	91
hsa_circ_0033155	Down	Proliferation(−);invasion and metastasis(−)	–	┤PTEN	92
hsa_circ_0008305	Down	invasion and metastasis(−)	miR-429,miR-200b-3p	┤TIF1γ	60

"┤"-inhibitory roles; "→"-stimulatory roles.

denote the potential of circRNAs as biomarkers for the diagnosis and prognosis of lung cancer.

Reportedly, hsa_circ_0013958 is upregulated in LAC tissues, cells, and plasma. In addition, hsa_ circ_0013958 levels are associated with the TNM stage and lymphatic metastasis. The area under the receiver operating characteristic curve was 0.815. The sensitivity and specificity of hsa_circ_0013958 for LUAD diagnosis were 0.755 and 0.796, respectively. The area under the curve (AUC) of plasma hsa_circ_0013958 was 0.794. Thus hsa_circ_0013958 may be superior in diagnosing early lung cancer than in diagnosing advanced lung cancer [67].

Echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (EML4-ALK) fusion gene is present in 4% of NSCLC cases. EML4-ALK produces the EML4-ALK fusion protein that activates alk-related oncogenic signaling and promotes NSCLC progression [68–70]. Increasing evidence indicates that circRNAs spliced from fusion genes may be an alternative entity involved in cancer development in addition to fusion proteins [71]. Tan et al. found a circRNA, *F-circEA-2a*, from *EML4-ALK-v3b* with an AA motif junction site [72]. In addition, F-circEA-2a has little effect on cell proliferation, but promotes migration and invasion of NSCLC cells. Further analysis revealed that *F-circEA* may be present in plasma and tumor tissues of *EML4-ALK*-positive patients. The mRNA of *EML4-ALK* is present only in tumor tissues and cannot be detected in plasma. This study pointed out that F-circEA, a fusion circRNA produced from the EML4-ALK fusion gene, could be a novel "liquid biopsy" biomarker to monitor NSCLC. Thus, F-circEA has a potential value in the diagnosis of EML4-ALK in NSCLC patients and in the use of crizotinib, an ALK inhibitor.

A circRNA derived from exon 5–7 of the phenylalanine-tRNA ligase subunit alpha (FARSA) gene, termed circFARSA, was significantly upregulated in cancer tissues and was abundant in corresponding plasma. The level of FARSA mRNA in plasma was found to be too low to detect [73]. Further analysis of the diagnostic value of plasma circFARSA in distinguishing NSCLC patients from non-cancer patients, indicated the area under the ROC curve to be 0.71, suggesting that plasma circFARSA may be used as a biomarker for non-invasive detection of NSCLC. Overexpression of circFARSA in lung cancer cell lines significantly promotes cell migration and invasion. In silico analysis revealed that circFARSA may sponge miR-330-5p and miR-326, leading to the attenuating of its inhibitory effect on oncogene fatty acid synthase.

In addition, some circRNAs show value in differential diagnoses between lung cancer tissues and adjacent normal tissues. Both Hsa_circ_0014130 [74] and hsa_circ_0079530 [75] are highly expressed in NSCLC tissues. The expression of hsa_circ_0014130 is associated with TNM staging and lymph node metastasis. The area under the ROC curve was 0.878, and the sensitivity and specificity were 87% and 84.8%, respectively. The expression level of hsa_circ_0075930 in NSCLC cell lines and tissues was significantly increased and was related to tumor size and lymph node metastasis. Area under the receiver operating characteristic curve (ROC) was 0.756, sensitivity was 76.2%, and specificity was 72.1%. The expression of circRNA_102231 was significantly up-regulated in LUAD tissues and was associated with low overall survival of patients with advanced TNM stage, lymph node metastasis and lung cancer. Its area under the ROC curve was 0.897, and circRNA_102231 showed good sensitivity and specificity of 81.2% and 88.7%, respectively [76]. The areas under the hsa_circ_0000792 and miR-375 ROC curves were 0.815 and 0.772, respectively [77]. In addition, circRNA-FOXO3 was down-regulated in NSCLC tissues and cell lines, its area under the ROC curve was 0.782, and sensitivity and specificity of diagnosis were 80.0 and 73.3%, respectively [78]. The circRNAs found to be associated with lung cancer diagnosis are shown in Table 2.

3.4. Prognostic evaluation of circRNAs in lung cancer

Prognostic evaluation plays an important role in prolonging the survival of cancer patients. Many studies have shown that circRNAs are involved in many pathological processes of lung cancer. Therefore, circRNAs are receiving increasing attention as potential prognostic biomarkers for lung cancer.

Reportedly, circRNA_100876 has prognostic value in patients with lung cancer. Yao et al. tested 101 NSCLC samples, including 51 squamous cell carcinoma (SCC) samples and 50 adenocarcinoma (ADC)

Table 2
Deregulated circRNAs in lung cancer as diagnostic biomarkers.

No.	Deregulation of CircRNA	Histological types	Patientns (No.)	ROC curve			Refs.
				AUC	Sensitivity	Specificity	
1	hsa_circ_0014130	NSCLC	36	0.878	0.87	0.848	74
2	hsa_circ_0075930	NSCLC	92	0.756	0.762	0.721	75
3	circFARSA	NSCLC	50	0.71			73
4	hsa_circ_0013958	LUAD	49	0.815	0.755	0.796	67
5	hsa_circ _0102231	LUAD	57	0.897	0.812	0.887	76
6	hsa_circ_0000792	LUAD	42	0.815			77

samples [79]. Compared with normal tissues, the expression level of circRNA_100876 was up-regulated by 1.23 times in tumor tissues, and positively correlated with lymph node metastasis, TNM stage of lung cancer with lymph node metastasis and tumor stage. The overall survival of NSCLC patients with a high circRNA 100876 expression was significantly shorter than that of patients with low circRNA 100876 expression, suggesting that circRNA_100876 may be one of the risk factors for predicting prognosis.

In NSCLC tissues with up-regulated hsa_circ_0003998 [80], hsa_circ_001569 [81], hsa_circRNA_103809 [82], hsa_circ_0016760 [83], hsa_circ_0067934 [84,85], hsa_circ_0020123 [86], circFADS2 [87] and circFGFR3 [88] expression, the overall survival rate of patients was short. Among these, hsa_circ_0003998 was associated with increased tumor volume and lymph node metastasis. Furthermore, upregulation of hsa_circ_0067934, hsa_circ_001569, hsa_circ_0016760, hsa_circ_0067934 and circFGFR3 expression was associated with advanced TNM stages and lymph node metastasis. High expression levels of circFADS2 and hsa_circ_0020123 were associated with advanced TNM stages, lymph node metastasis, and poor differentiation. Hsa_circ_0000064 was up-regulated in lung cancer tissues and its aberrant expression was correlated with several clinical characteristics, including T stage, lymphatic metastasis, and TNM stage [89].

The expression of circPRKCI was upregulated in LUAD tissues and positively correlated with tumor size and TNM stage. Kaplan Meier survival curves showed that patients with higher circPRKCI levels had shorter overall survival time and that circPRKCIs were independent, poor prognostic factors in LUAD patients [90]. Kaplan-Meier survival analysis in SCC showed high expression of Hsa_circRNA_103827 and low expression of hsa_circRNA_000122 in LSCC, where the overall survival time of patients was significantly shortened [41].

In addition, the expression of hsa_circ_0001649 [91], hsa_circ_0033155 [92] and hsa_circ_100395 [93] was decreased in NSCLC tissues, and the down-regulation of hsa_circ_0001649 was associated with advanced TNM stage, positive lymph node metastasis, and poor prognosis. Down-regulation of hsa_circ_0033155 was associated with lymphatic metastasis.

Based on these findings, circRNAs demonstrated potential for diagnosis and prognosis of lung cancer. More research may be needed before these findings can be applied to patients under clinical conditions. The circRNAs found to be associated with lung cancer prognosis are shown in Table 3.

3.5. Therapeutic potential of circRNAs in lung cancer

Many circRNAs have been shown to be involved in the proliferation and progression of lung cancer and their potential role as targets in the treatment of lung cancer has also been shown.

Lin et al. established a nude mouse xenograft model. Compared with the control, siRNA transfected cell-derived tumors and si-circPRKCI transfected cell-derived tumors were smaller and lighter in weight [90]. Patient-derived tumor xenografts (PDTX) better maintained the cell differentiation, morphology, and structure of primary patient tumors. The therapeutic potential of circPRKCI was evaluated via intratumoral injection of cholesterol-conjugated si-circPRKCI and control siRNA. The results indicated that si-circPRKCI significantly inhibited the growth of PDTX in vivo, suggesting that circPRKCI may be a promising therapeutic target for LUAD. EGFR tyrosine kinase inhibitor (EGFR-TKI) has been widely used in EGFR-mutant LUAD patients, and proliferation experiments indicated that gefitinib combined with circPRKCI silenced compared to gefitinib or si-circPRKCI alone. It has a strong inhibitory effect, suggesting that combining the inhibitory effects of EGFR and circPRKCI may lead to synergistic inhibition, indicating that circPRKCI may be a potential therapeutic target.

Zhang et al. reported that CDR1 expression was the highest in NSCLC tissues and negatively correlated with miR-7 expression, which was associated with TNM staging, lymph node metastasis, and a short overall survival time (OS) [94]. CDR1 levels are independent, prognostic factors in patients with NSCLC. CDR1as induces cell viability and growth, affects apoptosis and G1/S block, and adsorbs the miR-7 key target genes, EGFR, CCNE1, and PIK3CD, via sponge action. Several studies have shown that miR-7 may be an important regulator of EGFR-mediated tumorigenesis, suggesting that CDR1as/miR-7 may be a new potential therapeutic target for lung cancer [95,96].

3.6. CircRNAs and lung cancer resistance

Targeted therapy and chemotherapy are effective strategies for clinical treatment of lung cancer. However, the efficacy of drugs is reduced due to drug resistance, leading to treatment failure and poor prognosis of lung cancer patients. Therefore, it is important to understand the molecular mechanisms underlying resistance to chemotherapy in lung cancer.

Because NCSLC lacks sensitive biomarkers, many patients are diagnosed at an advanced stage of the disease, limiting chances of surgical resection. Paclitaxel is a class of diterpenoid alkaloids with effective anti-tumor activity and plays an important role in the treatment of lung cancer; however, paclitaxel treatment is currently facing challenges [97–99]. Xu et al. used high-throughput circRNA microarrays to study circRNA expression profiles of parental A549 and taxol-resistant A549/Taxol cells. They detected 2909 significantly upregulated and 8372 down-regulated circRNAs in A549/Taxol cells compared to those in A549 cells [100]. Compared to A549 cells with downregulated circRNAs, subsequent application of bioinformatics analysis found that many miRNAs that regulate chemosensitivity of lung cancer may interact with the differentially expressed circRNAs. Notably, upregulation of hsa_circ_0071799 was associated with miR-141, and downregulation of the circRNA, hsa_circ_0091931, was associated with miR-34c-5p. Downregulation of miR-141 in ovarian cancer cells by E-cadherin and vimentin led to fibronectin upregulation, triggering of mesenchymal transition and up-regulation of the β-tubulin isotype TUBB3, causing cells to develop resistance to paclitaxel and card Platinum [101]. In lung cancer, MiR-34c-5p inhibits paclitaxel-mediated apoptosis by down-regulating p53 via silencing of its target genes bcl-2 modifier (Bmf) and c-myc [102].

Currently, epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs), which mainly include erlotinib, icotinib and gefitinib,

Table 3
Deregulated circRNAs in lung cancer as prognostic biomarkers.

No.	Deregulation of CircRNA	Histological types	Correlation with clinical characteristics	Patientns (No.)	Kaplan-Meier overall survival curves (Prognostic ability)	Refs.
1	hsa_circ_103809↑	LC	–	44	Poor survival	82
2	hsa_circ_0000064↑	LC	T stage, lymphatic metastasis, TNM stage	50	–	89
3	hsa_circ_100876↑	NSCLC	lymph node metastasis, tumor staging	101	Poor survival	79
4	hsa_circ_0067934↑	NSCLC	TNM stage	79	Poor survival/independent factor (Cox regression analysis) RR 2.133;95% CI: 1.677–3.251; $P = 0.001$	84
5	hsa_circ_0067934↑	NSCLC	TNM stage, lymph node status, distant metastasis	159	Poor survival/independent factor (Cox regression analysis) RR: 3.198;95% CI: 1.293–5.673; $P = 0.004$	85
6	hsa_circ_001569↑	NSCLC	Tumor differentiation, lymph node metastasis, TNM classification	56	Poor survival	81
7	hsa_circ_0003998↑	NSCLC	Tumor size, lymph node metastasis	60	Poor survival	80
8	hsa_circ_0016760↑	NSCLC	TNM stages, lymph node metastasis,	83	Poor survival/independent factor (Cox regression analysis) HR 1.910;95% CI: 1.119–3.259; $P = 0.018$	83
9	hsa_circ_0020123↑	NSCLC	Differentiation degree, lymph node metastasis, TNM stage	80	Poor survival	86
10	circFADS2↑	NSCLC	TNM stage, lymph node metastasis, differentiation	43	Poor survival	87
11	CircFGFR3↑	NSCLC	TNM stage, lymph node metastasis, differentiation	63	Poor survival	88
12	circPRKCI↑	LUAD	T stage, TNM stage	89	Poor survival	90
13	hsa_circ_103827↑	LSCC	–	40	Poor survival	41
14	hsa_circ_100395↓	LC	TNM stage, metastases	69	Poor survival	93
15	hsa_circ_0001649↓	NSCLC	TNM stage, lymph node metastasis	53	Poor survival/independent factor (Cox regression analysis) HR 2.123;95% CI: 1.071–4.202; $P = 0.031$	91
16	hsa_circ_000122↓	LSCC	–	40	Poor survival	41
17	hsa_circ_0033155↓	NSCLC	Lymphatic metastasis	40	–	92

are the first-line drugs for EGFR-mutant NSCLC [103]. There is evidence that EGFR-TKIs treatment is significantly limited in its clinical efficacy in patients with NSCLC, and the exact pathogenesis and mechanism of resistance to EGFR-TKIs remain unclear [104]. Zhou et al. found that hsa_circ_0004015 was up-regulated in NSCLC tissues and the TKI-resistant NSCLC cell line, HCC827I/R, which promoted the viability, proliferation and invasion of lung cancer cells. Functional analysis indicated that hsa_circ_0004015 significantly enhanced HCC827 cell resistance to gefitinib. Silencing hsa_circ_0004015 enhances the sensitivity of HCC827I/R cells to gefitinib [105]. Further analysis of the sponge targeting PDPK1 of miR-1183, indicated that PDPK1 may mediate the regulation of AGC protein kinase family in cell proliferation, metabolism, and apoptosis, and thus, may function as an important component of the Akt-mTOR signaling pathway [106]. These results suggest that hsa_circ_0004015 may play a role in tumorigenesis and drug resistance of NSCLC.

Another study demonstrated that down-regulation of circRNA CCDC66 expression did not affect the resistance of EGFR-mutant H1975 cells to gefitinib or erlotinib, but increased the resistance of H23 cells, with low EGFR expression, to cisplatin, while circRNA CCDC66 expression was regulated by HGF/c-Met [107]. It has been reported that LADC patients with higher HGF levels are more tolerant to TKIs [108]. Yano et al. demonstrated that resistance to gefitinib was mediated by PI3K/AKT activation via the HGF/c-Met pathway [109].

3.7. Role of circRNAs in small cell lung cancer

Compared with NSCLC, SCLC exhibits rapid doubling time and early extensive metastasis. However, research on circRNAs in SCLC is scanty.

A recent study showed that FLI1 exonic circRNAs (FECRs), FECR1 (exons 4-2-3) and FECR2 (exons 5-2-3-4), were up-regulated in SCLC tissues and positively correlated with lymph node metastasis [110]. Inhibition of FECR expression in SCLC cells may significantly inhibit cell migration and reduce metastasis of xenografts in vivo. Functional analysis indicated that FECRs adsorbed miR584-3p to activate Rho Associated Coiled-Coil Containing Protein Kinase 1 gene (ROCK1). In addition, it was also found that serum exocytosis in serum exosomes of FECR1 was associated with low survival rates and response to clinical chemotherapy. These results indicated that FLI1 exonic circRNAs may be carcinogenic drivers of SCLC.

Sry is a circular transcript from the sex determining region of the Y chromosome, with 16 miR-138 conserved binding sites. In SCLC cells, miR-138 targets H2A histone family member X (H2AX), which regulates DNA damage response, leading to a significant decrease in cell proliferation and cell cycle arrest, suggesting that the Sry/miR138/H2AX axis may be associated with the regulation of SCLC, but the specific mechanism involved may need further verification [111].

4. Conclusions and outlook

circRNAs, a class of non-coding RNAs, exhibit functions related to sponge activity, splicing, transcription, protein interaction, translation, and tumor regulation. Clinical value of circRNAs has been explored. This article reviews the expression, proliferation, apoptosis, invasion and diagnosis, as well as biomarker and therapeutic potential of lung cancer-associated circRNAs. It discusses new research and the role of circRNAs in the pathogenesis, diagnosis, treatment, and drug resistance of lung cancer. There are still many problems surrounding circRNAs that remain to be clarified: (1) Further studies of circRNA regulatory networks may elucidate mechanisms underlying related diseases. (2) Although circRNAs have multiple effects, little is known about their other roles in lung cancer. (3) Current circRNA studies must be expanded to include non-invasive and disease-related samples. (4) CicrRNAs show potential therapeutic effects. Development of stable circRNAs capable of accurately targeting the site of action is important. In-depth studies may improve the understanding of circRNA function in lung cancer.

Conflicts of interest

The authors declare that they have no conflict of interests.

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