

CircRNA in non-small cell lung cancer: Potential biomarkers and therapeutic targets (Review)

ZUOKUN WU*, ZHENGFENG ZHU*, PENGFEI ZHAO, YONGXIANG SONG and XIXIAN KE

Department of Thoracic Surgery, Affiliated Hospital of Zunyi Medical University, Zunyi, Guizhou 563000, P.R. China

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Abstract. Lung cancer is one of the most common malignant tumors, characterized by high incidence and mortality rates. Non-small cell lung cancer (NSCLC) is the predominant histological type of lung cancer. Due to the lack of effective early diagnostic methods, the majority of patients with lung cancer present with distant metastasis at the time of initial diagnosis, often rendering treatments such as surgery and pharmacotherapy ineffective. Consequently, there is an urgent need for a more in-depth understanding of the pathogenesis of NSCLC and the identification of novel therapeutic targets to enable more precise prediction and treatment of the disease. circular RNAs (circRNAs) are specifically expressed in tissues, owing to their high stability and specificity. The dysregulation of circRNA expression has been implicated in cancer progression, where circRNAs function as microRNA sponges, RNA-binding protein sponges, gene splicing and transcriptional regulators and protein/peptide translational modulators. These molecules may serve as potential biomarkers for cancer prognosis and predictive indicators, as well as novel therapeutic targets. The present review summarizes the biogenesis and mechanistic functions of circRNAs, outlines their potential role in the initiation and progression of NSCLC and discusses their application as therapeutic targets in cancer treatment. The present review aimed to provide new perspectives for the development of emerging diagnostic or prognostic biomarkers and potential therapeutic targets for NSCLC.

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1. Introduction

According to the latest statistical data released by the Global Cancer Center, lung cancer is one of the most common malignant tumors (1), characterized by high incidence and mortality rates (2). Based on histological classification, lung cancer is divided into two pathological subtypes: Non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), with NSCLC accounting for ~85% of lung cancer cases (3). The primary pathological subtypes of NSCLC include lung adenocarcinoma and squamous cell carcinoma. Although recent advancements made in surgical treatment, radiotherapy, chemotherapy, molecular targeted therapies and anti-angiogenesis treatments have improved survival rates of patients with NSCLC (4), the characteristics of NSCLC, such as late detection, high metastatic potential, epithelial-to-mesenchymal transition (EMT) and uncontrolled proliferation, limit the effectiveness of early diagnosis and treatment. Consequently, the 5-year overall survival rate of patients with NSCLC remains low (5). Therefore, there is need for the identification of effective and specific biomarkers for diagnosis and prognosis, as well as for the discovery of novel therapeutic targets to improve the diagnosis and treatment of patients with NSCLC (6).

Circular RNAs (circRNAs) were first identified in RNA viruses in 1979 (7). Initially, circRNAs were primarily considered to be 'junk' products arising from aberrant splicing events (8). However, with the advancement of high-throughput RNA sequencing (RNA-seq) and circRNA-specific bioinformatics algorithms, thousands of distinct circRNA species have now been identified in eukaryotic organisms (9). As research into the biological properties and functions of circRNAs broadens, these molecules have increasingly garnered attention as a class of non-coding RNAs pivotal to human disease studies. In comparison with normal surrounding tissues, the expression of circRNAs in tumor cells may be either upregulated or downregulated (10). Although circRNAs exert

Correspondence to: Dr Yongxiang Song or Dr Xixian Ke, Department of Thoracic Surgery, Affiliated Hospital of Zunyi Medical University, 149 Dalian Road, Zunyi, Guizhou 563000, P.R. China
E-mail: songtan@163.com
E-mail: kexixian@zmu.edu.cn

*Contributed equally

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differential effects on gene expression regulation across various types of cancer or stages, they predominantly influence downstream gene expression levels and the cascading responses of signaling molecules by forming intricate post-transcriptional regulatory networks, thereby affecting tumor progression. For instance, the study by Zhang *et al* (11) demonstrated that circSATB2 promotes the progression of NSCLC cells, while the study by Li *et al* (12) demonstrated that circNDUFB2 can stabilize insulin-like growth factor-2 mRNA-binding protein (IGF2BP) and activate anti-tumor immunity, thus impeding NSCLC progression.

An increasing body of research has revealed that circRNAs not only function as microRNA (miRNA/miR) sponges, but also carry out key roles in the development of various human diseases through mechanisms, such as gene splicing, transcriptional regulation (13), RNA-binding protein sponging and the modulation of protein/peptide translation (14). The versatility of the biological functions of circRNAs provides new insight into the pathogenesis of diseases. circRNAs are differentially expressed in different types of cancer, where they can function as either tumor suppressors or oncogenes, carrying out an indispensable role in tumorigenesis (15). As the comprehensive study of circRNA expression and function progresses, the notable regulatory roles of circRNAs in numerous diseases are becoming increasingly apparent (16-18). In the context of cancer, circRNAs are integral to the initiation and progression of malignancies and hold promise as potential biomarkers for cancer diagnosis, prognosis and therapy (19-20). The present review summarizes the currently available knowledge on the biogenesis and biological functions of circRNAs, and discusses their impact on the occurrence and development of NSCLC. Furthermore, the present review discusses the potential of circRNAs as therapeutic targets for cancer. circRNAs may be utilized as biomarkers, or even therapeutic targets, for NSCLC, thus providing new perspectives or strategies for the early detection, diagnosis and treatment of this disease.

2. Mechanism of circRNA circularization and its basic functions

circRNAs are primarily located in the cytoplasm of eukaryotic cells or stored in exosomes, where they participate in intercellular communication, cell development and differentiation, and cellular signal transduction (21). circRNAs are a class of non-coding RNA molecules that are abundant and evolutionarily conserved, and they are stably present in various body fluids, such as exosomes, blood, saliva and urine in eukaryotes (22). circRNAs are characterized by their abundance and evolutionary conservation. Their formation is regulated by both *cis*- and *trans*-acting elements and primarily occurs through a back-splicing mechanism (23). These molecules are highly stable and conserved with a closed circular structure, and can be categorized into four major types: Exonic circular RNAs, intronic circular RNAs, exon-intron circular RNAs and tRNA intronic circular RNAs, with exonic circular RNAs being the most prevalent (24). Unlike conventional linear RNAs, circRNAs lack a 5' cap and a 3' Poly(A) tail. The unique circular structure formed by splicing renders circRNAs resistant to degradation by exonucleases, allowing them to exhibit greater stability and longer half-lives compared with the

parent gene expression. Furthermore, the circular structure of circRNAs endows them with stability, tissue specificity and conservation (25), rendering circRNAs potential biomarkers for diagnosis and prognosis.

Formation mechanisms of circRNAs. circRNAs can be classified into intronic and exonic types based on the mechanism of circularization. However, the majority of circRNAs are primarily formed through exonic circularization, resulting in a covalently closed circular structure. The process of circRNA circularization can be categorized into four distinct biogenesis mechanisms based on the patterns of circular structure formation: i) Intron pairing-driven circularization: Complementary pairing of the intronic sequences flanking the exons drives the circularization process, which occurs through alternative splicing to generate circular RNA; ii) RNA-binding protein (RBP)-driven circularization: During RBP-mediated circularization, the dimerization of RBPs interacts with the intronic sequences flanking the exons, promoting the proximity of the two intronic regions, which facilitates the back-splicing of exons into a circular structure; iii) Lasso-driven circularization: In this mechanism, the classical GU/AG splicing of precursor mRNAs can result in cross-exonic splicing, generating an intermediate lasso structure that contains both introns and exons. This intermediate is then subjected to back-splicing, forming a circular RNA; iv) tRNA intronic circular (tricRNA) splicing pathway: In this pathway, tRNA splicing enzymes cleave precursor tRNA into two exonic halves and an intron, with one portion forming tRNAs and the other generating tricRNAs (26,27). The possible mechanisms of circRNA circularization are illustrated in Fig. 1.

Functions of circRNAs. circRNAs primarily function as miRNA sponges, interact with RBPs and regulate alternative splicing, transcription and translation (28-31) (Fig. 2). Additionally, circRNAs have been revealed to regulate gene expression through epigenetic mechanisms and selective splicing (32).

circRNAs as molecular 'sponges' for miRNAs. Studies have revealed that the circular structure of circRNAs is rich in miRNA binding sites, allowing circRNAs to function as molecular sponges by adsorbing miRNAs (28,33). This reduces the ability of miRNAs to bind to the 3' untranslated regions (UTRs) of target mRNAs, thereby alleviating the suppressive effect of miRNAs on their target genes and promoting the expression of those genes. This mechanism is referred to as the competitive endogenous RNA (ceRNA) mechanism (34).

circRNAs can sponge miRNAs through miRNA response elements (35), thereby preventing miRNAs from binding to target mRNAs and influencing downstream target genes. For example, circ-CSPP1 functions as a molecular sponge for miR-1236-3p, promoting proliferation, invasion and migration in ovarian cancer (36). Additionally, circBACH2 (hsa_cir_0001625) has been revealed to function as a sponge for hsa-miR-944, and through the circBACH2/hsa-miR-944/HNRNPC axis, it promotes cell proliferation in breast cancer (37). The study by Yang *et al* (38) revealed that CircHIPK3 promotes gastric cancer progression through the miR-637/AKT1 pathway. Cheng *et al* (39) reported that circTP63 facilitates the progression of lung squamous

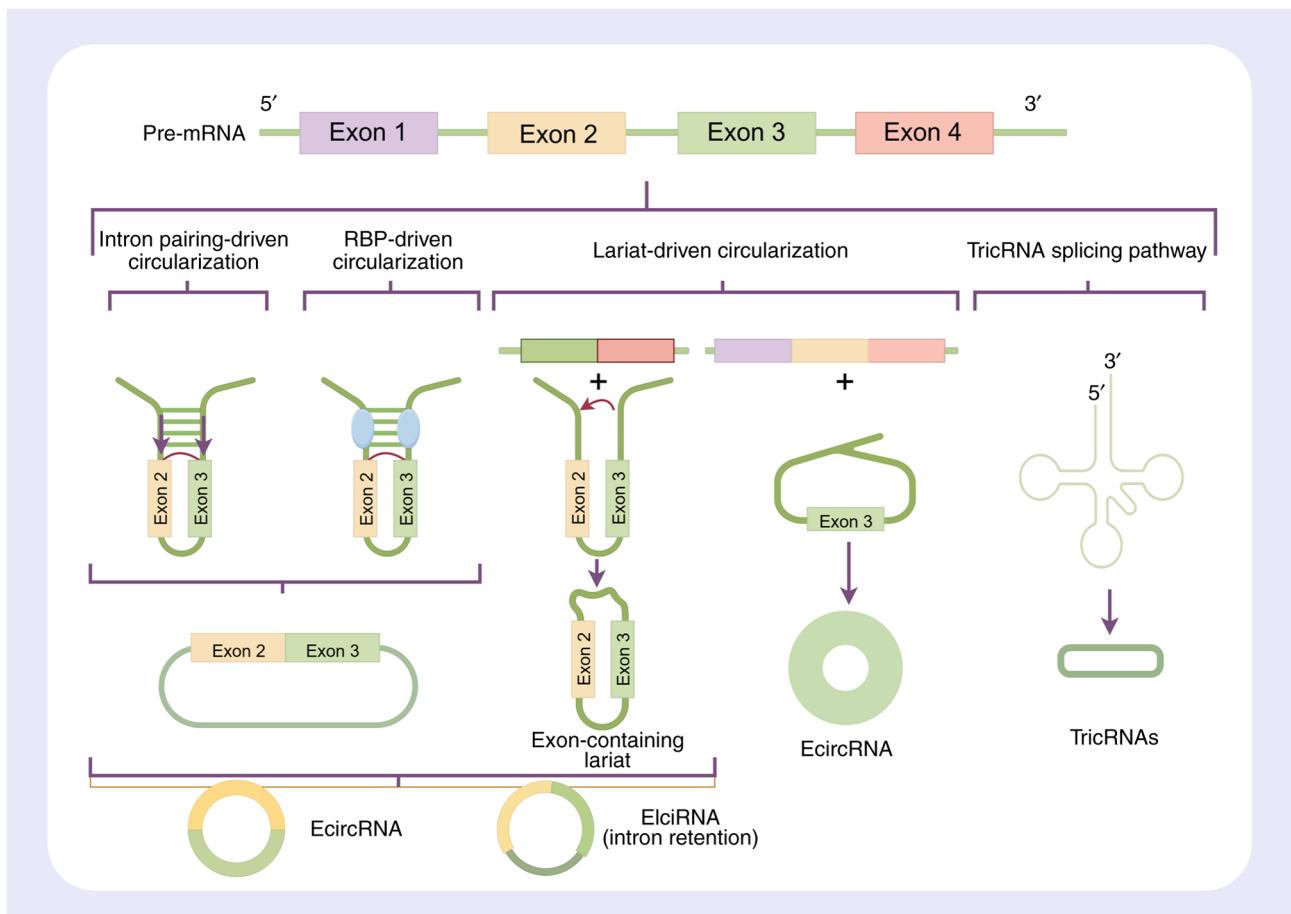


Figure 1. Biogenesis of circRNAs. circRNA biogenesis is mainly regulated by four different mechanisms: i) Intron pairing-driven circularization. ii) RBP-driven Circularization. iii) Lasso-driven circularization. ii) TricRNA splicing pathway. CircRNAs, circular RNAs; RBP, RNA-binding protein; tricRNA, tRNA intronic circular RNAs; EcircRNA, exonic circular RNA; EliciRNA, Exon-intron circular RNA.

cell carcinoma by sponging miR-873-3p and preventing the downregulation of FOXM1. The ceRNA regulatory network composed of circRNA/miRNA/mRNA carries out a key role in cancer initiation and progression, providing new insight and potential targets for cancer prevention and treatment (40).

circRNAs interacting with proteins. Increasing research into circRNAs has revealed that circRNAs can function as 'protein decoys', binding to specific proteins to form circRNA-protein complexes (41-43). Additionally, circRNAs may function as protein scaffolds, where they bind to individual proteins or coordinate interactions with multiple proteins to form multi-component circRNA-protein complexes. These complexes can directly or indirectly influence the subcellular localization of proteins, the activity of associated proteins and the transcription of parent or associated genes (44). For example, the ectopic expression of circ-Amotl1 promotes the nuclear translocation of c-myc (45). Research has demonstrated that circEIF3J and circPAIP2 can form RNA-protein complexes by interacting with RNA polymerase II, thereby promoting the transcription of EIF3J and PAIP2 (46). Furthermore, Du *et al* (47) demonstrated that the circFoxo3-p21-CDK2 ternary complex enhances the binding of CDK2 with p21 (CDK inhibitor 1A), thereby inhibiting the phosphorylation activity of CDK2 and causing G1-phase cell cycle arrest.

That study highlights the ability of circRNAs to function as protein sponges and regulate protein interactions. The study by Liang *et al* (48), revealed that circDCUN1D4 functioned as a scaffold, forming the circDCUN1D4-HuR-TXNIP RNA-protein ternary complex, which increased the stability of TXNIP mRNA and suppressed the metastasis and glycolysis of NSCLC. These findings indicate that circRNAs can serve as protein regulators, modulating various biological processes.

The interaction between circRNAs and proteins has expanded the scope of circRNA research and increased its potential for clinical translation. However, due to theoretical and technical limitations, research on the interaction between circRNAs and proteins remains relatively limited. Previous studies mainly focus on circRNAs influencing protein-protein interactions through the formation of circRNA-mRNA-protein ternary complexes (49,50). The specific mechanisms underlying the biological interactions between circRNAs and proteins require further investigation and gradual translation into clinical applications.

circRNAs regulate alternative splicing, transcription and translation. Alternative splicing is a key post-transcriptional regulatory mechanism that contributes to gene expression and the diversification of gene products (51). For example, circRNAs derived from SEPALLATA3 can form an R-loop

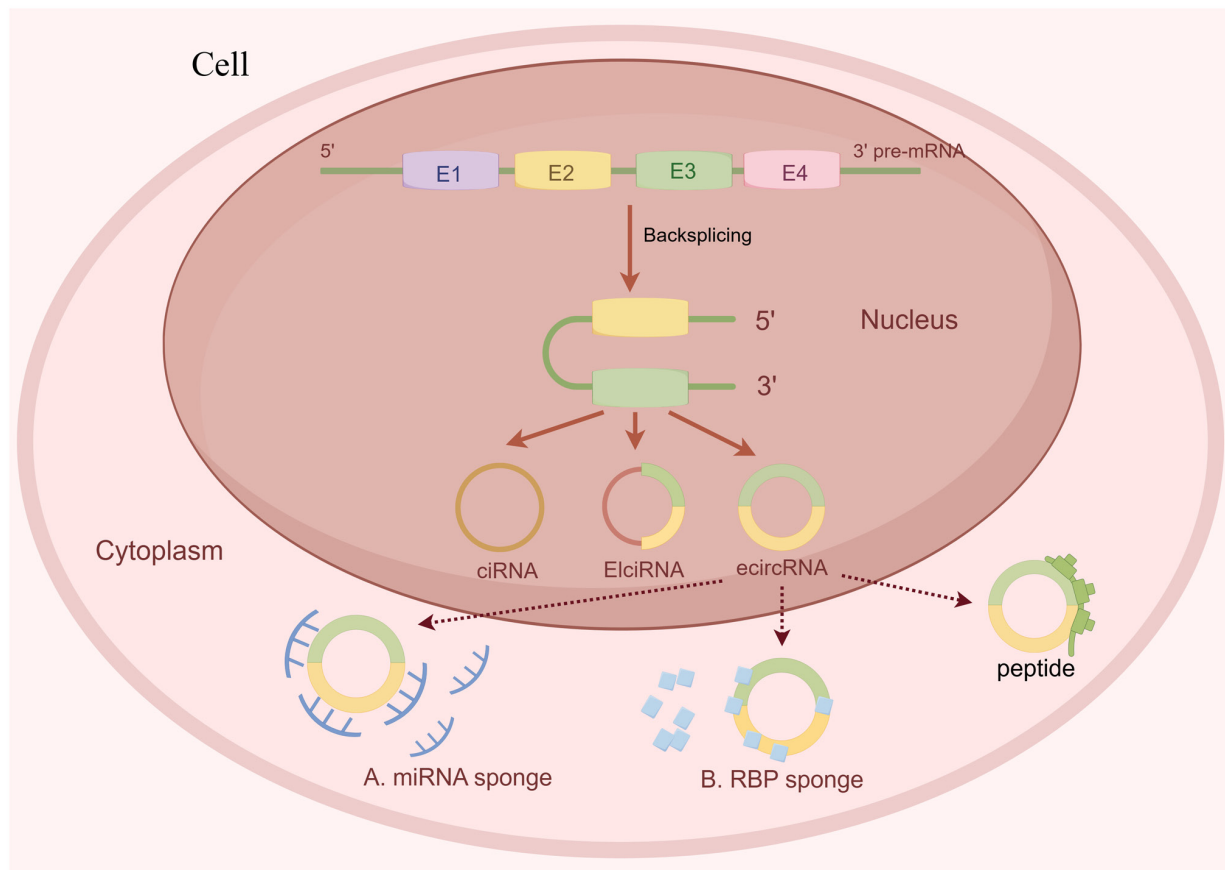


Figure 2. Functional mechanisms of circRNA. circRNAs primarily function as miRNA sponges, interact with RBPs and regulate alternative splicing, transcription and translation. miRNA, microRNA; RBPs, RNA-binding proteins; EcircRNA, Exonic circular RNA; ElciRNA, Exon-intron circular RNA.

structure to regulate the splicing of its homologous mRNA (52). CircURI1 has been revealed to regulate the alternative splicing of the vascular endothelial growth factor A gene (53). Furthermore, interactions between linear splicing and nuclear circRNAs can mutually regulate alternative splicing by competing for splicing sites (54). Through the modulation of alternative splicing pathways, circRNAs carry out key roles in cancer development. Additionally, circRNAs can function as *cis*-regulatory factors in various pathological processes to modulate gene expression at the transcriptional level. For instance, circRHOT1 recruits TIP60 to the NR2F6 promoter, thereby promoting NR2F6 transcription and inhibiting the progression of hepatocellular carcinoma (55). Other research has demonstrated that circEIF3J and circPAIP2 promote the transcription of PAIP2 and EIF3J by interacting with U1 small nuclear ribonucleoproteins and RNA polymerase II (56). However, further investigations are required to determine whether other nuclear-retained circRNAs can regulate transcription and splicing.

In previous studies, circRNAs were classified as non-coding RNAs due to their lack of a 5' cap, and they were largely considered to lack the capacity to associate with ribosomes for translation (57,58). However, reports have demonstrated that circRNAs containing internal ribosome entry site (IRES) elements can initiate translation independent of the conventional cap-dependent mechanism (59). Although endogenous IRES elements are rare, studies have uncovered the translation of circRNAs driven by m6A epitranscriptomic

modifications. Certain circRNAs in tumor cells are translated via m6A-mediated initiation, and hundreds of translatable endogenous circRNAs have been identified, marking a notable advancement in the field of translation (60,61).

Proteins derived from circRNAs have been revealed to participate in various physiological functions in animals and humans. For example, the translatable circ-ZNF609 regulates myoblast proliferation in mice and humans in an IRES-dependent manner (62). Moreover, the translation of circFNDC3B results in the production of circFNDC3B-218aa, which suppresses tumor progression and EMT in colon cancer by modulating Snail expression (63). Additionally, studies have demonstrated that circ-EIF6 encodes EIF6-224aa, which promotes triple-negative breast cancer progression by stabilizing MYH9 and activating the Wnt/ β -catenin pathway (64). These findings suggest that circRNAs may serve as effective transcriptional templates for protein expression. Although the translation efficiency of circRNAs may be limited (65,66), their potential to encode proteins broadens the current understanding of their molecular functions, providing new pathways for cancer diagnosis and treatment.

3. Impact of circRNAs on the biological behavior of NSCLC

The initiation and progression of NSCLC involve a complex interplay of multiple factors, including cancer cell proliferation, apoptosis, invasion and metastasis, tumor energy metabolism, angiogenesis, genomic mutations, immune evasion, and the

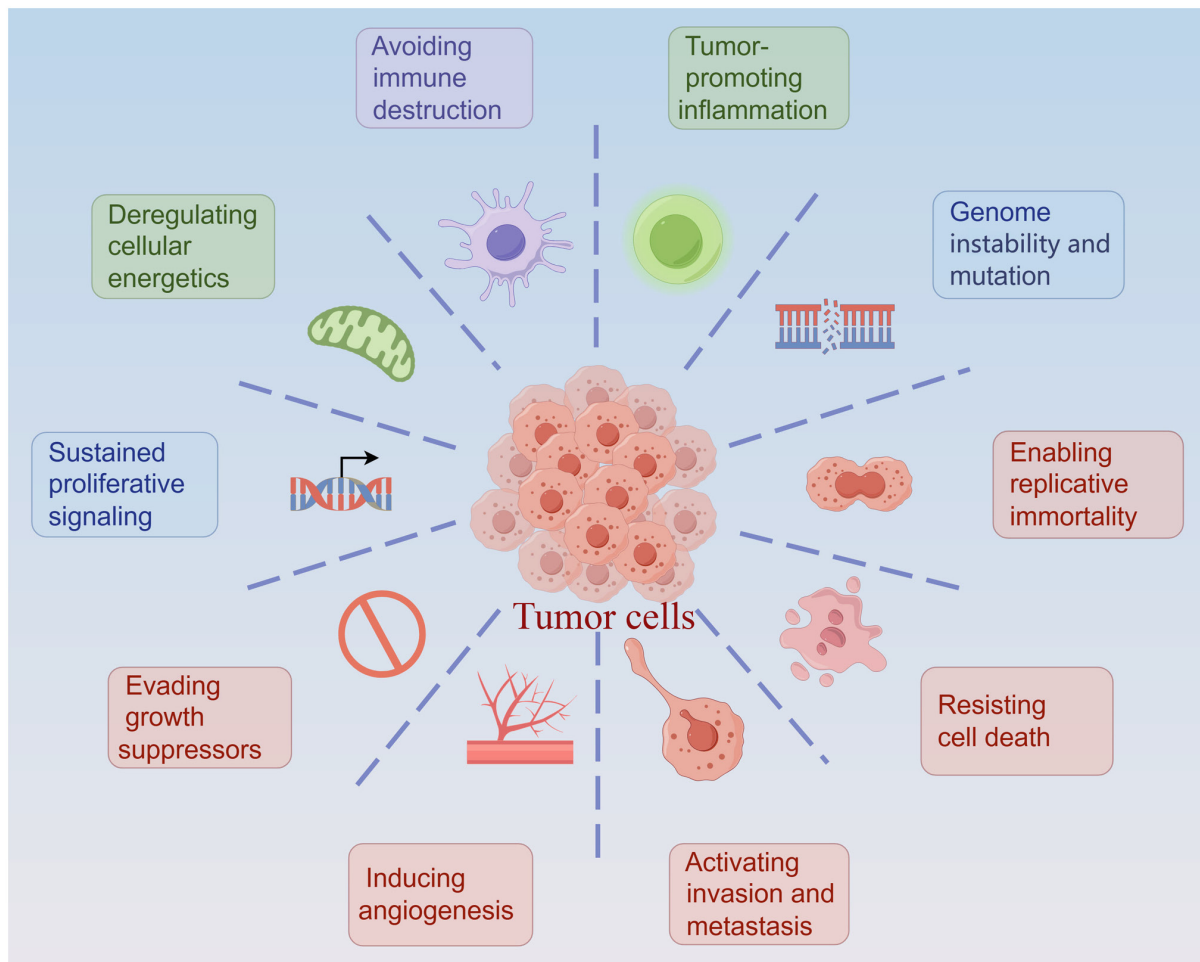


Figure 3. Effects of circular RNA on the biological behavior of non-small cell lung cancer.

tumor microenvironment (TME). These factors collectively determine the malignant biological behavior of NSCLC (67,68).

In recent years, with the continuous exploration of tumor-related RNA in NSCLC and the advancement of technologies, such as gene microarrays, numerous studies have revealed that circRNAs are highly specifically expressed in NSCLC (69,70). Furthermore, circRNAs function as either oncogenes or tumor suppressors, carrying out a key role in the malignant biological behaviors of NSCLC (Fig. 3). Increasing *in vitro* and *in vivo* evidence further indicates that circRNAs regulate the malignant biological behavior of NSCLC through various mechanisms. A more in-depth understanding of the functional mechanisms of circRNAs could provide potential biomarkers and therapeutic targets for patients with NSCLC, paving the way for a new paradigm in the precision treatment of NSCLC. However, the underlying causes of circRNA dysregulation remain unclear and require further investigation (71).

Regulation of NSCLC cell growth and proliferation by circRNAs. Abnormally expressed circRNAs in NSCLC can function as either oncogenes or tumor suppressors, carrying out a key role in the initiation and progression of the tumor (72). For example, the study by Zhang *et al* (73) demonstrated that circFGFR1 functions as a sponge for miR-381-3p, promoting the migration, invasion and proliferation of NSCLC

cells. The study by Hong *et al* (74) revealed that circ-CPA4 regulates NSCLC cell growth through interactions with the let-7 miRNA family. Additionally, Wang *et al* (75) discovered that circRNAs can modulate NSCLC progression by either inhibiting or activating autophagy through autophagy-related pathways. Furthermore, the study by Wei *et al* (76) verified that circPTPRA inhibits the growth and metastasis of NSCLC cells *in vivo* by sequestering miR-96-5p and upregulating RASSF8, using a nude mouse xenograft model. These studies underscore the considerable role of circRNAs in regulating the growth and proliferation of lung cancer cells. They also highlight the potential of circRNAs as biomarkers for NSCLC screening and as therapeutic targets for NSCLC treatment.

Impact of circRNAs on EMT in NSCLC. EMT is the process through which epithelial cells lose their adhesion properties and transition into cells with a mesenchymal phenotype. During this process, epithelial cell polarity is lost, and adhesion to the basement membrane decreases, which carries out a key role in the invasion and distant metastasis of various types of cancer (77).

Numerous studies have demonstrated that circRNAs regulate the EMT process in cancer, either positively or negatively. For instance, circ_0067934 has been revealed to function as a sponge for miR-1182, thereby reducing the expression of the miR-1182/KLF8 axis and promoting EMT and distant

metastasis in NSCLC (78). In the study by Wang *et al* (79), the overexpression of circPTK2 enhanced the expression of transcription intermediary factor 1 γ (TIF1 γ), thereby inhibiting TGF- β -induced EMT and NSCLC cell invasion. Additionally, research has revealed that circAGFG1 functions as a sponge for miR-203, upregulating ZNF281 expression, which in turn promotes EMT and the metastasis of NSCLC cells (80). EMT facilitates cancer cell invasion and increases the permeability of endothelial cells, thereby promoting the formation of metastatic foci. This process is a key mechanism for tumor invasion and metastasis, and cancer metastasis is a major factor contributing to the poor prognosis of patients (81). Research on the impact of circRNAs on EMT may provide novel therapeutic targets to inhibit NSCLC tumor cell metastasis, which may improve the prognosis of patients with NSCLC.

Impact of circRNAs on immune evasion in NSCLC. Immune systems in healthy organisms carry out immune surveillance, which enables them to recognize tumor antigens and specifically eliminate tumor cells that arise in the body, thereby defending against tumor initiation and progression. However, in certain conditions, tumor cells evade recognition and attack by the immune system through various mechanisms, thereby escaping immune clearance (82).

Recent studies have revealed that circRNAs carry out a key role in immune evasion in NSCLC, accelerating tumor cell proliferation and metastasis (83,84). For instance, in the study by Liu *et al* (85), circIGF2BP3 was revealed to inhibit the ubiquitination of programmed death-ligand 1 (PD-L1), thereby suppressing the cytotoxic effect of CD8⁺ T-cells and promoting immune evasion in NSCLC, which in turn facilitated tumor progression. Additionally, other studies have demonstrated that circ_00167 regulates the miR-326/ZEB1 signaling axis, which activates the PD-1/PD-L1 pathway, promoting the apoptosis of CD8⁺ T-cells and inducing the immune evasion of NSCLC cells (86-88). Although tumor growth and differentiation in patients with NSCLC vary due to tumor heterogeneity, the refractory nature and recurrence of the majority of NSCLCs suggest immune evasion as a key factor. Immunotherapies targeting immune checkpoints, such as PD-1 and PD-L1, have shown promising clinical results and several antitumor immune strategies are under development (89,90). However, the efficacy of these therapies in eliminating tumor cells remains limited, and immune-related side-effects cannot be overlooked, particularly in advanced solid tumors. Thus, immunotherapy is often used as an adjunctive treatment in clinical settings.

Studies have also revealed that exogenous circRNAs can induce the activation of antigen-specific T-cells and antibody production, and serve as effective adjuvants in antitumor immune vaccines (91-93). This suggests that circRNAs may hold potential as a strategy for immune therapy in NSCLC. By further exploring the molecular biological functions and mechanisms through which circRNAs activate immune evasion, new insight can be gained to enhance immune therapeutic strategies for NSCLC.

circRNAs and the TME in NSCLC. TME is the direct ecological environment in which tumors grow, and it carries out a key role in tumor growth, metastasis and responses to therapy (94).

Tumor cells can remodel the TME through autocrine and paracrine signaling, altering and maintaining changes within the TME that favor their own survival and development. These interactions are mutually reinforcing and carry out a key role in the growth and progression of tumors.

Tumor cells primarily rely on aerobic glycolysis to obtain energy, which serves as the main energy source for tumor cell growth and survival. The metabolic reprogramming of the TME has profound effects on resistance to cancer therapeutics (95). By regulating the metabolic reprogramming of the TME, circRNAs can influence energy metabolism, cell proliferation and metastasis in NSCLC. Research has demonstrated that silencing circAKT3 can target the miR-516b-5p/STAT3 axis, markedly reducing hypoxia inducible factor-1 α -dependent glycolysis and enhancing the sensitivity of NSCLC cells to cisplatin (96). Additionally, the upregulation of circ_0000376 in NSCLC is associated with the poor overall survival of patients with NSCLC and promotes the glycolysis and viability of NSCLC cells (97). Furthermore, tumor-derived exosomal circFARSA mediates M2 macrophage polarization via the PTEN/PI3K/AKT pathway, promoting the metastasis of NSCLC (98). Tumor-associated macrophages, which are the most abundant immune cells in the TME, exert unique immune regulatory effects that either promote or inhibit tumor development. An increasing number of studies have highlighted the key role of circRNAs in regulating multiple biological processes within the TME (99-101). circRNAs can recruit and reprogram key components of the TME, and their interactions with the TME form complex signaling networks that influence the initiation and progression of NSCLC. Targeting the co-activation of circRNAs and TME components may enhance the efficacy of NSCLC therapeutics (102).

circRNAs as therapeutic targets in cancer. Dysregulation of circRNA expression underscores their potential as therapeutic targets and biomarkers, opening new avenues for the development of novel cancer treatments. For example, synthetically engineered circRNAs can function as miR-21 sponges, inhibiting the proliferation of gastric cancer cells (103). Synthesis of therapeutic circRNAs is achieved through chemical synthesis, enzymatic reactions and ribozyme-based methods (104-106). Furthermore, exogenous synthetic circRNAs can be delivered at the tissue, cellular and subcellular levels using both viral and non-viral delivery systems. However, these synthetic approaches inevitably lead to the generation of by-products (107). Future efforts should focus on developing more efficient circRNA production methods with fewer drawbacks to meet therapeutic needs. In addition, gene editing, gene silencing, circRNA vaccines and other therapies targeting carcinogenic circRNA have been developed (108-110). However, the specificity and immunogenicity of the target are issues which remain to be resolved.

Discussion

NSCLC is a multifactorial disease. Despite continuous advancements being made in its diagnosis and treatment, the therapeutic outcomes of patients with NSCLC remain suboptimal due to the recurrence and metastasis of tumor cells, as well as drug resistance. Identifying sensitive biomarkers and

developing effective therapeutic targets are key to improve clinical efficacy and patient prognosis (111).

Increasing evidence from functional experiments have confirmed that circRNAs carry out a key regulatory role in various aspects of NSCLC, including tumor cell proliferation and apoptosis, cell cycle regulation, metastasis, angiogenesis, drug sensitivity and immune suppression (112,113). Due to their unique circular structure, circRNAs exhibit marked conservation, stability and specificity, rendering them promising candidates as biomarkers for early diagnosis and prognosis in NSCLC, as well as potential targets for molecular therapies. Notably, certain circRNAs are dysregulated in various types of cancer, suggesting they may serve as universal therapeutic targets across multiple types of cancer (114). However, it is important to note that circRNAs may carry out different functions in different types of cancer. For example, circRAPGEF5 promotes thyroid cell proliferation through the regulation of the miR-198/FGFR1 axis (115); however, it is downregulated in renal cell carcinoma, where it exerts tumor-suppressive effects by inhibiting growth and metastasis (116). Therefore, further studies are required to explore NSCLC-specific circRNAs as biomarkers.

CircRNA sequencing can be used to identify circRNAs that are specifically expressed in different NSCLC subtypes. This can address the differences in circRNA mechanisms across these subtypes. High-throughput sequencing can be used to conduct circRNA expression profile sequencing on tissue samples of different NSCLC subtypes and normal lung tissues. This can directly obtain circRNA expression data in different NSCLC subtypes, providing raw data for mechanism research. In addition, circRNA-seq data can be integrated with other omics data (such as, genomics, transcriptomics and proteomics) to construct networks between circRNAs and other molecules. This can comprehensively reveal the functional mechanisms and potential application value of circRNAs in NSCLC.

The unique biological characteristics of circRNAs present immense clinical potential (117). With the advancement of technologies, such as gene chips, circRNAs are emerging as a new frontier within the non-coding RNA family. While clinical translation in NSCLC is still in the early stages, the field holds promise for future clinical applications. It is anticipated that with the development of high-throughput sequencing, bioinformatics, liquid biopsy and other technologies, circRNAs will carry out a key role in the precision treatment of NSCLC.

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Authors' contributions

ZW and ZZ conceived and designed the review. ZW, ZZ and PZ wrote the manuscript. YS and XK revised the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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