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Review

# *Mechanisms of circular RNA in drug resistance of lung cancer: therapeutic targets, biomarkers, and future research directions

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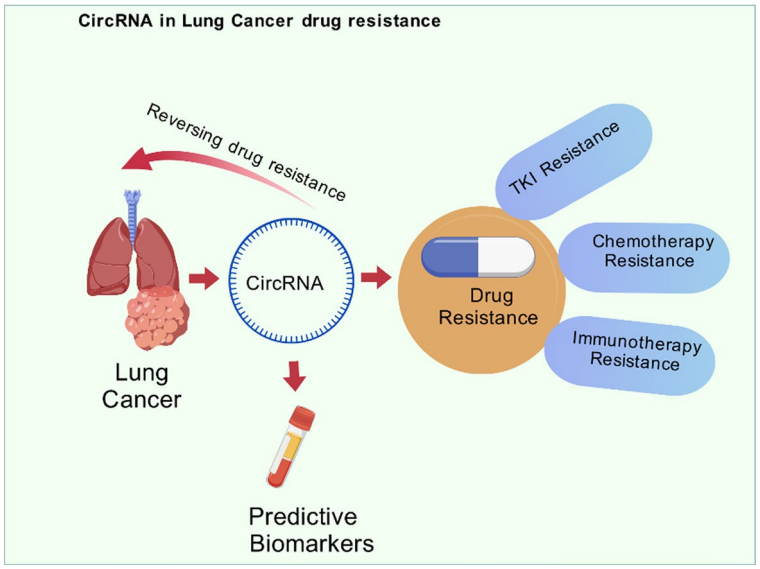
**Abstract**

Lung cancer is one of the most prevalent malignant tumors globally, posing significant challenges to treatment outcomes. Circular RNAs (circRNAs), a novel class of non-coding RNAs, have emerged as crucial regulators in cancer biology, influencing drug resistance, progression, and prognosis. Due to their closed-loop structure, circRNAs demonstrate high stability and resistance to degradation, making them promising diagnostic and therapeutic targets. Here we summarize the mechanisms by which circRNAs mediate drug resistance in lung cancer, focusing on their roles in chemotherapy, targeted therapies, and immunotherapy. We highlight how circRNAs interact with microRNAs (miRNAs) and proteins to regulate signaling pathways and alter drug sensitivity. Additionally, circRNA expression patterns hold potential as biomarkers for predicting treatment response. By synthesizing the latest research, we offer new insights into circRNA functions and suggest future directions for overcoming drug resistance in lung cancer.

**Graphical Abstract**

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**Keywords** CircRNA · Lung cancer · Drug resistance · Chemotherapy · Targeted therapy · Biomarkers

## 1 Introduction

Lung cancer is one of the most common malignant tumors worldwide, with a high incidence and poor survival rate. Despite advancements in diagnostic tools and therapies, the overall five-year survival rate remains unsatisfactory, particularly due to the development of drug resistance [1].

CircRNAs, a novel class of non-coding RNAs, have emerged as critical players in cancer biology, influencing tumor progression, prognosis, and drug resistance [2]. Due to their unique closed-loop structure, circRNAs are resistant to exonucleases, exhibit high stability, and are abundantly expressed in various tissues [3]. These properties make them valuable as biomarkers for early diagnosis and monitoring therapeutic responses [4].

CircRNAs modulate cancer biology by interacting with miRNAs and proteins, impacting signaling pathways such as PI3K/Akt and Wnt/β-catenin [5, 6]. These interactions affect not only cancer proliferation and invasion but also resistance to chemotherapy, targeted therapy, and immunotherapy [7, 8]. Drug resistance is a major obstacle in the clinical management of lung cancer, and understanding how circRNAs contribute to this phenomenon is essential for developing effective treatment strategies.

In lung cancer, circRNAs have been implicated in the initiation and progression of the disease by regulating key signaling pathways and influencing tumor microenvironments. They play a crucial role in modulating gene expression, sponging miRNAs, and interacting with proteins that drive tumor growth, metastasis, and resistance to therapies. CircRNAs such as hsa_circ_0002130 and hsa_circ_0004015 have been shown to contribute to the development of resistance to targeted therapies and chemotherapy by regulating key pathways like PI3K/Akt and Wnt/β-catenin.

This review focuses on the role of circRNAs in lung cancer drug resistance, with particular attention to their interactions with the miRNA-protein axis. We also explore the potential of circRNAs as biomarkers for predicting treatment response and as therapeutic targets for reversing drug resistance. Future research directions are discussed to provide insights into how circRNAs can help overcome drug resistance and improve patient outcomes [9].

## 2 Overview of circular RNAs: structure, biogenesis, and functions

CircRNAs are a class of covalently closed non-coding RNAs characterized by their unique circular structure, which provides exceptional stability against exonucleases such as RNase R [10]. This stability allows circRNAs to accumulate in cells with low turnover rates, such as neurons [11, 12]. CircRNAs are primarily generated through a process called backsplicing, in which the 5′ splice donor site of a downstream exon is ligated to the 3′ splice acceptor site of an upstream exon, creating a continuous loop [13, 14]. The backsplicing process is regulated by cis-elements, such as intronic complementary sequences, and trans-acting factors, including RNA-binding proteins (RBPs) like QKI and ADAR1 [15, 16].

CircRNAs are classified into three main types based on their genomic composition. Exonic circRNAs (ecircRNAs) are derived from exons and constitute the majority of circRNAs [17]. They often function as miRNA sponges or interact with RBPs to regulate gene expression [18]. Intronic circRNAs (ciRNAs), formed from retained introns, primarily modulate transcriptional activity [19]. Exon–intron circRNAs (EIciRNAs) contain both exonic and intronic sequences, and they interact with RNA polymerase II to enhance the transcription of their parent genes [20].

CircRNAs regulate various cellular processes through diverse mechanisms. One of their key functions is miRNA sponging, where circRNAs like CDR1 as sequester specific miRNAs, such as miR-7, to influence neuronal functions [21, 22]. CircRNAs also bind to RBPs, such as HuR, to regulate processes like translation, autophagy, and stress responses [23]. Some circRNAs possess internal ribosome entry sites (IRES) that allow them to encode functional peptides, adding another layer of regulatory potential [24]. Additionally, circRNAs are involved in modulating signaling pathways, including oncogenic pathways such as PI3K/Akt and Wnt/β-catenin, which play crucial roles in cancer development and progression [25, 26, 27].

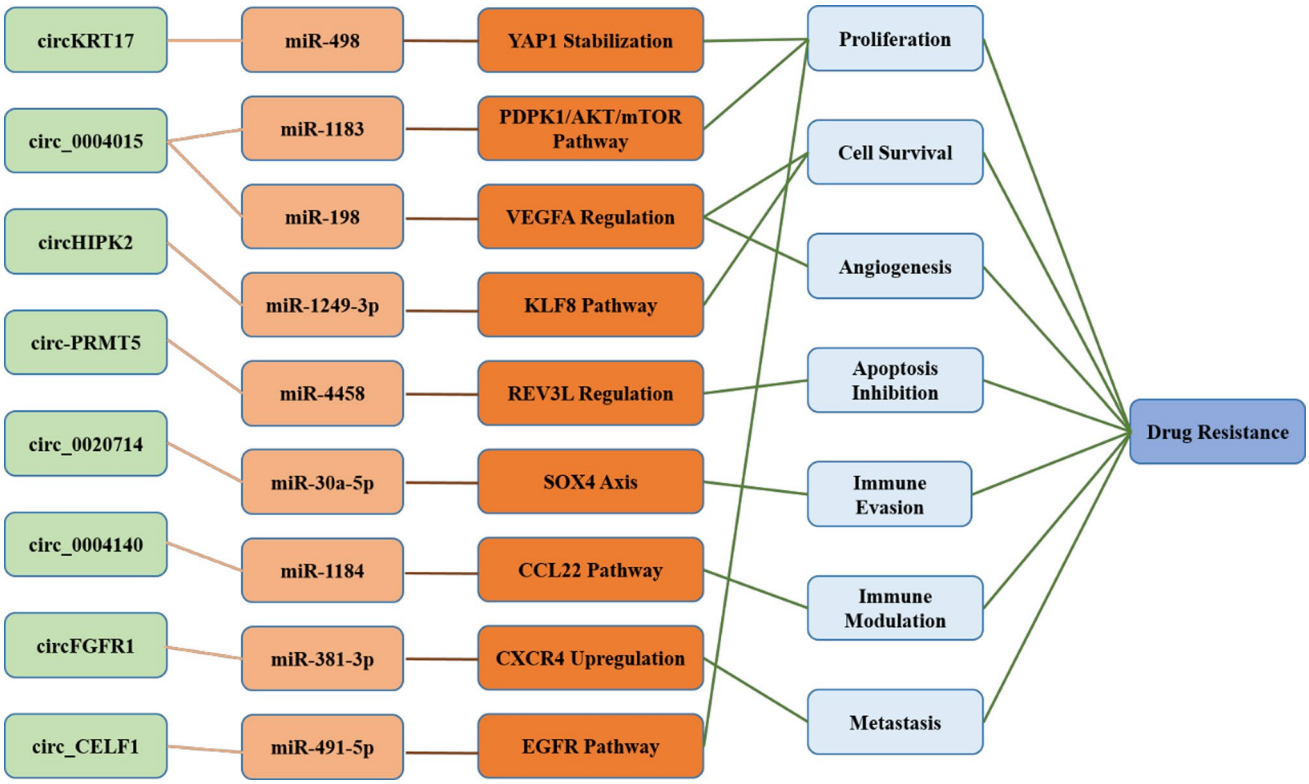


**Fig.1** CircRNA and Mechanisms of Drug Resistance in Lung Cancer

## 3 CircRNA and mechanisms of drug resistance in lung cancer

CircRNA, as a special type of non-coding RNA molecule, plays an important role in drug resistance in lung cancer. Relevant studies have revealed the molecular mechanisms through which circRNAs contribute to both drug resistance and its reversal in lung cancer, which is crucial for understanding their biological functions. This section categorizes the research on circRNAs and lung cancer drug resistance based on targeted therapy, chemotherapy, and immunotherapy, shedding light on the latest findings (Fig. 1).

### 3.1 Mechanism of circRNA in lung cancer TKI resistance

Tyrosine kinase inhibitors (TKIs) are a class of oral drugs developed to target specific proteins involved in tumor signaling. TKIs target specific molecular sites to modulate cellular signaling pathways, thereby inhibiting tumor growth, reducing side effects, and improving patient outcomes. These drugs have become the first-line treatment for advanced non-small cell lung cancer (NSCLC) patients with gene mutations such as EGFR and ALK [28].

Several molecular targets have been identified for TKI therapy, including EGFR, ALK, MET, RET, VEGF, NTRK, ROS1, KRAS, and BRAF [29] (Table 1).

The introduction of TKIs has significantly extended the survival time of patients with advanced NSCLC, with third-generation EGFR-TKIs such as osimertinib achieving a progression-free survival (PFS) of up to 19.3 months in clinical trials [36]. EGFR is the most common mutation in Asian populations, with about 50% of cases showing EGFR gene mutations [37]. Currently, three generations of EGFR-TKI drugs have been developed. First-generation drugs include gefitinib and erlotinib; second-generation drugs include afatinib and dacomitinib; and third-generation drugs include osimertinib, aumolertinib, and furmonertinib [38]. Fourth-generation targeted therapies, such as EAI045 and JBJ-04–125-02, are also under development. These EGFR-TKIs have greatly extended the survival time of patients with advanced lung cancer, significantly improving their quality of life. For example, osimertinib can achieve a progression-free survival (PFS) of 19.3 months, whereas ceritinib may exceed two years in PFS for patients without brain metastases [36]. However, resistance to EGFR-TKIs often develops after around one year, which diminishes treatment effectiveness, highlighting the need

**Table 1** The regulatory mechanisms of circRNAs in EGFR-TKI resistance in lung cancer

| circRNA | Expression Level | Potential Regulatory Mechanism | References |
|---|---|---|---|
| circKRT17 | Upregulated | METTL3 initiates m6A modification of circKRT17, recruiting EIF4A4 to enhance YAP1 stability;leading to resistance | [30] |
| hsa_circ_0004015 | Upregulated | —— | [31] |
| hsa_circ_0002130 | Upregulated | hsa_circ_0002130 sponges miR-498 to upregulate GLUT1, HK2, and LDHA expression, leading to resistance | [32] |
| HIF1A-AS2 | Upregulated | HIF1A-AS2 sponges miR-146b-5p, disrupting miR-146b-5p's inhibition of IL-6 expression, leading to resistance | [33] |
| CircSETD3 | Upregulated | Inhibits miR-520e/BCL-xL signaling pathway function, leading to resistance | [34] |
| CircHIPK3 | Upregulated | CircHIPK3 transmits anti-apoptotic signals through the miR-124-SphK1/STAT3/CDK4 signaling axis, leading to resistance | [35] |
| hsa_circ_0004015 | Upregulated | hsa_circ_0004015 sponges miR-1183 to regulate PDPKI/AKT/mTOR signaling pathway, leading to resistance | [31] |

for novel strategies [39, 40]. EGFR-TKI resistance can be classified into primary and acquired types. Primary resistance occurs when patients show no initial response to EGFR-TKIs, often due to KRAS or BRAF mutations, BIM polymorphisms, or co-mutations with other genes [41]. Acquired resistance, developing after initial treatment success, is typically linked to T790M mutations, C-MET amplification, PIK3CA mutations, or small cell lung cancer (SCLC) transformation. Other mechanisms include epithelial-mesenchymal transition (EMT), oncogene fusions, and cell cycle changes [42]. Additionally, IGF-1R and EGFR signaling interactions, or VFEN loss, activate the PI3K/Akt/mTOR pathway, contributing to apoptosis resistance, while high BCRP/ABCG2 expression is linked to resistance in EGFR wild-type cases [43]. Many mechanisms of circRNA-mediated resistance to EGFR-TKIs have been reported, suggesting a novel layer of complexity in resistance pathways. CircKRT17 was found to be highly expressed in osimertinib-insensitive lung adenocarcinoma tissues and cells. The m6A modification of circKRT17 mediated by METTL3 enhances YAP1 stability by recruiting EIF4A4, thereby promoting osimertinib resistance [30]. Another study demonstrated that hsa_circ_0004015 is highly expressed in NSCLC tissues, and its overexpression in HCC827 cells induces resistance to gefitinib. Knocking down hsa_circ_0004015 in HCC827I/R cells increased their sensitivity to gefitinib [31]. CircRNAs can also regulate drug resistance by modulating the circRNA-miRNA-protein axis. For example, MALAT1 was highly expressed in drug-resistant lung adenocarcinoma cells, while mir-125a-5p was downregulated, and rab25 expression was upregulated. Overexpression of MALAT1 promoted resistance to erlotinib by sponging mir-125a-5p and upregulating rab25 [44]. Similarly, hsa_circ_0002130 sponged mir-498 to upregulate GLUT1, HK2, and LDHA, promoting osimertinib resistance [32]. In another example, HIF1A-AS2 sponged miR-146b-5p, disrupting its inhibitory effect on IL-6 expression, thereby promoting osimertinib resistance in lung adenocarcinoma cells [45]. CircSETD3 was shown to inhibit miR-520e, preventing the regulation of BCL-xL, and thus promoting gefitinib resistance in lung cancer cells [34]. CircHIPK3 transmitted apoptotic resistance signals via the miR-124-SphK1/STAT3/CDK4 axis, promoting drug resistance in lung cancer [31]. Hsa_circ_0004015 also regulated the PDPK1/AKT/mTOR pathway by sponging mir-1183, further contributing to gefitinib resistance.

Anaplastic lymphoma kinase (ALK) mutations play a crucial role in NSCLC, with approximately 3%–7% of cases exhibiting ALK gene fusions. Common fusion mutations include EML4-ALK, NPM-ALK, and TPM3-ALK, with EML4-ALK being the most frequent type [46]. These ALK fusions cause continuous activation of tyrosine kinases, which in turn activate downstream signaling pathways, promoting tumor proliferation and metastasis [47]. ALK-TKIs (tyrosine kinase inhibitors) function by inhibiting these downstream pathways to block tumor progression effectively. There are currently three generations of ALK-TKIs. First-generation drugs include crizotinib; second-generation drugs include ceritinib, alectinib, brigatinib, and ensartinib; and third-generation drugs include lorlatinib [48]. These inhibitors have greatly enhanced the survival time and quality of life for patients. ALK mutations, often referred to as "diamond mutations," are known for their low frequency but high response to treatment [47]. Studies show that alectinib treatment can achieve a progression-free survival (PFS) of 34.1 months, with PFS extending to 38.6 months in patients without brain metastases. Similarly, ensartinib has a median PFS (mPFS) of 31.3 months and an overall response rate (ORR) of 75%, with the added benefit of delaying brain metastasis [46]. Despite their efficacy, resistance to ALK-TKIs inevitably develops over time, significantly limiting therapeutic outcomes. ALK-TKI resistance can be classified into primary resistance (when patients show no response to the initial treatment) and acquired resistance (when patients develop

resistance over time) [49]. Acquired resistance mechanisms are further divided into several categories: (1) Mutations within the ALK kinase domain, such as G1202R/K and L1196M mutations, which interfere with drug binding; (2) Bypass activation of other signaling pathways, including EGFR amplification, IGF1R overexpression, HER2 amplification, MET amplification, and BRAF-V600E mutations [47]; (3) Histological transformation from adenocarcinoma to small cell lung cancer (SCLC); and (4) Pharmacokinetic factors, such as insufficient drug levels due to metabolism-related issues with first-generation ALK-TKIs [49]. Recent studies have identified circRNAs as a new factor influencing ALK-TKI resistance by modulating downstream signaling pathways. These findings indicate that circRNAs play an essential role in resistance and may represent a novel mechanism distinct from previously known mutations. For instance, circ-FOXM1 has been shown to reduce the inhibitory effect of crizotinib on lung cancer cells by activating the PI3K/AKT signaling pathway, which promotes cell survival and drug resistance [50]. This suggests that targeting circRNAs could offer new strategies for overcoming resistance.

Future research should leverage bioinformatics tools and high-throughput sequencing technologies to further explore resistance mechanisms, identify new targets, and investigate how to reverse resistance pathways effectively. This approach could open new avenues for improving patient outcomes by overcoming drug resistance in ALK-positive lung cancer [51].

### 3.2 CircRNA mechanisms in chemotherapy resistance of lung cancer

For lung cancer patients without gene mutations, chemotherapy remains the primary treatment option. Chemotherapy works by disrupting the proliferation and replication of tumor cells, thus preventing tumor growth and spread. As a traditional treatment, chemotherapy can improve patient survival time and prognosis and has been widely used. Cisplatin-based chemotherapy regimens are considered the standard first-line treatment. The anti-tumor mechanisms of cisplatin include: (1) inducing oxidative stress, (2) inducing p53 signaling pathway expression and cell cycle arrest, (3) regulating the expression of oncogenes and anti-apoptotic proteins, and (4) activating endogenous and exogenous apoptotic pathways [35]. However, chemotherapy resistance limits the effectiveness of these drugs in treating lung cancer.

Cisplatin resistance is divided into primary and acquired resistance. The main mechanisms of cisplatin resistance include abnormalities in DNA damage repair, altered drug accumulation in cells, intracellular drug inactivation (reduced drug uptake and increased drug efflux), autophagy, effects on apoptotic pathways, and changes in resistance-related genes [52].

Current research shows that circRNAs are closely associated with cisplatin resistance and may represent another mechanism of resistance. This mechanism involves the regulation of the circRNA-miRNA-protein axis, leading to drug resistance. One study found that circHIPK2 and VEGFA were abnormally overexpressed in cisplatin-resistant NSCLC tissues and cell lines, while miR-1249-3p was underexpressed. Knockdown of circHIPK2 or overexpression of miR-1249-3p inhibited cisplatin resistance in NSCLC. Mechanistically, circHIPK2 promotes chemotherapy resistance in NSCLC through the miR-1249-3p/VEGFA network [53]. Emerging evidence suggests that epigenetic changes, including modifications of circRNAs, play critical roles in regulating cancer cells' responses to chemotherapy, further complicating resistance mechanisms [33].

Another study found that circ_0004015 was upregulated in resistant NSCLC tissues and cells. Silencing circ_0004015 inhibited the proliferation, migration, and invasion of cisplatin-resistant NSCLC cells and induced apoptosis. Mechanistically, circ_0004015 mediates cisplatin resistance through the miR-198/KLF8 pathway [54].

In addition, circ-PRMT5 and REV3L were significantly overexpressed in cisplatin-resistant tissues and cells, while miR-4458 was significantly underexpressed. Knockdown of circ-PRMT5 enhanced apoptosis and cisplatin sensitivity while reducing metastasis. Mechanistically, circ-PRMT5 sponges miR-4458 and regulates REV3L through miR-4458, thereby promoting cisplatin resistance [32]. Another study pointed out that circ_0002360 targets miR-6751-3p and regulates ZNF300 levels, thereby increasing cisplatin resistance in lung cancer cells [55]. Similarly, circ_PIP5K1A promotes cisplatin resistance and tumor progression in NSCLC by targeting miR-493-5p and upregulating ROCK1 expression [56].

Current studies have elucidated some of the mechanisms by which circRNAs contribute to chemotherapy resistance. However, as cisplatin-based regimens dominate chemotherapy treatments, most research on chemotherapy resistance focuses on cisplatin, while studies on other chemotherapeutic agents remain limited. As a result, the mechanisms of resistance to various chemotherapy drugs are not well connected, leading to single and generally less effective chemotherapy regimens. Research on the resistance mechanisms of different chemotherapy drugs, drug interactions when

**Table 2** Regulatory mechanisms of circRNAs in lung cancer chemotherapy resistance

| circRNA | Expression Level | Potential Regulatory Mechanism | Reference |
|---|---|---|---|
| circHIPK | Upregulated | Promotes resistance through the miR-1249-3p/VEGFA network | [53] |
| circ_0004015 | Upregulated | Mediates cisplatin resistance via the miR-198/KLF8 pathway | [54] |
| circ-PRMT5 | Upregulated | Regulates REV3L through miR-4458, promoting cisplatin resistance | [57] |
| circ_0002360 | Upregulated | Regulates ZNF300 levels via miR-6751-3p, promoting cisplatin resistance | [58] |
| circ_PIP5K1A | Upregulated | Upregulates ROCK1 expression by targeting miR-493-5p, promoting cisplatin resistance | [59] |

multiple chemotherapy drugs are used together, and how to reverse cisplatin resistance will be important future directions (Table 2).

### 3.3 Mechanisms of circRNA in lung cancer immunotherapy resistance

For NSCLC patients without driver gene mutations, immunotherapy, especially immune checkpoint inhibitors, can be an effective treatment option. Immunotherapy aims to activate the body's immune system, relying on the immune response to kill cancer cells and tumor tissues. Immune drugs include PD-1 (programmed death receptor-1) and PD-L1 (programmed death ligand-1) inhibitors. Currently, PD-1 inhibitors such as pembrolizumab (Keytruda), nivolumab (Opdivo), camrelizumab, toripalimab, sintilimab, and tislelizumab are available. PD-L1 inhibitors include atezolizumab (Tecentriq), durvalumab, avelumab, sugemalimab, and envafolimab [60].

The introduction of immune inhibitors has significantly improved the prognosis of NSCLC patients without driver gene mutations. In a study named CameL, camrelizumab combined with chemotherapy as a first-line treatment for advanced non-squamous NSCLC resulted in a median overall survival (mOS) of 27.1 months, with a 4-year overall survival (OS) rate of 37.2% and a progression-free survival (PFS) rate of 15.6%. Meanwhile, the chemotherapy group showed a mOS of 19.8 months and a 4-year OS rate of 25.6%. Immunotherapy significantly controlled disease progression [60]. Another study on 250 small cell lung cancer (SCLC) patients treated with PD-1 or PD-L1 inhibitors showed a median PFS of 7.6 months and a median OS of 18.2 months, with 1-year and 2-year survival rates of 66.4% and 49.2%, respectively, highlighting the superior efficacy of immunotherapy compared to chemotherapy alone [61].

Although PD-1 and PD-L1 immunotherapy has improved the prognosis of NSCLC patients, resistance remains inevitable, limiting its effectiveness. Immunotherapy resistance can be divided into primary, acquired, and adaptive resistance (where tumor cells are recognized by the immune system but evade death by adapting to immune attack). Mechanisms of immune resistance include insufficient immunogenicity of tumor antigens, dysfunction of major histocompatibility complexes, epigenetic modifications and gene mutations, abnormal IFN-γ signaling, severe exhaustion of CD8 + T cells, and changes in the tumor microenvironment [61].

Recent studies have confirmed that circRNAs play key regulatory roles in tumor immune resistance and immune evasion. The mechanisms discovered so far include circRNA expression changes that induce immune evasion through the circRNA-miRNA-protein signaling axis. A study identified hsa_circ_0020714, which is highly expressed and associated with immune evasion in NSCLC. Knockdown and overexpression experiments showed that hsa_circ_0020714 regulates NSCLC sensitivity to PD-1 immunotherapy. Mechanistically, hsa_circ_0020714 induces immune evasion and resistance to PD-1 therapy through the miR-30a-5p/SOX4 axis [62]. Another study demonstrated that circ_0004140 overexpression promotes tumor progression and immune resistance in lung adenocarcinoma cells through the circ_0004140/miR-1184/CCL22 axis, leading to immune resistance [63]. Additionally, research indicates that dysregulated circRNA expression may alter immune cell infiltration in the tumor microenvironment, weakening the effectiveness of immune checkpoint inhibitors [64].

CircRNA-induced resistance may also occur by altering PD-L1 expression. One study revealed that overexpression of hsa_circ_0000190 promotes tumorigenesis and immune evasion in NSCLC by upregulating soluble PD-L1, leading to resistance to immune therapy [65]. Additionally, circRNAs can act as miRNA sponges, regulating the expression of miRNA target genes and inducing resistance. A study concluded that circFGFR1 directly interacts with miR-381-3p and acts as a miRNA sponge to upregulate the expression of CXCR4, promoting NSCLC progression and resistance to PD-1 therapy [66]. Another study reported that circ_CELF1 interacts with miR-491-5p as a miRNA sponge, increasing the expression of EGFR, ultimately promoting NSCLC progression and enhancing tumor cell resistance to immune inhibitors [61].

**Table 3** Regulatory mechanisms of circRNAs in lung cancer immune therapy resistance

| circRNA | Expression Level | Potential Regulatory Mechanism | References |
|---|---|---|---|
| hsa_circ_0020714 | Upregulated | Acts as a miR-30a-5p sponge, upregulating SOX4 expression, inducing immune evasion in NSCLC | [67] |
| circ_0004140 | Upregulated | Promotes immune resistance through the circ_0004140/miR-1184/CCL22 axis | [63] |
| hsa_circ_0000190 | Upregulated | Promotes tumorigenesis and immune evasion in NSCLC by upregulating soluble PD-L1 expression | [68] |
| circFGFR1 | Upregulated | Acts as a miRNA sponge to upregulate miR-381-3p target gene (CXCR4) expression, promoting immune resistance | [62] |
| circ_CELF1 | Upregulated | Acts as a miRNA sponge, increasing miR-491-5p expression, enhancing tumor resistance to immunotherapy | [64] |

Research on immune therapy resistance has made preliminary progress. In future studies, unraveling the mechanisms of immune evasion will be key to overcoming immune resistance and improving the efficacy of immunotherapy. Whether circRNA regulation can reverse immune resistance also warrants further exploration. Additionally, further studies on the mechanisms and efficacy of dual immune combination therapies, immune + chemotherapy, immune + VEGFR inhibitors, immune + radiotherapy, or even immune + targeted therapies will provide evidence for the combination of various drugs and treatment strategies (Table 3).

### 3.4 Mechanisms of circRNAs in reversing lung cancer drug resistance

CircRNAs are not only closely related to the mechanisms of drug resistance in lung cancer but can also enhance the sensitivity of lung cancer cells to drugs, thereby reversing resistance. CircRNAs have been shown to reverse TKI resistance (Table 4). The mechanism may involve altering the circRNA-miRNA-protein signaling pathway to reverse resistance. A study found that circF-BXW7 regulates the Wnt pathway function by ubiquitinating and inhibiting β-catenin via circFBXW7-185AA, effectively suppressing the stem cell-like properties of lung adenocarcinoma cells and reversing TKI resistance [69]. Another study revealed that circASK1 (hsa_circ_0007798) is significantly downregulated in gefitinib-resistant cells, and upregulation of circASK1 enhances the sensitivity of lung adenocarcinoma cells to gefitinib. Mechanistically, a novel protein encoded by circASK1, ASK1-272a.a, was found to be crucial for the activation of the ASK1/JNK/p38 signaling pathway, mediating the chemosensitivity effect of circASK1 in LUAD. ASK1 and ASK1-272a.a competitively bind to Akt1, antagonizing Akt1-induced phosphorylation and inactivation of ASK1, thereby activating ASK1-induced apoptosis and reducing gefitinib resistance [70]. Studies also suggest that certain circRNAs may regulate the phosphorylation of stress-related kinases, further enhancing the sensitivity of drug-resistant cancer cells to treatment [71]. Another mechanism involves circRNA_100146, which was reported to reverse osimertinib resistance by sponging miR-361-3p and regulating FOXM1 expression, leading to restored apoptosis in resistant NSCLC cells. This suggests that targeting circRNA-miRNA interactions can enhance drug sensitivity [72]. Moreover, circGSK3β was found to regulate the miR-485-3p/SOX7 axis, promoting apoptosis and enhancing gefitinib sensitivity in LUAD cells. This highlights the therapeutic potential of circRNA-mediated regulation of key pathways to overcome resistance [73]. These findings illustrate that circRNAs can modulate multiple signaling pathways to reverse resistance, offering new directions for overcoming TKI resistance and improving treatment outcomes.

CircRNAs can inhibit and reverse cisplatin resistance through mechanisms related to the circRNA-miRNA-protein signaling pathway (Table 5). A study found that circANKRD28 is significantly downregulated in NSCLC. Overexpression of circANKRD28 can inhibit cisplatin resistance in NSCLC cells by regulating tumor progression and cisplatin sensitivity

**Table 4** Regulatory mechanisms of circRNAs in reversing TKI resistance in lung cancer

| circRNA | Expression Level | Potential Regulatory Mechanism | References |
|---|---|---|---|
| circF-BXW7 | Upregulated | Regulates Wnt pathway function by ubiquitinating β-catenin via circFBXW7-185AA, reversing resistance | [74] |
| circASK1 | Upregulated | Competitively binds to Akt1, antagonizing ASK1 phosphorylation and inactivation, activating apoptosis to reverse resistance | [75] |

**Table 5** Regulatory mechanisms of circRNAs in reversing cisplatin resistance in lung cancer

| circRNA | Expression Level | Potential Regulatory Mechanism | References |
|---|---|---|---|
| circANKRD28 | Upregulated | Regulates tumor progression and cisplatin sensitivity via the miR-221-3p/SOCS3 axis | [76] |
| circ_0030998 | Upregulated | Inhibits cisplatin resistance by regulating the miR-1323/PDCD4 axis | [77] |

via the miR-221-3p/SOCS3 axis [76]. Further evidence highlights that circRNAs interacting with tumor suppressors may modulate apoptotic pathways, restoring drug sensitivity in lung cancer cells [66]. Another study indicated that the upregulation of circ_0030998 can inhibit cisplatin resistance in NSCLC cells and trigger apoptosis. Mechanistically, circ_0030998 inhibits cisplatin resistance and NSCLC progression by regulating the miR-1323/PDCD4 axis, restoring the sensitivity of lung cancer cells to cisplatin [57].

These findings suggest that targeting specific circRNAs involved in the regulation of miRNA-protein signaling networks could provide new therapeutic strategies to reverse drug resistance in NSCLC.

In summary, current research demonstrates that circRNAs can enhance the sensitivity of lung cancer cells to drugs by regulating the circRNA-miRNA-protein signaling pathway, thereby alleviating resistance to TKIs and cisplatin [57, 69, 70, 76]. These mechanisms provide new targets for lung cancer treatment by modulating the expression of specific circRNAs, offering promising strategies to combat drug resistance and improve long-term patient survival. However, no circRNAs have yet been identified that are capable of reversing resistance to immunotherapy through these pathways [61]. Further research is needed to explore how to overcome immune resistance and investigate alternative pathways that could help reverse drug resistance and enhance therapeutic efficacy.

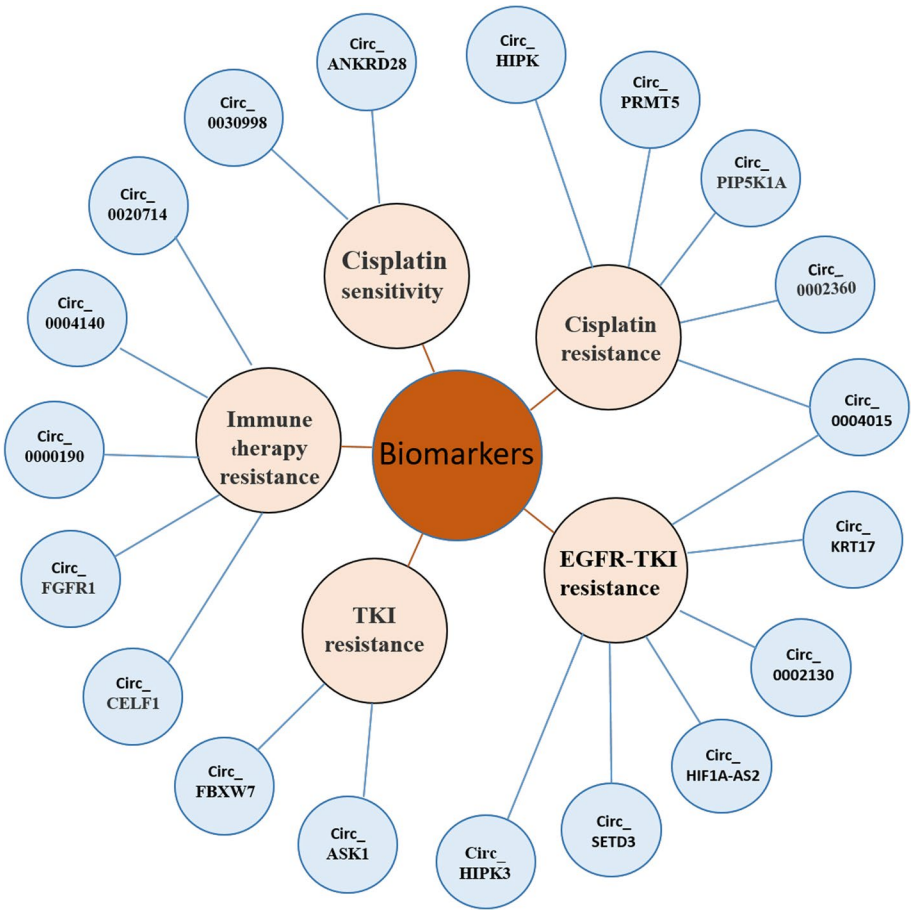


**Fig.2** CircRNAs as predictive biomarkers for drug sensitivity and treatment outcomes

## 4 CircRNAs as predictive biomarkers for drug sensitivity and treatment outcomes

Recent studies show that circRNAs not only correlate with drug resistance but can also predict overall treatment outcomes and patient survival, further highlighting their clinical relevance [65]. Specific circRNAs have been linked to the efficacy of combination therapies, underscoring the need for more comprehensive studies in this area [4]. CircRNAs as predictive biomarkers for drug sensitivity and treatment outcomes are summarized in Fig. 2.

Emerging clinical validations have highlighted the dynamic monitoring capabilities of circRNAs in treatment response [78]. In the KEYNOTE-789 trial subset, levels of hsa_circ_0020714 showed increase at radiographic progression compared to baseline, suggesting its potential for real-time tracking of immunotherapy resistance [67]. The phase I/II NCT04858321 trial demonstrated that circHIPK2 in liquid biopsies achieved sensitivity and specificity in predicting cisplatin response in NSCLC [79]. Notably, circSETD3 exhibits tissue-specific expression—elevated in TKI-resistant tumor biopsies but undetectable in matched plasma—offering potential for dual diagnostic and therapeutic applications [80].

Recent breakthroughs in delivery systems have significantly improved the precision of circRNA targeting [81–83]. Poly(β-amino ester) nanoparticles loaded with si-circMDK achieved a tumor growth inhibition in hepatocellular carcinoma patient-derived xenograft (PDX) models [84]. PLGA-PEG nanocarriers delivering si-circROBO1 induced apoptosis in gastric cancer cells [85]. Furthermore, liver-optimized lipid nanoparticles exploit hepatic accumulation to modulate circRNAs specifically for HCC treatment [86].

Cross-cancer analyses have revealed conserved regulatory networks. For instance, circRNA_0023685 promotes gastric cancer via activation of the miR-195-5p/APP axis [87]. CircHIPK3 mediates 5-FU resistance in colorectal cancer by sponging miR-7, and circPVT1 stabilizes c-Myc to drive lung cancer metastasis [88]. However, challenges in standardization remain, particularly with inter-platform quantification variability, with differences [89]. Disease-specific expression patterns are also a concern; for example, circMTO1 shows inverse trends in coronary artery disease (CAD) versus HCC [90]. Additionally, exosome loading efficiency remains below, although cationic nanoparticles improve payload efficiency [91].

CircRNA-guided combination therapies, currently being investigated in ongoing clinical trials such as NCT04858321 and NCT05167242, hold significant promise for enhancing treatment outcomes in cancer therapy [92]. However, multicenter validation of additional circRNA panels is essential to establish their clinical applicability and ensure consistent, reliable results across diverse patient populations.

## 5 Discussion

In summary, we have found that circRNAs hold significant theoretical and practical importance in lung cancer treatment. Further research on circRNAs will play a crucial role in the treatment of lung cancer and present important prospects for clinical applications. Current research demonstrates that circRNAs play an essential role in both drug resistance and the reversal of resistance in lung cancer. The mechanisms by which circRNAs influence drug resistance are diverse and complex, involving multiple signaling pathways and interaction networks. CircRNAs regulate biological processes such as tumor cell proliferation and apoptosis by interacting with miRNAs, signaling pathways, proteins, and by modulating their own expression. This regulation contributes to both the development of resistance and the reversal of resistance to TKI, chemotherapy, and immunotherapy in lung cancer cells [69, 70].

While significant progress has been made in circRNA research related to lung cancer treatment, several gaps remain. Future research should explore the involvement of circRNAs in the development and progression of lung cancer, their potential as predictive biomarkers for treatment efficacy, and their use in therapeutic strategies.

CircRNAs have been implicated in lung cancer progression through their regulation of gene expression, signaling pathways, protein transcription, translation, and binding. These mechanisms include: Regulating miRNA Expression: CircRNAs such as circ_0001368, circ_0081666, circMTO1, and CircNFIX modulate miRNA expression to influence tumor cell proliferation, migration, and invasion. Regulating Signaling Pathways: CircRNAs impact critical signaling pathways associated with cancer progression, including the Wnt/β-catenin, miR-1184/miR-548I/AGO1, miR-142-3p/HMGB1, and hsa_circ_0016600/miR-1298/TGFA pathways. These pathways are known to regulate tumor growth and metastasis [76]. Regulating Protein Function: CircRNAs also affect the activity of proteins essential for cancer development, thereby contributing to tumor progression and drug resistance [57]. Regulating Their Own Expression: Changes in the expression of circRNAs like circ_CELF1, circCCDC66, and circ-DCAF6 further influence tumor growth and progression by modulating

key cellular pathways [70]. CircRNAs also show potential as predictive biomarkers for drug sensitivity and treatment outcomes. They could help clinicians tailor therapies based on the predicted response to different treatments:

TKI Sensitivity and Resistance: CircRNAs such as circSETD3, hsa_circ_0030591, hsa_circ_0040348, and hsa_circ_0109320 have been identified as predictors of TKI resistance and treatment efficacy, highlighting their potential for improving patient outcomes [69].

Chemotherapy Sensitivity: CircRNAs including circ_0000620, hsa_circ_0085131, circRNA CDR1as, and circAKT3 are associated with cisplatin resistance. Their expression levels correlate with treatment outcomes, suggesting their potential as biomarkers for predicting chemotherapy success [57].

Although biomarkers such as PD-L1 expression (TPS, CPS), tumor mutational burden (TMB), microsatellite instability (MSI), and tumor-infiltrating lymphocytes (TIL) are currently used to predict immunotherapy efficacy, their specificity and accuracy are limited. Recent studies suggest that circRNAs could serve as novel biomarkers for immunotherapy outcomes. For instance, changes in hsa_circ_0000190 and circZNF451 are associated with poor prognosis in lung adenocarcinoma patients undergoing immunotherapy and could serve as valuable indicators for monitoring disease progression and treatment efficacy [61]. Research on circRNAs in lung cancer treatment shows promising prospects. With further investigation and development, circRNAs are expected to play a more significant role in clinical practice, offering more effective strategies to combat drug resistance and improve patients' survival and quality of life. Expanding research efforts to identify additional therapeutic targets and integrating circRNA-based approaches with current immunotherapy, chemotherapy, and targeted therapy will provide innovative treatment strategies and improve patient outcomes.

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**Data availability** The data supporting the findings are available from the corresponding author.

## Declarations

**Ethics approval and consent to participate** This study did not involve human participants or animals, so ethics approval was not required.

**Competing interests** The authors declare no competing interests.



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