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Original Article

The emerging role of circular RNAs in non-small cell lung cancer

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Abstract: Lung cancer (LC) is one of the most important malignant and devastating tumors, the leading cause of cancer-related deaths worldwide. The most frequent type of lung cancer is non-small cell lung cancer (NSCLC). Moreover, circRNAs, as covalently closed circular RNA molecules resistant to RNA exonuclease or RNase R with high stability, play a vital role in the tumorigenesis progression of NSCLC. Recent studies have indicated that upregulated circRNAs and downregulated circRNAs are related with proliferation, invasion, migration and apoptosis in NSCLC patients. The current study briefly summarized the latest studies regarding classification, biogenesis, biological functions, up/down-regulation mechanisms, and the diagnostic role and prognostic value of circRNAs, with a focus on their biological roles in NSCLC. This study found more upregulated circRNAs than downregulated circRNAs in tumor tissues, relative to adjacent noncancerous tissue samples, and more promising diagnostic biomarkers of circRNAs with high sensitivity and specificity for NSCLC. In addition, this study found that patients with higher expression of upregulated circRNAs and lower expression of downregulated circRNAs had shorter overall survival times in NSCLC. Moreover, ciRS-7/CDR1as and circPRKCI are potential therapeutic targets for NSCLC. Through the continuous efforts of researchers studying the relationships, regulatory networks, and signaling pathways between circRNAs and NSCLC, circRNAs may emerge as another potential powerful biomarker for diagnosis and treatment of lung cancer.

Keywords: Circular RNAs, lung cancer, NSCLC, miRNA sponge, diagnostic, prognostic, biomarker

Introduction

Lung cancer (LC) is one of the most important malignant tumors, the leading cause of cancer-related deaths around the world [1, 2]. The most frequent type of this devastating tumor is non-small cell lung cancer (NSCLC), which accounts for approximately 80% of all lung cancers. NSCLC, a highly heterogeneous group, is mainly organized into 3 subtypes, lung adenocarcinoma (LUAD), lung squamous carcinoma (LUSC), and large-cell lung carcinoma. Although treatments, including surgery, radiotherapy, and chemotherapy, are improving, 5-year overall survival rates are still under 20% [3-5]. Despite the advent of drugs targeting proteins encoded by major driver oncogenes of EGFR, KRAS, ALK and ROS1, along with immunotherapy related to immune checkpoints, such as PD-1, PD-L1, and CTLA-4, the ensuing drug-resistant issues of NSCLC are inevitable and obvious [6, 7]. Therefore, it is necessary to further and thoroughly explore molecular mechanisms behind tumorigenesis and progression of NSCLC, aiming to discover novel and efficient therapeutic targets.

With the development of high-throughput sequencing and continuous updating algorithms, non-coding RNAs (ncRNAs), including long non-coding RNAs (lncRNAs) and microRNAs (miRNAs), have been shown to play an important role in a wide diversity of biological processes, including progression of NSCLC. However, the mechanisms of circular RNAs (circRNAs, a new type of ncRNAs) remain to be elucidated [8-10].

Unlike the well-known linear RNAs, circRNAs are characterized by a single-stranded covalently closed continuous loop structure resistant to RNA exonuclease or RNase R without termination at 5' caps or 3' poly (A) tails, preventing them from degradation through RNA exonucleases. They were was first discovered in 1976 in RNA viruses by electron microscopy, displaying higher stability [11-13]. Emerging evidence has revealed that circRNAs can function as miRNA (microRNA) sponges, regulating the transcription and post-transcription of target genes through interaction with RBPs (RNA-binding proteins) [14, 15]. Although previous studies have indicated that circRNAs are strongly correlated with proliferation, invasion, and apoptosis of various tumors, further circRNA studies of biological functions and regulatory network mechanisms in NSCLC are still warranted [16-18]. Studies of cancer-related circRNAs has provided a new perspective regarding diagnosis, treatment, and prognosis of NSCLC. Taking lung cancer-related biological functions and up/down-regulation mechanisms of circRNAs into account, the present study provides potential novel diagnostic biomarkers, therapeutic targets, and prognostic value for NSCLC.

Features of circRNAs

Classification and biogenesis of circRNAs

Early studies have reported that circRNAs are predominantly derived from various protein-coding genes. Recent studies have found that non-coding regions, introns, and antisense regions can participate in circRNAs formation. Spliceosome-mediated precursor mRNA (pre-mRNA) with back-splicing connects a downstream 5' splice site to upstream 3' splice site to generate circRNAs [6, 11, 19, 20]. In addition, through alternative back-splicing junctions or alternative splice junctions, a single locus can produce various circRNAs. On the basis of their origin and constituent parts, circRNAs can be classified into 3 categories, exonic circRNAs (EcircRNAs), exon-intron circRNAs (EIciRNAS), and circular intronic RNAS (CiRNAs) [6, 21]. Although the exact mechanisms of circRNAs generation remain indistinct, scientists have put forward 3 potential mechanisms of EcircRNAs (only single or several exons, majority of identified circRNAs) formation, including direct back-splicing or intron-pairing circularization, exon skipping or lariat-driven circularization, and RBP quaking circularization [22]. Moreover, ciRNAs are composed of only introns possessing conserved motifs at both ends with 11 nt C-rich element close to 3-branching site and 7 nt Gu-rich motifs near the 5' splice, along with a lack of miRNA target sites [20]. EIciRNAS consist of both introns and exon. They share a similar splicing mechanism with EcircRNAs, to some degree, and a lack of miRNA target sites. However, their regulatory functions are different [23].

Biological function of circRNAs

Recent studies have suggested that circRNAs have several biological functions. The first function is acting as miRNA sponges. In 2013, Hansen et al. first reported that CDR1as/ciRS-7 could suppress the activity of miR-7 significantly, finding that ciRS-7 contains more than 70 miRNA target sites [24]. The second function is interaction with rbps (RNA-binding proteins). Albrecht et al. first discovered that 12 circRNAs can bind to RBPs, such as IMP3, to form RNA protein complexes [25]. Also, circRNAs have been regarded as "super sponges" because of their interactions with high density binding sites for a certain RBP [26]. Interactions between RBPs and circRNAs may let circRNAs participate in various biological processes of tumors. Transcription regulation is the third function. Moreover, ciRNAs and EIciRNAs function at the transcriptional level, as they are predominantly located in the nucleus, while EcircRNAs are mainly located in the cytoplasm. Li et al. reported that circEIF3J (one type of EIciRNAs) can upregulate their parental gene expression in cis by combining with U1 mall nuclear ribonucleic protein (snRNP) via RNA-RNA interaction and with the RNA polymerase II (RNA Pol II) complex [27]. The fourth function is protein translation. Yang et al. demonstrated that large number of endogenous circRNAs are driven by N (6)-methyladenosine (m6A), the most abundant internal modification of RNA, which can translate proteins [28].

Biological roles of circRNAs in NSCLC

Expression profiling of circRNAs is essential for the dissection and identification of their biological roles, including carcinogenic factor or tumor suppressor, functions, and mechanisms. Zhao et al. found that high-throughput of circRNA

microarrays were employed to demonstrate 152 downregulated circRNAs and 204 upregulated circRNAs in lung adenocarcinoma samples, predicting potential miRNA-circRNA interactions [29]. One later study reported that 2,909 circRNAs were significantly upregulated and 8,372 circRNAs were downregulated in A549/Taxol, compared with A549, in human NSCLC cell lines, revealing that circRNAs exert strong biological effects by absorbing and sequestering miRNA molecules [30]. Recent studies have indicated that novel tumor suppressors and oncogenic circRNAs are significantly related with proliferation, migration, invasion, and apoptosis in the pathogenesis process and development of NSCLC. Published and up-to-date NSCLC-related circRNAs from 42 studies were classified into upregulated (carcinogenic) and downregulated (tumor suppressor) circRNAs.

*Upregulated circRNAs in NSCLC (**Table 1**)*

A total of 30 studies, relevant to upregulated circRNAs in NSCLC, were enrolled in the current review [31-60]. Information, such as circRNA name, gene symbol, function, miRNA sponge, target gene/signaling pathways, was extracted (**Table 1**). The table demonstrates that these circRNAs were upregulated in tissues and cell lines, modulating various processes or hallmark events, including promotion of tumor cell proliferation, migration, and invasion and inhibition of apoptosis in NSCLC.

Twenty-two of these circRNAs were found to have the potential to serve as miRNA sponges, regulating expression of miRNA targets. circRNA 100876 and MMP13 (the 3-UTR of matrix metalloproteinase 13) both bind to miR-136. Suppression of circRNA 100876 with siRNA lowers MMP13 expression, thus suggesting that circRNA 100876 may modulate MMP13 indirectly via sponging miR-136 [31]. Bio-informatic prediction, luciferase reporter assays, and RIP have illustrated that circHIPK3 may act as a sponge for different miRNAs, such as miR-379 and miR-124, to regulate corresponding gene IGF1 and STAT3 expression [32, 56]. Hsa_-circ_0013958 serves as a sponge to absorb miR-134 and upregulates expression of proto-oncogene cyclin D1, thus promoting tumor cell proliferation and invasion, as well as inhibiting apoptosis in NSCLC [33]. Hsa_circ_0043256 acts as sponge to bind competitively to miR-1252, affecting Wnt signaling pathways to upregulate ITCH expression, while hsa_-circ_0043256/miR-1252/ITCH axis provides a novel target for NSCLC treatment [34]. Circular RNA UBAP2 silencing inhibits proliferation and invasion and induces apoptosis of tumor cells via sponging miR-339-5p, miR-96-3p, and miR-135b-3p, downregulating metastasis-associated proteins (FAK, Rac1, and MMP2) and apoptosis-associated proteins (CDK6, cyclin D1, c-IAP1, Bcl-2, and survivin), and upregulating expression levels of p27 and Bax relevant to cell cycle and apoptosis [36]. ciRS-7, located on the opposite strand of the gene CDR1, was the first and one of most studied circRNAs to be illustrated to have a miRNA sponge function for miR-7. Moreover, ciRS-7/CDR1 can inhibit miR-7 activity significantly [37, 51]. Hsa_circ_0012673 serves as a miR-22 sponge to regulate ErbB3 (erb-b2 receptor tyrosine kinase 3) expression, promoting lung adenocarcinoma cells proliferation via the hsa_circ_0012673/miR-22/ErbB3 axis [38]. Hsa_circ_0007385 acts as a sponge for miR-181, which may be a regulatory pathway for hsa_circ_0007385 [39]. Hsa_circ_0014130 acts as a sponge of 3 related miRNAs containing miR-216a-3p, miR-493-5p, and miR-200c-5p in cancer progression [40]. circMAN2B2 upregulates FOXK1 expression via sponging miR-1275, which promotes tumor cell proliferation and invasion in a cancer-promoting role [41]. circPRKCI, related with lymph node metastasis, TNM stage, and tumor size, serves as a miRNA sponge of miR-545/589, directly binding to the 3'-UTR of E2F7 to inhibit expression of E2F7 genes, promoting tumor cell proliferation and migration via the circPRKCI-miR-545/589-E2F7 signaling pathway [42]. Hsa_circRNA_103809 participates in the regulation of lung cancer via the miR-4302/ZNF121/MYC pathway. Knockdown of hsa_circRNA_103809 promotes miR-4302 expression significantly, while overexpression of miR-4302 inhibits expression levels of ZNF121 interacting with MYC directly [45]. Hsa_circ_0000729 has been related with a novel microRNA, miR375, closely, revealing an interaction between pivotal circRNAs and miRNAs in lung cancer [48]. circ-BANP can play regulatory roles, such as promoting cell invasion, proliferation, and metastasis in NSCLC through miR-503/LARP1 signaling pathways [49]. circ_0016760 represents unfavorable prognosis in NSCLC and promotes cell proliferation, migration, and invasion, as

Table 1. Upregulated circRNAs in NSCLC and their functions

First author	CircRNA	Gene Symbol	Expression level	Function	miRNA sponge	Target gene/pathway	Ref
Yao J	CircRNA 100876	RNF121	Upregulated in tissues	Invasion (+)	Sponge miR-136	MMP1	[31]
Tian F	Circ_0000284	HIPK3	Upregulated in cells	Proliferation (+)	Sponge miR-379	IGF1	[32]
Zhu X	Circ_0013958	ACP6	Upregulated in tissues, cells, and plasma	Proliferation (+), invasion (+), apoptosis (-)	Sponge miR-134	Cyclin D1	[33]
Tian F	Hsa_circ_0043256	ACACA	Upregulated in cells in response to CA treatment	Proliferation (-), apoptosis (+)	Sponge miR-1252	ITCH; Wnt/β-catenin	[34]
Luo Y	Hsa_circ_0000064	B4GALT2	Upregulated in tissues and cell lines	Proliferation (+), apoptosis (-)	-	Caspase-3, caspase-9, bax, p21, CDK6, cyclin D1, MMP-2, MMP-9 and bcl-2	[35]
Yin Y	Circular RNA UBAP2	UBAP2	Upregulated in tissues	Proliferation (+), invasion (+), apoptosis (-)	Sponge miR-339-5p, miR-96-3p and miR-135b-3p	CDK6, cyclin D1, c-IAP1, Bcl-2, Survivin, FAK, Rac1, MMP2, JNK, ERK1/2, p27 and Bax	[36]
Su C	CiRS-7	CDR1as	Upregulated in tissues and cell lines	Proliferation (+), migration (+), invasion (+), apoptosis (-)	Sponge miR-7	NF-kB	[37]
Wang X	Hsa_circ_0012673	DHCR24	Upregulated in tissues	Proliferation (+)	Sponge miR-22	ErbB3	[38]
Jiang M	Hsa_circ_0007385	MEMO1	Upregulated in tissues and cells	Proliferation (+), migration (+), invasion (+)	Sponge miR-181	-	[39]
Zhang S	Hsa_circ_0014130	PIP5K1A	Upregulated in tissues	-	Sponge miR-216a-3p, miR-493-5p and miR-200c-5p		[40]
Ma X	CircMAN2B2	MAN2B2	Upregulated in tissues and cell lines	Proliferation (+), invasion (+)	Sponge miR-1275	FOXK1	[41]
Qiu M	CircPRKCI	PRKCI	Upregulated in tissues	Proliferation (+), migration (+)	Sponge miR-545 and miR-589	E2F7	[42]
Zong L	CircRNA_102231	-	Upregulated in tissues	Proliferation (+), invasion (+)	-	-	[43]
Li J	Hsa_circ_0079530	TWIST1	Upregulated in tissues and cell lines	Proliferation (+), migration (+), invasion (+)	-	-	[44]
Liu W	Hsa_circRNA_103809	-	Upregulated in tissues and cell lines	Proliferation (+), invasion (+)	Sponge miR-4302	ZNF121; MYC	[45]
Wang J	Circ_0067934	PRKCI	Upregulated in tissues and cell lines	Proliferation (+), migration (+), invasion (+)	-	EMT	[46]
Ding L	Circ_001569	-	Upregulated in tissues	Proliferation (+)	-	Wnt/β-catenin	[47]
Li S	Hsa_circ_0000729	GAS8	Upregulated in tissues	-	Sponge miR-375	-	[48]
Han J	Circ-BANP	BANP	Upregulated in tissues	Proliferation (+), migration (+), invasion (+)	Sponge miR-503	LARP1	[49]
Qi Y	Hsa_circ_0007534	DDX42	Upregulated in tissues and cell lines	Proliferation (+), migration (+), invasion (+), apoptosis (-)	-	EMT	[50]
Zhang X	Circular RNA ciRS-7/ CDR1as	CDR1as	Upregulated in tissues	Proliferation (+), migration (+), apoptosis (-)	Sponge miR-7	Ki-67, EGFR, CCNE1 and PIK3CD	[51]
Li Y	Circ_0016760	SNAP47	Upregulated in tissues and cell lines	Proliferation (+), migration (+), invasion (+), apoptosis (-)	Sponge miR-1287	GAGE1	[52]
Qu D	Hsa_circ_0020123	PDZD8	Upregulated in tissues and cell lines	Proliferation (+), migration (+), invasion (+)	Sponge miR-144	ZEB1/EZH2	[53]
Yu W	Hsa_circ_0003998	ARFGEF2	Upregulated in tissues and cell lines	Proliferation (+), migration (+)	Sponge miR-326	Notch1	[54]
Zou Q	Circ_0067934	PRKCI	Upregulated in tissues and cell lines	Proliferation (+)	-	-	[55]
Yu H	Circular RNA HIPK3	HIPK3	Upregulated in tissues and cell lines	Proliferation (+), apoptosis (-)	Sponge miR-124		[56]
Tian X	Hsa_circ_0008717	ABCB10	Upregulated in cell lines	Proliferation (+), migration (+)	Sponge miR-1252	FOXR2	[57]
Hang D	CircFARSA	FARSA	Upregulated in tissues and plasma	Migration (+), invasion (+)	Sponge miR-330-5p and miR-326	-	[58]
Zhao F	CircFADS2	FADS2	Upregulated in tissues	Proliferation (+), migration (+), invasion (+)	Sponge miR-498	-	[59]
Xu J	CircRNA_103827	-	Upregulated in tissues	-	-	-	[60]

well as inhibiting apoptosis through the miR-1287/GAGE1 axis [52]. Hsa_circ_0020123 plays an important role in biological functions, such as proliferation and migration, regulating its targets via miR-144-ZEB1/EZH2 axis [53]. Hsa_circ_0003998, serving as a sponge for miR-326, upregulates Notch1 (the miR-326 target gene) expression. Moreover, miR-326 inhibitor can block tumor-inhibiting effects of hsa_circ_0003998 silencing [54]. circABCB10 promotes FOXR2 expression by sponging miR-1252 and circABCB10 knockdown, significantly inhibiting tumor growth [57]. circFARSA functions as a sponge for miR-330-5p/miR-326 to promote tumor cell migration and invasion in NSCLC [58]. circFADS2 promotes NSCLC cell proliferation and invasion by acting as a sponge of miR-498, negatively correlating with circFADS2 expression. It could serve as a target for lung cancer treatment [59]. The authors of these studies have found the important function of circRNAs sponging circRNAs. However, the specific mechanisms of circRNA-miRNA-mRNA networks in the development and progression of NSCLC should be further elucidated.

*Downregulated circRNAS in NSCLC (**Table 2**)*

A total of 12 studies related to downregulated circRNAs in NSCLC were enrolled in the current review [60-71]. The same information as with upregulated circRNAs in NSCLC was extracted (**Table 2**). This table indicates that these circRNAs are tumor suppressors and are downregulated in tissues and cell lines, modulating various processes or hallmark events, including inhibition of tumor cell proliferation, migration, and invasion in NSCLC.

Nine of these circRNAs were proven to have the potential to function as miRNA sponges, regulating expression of miRNA targets. cir-ITCH serves as a sponge to absorb miR-214 and miR-7, thereby regulating expression levels of ITCH, which inhibits Wnt/β-catenin signaling pathways. The pathway is enhanced, promoting the development and progression of NSCLC through downregulation of cir-ITCH expression [61]. circRNA-FOXO3 acts as a tumor suppressor through the miR-155/FOXO3 pathway and promotes FOXO3 expression by adsorbing miR-155. Overexpression of circRNA-FOXO3 can inhibit cell proliferation, invasion, and metastasis of NSCLC, significantly [62]. circ_0046264 acts as a sponge to absorb miR-1245 to inhibit cell proliferation, invasion, and induce apoptosis of NSCLC by upregulating BRCA2 expression [63]. circ_0001649 exerts biological functions via sponging both miR-331-3p and miR-338-5p in NSCLC. Rescue experiments indicated that silence of circ_0001649, co-transfected with either miR-338-5p or miR-331-3p inhibitor, could obviously rescue oncogenic properties which were induced by si-circ_0001649 [64]. Hsa_circ_100395 acts as a sponge for miR-1228 and inhibits cell proliferation, migration, and invasion via modulating miR-1228/TCF21 pathways [66]. circPTK2 serves as a sponge of miR-429 and miR-200b-3p, promoting TGF-β-induced EMT and NSCLC cell invasion by targeting TIF1γ [68]. circRNF13 and miR-93-5p were significantly enriched in RNAs retrieved from the AGO2 (argonaute 2) antibody, confirming that both could be combined directly and that circRNF13 could act as a sponge for miR-93-5p [69]. circ0006916 functions as a sponge for miR-522-3p and inhibits PHLPP1 (PH domain and leucine rich repeat protein phosphatase 1) activity, therefore inhibiting cell proliferation. In addition, circ0006916 biogenesis was regulated by TNRC6A (trinucleotide repeat-containing 6A), binding to the flanked intron region of circ0006916 [70]. Hsa_circ_0006427 functions as miR-6783e3p and inactivates Wnt/β-catenin signaling pathways by upregulating DKK1, inhibiting lung adenocarcinoma progression via the miR-6783e3p/DKK1 axis [71].

*Diagnostic biomarkers of circRNAs in NSCLC (**Table 3**)*

Early detection and diagnosis are of great significance in the treatment of lung cancer. Previous findings have demonstrated that circRNAs may be potential stable biomarkers for diagnosis of NSCLC. Seven studies clearly reported the value of an area under ROC (receiver operating characteristic) curve and were enrolled in the current review [33, 40, 43, 44, 48, 58, 62]. Zhu et al. first demonstrated that circ_0013958 was significantly related with lymphatic metastasis and TNM stage. It is elevated in NSCLC and serves as a potential diagnosis biomarker, with an area under receiver operating characteristic (ROC) curve of 0.815, sensitivity of 0.755, and specificity 0.796, respectively [33]. Zhang S et al. showed that hsa_circ_0014130 has good diagnostic potential in NSCLC, with an area under the ROC curve (AUC)

Table 2. Downregulated circRNAs in NSCLC and their functions

First author	CircRNA	Gene Symbol	Expression level	Function	miRNA sponge	Target gene/pathway	Ref
Wan L	Circular RNA-ITCH	ITCH	Downregulated in tissues	Proliferation (-)	Sponge miR-7 and miR-214	Wnt/β-Catenin	[61]
Zhang Y	CircRNA-FOXO3	FOXO3	Downregulated in tissues and cell lines	Proliferation (-), migration (-), invasion (-)	Sponge miR-155	-	[62]
Yang L	Hsa_circ_0046264	P4HB	Downregulated in tissues and cell lines	Proliferation (-), invasion (-)	Sponge miR-1245	BRCA2	[63]
Qin M	Circ-UBR5	UBR5	Downregulated in tissues	-	-	-	[64]
Liu T	Circ_0001649	SHPRH	Downregulated in tissues and cell lines	Proliferation (-), migration (-), invasion (-)	Sponge miR-331-3p and miR-338-5p		[65]
Chen D	Hsa_circ_100395	-	Downregulated in tissues	Proliferation (-), migration (-), invasion (-)	Sponge miR-1228	TCF21	[66]
Gu X	Hsa_circ_0033155	EML1	Downregulated in tissues and cell lines	Proliferation (-), invasion (-)	-	PTEN	[67]
Wang L	hsa_circ_0008305	PTK2	Downregulated in tissues and cell lines	Migration (-); invasion (-)	Sponge miR-429/miR-200b-3p	EMT	[68]
Wang L	CircRNF13	RNF13	Downregulated in tissues	Proliferation (-)	Sponge miR-93-5p	-	[69]
Dai X	Circ0006916	HOMER1	Downregulated in cell lines	Proliferation (-)	Sponge miR-522-3p	PHLPP1, TNRC6A	[70]
Xu J	CircRNA_000122	-	Downregulated in tissues	-	-	-	[60]
Yao Y	Has_circ_0006427	BCAR3	Downregulated in tissues	Proliferation (-), migration (-), invasion (-)	Sponge miR-6783-3p	DKK1	[71]

Table 3. Diagnostic biomarkers of circRNAs in NSCLC

First author	CircRNA	Gene Symbol	Expression level	Function	Case (n)	Control (n)	AUC	SEN	SPE	Cut-off	Ref
Zhu X	Circ_0013958	ACP6	Upregulated	Proliferation (+), invasion (+), apoptosis (-)	49	49	0.815	0.755	0.796	0.00101	[33]
Zhang S	Hsa_circ_0014130	PIP5K1A	Upregulated	-	46	46	0.878	0.87	0.848	0.573	[40]
Zong L	CircRNA_102231	-	Upregulated	Proliferation (+), invasion (+)	57	57	0.897	0.812	0.887	-	[43]
Li J	Hsa_circ_0079530	TWIST1	Upregulated	Proliferation (+), migration (+), invasion (+)	92	92	0.756	0.762	0.721	1.9	[44]
Li S	Hsa_circ_0000729	GAS8	Upregulated	-	42	42	0.815	-	-	-	[48]
Hang D	CircFARSA	FARSA	Upregulated	Migration (+), invasion (+)	50	50	0.71	-	-	-	[58]
Zhang Y	CircRNA-FOXO3	FOXO3	Downregulated	Proliferation (-), migration (-), invasion (-)	45	45	0.782	0.8	0.733	-	[62]

Table 4. Prognostic value of circRNAs in NSCLC

First author	CircRNA	Gene Symbol	Prognostic value	circRNA type	Case (High)	Control (Low)	Follow-up time (m)	OSHR	OSHRL	OSHRH	Ref
Su C	CiRS-7	CDR1as	Higher expression level indicated poorer survival outcome	Oncogenic	77	51	60	1.705	1.02	2.86	[37]
Qiu M	CircPRKCI	PRKCI	Higher expression level indicated poorer survival outcome	Oncogenic	55	34	80	2.664	1.327	5.347	[42]
WANG J	Circ_0067934	PRKCI	Higher expression level indicated poorer survival outcome	Oncogenic	79	80	60	3.198	1.293	5.673	[46]
Qi Y	Hsa_circ_0007534	DDX42	Higher expression level indicated poorer survival outcome	Oncogenic	56	42	60	1.969	1.177	3.293	[50]
Zhang X	Circular RNA ciRS/7CDR1as	CDR1as	Higher expression level indicated poorer survival outcome	Oncogenic	41	19	60	6.132	2.923	7.556	[51]
Li Y	Circ_0016760	SNAP47	Higher expression level indicated poorer survival outcome	Oncogenic	45	38	60	1.91	1.119	3.259	[52]
Zou Q	Circ_0067934	PRKCI	Higher expression level indicated poorer survival outcome	Oncogenic	41	38	60	2.133	1.677	3.251	[55]
Yang L	Hsa_circ_0046264	P4HB	Lower expression level indicated poorer survival outcome	Tumor suppressive	55	44	16	1.89	0.97	3.67	[63]
Liu T	Circ_0001649	SHPRH	Lower expression level indicated poorer survival outcome	Tumor suppressive	22	31	60	2.123	1.071	4.202	[65]

of 0.878, along with a sensitivity and specificity of 87.0% 84.8% [40]. Zong et al. reported the higher value of AUC was 0.897, with a sensitivity and specificity of 81.2% and 88.7%, respectively, indicating that circRNA_102231 expression levels have potential clinical significance in diagnosis and therapeutic efficacy as a tumor marker [43]. Li et al. revealed that a ROC curve was constructed for differentiating NSCLC tissues from normal controls up to 0.756, with 76.2% sensitivity and 72.1% specificity [44]. The area under the ROC curve (AUC) for hsa_circ_0000729 and circFARSA was 0.815 and 0.71, respectively [48, 58]. The above diagnostic biomarkers of circRNAs were upregulated in NSCLC, but circRNA-FOXO3 was downregulated in tissues and cell lines [62]. The AUC of circRNA-FOXO3 was 0.782, with 80% sensitivity and 73.3% specificity. It may serve as a tumor biomarker to diagnose NSCLC and evaluate prognosis [62]. Each of these studies had no more than 100 NSCLC and paired adjacent normal samples. A larger cohort of patients is necessary to confirm its diagnostic value.

*Prognostic value of circRNAs in NSCLC (**Table 4**)*

Emerging evidence has demonstrated that circRNAs have prognostic value in NSCLC patients. Seven studies of oncogenic circRNAs and 2 studies of tumor suppressive circRNAs, with explicitly reported HR values, were included. Only Kaplan-Meier overall survival curves without HR scores were excluded. Other information, containing the name, gene symbol, prognostic value, oncogenic or tumor suppressive type, follow-up time, OSHR, OSHRL, and OSHRH, is summarized in **Table 4**. Two studies demonstrated that ciRS-7/CDR1 be positively associated with TNM stage or advanced histopathological grade and lymph node metastasis (LNM) ($P < 0.05$). Kaplan-Meier analysis of these 2 studies showed that overexpression of ciRS-7/CDR1 was an independent prognostic factor for the 5-year overall survival of patients in NSCLC, with HR: 1.705 (1.02-2.86) and HR: 6.132 (2.923-7.556), respectively. It predicted poor clinical outcomes of NSCLC patients [37, 51]. Three studies related to circPRKCI, the gene symbol of circ_0067934, indicated that high circPRKCI expression level is an independent poor prognosis factor for NSCLC outcomes (HR=2.664, 95% CI: 1.327-5.347; HR=3.198, 95% CI: 1.239-5.673; HR=2.133, 95% CI= 1.677-3.251, respectively) [42, 46, 55]. EGFR-TKIs (EGFR tyrosine kinase inhibitors) have been widely used in EGFR mutations of lung adenocarcinoma patients. Qiu et al. performed a proliferation assay and reported that combining silencing circPRKCI with Gefitinib together showed significantly stronger inhibitory effects than si-circPRKCI or Gefitinib alone. This suggests that circPRKCI is a potential therapeutic target for NSCLC [42]. In addition, survival curves demonstrated that high expression levels of hsa_circ_0007534 and circ_0016760 predict shorter 5-year overall survival rates for NSCLC patients (HR=1.969, 95% CI: 1.177-3.293; HR=2.133, 95% CI: 1.677-3.251, separately). Kaplan-Meier analysis indicated that patients with lower expression of circ_0046264 and circ_0001649 had shorter overall survival times, validated as independent prognostic biomarkers for poor clinical outcomes in NSCLC patients (HR=1.89, 95% CI: 0.97-3.67; HR= 2.123, 95% CI: 1.071-4.202, respectively).

Conclusion and future perspectives

It is evident that circRNAs are a new frontier in NSCLC-related research. With the rapid development of high-throughput sequencing technologies and bioinformatics, emerging evidence has demonstrated that various kinds of circRNAs are upregulated or downregulated in NSCLC tissues and cell lines. These circRNAs have a significant relationship with TNM stage, lymph node metastasis (LNM), and survival outcomes, playing strong biological roles in the progression of tumorigenesis, proliferation, metastasis, migration, invasion, and apoptosis of NSCLC. Recent studies have indicated that circRNAs can act as miRNA and RBP sponges, playing a vital role in transcription regulation and protein translation and contributing to NSCLC progression.

Considering the stability characteristics of circRNAs, some upregulated and downregulated circRNAs are expected to become promising diagnostic and prognostic biomarkers for NSCLC. Upregulated circRNAs, such as circ_0013958, circ_0014130, circRNA_102231, circ_0079530, circ_0000729, and circFARSA, are potential diagnostic biomarkers for NSCLC, with AUC values ranging from 0.71 to 0.897 and an area under the ROC curve (AUC) of 0.878. circRNA-FOXO3 was only downregulated circRNAs with certain AUC value of 0.782. It may

be a potential diagnostic biomarker for NSCLC. In circRNAs studies, ciRS-7/CDR1 and circPRKCI have been the star circRNAs in NSCLC-related research. These circRNAs are upregulated in tumor tissues and their high expression levels indicate worse survival outcomes. Downregulated circRNAs, such as circ_0046264 and circ_0001649, with low expression levels, reveal shorter overall survival times. It is necessary and important to figure out more suitable molecular circRNAs with high sensitivity and specificity to confirm clinic diagnostic and prognostic roles in NSCLC.

Compared with other noncoding RNAs, including mRNAs and lncRNAs, studies concerning circRNAs in NSCLC are just beginning. Growing numbers of circRNAs have been found, but most studies have focused on their function as miRNA sponges in the proliferation, migration, invasion of NSCLC cells. Only a few circRNAs have been investigated mechanistically. circRNA ciRS-7, which was the first discovered circRNA and transcribed from the CDR1 locus, functions as a miR-7 sponge/inhibitor. It is frequently detected in lung carcinomas [72]. CDR1as overexpression could inhibit miR-7-induced growth arrest apoptosis through upregulating miR-7 targets, including EGFR, CCNE1, and PIK3CD [51]. ciRS-7/CDR1as/miR-7 axis will play probably a significant role in therapeutic targets for lung cancer. Through circPRKCI-miR-545/589-E2F7 pathways, circPRKCI participates in tumor cell regulation in NSCLC. Gefitinib combined with si-circPRKCI was shown to be more effective than si-circPRKCI or gefitinib alone, indicating that circPRKCI is another potential therapeutic target for NSCLC [18, 42]. Furthermore, circ_0012673 can regulate ErbB3 and exert functions in the development of therapies against NSCLC [38]. Previous studies have demonstrated that circRNAs play an important role in tumor progression, metastasis, and chemo-resistance through EMT (epithelial-mesenchymal transition) pathways [46, 50, 68]. Improved EMT-associated secretory phenotypes indicate NSCLC patient (including adenocarcinoma and squamous carcinoma patients) survival [73]. Moreover, circRNAs function in EMT should be further investigated, examining their roles in NSCLC.

Although a significant relationship between circRNAs and NSCLC has been demonstrated. according to previous studies, the complete biological functions and molecular mechanisms have not yet been elucidated and validated. In the future, with reduced costs of second-generation sequencing technology, large-scale comparative studies on circRNAs in the different types of lung cancer will be carried out. Diagnostic experiments need to be combined with or compare well-known clinic tumor markers, such as CEA, CA125, CA199, and NSE. Prognostic experiments need to be focus on combining with si-circ and gefitinib or using one alone to investigate survival outcomes. It is important to improve the circRNAs-miRNAs-mRNAs network to elucidate the tumorigenesis progression. It is imperial and urgent to explore more suitable circRNAs, elucidating their biological functions and mechanisms in the diagnosis, prediction, prevention, and treatment of lung cancer. Through the continuous efforts of researchers focusing on the relationship between circRNAs and NSCLC, circRNAs may become another powerful biomarker for diagnosis and treatment of lung cancer.

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Disclosure of conflict of interest

None.

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