Molecular Therapy
Nucleic Acids
Review

Biogenesis, functions, and clinical implications of circular RNAs in non-small cell lung cancer

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Lung cancer (LC) is the leading cause of cancer-related deaths worldwide, with high morbidity and mortality. Non-small cell lung cancer (NSCLC) is a major pathological type of LC and accounts for more than 80% of all cases. Circular RNAs (circRNAs) are a large class of non-coding RNAs (ncRNAs) with covalently closed-loop structures, a high abundance, and tissue-specific expression patterns. They participate in various pathophysiological processes by regulating complex gene networks involved in proliferation, apoptosis, migration, and epithelial-to-mesenchymal transition (EMT), as well as metastasis. A growing number of studies have revealed that the dysregulation of circRNAs contributes to many aspects of cancer progression, such as its occurrence, metastasis, and recurrence, suggesting their great potential as efficient and specific biomarkers in the diagnosis, prognosis, and therapeutic targeting of NSCLC. In this review, we systematically elucidate the characteristics, biogenesis, and functions of circRNAs and focus on their molecular mechanisms in NSCLC progression. Moreover, we highlight their clinical implications in NSCLC treatment.

INTRODUCTION

Lung cancer (LC) is one of the most common malignant diseases of the respiratory system and the leading cause of cancer-related deaths worldwide.[1] In recent years, the mortality of LC has decreased due to the introduction of screening guidelines and reductions in tobacco use. However, it is still a major public health problem, with poor 5-year overall survival (less than 20%).[2,3] According to its pathological features, LC is usually classified into two subtypes: small cell LC and non-small cell LC (NSCLC). NSCLC is a major pathological type of LC and accounts for more than 80% of all cases, including lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC).[3] Clinically, it is difficult to observe the early symptoms of NSCLC due to its pathophysiological characteristics, leading to a large number of patients diagnosed at an advanced stage. In addition, incomplete treatment, as well as metastases or relapse in certain patients, contributes to the poor prognosis of patients with NSCLC.[4] Therefore, the identification of efficient and specific biomarkers for diagnosis and prognosis, as well as the discovery of new therapeutic targets, is urgently needed to improve the diagnosis and treatment of NSCLC patients.

Circular RNAs (circRNAs) are a large class of non-coding RNAs (ncRNAs) and are characterized by the formation of covalently closed-loop structures without 5′ caps and 3′ poly(A) tails.[5] Compared with linear RNAs, they are relatively more stable and not easily degraded by RNase.[6] The first circRNA molecule was identified in RNA viruses via electron microscopy in the early 1970s.[7] They were initially considered to be aberrant by-products of splicing without any important function in biological processes.[4] However, with the rapid development of high-throughput sequencing technologies and bioinformatics, a large number of circRNAs have been identified in eukaryotes. Many of these circRNAs are shown to be involved in the regulation of many physiological processes of higher organisms.[8]

In recent years, a growing amount of evidence has shown that the dysregulation of circRNAs is involved in the occurrence and development of many cancer types, including NSCLC.[9–12] circRNAs play crucial roles in the regulation of cancer progression by modulating the expression of key genes involved in proliferation, apoptosis, migration, and epithelial-to-mesenchymal transition (EMT), as well as metastasis.[13] Moreover, the distinct covalently closed-loop structure of circRNAs grants them multiple characteristics, including stability, tissue specificity, and conservation in humans. These characteristics endow circRNAs with great potential as biomarkers for the early diagnosis and prognosis of cancer patients. They may even act as therapeutic targets for cancer. However, studies on NSCLC-related circRNAs are still lacking, and the detailed mechanisms of these molecules in NSCLC are also unclear.

In this review, we provide a detailed description of recent findings regarding the biogenesis, features, and functional roles of circRNAs and highlight their potential as biomarkers and therapeutic targets in the diagnosis and treatment of NSCLC.

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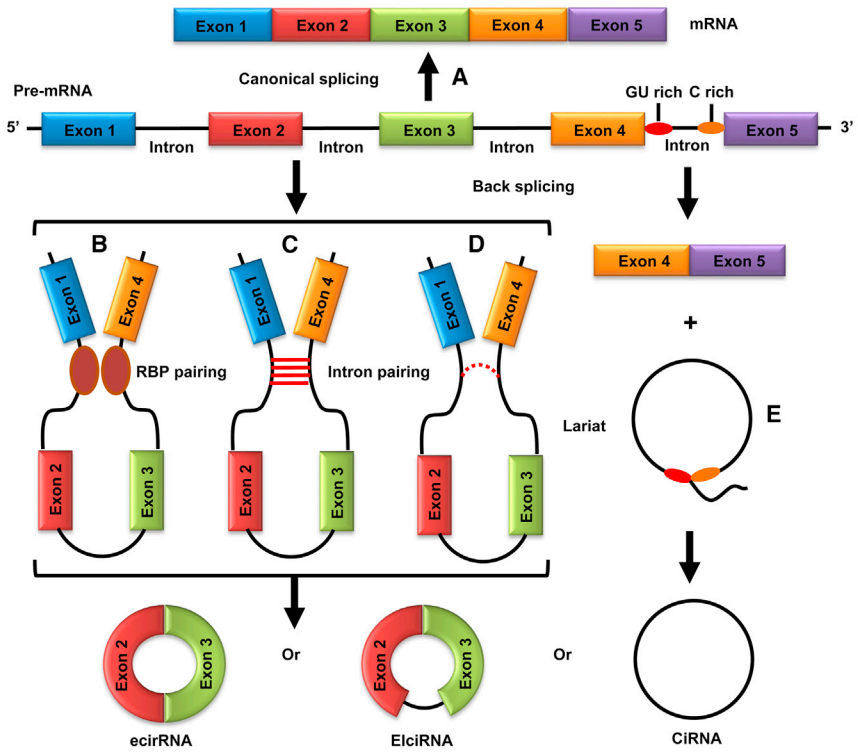

Figure 1. Biogenesis of circRNAs

(A) Canonical splicing mediated by the spliceosome generates liner mRNA. (B) In RBP-driven circularization, RBPs regulate the formation of ecirRNA or ElciRNA by binding to a specific sequence of introns. (C) In intron-pair-driven circularization, the generation of ecirRNA or EIciRNA is modulated via complementary base pairs in introns. (D) In lariat-driven circularization, the binding between the splicing donor and the splicing acceptor leads to the formation of a lariat; then, the intron sequence is removed or retained to generate ecirRNA or ElciRNA. (E) In the formation of ciRNA, the intron lariat is formed depending on consensus motifs near both ends, and then the exons and introns in the lariat are removed by the spliceosome.

OVERVIEW OF circRNAs

Biological characteristics of circRNAs

As a novel type of ncRNAs, a large number of circRNAs have been identified in different eukaryotic cells. circRNAs share several noteworthy biological features, including the following: (1) A diverse range of circRNAs have been widely detected in a series of species, including yeasts, plants, fungi, mouse, rat, monkey, fruit fly, human, and many other organisms.[14] Moreover, circRNAs could be generated from a total of 5.8%–23% of actively transcribed human genes.[15] It has been reported that approximately 20% of the genes in the human brain generate circRNAs, whereas in the heart, approximately 9% of the expressed genes produce circRNAs.[16] (2) Due to their unique covalently closed-loop structure, circRNAs are more stable and have longer half-lives in tissues and plasma than linear RNAs, which are easily degraded by RNase R.[17] This feature contributes to the accumulation of circRNAs in cells and their extensive biological functions. (3) circRNAs are generally expressed at a low level compared with their corresponding linear mRNAs.[18] However, some studies have reported that the expression of a circRNA does not correlate with the expression of its cognate linear mRNA; in fact, under certain circumstances, circRNAs are expressed at a much higher level than their linear counterparts, even by several-fold.[18,19] (4) The majority of circRNAs appear to be highly conserved regardless of the evolutionary distance between species,[20] which may result from the conservation of back-splicing junctions in circRNAs. For instance, approximately 5%–10% of circRNAs are orthologous between the human brain and the porcine brain.[17] (5) Different genomic origins of circRNAs exhibit diverse distributions in the compartments of eukaryotes. circRNAs generated from exons are mainly localized in the cytoplasm, while circRNAs generated from introns are localized in the nucleus.[21] (6) circRNAs are often expressed in cell-, tissue-, and developmental-stage-specific patterns in different species.[22] For instance, circRNAs appear to have a higher expression level in low-proliferating cells, such as cardiomyocytes, compared with the high-proliferating cells of the liver.[23] Increased levels of circRNAs have been observed in developing organs, such as heart, lung, and brain tissues.[24] This feature indicates their crucial roles in the regulation of different biological processes.

Biogenesis of circRNAs

circRNAs are mainly produced from precursor mRNAs (pre-mRNAs) via a back-splicing process that ligates an upstream 3′ splice site with a downstream 5′ splice site to form a single-strand, covalently closed-loop structure.[15] According to their genomic origin, circRNAs are generally divided into three classes: exonic circRNAs (ecirRNAs), intronic circRNAs (ciRNAs), and exon-intron circRNAs (EIciRNAs).[25] Among them, ecirRNAs are the most abundant, accounting for nearly 85% of all identified circRNAs. ecirRNAs are mainly located in the cytoplasm after biogenesis, whereas the majority of ciRNAs and EIciRNAs are located in the nucleus.[3]

Canonical splice signals and canonical spliceosomal machinery are reported to be necessary components of back-splicing circularization;[26] however, the detailed mechanisms involved in spliceosome action in the back-splicing process are still not fully clarified. Currently, three hypothetical models of circRNA formation are proposed to explain the back-splicing process: lariat-driven circularization, intron-pair-driven circularization, and RNA-binding protein (RBP)-driven circularization (Figure 1). These models can be further summarized into two mechanisms according to the order in which the direct back-splicing or exon skipping occurs. In the model of lariat-driven circularization, exon skipping occurs first, and the

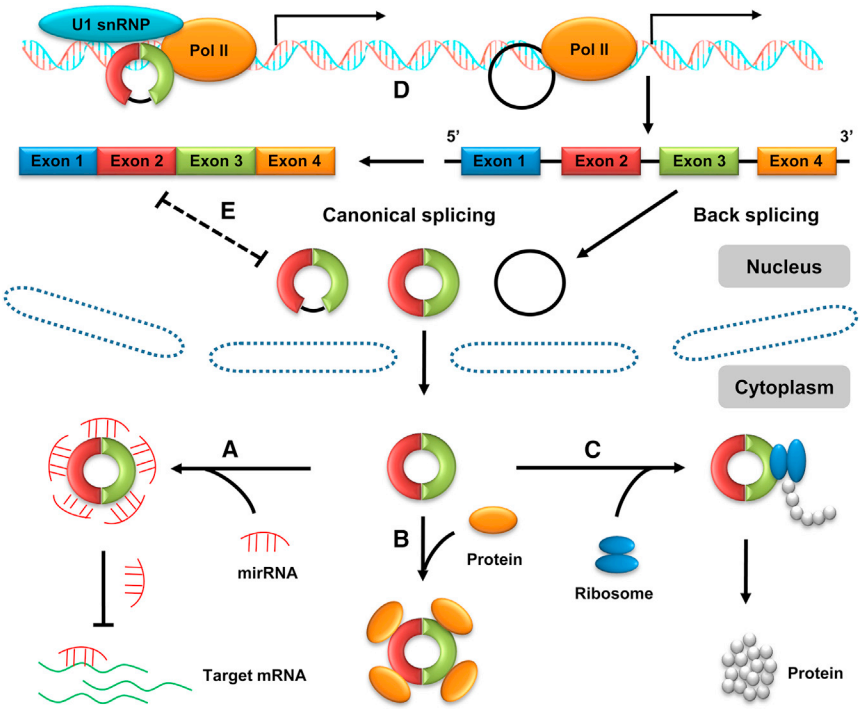

Figure 2. Molecular functions of circRNAs

(A) circRNAs can serve as miRNA sponges to regulate the expression of target genes by binding to miRNAs. (B) circRNAs can act as protein sponges, decoys, or scaffolds to regulate the cellular functions of proteins by directly binding to them, thereby affecting the related processes. (C) circRNAs can be translated into proteins in a cap-independent manner. (D) circRNAs can positively regulate the transcription of genes by interacting with the RNA Pol II complex or transcription-related factors. (E) circRNAs compete with linear RNAs to maintain the transcript's dynamic balance.

downstream splicing donor of an exon covalently binds to the upstream splice acceptor of another non-adjacent exon to form a lariat intermediate by exon skipping. Subsequently, the intron sequence in the lariat intermediate is removed through spliceosome-mediated splicing, thus forming ecirRNAs.[27] In some certain cases, the intron between the exons may not be spliced out completely but preserved, leading to the formation of EIciRNAs.[28] In models of intron-pair-driven circularization and RBP-driven circularization, back-splicing occurs first, and the two flanking introns generate a circular structure by direct base-pairing. This process is promoted by repeated Alu complementary elements or RBPs. Subsequently, all or part of the introns between the exons are excised to generate ecirRNA or EIciRNA.[18,29] The biogenesis of ciRNAs occurs in a lariat-derived manner. Different from ecirRNAs and EIciRNAs, the formation of ciRNAs mainly depends on conserved motifs containing a 7-nt GU-rich element near the 5′ splice site and an 11-nt C-rich element near the branchpoint site. In the process of back-splicing, the two elements combine to form a lariat structure, and then the exons and introns in the lariat structure are removed by the spliceosome, leading to the formation of stable ciRNAs.[29]

The biogenesis of circRNAs is widely regulated by general *cis*-regulatory elements (non-coding binding regions capable of regulating transcription) and *trans*-acting factors.[21] For instance, a reverse complementary sequence or inverted tandem repeating in flanking introns, such as Alu elements, is reported to facilitate intron pairing and the formation of exon-retaining circRNA.[30] Moreover, RNA pairing across flanking introns or within individual introns can also modulate the efficiency of circRNA biogenesis.[31] In addition, RBPs, such as muscleblind (MBL), quaking (QKI), adenosine deaminase acting on RNA (ADAR), and heterogeneous nuclear ribonucleoprotein L (HNRNPL), can act as *trans*-acting factors to play crucial roles in the regulation of circRNA biogenesis. They may serve as switches to promote or inhibit circRNA formation. For instance, MBL has been shown to bind to conserved MBL binding sites in the second exon of its own pre-mRNA and promote the generation of circMBL. Consistent with this, the mutation of MBL binding sites in MBL pre-mRNA leads to the significant downregulation of circMBL production.[31] The QKI protein links two introns together by binding to specific sequences within the flanking introns of the pre-mRNA and then promotes the biogenesis of circRNAs. Further study showed that both the silencing of QKI and the insertion of QKI-binding sites into the introns significantly affected circRNA production.[32] ADAR is a kind of negative RBP that can antagonize circRNA generation by adenosine-to-inosine (A-to-I) RNA editing. The knockdown of ADAR has been shown to upregulate the expression of intracellular circRNAs.[33] HNRNPL is a newly identified RBP that directly modulates the alternative splicing of a set of RNAs. It has been reported that HNRNPL can either positively or negatively regulate circRNA formation by binding at the flanking introns or within the circRNAs.[34]

Collectively, the biogenesis of circRNAs and the regulation mechanisms involved in this process remain inconclusive. Further studies are required to understand these processes in depth.

Functions of circRNAs

With continuous in-depth studies on circRNAs, their biological functions have been gradually revealed in recent years (Figure 2). An increasing amount of evidence demonstrates that circRNAs are involved in the regulation of a series of pathophysiology processes.

circRNAs act as miRNA sponges

MicroRNAs (miRNAs) belong to the ncRNA family and are 20–25 nt in length.[35] They are crucial regulators of gene expression, binding to specific miRNA-response elements (MREs) of target mRNAs to block

their translation or facilitate their degradation.[36,37] It has been reported that a large number of circRNAs contain MREs and can act as intracellular competitive endogenous RNAs (ceRNAs) or miRNA sponges to weaken the effects of miRNAs on downstream target mRNAs, thereby regulating the expression of correlated genes.[38]

CiRS-7, also known as CDR1as, was the first identified circRNA with a powerful miRNA sponge function. It contains more than 70 conserved miR-7 binding sites and functions as a super-sponge to inhibit the biological activity and functions of miR-7.[39,40] In recent years, the existence and importance of ciRS-7 serving as a miR-7 sponge have been demonstrated in the regulation progression of several types of cancer, including esophageal squamous cell carcinoma, NSCLC, gastric cancer, pancreatic cancer, colorectal cancer, papillary thyroid cancer, hepatocellular carcinoma, laryngeal squamous cell carcinoma, and ovarian cancer.[41–50] Moreover, ciRS-7 also harbors a number of complementary miR-671 binding sites. By binding to miR-671, ciRS-7 induces its own degradation to release miR-7.[51] Mouse testicular-specific circRNA Sry is another typical case that can also serve as an RNA sponge. circRNA Sry contains 16 conserved miR-138 binding sites. It has been reported that the overexpression of circRNA Sry inhibits the activity of miR-138, leading to the upregulation of the miR-138 target gene miR-769.[39] In addition, our previous study showed that circ-ZKSCAN1 (hsa_circ_0001727) significantly upregulated the expression of FAM83A by sponging miR-330-5p, leading to the suppression of the mitogen-activated protein kinase (MAPK) signaling pathway.[52]

In recent years, an increasing number of circRNAs have been confirmed to act as miRNA sponges.[53] Some circRNAs also include multiple types of MREs, indicating that they can simultaneously modulate the expression of multiple target genes by targeting different miRNAs.[54] However, not all circRNAs possess this function because some certain circRNAs contain few or even no binding sites for a single miRNA.

circRNAs interact with proteins

Serving as protein sponges, decoys, or scaffolds is another crucial role of circRNAs. They can regulate the cellular functions of proteins by physically interacting with them, thereby being involved in pathological and physiological processes. For instance, Tsitsipatis et al. showed that the overexpression of circPCNX inhibits the proliferation of human cervical carcinoma HeLa cells. Mechanistically, circPCNX serves as a protein sponge to prevent the binding of AUF1 to p21 mRNA by physically interacting with AUF, thereby promoting p21 mRNA stability and upregulating p21 expression, a major inhibitor of cell proliferation.[55] Zhu et al. revealed that circZKSCAN1 competitively interacts with FMRP to block the binding of FMRP to β-catenin-binding protein-cell cycle and apoptosis regulator 1 (CCAR1) mRNA, leading to the inhibition of the Wnt signaling pathway in hepatocellular carcinoma.[56] Moreover, circ-Amotl1 can serve as a decoy to enhance c-Myc stability and its retention in the nucleus by directly interacting with c-Myc, leading to increased cell proliferation and decreased apoptosis in breast cancer.[57] In addition, some circRNAs have been shown to function as scaffolds to promote the contact between two or more proteins. For instance, circNDUFB2 acts as a scaffold to interact with E3 ubiquitin-protein ligase (TRIM25) and insulin-like growth factor 2 mRNA-binding proteins (IGF2BPs) to promote the ubiquitin-dependent degradation of IGF2BPs, resulting in the inhibition of IGF2BP-mediated proliferation and metastasis of NSCLC cells.[58] The interactions between circRNAs and proteins expand the regulatory functions of circRNAs, but the mechanisms are still inconclusive and require further study.

Translation of circRNAs into proteins

In eukaryotes, the canonical translation initiation is a complex process in which the open preinitiation complex (PIC) first binds to mRNA and then scans along it to locate the start codon. During this process, the 5′ terminal cap structure of the mRNA mediates the interaction of PIC with mRNA.[59] Therefore, circRNAs were initially considered to be untranslatable due to a lack of a 5′ cap. However, with the deepening of the study, some circRNAs have been reported to contain the initiation codon AUG and putative open reading frames (ORFs),[12] indicating that they possess great potential to translate into proteins or functional peptides.

In 1995, Chen et al. first reported that eukaryotic ribosomes could initiate translation on engineered circRNAs inserting internal ribosome entry site (IRES) elements in an *in vitro* study.[60] However, it was not until 2017 that Legnini et al. provided the first proof that endogenous circRNAs can, in fact, encode proteins in humans. They identified a functional circRNA, circ-ZNF609, which contains an IRES and can bind to the ribosome, thus being translated into a protein in a splicing-dependent but cap-independent manner.[61] In addition to IRESs, N6-methyladenosine (m^6A) modification can also drive the translation of circRNAs in a cap-independent manner. Yang et al. showed that m^6A modification initiates the translation of circRNAs by recruiting the m^6A recognition protein YTHDF3 and the translation initiation factor eIF4G2. This process can be promoted by the methyltransferase METTL3/14 and suppressed by the demethylase fat mass and obesity-associated gene (FTO).[62] These studies strongly support the coding potential of circRNAs. However, there are only a few endogenous circRNAs that have been confirmed to possess this ability, which may be due to the low translation initiation efficiency of cap-independent translation. In addition, the functions of circRNA-encoded proteins are still unclear. Collectively, further studies are needed to identify a series of uncharacterized proteins and elucidate the mechanisms in which they are involved.

Regulation of circRNAs on gene expression

circRNAs have been shown to regulate gene expression in multiple ways, such as transcription, post-transcription, and alternative splicing. Different from ecirRNAs, the majority of EIciRNAs and ciRNAs are localized in the nucleus and tend to function at the transcriptional or post-transcriptional level. For instance, Li et al. showed that EIciRNA (e.g., circEIF3J or circPAIP2) combines with U1 small nuclear ribonucleoproteins (U1 snRNPs) via an RNA-RNA interaction to form an EIciRNA-U1 snRNP compound, which further interacts with the polymerase II (Pol II) complex to facilitate the transcription

Table 1. Databases for circRNAs

Database	Resource available	Website	Reference
circBase	the merged and unified datasets of circRNAs from multiple species, including *H. sapiens*, *C. elegans*, *D. melanogaster*, *M. musculus*, and *L. chalumnae*	http://circrna.org/	Glazar et al.[65]
Circ2Traits	prediction of potential interaction networks among miRNA, circRNA, mRNA, and lncRNA	http://gyanxetbeta.com/circdb/	Ghosal et al.[66]
circNet	prediction of novel circRNAs, integrated miRNA-target networks, and tissue-specific circRNA expression profiles	http://circnet.mbc.nctu.edu.tw/	Liu et al.[67]
deepBase v.3.0	expression features of circRNAs in cancer and normal tissues, survival analysis of circRNAs in cancer patients, and evolutional conservation analysis of circRNAs across species	http://rna.sysu.edu.cn/deepbase3/	Xie et al.[68]
CircInteractome	prediction and mapping of binding sites for RBPs and miRNAs on known circRNAs	http://circinteractome.nia.nih.gov/	Dudekula et al.[69]
CSCD	prediction of potential interactions of miRNAs and RBPs with circRNA in various types of cancer, comparison of the expression levels of circRNA-associated RBPs and microRNAs among different cancers, and prediction of potential ORFs in circRNAs	http://gb.whu.edu.cn/CSCD	Xia et al.[70]
CIRCpedia v.2	expression features of circRNAs in various cell types and tissues, including disease samples; conservation analysis of circRNAs between humans and mice; and comparison of circRNA expression between samples	http://www.picb.ac.cn/rnomics/circpedia	Dong et al.[71]
circRNADb	annotation of circRNAs with protein-encoding ability	http://reprod.njmu.edu.cn/circrnadb	Chen et al.[72]
circlncRNAnet	functional analysis of circRNAs and lncRNAs from users	http://app.cgu.edu.tw/circlnc/	Wu et al.[73]
circRNA disease	annotation of published disease-associated circRNAs, including basic information of circRNAs and disease and functional description of circRNAs	http://cgga.org.cn:9091/circRNADisease/	Zhao et al.[74]
StarBase v.2.0	pan-cancer analysis of RNA-RNA and RBP-RNA interactions; survival and differential expression analysis of circRNAs, miRNAs, lncRNAs, pseudogenes, and mRNAs	http://starbase.sysu.edu.cn/	Li et al.[75]
CIRCexplore2	identification and characterization of circRNAs	https://github.com/YangLab/CIRCexplorer2	Zhang et al.[76]
ExoRBase	annotation, expression level, and possible original tissue analysis of circRNAs in human blood exosomes	http://www.exoRBase.org	Li et al.[77]
TRCirc	regulatory information of transcription factors on circRNAs and correlation information, such as methylation level, H3K27ac signals, super-enhancers, and expression of circRNAs	http://www.licpathway.net/TRCirc	Tang et al.[78]

of an EIciRNA parental gene.[63] Similarly, ciRNAs such as ci-ankrd52 and ci-sirt7 can also facilitate the transcription of their parental genes by interacting with the RNA Pol II complex. Consistent with this, the silencing of ciRNAs derived from the introns of ANKRD52 and SIRT7 results in the downregulation of their parent genes.[64] circRNAs are also involved in the regulation of gene expression by influencing alternative splicing. It has been reported that back-splicing can compete with canonical splicing to regulate alternative splicing in the pre-mRNA splicing process.[31] For instance, circMBL, generated from the second exon of MBL pre-mRNA, competes with the canonical splicing of MBL pre-mRNA, thus decreasing the formation of linear RNA.[31] These studies suggest that the regulation of gene expression may be a common mechanism for circRNAs.

Online databases of circRNAs

To facilitate the development of circRNA investigation, many online databases have been established (Table 1). These databases provide predictions of biological roles or regulatory networks of circRNAs

Table 2. Dysregulated circRNAs in NSCLC

CircRNA	Expression	Sponge target	Types of NSCLC tissues and cell lines	Function	Reference
circPTPRA	down	miR-96-5p	114 NSCLC tissue samples with various clinicopathologic features; H23, H1755, and H522 NSCLC cell lines	downregulation of circPTPRA is associated with metastasis and inferior survival outcomes of NSCLC patients; overexpression of circPTPRA inhibits NSCLC cell EMT and metastasis by sponging miR-96-5p to upregulate RASSF8 expression	Wei et al.[79]
circRNA_101237	up	miR-490-3p	303 NSCLC tissue samples with various clinicopathological features; A549 and H1299 NSCLC cell lines	upregulation of circRNA_101237 predicts poor survival in NSCLC; circRNA_101237 overexpression promotes cancer cell proliferation, migration, and invasion by sponging miR-490-3p to upregulate MAPK1 expression	Zhang et al.[80]
circPTK2	down	miR-429, miR-200b-3p, miR-429, miR-200b-3p	73 NSCLC tissue samples; A549, H1299, H1650, SPC-A1, Calu3, H226, H520, and SK-MES-1 NSCLC cell lines	circPTK2 inhibits TGF-β-induced EMT and metastasis in NSCLC by sponging miR-429/miR-200b-3p and miR-429/miR-200b-3p to increase TIF1γ expression	Wang et al.[81]
circFGFR1	up	miR-381-3p	210 NSCLC tissue samples with various clinicopathologic features; H358, H1299, A549, HCC827, H1650, H838, and H292 NSCLC cell lines	downregulation of circFGFR1 is associated with poor prognosis of NSCLC patients; overexpression of circFGFR1 promotes NSCLC cell migration, invasion, proliferation, and immune evasion by sponging miR-381-3p to upregulate CXCR4 expression	Zhang et al.[82]
circ_ZFR	up	miR-195-5p	64 NSCLC tissue samples; A549 and H460 NSCLC cell lines	silencing circ_ZFR inhibits PTX resistance, cell-cycle process, proliferation, migration, and invasion and promotes apoptosis in PTX-resistant NSCLC cells by sponging miR-195-5p to upregulate KPNA4 expression	Li et al.[83]
circGFRA1	up	miR-188-3p	30 NSCLC tissue samples; A549 and H803 NSCLC cell lines	upregulation of circGFRA1 promotes cancer cell proliferation by sponging miR-188-3p to activate the PI3K/AKT signaling pathway	Yao et al.[84]
hsa_circ_0014130	up	miR-136-5p	30 NSCLC tissue samples; A549 and PC-9 NSCLC cell lines	downregulation of hsa_circ_0014130 suppresses NSCLC progression by sponging miR-136-5p to increase Bcl-2 expression	Geng et al.[85]
hsa_circ_0062389	up	miR-103a-3p	33 NSCLC tissue samples with various clinicopathologic features; H1650, H23, H522, A549, H1703, and H460 NSCLC cell lines	high expression of hsa_circ_0062389 is associated with advanced TNM stage and lymph node metastasis in NSCLC patients; downregulation of hsa_circ_0062389 inhibits NSCLC cell proliferation and arrests cell cycle in G0/G1 phase by sponging miR-103a-3p to upregulate CCNE1 expression	She et al.[86]
hsa_circ_0018818	Up	miR-767-3p	30 NSCLC tissue samples with various clinicopathologic features; A549, PC-9, NCI-H441, and NCI-H1650 NSCLC cell lines	silencing hsa_circ_0018818 inhibits the proliferation and invasion of NSCLC cells and promotes apoptosis by sponging miR-767-3p to increase NID1expression; hsa_circ_0018818 knockdown also inhibits the EMT process and PI3K/Akt signaling pathway	Xu et al.[87]

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Table 2. *Continued*

CircRNA	Expression	Sponge target	Types of NSCLC tissues and cell lines	Function	Reference
circ_100565	Up	miR-506-3p	50 NSCLC tissue samples; Calu-3, Calu-6, A549, and H1299 NSCLC cell lines	high expression of circ_100565 is associated with poor overall survival in NSCLC patients; downregulation of hsa_circ_0062389 inhibits the proliferation, migration, and invasion of NSCLC cells *in vitro* and reduces the tumor growth of NSCLC by sponging miR-506-3p to upregulate HMGA2 expression	Li et al.[88]
circMET	Up	miR-145-5p	94 NSCLC tissue samples with various clinicopathologic features; A549, 95C, 95D, HBE, NCI-H1299, and NCI-H460 NSCLC cell lines	independent diagnostic and prognostic factor; overexpression of circMET promotes NSCLC cell proliferation, metastasis, and immune evasion by sponging miR-145-5p to upregulate CXCL3 expression	Pei et al.[89]
circMAGI3	Up	miR-515-5p	30 NSCLC tissue samples with various clinicopathologic features; H322, H460, A549, and H1299 NSCLC cell lines	high expression of circMAGI3 is associated with poor prognosis in NSCLC patients; circMAGI3 promotes the glycolysis and proliferation of NSCLC cells by sponging miR-515-5p to upregulate HDGF expression	Guo et al.[90]
circ_0072088	Up	miR-377-5p	45 NSCLC tissue samples; A549 and H1299 NSCLC cell lines	circ_0072088 inhibits proliferation and motility of NSCLC cells by sponging miR-377-5p to upregulate NOVA2 expression	Tan et al.[91]
circ_0007385	Up	miR-519d-3p	75 NSCLC tissue samples; A549, HCC827, H1975, and H2342 NSCLC cell lines	high expression of circ_0007385 is associated with poor prognosis in NSCLC patients; downregulation of circ_0007385 inhibits the proliferation, migration, invasion, and DDP resistance of NSCLC cells by sponging miR-519d-3p to upregulate HMGB1 expression	Ye et al.[92]
circRNA CDR1as	Up	miR-641	A549, H1299, and Calu6 NSCLC cell lines	silencing of circRNA CDR1as suppresses the stemness of DDP-resistant NSCLC cells by sponging miR-641 to downregulate HOXA9 expression	Zhao et al.[93]
circTUBA1C	Up	miR-143-3p	30 NSCLC tissue samples; A549 and Calu-3 NSCLC cell lines	knockdown of circTUBA1C inhibits cell proliferation and induces cell apoptosis in NSCLC by sponging miR-143-3p	Yang et al.[94]
circHIPK3	Up	miR-107	H1299, A549, and BEAS-2B NSCLC cell lines	circHIPK3 promotes the migration and proliferation of NSCLC cells by sponging miR-107 to upregulate BDNF expression	Hong et al.[95]
circ_0074027	up	miR-335-5p	60 NSCLC tissue samples; H358, H1299, H1581, and A549 NSCLC cell lines	circ_0074027 promotes cell viability, cell-cycle process, and colony formation and inhibits apoptosis in NSCLC cells by sponging miR-335-5p to increase GUL4B expression	Yu et al.[96]
circSEC31A	up	miR-376a	44 NSCLC tissue samples; A549 and H1299 NSCLC cell lines	circSEC31A promotes NSCLC cell migration, invasion, and glycolysis and inhibits apoptosis by sponging miR-376a to increase SEC31A expression	Cheng et al.[97]
hsa_circ_0046263	up	miR-940	45 NSCLC tissue samples; A549 and H1299 NSCLC cell lines	hsa_circ_0046263 knockdown promotes NSCLC cell proliferation, cell cycle, and metastasis and induces apoptosis by sponging miR-940 to upregulate NOVA2 expression	Li et al.[98]

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Table 2. *Continued*

CircRNA	Expression	Sponge target	Types of NSCLC tissues and cell lines	Function	Reference
circ-ABCB10	up	miR-584-5p	40 NSCLC tissue samples with various clinicopathologic features; SPC-A1, H1975, HCC827, H1650, PC9, and A549 NSCLC cell lines	high expression of circ-ABCB10 is associated with poor prognosis in NSCLC patients; upregulation of circ-ABCB10 promotes the migration, cell proliferation, and invasion of NSCLC cells by sponging miR-584-5p to upregulate E2F5 expression	Ma et al.[99]
hsa_circ_0102231	up	miR-145	A549, NCI-H358, NCI-H1650, HCC827, and NCI-H1299 NSCLC cell lines	hsa_circ_0102231 facilitates the proliferation and invasion of NSCLC cells by sponging miR-145 to increase RBBP4 expression	Cao et al.[100]
circ-FOXM1	up	miR-149-5p	72 NSCLC tissue samples; A549 and H1581 NSCLC cell lines	circ-FOXM1 promotes NSCLC cell viability, migration, and autophagy and inhibits cell apoptosis by sponging miR-149-5p to increase ATG5 expression	Wei et al.[101]
circ_0020123	up	miR-384	33 NSCLC tissue samples; A549 and H1581 NSCLC cell lines	circ_0020123 promotes the viability, migration, invasion, and EMT and inhibits apoptosis of NSCLC cells by sponging miR-384 to upregulate TRIM44 expression	Ma et al.[102]
circNDUFB2	down	–	55 NSCLC tissue samples with various clinicopathologic features; A549, H1299, HCC827, H1975, H1703, H460, and H1650 NSCLC cell lines	overexpression of circNDUFB2 suppresses the growth and metastasis of NSCLC cells by acting as a scaffold to enhance the interaction between TRIM25 and IGF2BPs	Li et al.[58]
circSATB2	up	miR-326	59 NSCLC tissue samples; A549, H460, H1299, H226, and MES-1 NSCLC cell lines	circSATB2 facilitates the proliferation, migration, and invasion of NSCLC cells, as well as inducing abnormal proliferation of normal human bronchial epithelial cells by sponging miR-326 to increase actin-bundling protein 1 expression	Zhang et al.[11]
circ-CPA4	up	let-7 miRNA	50 NSCLC tissue samples with various clinicopathologic features; A549, H1299, SK-MES-1, and Calu-3 NSCLC cell lines	circ-CPA4 promotes cell growth, mobility, EMT, and cell death in NSCLC cells by sponging let-7 miRNA to upregulate PD-L1 expression	Hong et al.[103]

circRNA, circular RNA; NSCLC, non-small cell lung cancer; EMT, epithelial-to-mesenchymal transition; DDP, cisplatin; RASSF8, Ras-association domain family 8; MAPK1, mitogen-activated protein kinase 1; TIF1γ, transcriptional intermediary factor 1γ; CXCR4, chemokine receptor 4; PTX, pentraxin; KPNA4, karyopherin subunit α4; CCNE1, cyclin E1; PI3K, phosphatidylinositol 3-kinase; HMGA2, high-mobility group AT-hook 2; CXCL3, chemokine (C-X-C motif) ligand 3; HDGF, hepatoma-derived growth factor; NOVA2, NOVA alternative splicing regulator 2; HMGB1, high-mobility group box 1; HOXA9, homeobox protein Hox-A9; BDNF, brain-derived neurotrophic factor; GUL4B, cullin 4B; SEC31A, SEC31 homolog A; RBBP4, retinoblastoma-binding protein 4; ATG5, autophagy-related 5; TRIM44, tripartite motif-containing protein 44; IGF2BPs, insulin-like growth factor 2 mRNA-binding proteins; PD-L1, programmed cell death ligand 1.

in human diseases, including cancer, which is of great benefit to circRNA identification, localization, characterization, and functional analysis, as well as tools for analyzing the association of circRNAs with their targets. However, there are still some limits, such as a little overlap in predictions and a clear lack of standardized nomenclature. Therefore, these databases still require to continual improvement. Also, the naming rules of circRNAs need to be unified.

circRNAs and NSCLC

circRNAs play crucial roles in the regulation of NSCLC development and progression by targeting cancer-related signaling pathways and/or regulating the expression of genes involved in the pathological progression of NSCLC, including cell proliferation, apoptosis, metastasis, and stemness, as well as resistance to therapy.[3] In addition, some circRNAs have been shown to be differentially expressed between NSCLC tissues and corresponding normal tissues, indicating their great potential as promising biomarkers for the early diagnosis and prognosis of NSCLC. Here, we summarize some dysregulated circRNAs that have been found to be associated with NSCLC (Table 2).

Expression profiles of circRNAs in NSCLC

With the development of detection techniques and bioinformatics, an increasing number of circRNAs have been identified in NSCLC. Many of them have aberrant expression levels and are closely associated with NSCLC progression. Zhang et al. conducted a circRNA microarray analysis and distinguished 171 differentially expressed circRNAs, among which 148 were upregulated and 23 were downregulated in NSCLC tissues compared with normal tissues.[104] Zhao et al. revealed

Table 3. circRNAs and their target signaling pathways in NSCLC

Signaling pathway	circRNA	Expression	Key message(s)	Reference
Wnt/β-catenin	hsa_circ_000984	up	high hsa_circ_000984 expression predicts poor prognosis in NSCLC patients, indicating its potential as diagnostic biomarker for NSCLC; knockdown of hsa_circ_000984 results in the inhibition of the Wnt/β-catenin signaling pathway by downregulating β-catenin, cyclin D1, and c-Myc expression in NSCLC cells	Li et al.[109]
	circ_0067934	up	silencing of circ_0067934 inactivates the Wnt/β-catenin signaling pathway by decreasing the expression of β-catenin, cyclin D1, and c-Myc in NSCLC cells; overexpression of circ_0067934 has the opposite effect on the Wnt/β-catenin signaling pathway	Zhao et al.[110]
	circ-ZNF124	up	knockdown of circ-ZNF124 downregulates the expression of β-catenin and c-Myc by targeting the miR-498/YES axis, leading to the inactivation of the Wnt/β-catenin signaling pathway; these findings suggest the potential of circ-ZNF124 as a therapeutic target for NSCLC	Gao et al.[111]
	circ_001569	up	high expression of circ_001569 predicts poor prognosis in NSCLC patients, suggesting its potential as a diagnostic biomarker for NSCLC; silencing of circ_001569 inhibits the Wnt/β-catenin pathway by reducing the expression of WNT1, β-catenin, and TCF4 in NSCLC cells	Ding et al.[112]
	hsa_circ_0043256	up	hsa_circ_0043256 inhibits the Wnt/β-catenin pathway by sponging miR-1252 to upregulate the expression of ITCH (Wnt/β-catenin pathway inhibitor protein), indicating that hsa_circ_0043256 might be a potential therapeutic target for NSCLC	Tian et al.[113]
PI3K/AKT	circPRKCA	up	high expression of circPRKCA is associated with TNM stage and lymph node metastasis in NSCLC patients; knockdown of circPRKCA upregulates the expression of PDK1 by sponging miR-330-5p, leading to the inactivation of the PI3K/AKT signaling pathway	Bai et al.[114]
	circGFRA1	up	overexpression of circGFRA1 significantly upregulates the expression of p-AKT in NSCLC cells, whereas LY294002 treatment blocks the increased expression of p-AKT caused by circGFRA1 overexpression	Yao et al.[84]
	circRNA_100876	up	silencing of circRNA_100876 inhibits the proliferation, migration, and invasion of NSCLC cells by sponging mir-636, leading to inhibition of the PI3K/Akt signaling pathway	Song et al.[115]
	hsa_circ_0018818	up	hsa_circ_0018818 promotes the proliferation and invasion of NSCLC cells and induces their apoptosis by targeting miR-767-3p to upregulate NID1 expression, leading to activation of the PI3K/Akt signaling pathway	Xu et al.[87]
	circFGFR3	up	circFGFR3 promotes the invasion and proliferation of NSCLC cells by sponging miR-22-3p to upregulate the expression of Gal-1, p-AKT, and p-ERK1/2	Qiu et al.[116]
	circ-ACACA	up	circ-ACACA promotes the proliferation and migration of NSCLC cells and decreases the glycolysis rate by targeting miR-1183 to activate the PI3K/Akt signaling pathway	Wu et al.[117]

(*Continued on next page*)

Table 3. *Continued*

Signaling pathway	circRNA	Expression	Key message(s)	Reference
MAPK	circ0001313	up	overexpression of circ0001313 promotes NSCLC cell proliferation and invasion by sponging miR-452 to upregulate the expression of HMGB3, leading to activation of the MAPK signaling pathway	Zhang et al.[118]
	circ-ZKSCAN1	up	high expression of circ-ZKSCAN1 predicts poor prognosis in NSCLC patients, suggesting its potential as a diagnostic biomarker for NSCLC; overexpression of circ-ZKSCAN1 inactivates the MAPK signaling pathway by sponging miR-330-5p to upregulate the expression of FAM83A, leading to the inhibition of NSCLC cell proliferation	Wang et al.[52]
	hsa_circ_0004050	down	high expression of hsa_circ_0004050 predicts good prognosis in NSCLC patients; hsa_circ_0004050 promotes apoptosis and inhibits proliferation of NSCLC cells by targeting miR-1233-3p to upregulate the expression of DUSP9, leading to the inhibition of the ERK/JNK signaling pathway	Wang et al.[119]
	circFGFR3	up	circFGFR3 facilities NSCLC cell invasion and proliferation by sponging miR-22-3p to upregulate the expression of Gal-1, p-AKT, and p-ERK1/2	Qiu et al.[116]
NER	hsa_circ_0001946	up	silencing of hsa_circ_0001946 promotes the viability, proliferation, migration, and invasion of NSCLC cells and induces apoptosis by upregulating the expression of XPA, XPC, Rad23B, RPA14, RPA32, RPA70, and ERCC1, leading to the activation of the NER signaling pathway	Huang et al.[120]
E2F2	circPVT1	up	circPVT1 promotes NSCLC cell proliferation, migration, and invasion and induces apoptosis by sponging miR-125b to upregulate the expression of E2F2	Li et al.[121]

circRNA, circular RNA; NSCLC, non-small cell lung cancer; PI3K, phosphatidylinositol 3-kinase; PDK1, phosphoinositide-dependent kinase 1; MAPK, mitogen-activated protein kinase; ERK, extracellular signal-regulated kinase; NER, nucleotide excision repair; XPC, xeroderma pigmentosum group C; RPA, replication protein A; ERCC1, excision repair cross-complementing 1; E2F2, E2F transcription factor 2; PVT1, plasmacytoma variant translocation 1; NID1, nidogen 1; Gal-1, galectin-1.

356 differentially expressed circRNAs between four paired NSCLC tissues and adjacent normal tissues, including 204 upregulated circRNAs and 152 downregulated circRNAs. Most of them were ecirRNAs.[105] In another study, by comparing NSCLC tumors with adjacent normal tissues, Wang et al. confirmed 50 differentially expressed circRNAs in LUAD tissues, 172 differentially expressed circRNAs in LUSC tissues, and 26 differentially expressed circRNAs in both LUAD and LUSC tissues.[106] Furthermore, Liu et al. identified 1,377 differentially expressed circRNAs via a microarray screening analysis, among which 989 were upregulated and 98 were downregulated in the plasma samples of gefitinib-effective NSCLC patients compared with gefitinib-ineffective NSCLC patients.[107] Li et al. reported 121 differentially expressed circRNAs using public NSCLC datasets obtained from the Gene Expression Omnibus (GEO) database, among which 43 were upregulated and 78 were downregulated in NSCLC tissues.[108]

circRNAs target signaling pathways in NSCLC

An increasing number of studies have shown that circRNAs are involved in NSCLC progression by targeting cancer-related signaling pathways, such as the Wnt/β-catenin, PI3K/AKT, and MAPK signaling pathways (Table 3). This may provide us with new insights into NSCLC progression in order to understand the exact effect and molecular mechanism of circRNAs in signaling pathway regulation. The Wnt/β-catenin signaling pathway is closely correlated with fundamental cellular functions, such as cell proliferation, apoptosis, and metastasis. The aberrant activation of the Wnt/β-catenin signaling pathway has been widely observed in a series of cancers, including NSCLC.[122,123] Some circRNAs have been reported to contribute to NSCLC progression by modulating the expression of key components in the Wnt/β-catenin signaling pathway. For instance, Li et al. found that the knockdown of circRNA hsa_circ_000984 in human NSCLC cell lines A549 and H1299 significantly decreases the expression of β-catenin, cyclin D1, and c-Myc at both the mRNA and the protein level, indicating that hsa_circ_000984 affects NSCLC progression by enhancing the Wnt/β-catenin signaling pathway.[109] Another study showed that silencing circ_001569 significantly downregulates the expression of Wnt1, β-catenin, and transcription factor 4 in NSCLC cells.[112]

Some other circRNAs have been shown to indirectly regulate the Wnt/β-catenin pathway by sponging miRNAs. For instance, hsa_circ_0043256 promotes the expression of Itchy E3 ubiquitin protein ligase (a negative regulator of the Wnt/β-catenin signaling pathway) by sponging miR-1252, leading to the inactivation of the Wnt/β-catenin signaling pathway.[113] Similarly, circ-ZNF124 upregulates the expression of YES proto-oncogene 1 (YES1) by sponging miR-498, resulting in the inactivation of the Wnt/β-catenin signaling pathway.[111]

The PI3K/AKT signaling pathway plays crucial roles in regulating various biological processes of cells, such as cell cycle, glucose transport, and carcinogenesis.[124–126] It has been reported that the dysregulation of PI3K/AKT is closely associated with NSCLC progression.[127] Several circRNAs have been shown to regulate the carcinogenesis of NSCLC by targeting the PI3K/AKT signaling pathway. For instance, Yao et al. found that circGFRA1 activates the PI3K/AKT signaling pathway by sponging miR-188-3p, leading to the promotion of the proliferation of NSCLC cell lines A549 and NCI-H838. Consistent with this, LY264002 (a classical PI3K inhibitor) can reverse the positive effect of circGFRA1 on the proliferation of NSCLC cells.[84] Bai et al. revealed that circPRKCA enhances the activity of AKT by binding to miR-330-5p in NSCLC cells.[114] Moreover, Xu et al. showed that the knockdown of circRNA_100876 significantly downregulates the expression of p-AKT, resulting in the inhibition of NSCLC progression. The negative effect of circRNA_100876 knockdown on the expression of p-AKT is reversed by miR-636 downregulation.[115] In addition, circFGFR3 and hsa_circ_0018818 have also been demonstrated to promote the progression of NSCLC by activating the PI3K/AKT signaling pathway.[87,116]

The MAPK signaling pathway is a classical carcinogenic pathway. The dysregulation of the MAPK/ERK cascade contributes to many aspects of cancer progression.[128] Wang et al. found that circ-ZKSCAN1 suppresses the growth of NSCLC cells. Mechanistically, circ-ZKSCAN1 upregulates the expression of FAM83A by sponging miR-330-5p, leading to the inhibition of the MAPK signaling pathway.[52] Moreover, hsa_circ_0004050 is reported to downregulate the expression of DUSP9 by sponging miR-1233-3p in the NSCLC cell line A549 and then inhibiting the ERK/JNK signaling pathway.[119] In our previous work, circ-ZKSCAN1 was found to be upregulated in both NSCLC tissues and cell lines. The overexpression of circ-ZKSCAN1 inhibits the MAPK signaling pathway by sponging miR-330-5p to increase FAM83A expression, leading to an enhancement in NSCLC cell growth.[52] circRNAs can also modulate NSCLC progression by targeting the nucleotide excision repair (NER) signaling pathway. For instance, the silencing of hsa_circ_0001946 decreases the sensitivity of NSCLC cells to the chemotherapeutic drug cisplatin (DDP) and increases the DNA repair ability by activating the NER signaling pathway.[120] Collectively, these studies indicate that circRNAs are key factors in the regulation of the NSCLC signaling pathways (Figure 3). Understanding the mechanisms of circRNAs in the regulation of NSCLC signaling pathways may provide new therapeutic strategies for NSCLC patients.

Roles of circRNAs in NSCLC progression

Continuous proliferation and evasion from apoptosis are characteristic changes in cancer cells.[129] However, the detailed mechanisms of these cellular processes are very complex and not fully elucidated. A large number of oncogenic circRNAs (e.g., circABCB10, circRNA_103993, and circ_0014130) have been demonstrated to facilitate proliferation and suppress apoptosis in NSCLC cells.[130–132] Consistent with this, the upregulation of these circRNAs has been observed in NSCLC tissues and cell lines. In contrast, some circRNAs (e.g., hsa_circ_0043265 and circ-LARP4) act as tumor suppressors to inhibit proliferation and facilitate apoptosis in NSCLC cells.[133,134] Their expression is downregulated in NSCLC tissues and cells. Moreover, Chen et al. showed that knockdown of circRNA 100146 inhibits the proliferation of NSCLC cells and promotes apoptosis. Mechanistically, circRNA 100146 regulates the expression of related genes involved in these processes by interacting with multiple members of the splicing factor family SF3 and sponging miR-361-3p and miR-615-5p.[135] Wang et al. found that the overexpression of hsa_circ_0004050 promotes the apoptosis and inhibits the proliferation of NSCLC cells by inhibiting the ERK/JNK signaling pathway.[119]

Invasion and metastasis are the main causes of cancer recurrence and are closely associated with the mortality of NSCLC patients, and circRNAs have been shown to be important regulators of invasion and metastasis in NSCLC. For instance, Li et al. showed that circFGFR1 is highly expressed in NSCLC tissues. The overexpression of circFGFR1 facilitates the migration and invasion of NSCLC cells by sponging miR-381-3p to promote the expression of C-X-C motif chemokine receptor 4 (CXCR4).[82] Chi et al. found that circPIP5K1A knockdown inhibits tumor growth and the pulmonary metastasis of NSCLC in mouse xenograft models. Mechanistically, circPIP5K1A facilitates the expression of HIF-1α by sponging miR-600, leading to the promotion of NSCLC proliferation and metastasis.[136] Moreover, *EML4-ALK* and *SLC34A2-ROS1* are oncogenic fusion genes that contribute to NSCLC carcinogenesis and progression. Peng et al. revealed that F-circEA-2a derived from *EML4-ALK* variant 3b promotes the migration and invasion of NSCLC cells, whereas it has little effect on cell proliferation.[137] They also identified two novel circRNAs (F-circSR1 and F-circSR2) generated from the *SLC34A2-ROS1* fusion gene and found that the two F-circSRs facilitate cell migration in NSCLC cells.[138] EMT is a crucial physiological process that endows cells with migratory and invasive features. The dysregulation of EMT has been shown to be closely correlated with invasion and metastasis during cancer progression.[129] An increasing number of studies have demonstrated that circRNAs can regulate the invasion and metastasis of NSCLC cells through the EMT process. For instance, the overexpression of circPTPRA in NSCLC cells increases the expression of E-cadherin (epithelial marker) and inhibits the expression of N-cadherin and vimentin (mesenchymal marker), whereas circPTPRA knockdown induces opposite molecular alterations, indicating the negative effect of circPTPRA on EMT. Further study demonstrated that circPTPRA inhibits the EMT process of NSCLC cells by sponging miR-96-5p to upregulate RASSF8 expression, leading to the suppression of

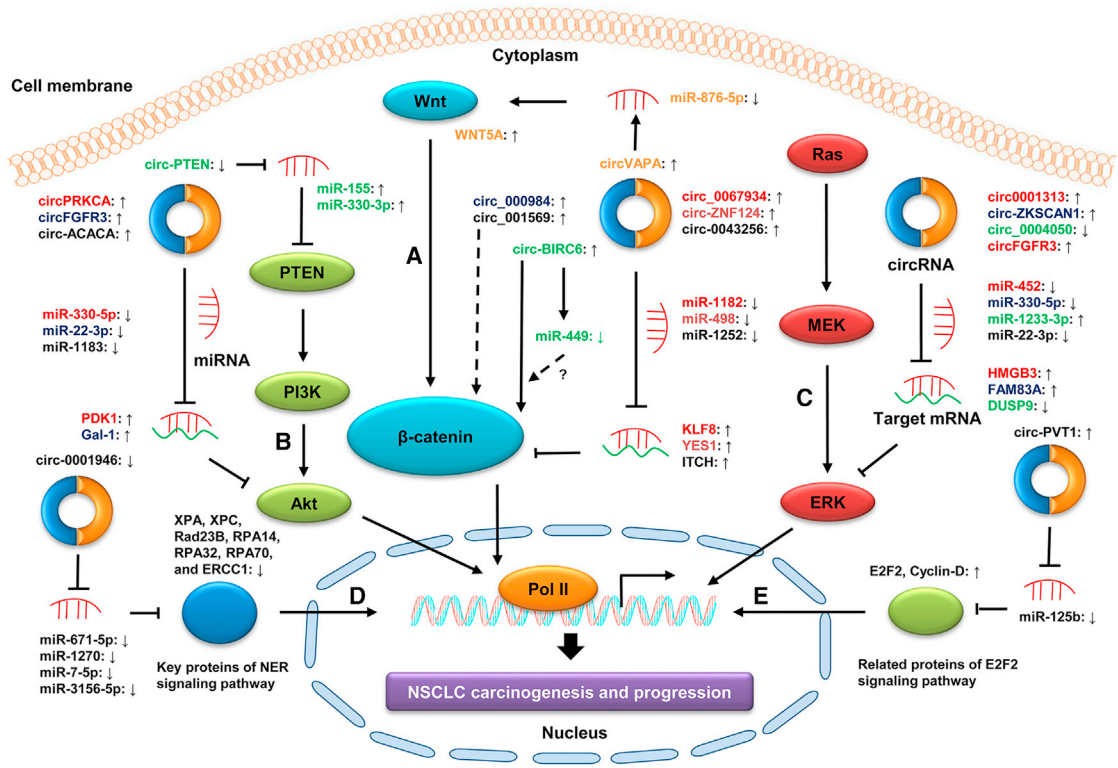

Figure 3. Regulation by circRNAs of signaling pathways in NSCLC

(A–E) circRNAs participate in the carcinogenesis and progression of NSCLC by regulating the expression of key components involved in cancer-related signaling pathways, including the Wnt/β-catenin (A), PI3K/AKT (B), MAPK (C), NER (D), and E2F2 (E) signaling pathways.

metastasis.[79] Another study showed that circAGFG1 upregulates the expression of ZNF281 by sponging miR-203, leading to the promotion of EMT progress and the metastasis of NSCLC cells.[139]

In addition, the oncogenic or anti-tumoral features of circRNAs are at least partly due to their cell-cycle modulation. Cyclin D1 is a key cell-cycle regulator that mediates the entrance of a cell into the proliferative stage.[140] Cui et al. showed that circ-CMPK1 upregulates the expression of cyclin D1 by sponging miR-302, thereby promoting the proliferation of NSCLC cells.[141] Lu et al. revealed that the knockdown of hsa_circ_0096157 in DDP-resistant NSCLC cells decreases the expression of CDK4, cyclin D1, and Bcl-2 by upregulating the P21 protein, resulting in the inhibition of cell-cycle progression. Consistent with this, the overexpression of hsa_circ_0096157 causes opposite cellular and molecular alterations in NSCLC cells.[142] Some other circRNAs, such as circ_0078767, circ_0072083, and circ-DENND2A, have also been reported to affect NSCLC progression by modulating the cell-cycle progress.[143–145] These studies suggest that circRNAs exert their oncogenic or anti-tumoral roles in NSCLC progression through diverse mechanisms.

circRNAs modulate the stemness of NSCLC cells

Cancer stem cells (CSCs) are a unique subset of self-renewable tumor cells that are characterized by their "stem-like" characteristics, such as differentiation, metastasis, and tumor initiation. An increasing amount of evidence shows that they are the main cause of chemotherapeutic drug resistance, metastasis, and cancer recurrence.[146,147] Therefore, the investigation of CSCs' regulation mechanism may provide new insights into the development of NSCLC therapeutic strategies. Recent studies have revealed that circRNAs are crucial factors in the modulation of NSCLC CSC stemness. For instance, Hong et al. found that circ-CPA4 enhances the stemness of NSCLC cell lines A549 and H1299. Further study revealed that circ-CPA4 upregulates the expression of stemness markers (OCT4, SOX2, Nanog, and ALDH1) by sponging let-7 miRNA to increase programmed cell death ligand 1 (PD-L1) expression.[103] Another study demonstrated that the silencing of circ_POLA2 reduces sphere-formation ability, ALDH1 activity, and stemness marker (Oct4 and Nanog) expression, indicating the positive role of circ_POLA2 in the promotion of NSCLC cell stemness. Mechanistically, circ_POLA2 upregulates the expression of G protein subunit β1 (GNB1) by sponging miR-326. Consistent with this, the overexpression of GNB1 reverses the inhibitory effect of circ_POLA2 knockdown on NSCLC cell stemness.[148]

circRNAs and autophagy in NSCLC

Autophagy is a conserved self-degradative process that plays a key role in regulating the degradation and recycling of organelles.[149] It

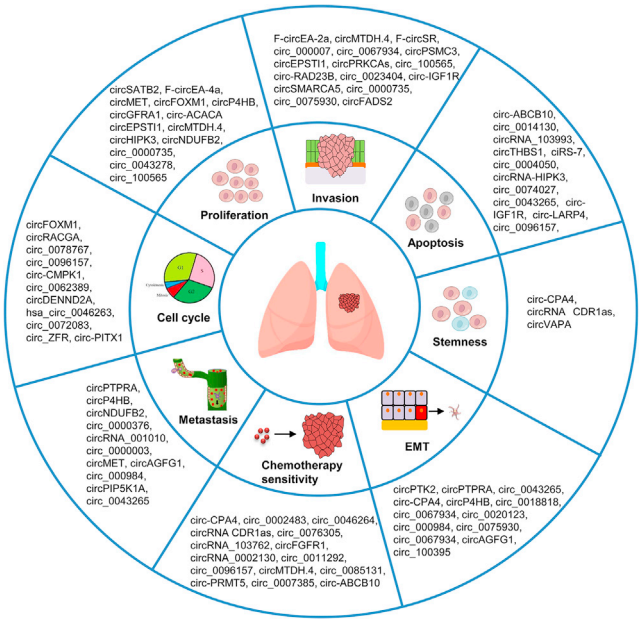

Figure 4. Effects of circRNAs on biological behaviors of NSCLC
circRNAs act as oncogenes or tumor suppressors to regulate NSCLC biological behaviors, including cell proliferation, invasion, apoptosis, metastasis, EMT, cell cycle, stemness, and chemotherapy sensitivity.

is recognized as a double-edged sword during cancer progression. On one hand, autophagy exerts its anti-tumoral function by eliminating oncogenic protein substrates, toxic unfolded proteins, and damaged organelles. On the other hand, it can promote cancer progression by mediating intracellular recycling, which provides substrates for metabolism and maintains the functions of the mitochondria.[150] Therefore, understanding the mechanism of autophagy regulation may provide us with new insights into autophagy-based therapeutic interventions for NSCLC. An increasing amount of evidence has shown that circRNAs are involved in the regulation of autophagy in NSCLC cells. For instance, Wei et al. demonstrated that the silencing of circ-FOXM1 inhibits the autophagy of NSCLC cells by sponging miR-149-5p to upregulate the expression of autophagy-related 5 (ATG5).[101] In another study, Chen et al. showed that the knockdown of circHIPK3 induces autophagy in STK11 mutant NSCLC cells. Mechanistically, circHIPK3 knockdown downregulates the expression of p-STAT3P by sponging miR-124-3p to increase RKAA expression, resulting in the induction of autophagy. Consistent with this, silencing STAT3 or the administration of a miR-124-3p mimic exhibits the opposite effect. Moreover, circHIPK3 has been shown to regulate autophagy by competing with linHIPK3.[151] In addition, Kong et al. found that hsa_circ_0085131 promotes the proliferation and DDP resistance of NSCLC cells and is closely associated with recurrence in NSCLC patients. Further study revealed that hsa_circ_0085131 induces autophagy in NSCLC cells by sponging miR-654-5p to increase the expression of autophagy-associated factor ATG7, thereby promoting cell chemoresistance.

Regulation effect of circRNAs on chemotherapy sensitivity in NSCLC

Chemotherapy is one of the main treatment modalities for cancer; however, with the development of chemotherapy resistance and multidrug resistance (MDR), the therapeutic effect of chemotherapy will gradually decline over time until its failure.[152] Therefore, in-depth research on the regulation mechanisms underlying NSCLC resistance may provide a novel theoretical basis for the improvement of NSCLC chemotherapy. Recent studies have shown that the dysregulation of circRNAs is involved in the regulation of NSCLC chemoresistance.[153] For instance, Xu et al. identified 11,281 differentially expressed circRNAs via a circRNA microarray in the taxol-resistant NSCLC cell line A549 compared with parental A549 cells, among which 2,909 were upregulated and 8,372 were downregulated. Further study revealed that the dysregulated circRNAs block the sensitivity of NSCLC to taxol by negatively regulating the expression of miRNA transcripts.[154] Li et al. showed that the overexpression of circ_0002483 enhances the sensitivity of NSCLC cells to taxol by sponging miR-182-5p to upregulate the expression of GRB2, FOXO1, and FOXO3.[155] In addition, circ_ZFR has been found to be upregulated in NSCLC tissues and cell lines. The knockdown of circ_ZFR inhibits the taxol resistance of NSCLC by sponging miR-195-5p to decrease KPNA4 expression.[83] Some circRNAs, such as circ_0007385 and circ-PRMT5, are reported to be involved in the regulation of the DDP resistance of NSCLC cells. circ_0007385 knockdown has been shown to repress the DDP resistance of NSCLC cells. Mechanistically, silencing circ_0007385 upregulates the expression of HMGB1 by sponging miR-519d-3p, leading to the inhibition of DDP resistance in NSCLC.[92] circ-PRMT5 promotes DDP resistance in NSCLC cells by sponging miR-4458 to upregulate the expression of the REV3-like DNA-directed polymerase ζ catalytic subunit (REV3L).[156] Moreover, Xiao et al. showed that circRNA_103762 is highly expressed in NSCLC tissues and cell lines. The knockdown of circRNA_103762 suppresses the MDR of NSCLC cells by upregulating the expression of DNA damage-inducible transcript 3.[157] In addition, hsa_circ_0004015 has been found to enhance the resistance of NSCLC cells to gefitinib by sponging miR-1183 to upregulate PDPK1 expression.[158] circFGFR1 has been shown to upregulate the expression of CXCR4 by sponging miR-381-3p, resulting in the resistance of NSCLC cells to anti-programmed cell death 1 (PD-1).[159] Taken together, these studies suggest that circRNAs play crucial roles in the regulation of chemotherapy resistance and MDR, indicating their great potential as therapeutic targets or drugs for improving chemotherapy resistance and MDR in NSCLC.

Collectively, circRNAs serve as oncogene or tumor suppressors to modulate NSCLC progression, including cell proliferation, invasion, apoptosis, metastasis, EMT, cell cycle, stemness, and chemotherapy sensitivity (Figure 4). The dual roles of circRNAs on NSCLC biological behaviors might be dependent on their diversity of function.

CLINICAL APPLICATIONS OF circRNAs IN NSCLC

circRNAs as diagnostic and prognostic biomarkers

Currently, it is difficult to observe the early symptoms of NSCLC due to its complex pathological characteristics, which results in most

Table 4. circRNAs as diagnostic and prognostic biomarkers in NSCLC

circRNA	Expression	Function	Clinical relevance	Reference
hsa_circ_0077837	Down	diagnostic biomarker	hsa_circ_0077837 shows the diagenetic value for NSCLC patients; AUC = 0.921, 95% CI 0.868–0.975	Wang et al.[106]
hsa_circ_0001821	Up	diagnostic biomarker	hsa_circ_0001821 shows the diagenetic value for NSCLC patients; AUC = 0.863, 95% CI 0.797–0.929	
circFARSA	Up	diagnostic biomarker	plasma circFARSA shows the diagenetic value for NSCLC patients; AUC = 0.71, gender, p = 0.048	Hang et al.[167]
circSATB2	up	diagnostic biomarker	circSATB2 is highly expressed in serumal exosomes with high sensitivity and specificity for clinical detection in NSCLC patients; AUC = 0.660 in serum from NSCLC patients; AUC = 0.797 in serum from metastatic NSCLC patients	Zhang et al.[11]
circRNA_100876	up	prognostic biomarker	high expression of circRNA_100876 predicts poor prognosis for NSCLC patients (OS, p < 0.001); lymph node metastasis, p = 0.001, and tumor staging, p = 0.001	Yao et al.[168]
ciRS-7	up	prognostic biomarker	high expression of ciRS-7 appears to be a powerful prognostic biomarker for NSCLC patients; HR 2.50, 95% CI 1.07–6.07, p < 0.001	Tian et al.[169]
circ_100565	up	prognostic biomarker	high expression of circ_100565 predicts poor prognosis for NSCLC patients; lymph node metastasis, p = 0.011, and TNM stages, p = 0.002	Li et al.[88]
circ_0000376	up	diagnostic biomarker	circ_0000376 expression is associated with unfavorable pathological parameters of NSCLC patients; T stage, p = 0.0449, and lymph invasion, p = 0.0371	Sun et al.[170]
hsa_circ_0109320	up	prognostic biomarker	upregulation of hsa_circ_0109320 predicts good prognosis in gefitinib-treated NSCLC patients; AUC = 0.81 for estimating the therapeutic effect of gefitinib	Liu et al.[107]
circMET	up	diagnostic and prognostic biomarker	a high level of circMET is associated with short OS and PFS in NSCLC patients; differentiation, p = 0.015; tumor size, p = 0.006; lymph node metastasis, p = 0.008; OS, p < 0.001; and PFS, p < 0.001	Pei et al.[89]
circ_0001649	down	prognostic biomarker	downregulation of circ_0001649 is associated with TNM stage (p = 0.010), lymph node metastasis (p = 0.029), and OS (p < 0.031)	Liu et al.[171]
hsa_circ_0033155	down	diagnostic biomarker	downregulation of hsa_circ_0033155 is associated with lymphatic metastasis (p = 0.0237)	Gu et al.[172]
hsa_circRNA_012515	up	diagnostic and prognostic biomarker	high expression of hsa_circRNA_012515 is associated with tumor stage (p = 0.013), lymphatic metastasis (p = 0.039), OS (p = 0.003), and PFS (p = 0.018); AUC = 0.89	Fu et al.[173]
hsa_circ_000984	up	prognostic biomarker	high expression of hsa_circ_000984 predicts poor prognosis for NSCLC patients; TNM stage, p = 0.004; lymph node metastasis, p = 0.005; OS, p = 0.0031; and PFS, p = 0.008	Li et al.[109]
circ-RAD23B	up	prognostic biomarker	high expression of circ-RAD23B predicts poor prognosis for NSCLC patients; lymph node metastasis, p = 0.019; differentiation grade, p = 0.010; and OS (p = 0.023)	Han et al.[174]

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Table 4. *Continued*

circRNA	Expression	Function	Clinical relevance	Reference
circ_0000079	down	prognostic biomarker	low expression of circ_0000079 predicts poor prognosis for NSCLC patients; depth of invasion, p = 0.041; differentiation, p = 0.005; and OS, p = 0.0018	Chen et al.[175]
hsa_circ_0109320	down	prognostic biomarker	high expression of hsa_circ_0109320 is associated with longer PFS in gefitinib-treated NSCLC patients; AUC = 0.8054, PFS, p = 0.02545	Liu et al.[107]
circ_0047921, circ_0056285, circ_0007761	up	diagnostic biomarkers	circ_0047921, circ_0056285, and circ_0007761 show significant diagnostic validity for NSCLC; AUC = 0.926, 95% CI 0.895–0.956	Xian et al.[176]
hsa_circ_0075930	up	prognostic biomarker	upregulation of hsa_circ_0075930 is associated with tumor size (p = 0.001) and lymph node metastasis (p = 0.038)	Li et al.[177]
hsa_circ_0043265	down	diagnostic biomarker	low expression of circ_0000079 is associated with tumor size (p = 0.0186), TNM stage (p = 0.0283), and lymph node metastasis (p = 0.0089)	Ren et al.[133]
hsa_circ_0014130	up	diagnostic biomarker	the expression of hsa_circ_0014130 is associated with TNM stage (p = 0.001) and lymphatic metastasis (p = 0.004); AUC = 0.878, 95% CI 0.804–0.951; p < 0.001	Zhang et al.[104]
circ_0000376	up	prognostic biomarker	high expression of circ_0000376 is associated with TNM stage (p = 0.0007), tumor size (p < 0.0001), and lymph node metastasis (p = 0.0016) and predicts poor prognosis in NSCLC patients (OS, p = 0.008)	Li et al.[178]
circ_0067934	up	prognostic biomarker	high expression of circ_0067934 is associated with TNM stage (p = 0.003), lymph node status (p = 0.000), and distant metastasis (p = 0.017) and predicts poor prognosis in NSCLC patients (OS, p = 0.001)	Wang et al.[179]
hsa_circ_0037515, hsa_circ_0037516	down	diagnostic biomarkers	hsa_circ_0037515 and hsa_circ_0037516 show diagnostic value in NSCLC patients; for hsa_circ_0037515, AUC = 0.81, sensitivity 0.57, and specificity 0.9; for hsa_circ_0037516, AUC = 0.82, sensitivity 0.65, and specificity 0.84; for the combination of hsa_circ_0037515 and hsa_circ_0037516, AUC = 0.9, sensitivity 0.87, and specificity 0.89	Zhao et al.[180]
hsa_circ_0102533	up	diagnostic biomarker	hsa_circ_0102533 shows diagnostic value for NSCLC patients; AUC = 0.744, 95% CI 0.622–0.867 (p = 0.001); high expression of hsa_circ_0102533 is associated with tumor type (p = 0.011), TNM stage (p = 0.010), lymph node metastasis (p = 0.001), and distant metastasis or recurrence (p = 0.021)	Zhou et al.[181]
circPVT1	up	prognostic biomarker	high expression of circPVT1 is associated with TNM stage (p = 0.007) and tumor size (p = 0.022) and predicts poor prognostic in NSCLC patients	Qin et al.[182]
circsSMARCA5	down	prognostic biomarker	low expression of circsSMARCA5 is associated with TNM stage (p = 0.012) and tumor size (p = 0.004) and predicts poor prognostic in NSCLC patients (OS, p = 0.022)	Zhang et al.[183]
novel_circ_0005280	down	diagnostic and prognostic biomarker	low expression of novel_circ_0005280 predicts poor prognosis in NSCLC patients; AUC = 0.944; cutoff 10.23; sensitivity 85.2%; specificity 95.1%; tumor diameter, p = 0.001; and age, p = 0.021	Li et al.[184]

(*Continued on next page*)

Table 4. *Continued*

circRNA	Expression	Function	Clinical relevance	Reference
hsa_circ_0002130	up	diagnostic biomarker	hsa_circ_0002130 is highly expressed in serum exosomes from osimertinib-resistant NSCLC patients and shows diagnostic value for NSCLC patients; AUC = 0.792, 95% CI 0.676–0.909 ($p < 0.005$)	Ma et al.[185]
hsa_circ_0046264	up	diagnostic and prognostic biomarker	high expression of hsa_circ_0046264 shows diagnostic and prognostic value for NSCLC patients; AUC = 0.971, sensitivity 95.1%, and specificity 97.3% in the tumor tissues; AUC = 0.915, sensitivity 92.7%, and specificity 95.7% in the serum of the patients; expression of hsa_circ_0046264 is associated with TNM stage ($p = 0.015$), age ($p = 0.03$), tumor size ($p = 0.017$), lymph node metastasis ($p = 0.004$), and OS ($p < 0.05$)	Liu et al.[186]
hsa_circ_0007385	up	prognostic biomarker	high expression of hsa_circ_0007385 shows diagnostic and prognostic value for NSCLC patients; AUC = 0.922, 95% CI 0.890–0.953, and OS ($p = 0.008$); high expression of hsa_circ_0007385 is associated with lymph node metastasis ($p = 0.007$), TNM stage ($p = 0.004$), and DFS ($p = 0.028$)	Lin et al.[187]

circRNA, circular RNA; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; AUC, area under the curve; TNM, tumor node metastasis; DFS, disease-free survival.

patients being diagnosed at an advanced stage, as well as the loss of the best opportunity for surgical treatment.[160] In addition, a poor prognosis assessment seriously affects the adjustment of treatment strategies for individual patients and the prolongation of their lifespan. In recent years, multiple conventional biomarkers, such as AFP, PD-L1, and ALK, have been applied to the diagnosis and prognosis evaluation of cancers, including NSCLC.[160–164] However, the low specificity and sensitivity of these protein biomarkers restrict their further utilization. For instance, AFP is the most efficient biomarker for hepatocellular carcinoma (HCC) diagnosis, but a study has shown that in up to 40% of patients with HCC, AFP expression is at a normal level, which reflects its low sensitivity.[165] miRNAs are also a class of biomarker candidates with great potential. However, the relatively short half-life and low stability of miRNAs limit their translation from basic research to clinical application. With the development of circRNA investigation, these limitations are being gradually overcome. For instance, Yu et al. identified a plasma circRNA panel (CircPanel) containing three circRNAs (hsa_circ_0000976, hsa_circ_0007750, and hsa_circ_0139897) from HCC patients and demonstrated that the CircPanel has a higher accuracy than AFP at distinguishing HCC patients from controls.[166] An increasing amount of evidence suggests that circRNAs are ideal biomarkers for the diagnosis and prognosis of cancers, including NSCLC, due to their high stability, specificity, and detectability.[3,4] Currently, quantitative real-time reverse transcription polymerase chain reaction (RT-PCR) is the favored method to detect circRNA and miRNA in clinical samples. Sequence-specific probes and primers are required in this system. Compared with circRNA, it is more difficult to design effective specific primers and probes for miRNAs due to their short length, which makes circRNA a more ideal biomarker. circRNAs that might serve as diagnostic and prognostic biomarkers in NSCLC are listed in Table 4.

Pei's study revealed that circMET is upregulated in NSCLC tissues compared with the normal control, and its upregulation in NSCLC is closely associated with differentiation, tumor size, and lymph node metastasis. Moreover, the overexpression of circMET has been shown to promote the proliferation, metastasis, and immune evasion of NSCLC cells. Furthermore, NSCLC patients exhibit poor overall survival (OS) and progression-free survival (PFS) after surgery. circMET can be used as a promising novel prognostic biomarker for NSCLC.[89] In addition, the expression of circSATB2 is upregulated in NSCLC tissues and cell lines compared with healthy controls. Further analysis showed that circSATB2 promotes the proliferation, migration, and invasion of NSCLC cells and is closely associated with metastasis in NSCLC. Clinically, circSATB2 is highly expressed in serum exosomes from NSCLC patients with a high sensitivity and specificity for clinical detection, indicating its great potential as a new diagnostic biomarker for NSCLC.[11] Moreover, hsa_circ_0102533 has proven to be upregulated in NSCLC tissues and in whole blood. The knockdown of hsa_circ_0102533 significantly suppresses proliferation and induces apoptosis in NSCLC cells. Receiver operating characteristic (ROC) analysis showed that the area under the curve (AUC) value of hsa_circ_0102533 is 0.774 in stage I–II NSCLC patients and 0.728 in stage III–IV NSCLC patients. hsa_circ_0102533 may become a promising early diagnostic biomarker of NSCLC.[181]

In addition, Xian's group found that exosomal circ_0047921, circ_0056285, and circ_0007761 have significant diagnostic value

for NSCLC in the Chinese population. In their study, the expression levels of circ_0047921 and circ_0056285 were downregulated, whereas circ_0007761 was upregulated in NSCLC cases compared with controls. Correspondingly, the expression of circ_0047921, circ_0056285, and circ_0007761 distinguishes NSCLC patients from healthy controls with AUCs of 0.757, 0.625, and 0.750, respectively. Surprisingly, the panel of the three circRNAs showed AUC values of 0.926.[176] Moreover, circRNA_100876 has been shown to be significantly upregulated in NSCLC tissues compared with their adjacent non-tumorous tissues, and its high expression is associated with lymph node metastasis and tumor staging. In addition, the NSCLC patients with high circRNA_100876 expression showed significantly shorter OS time compared with patients with low circRNA_100876 expression, indicating that circRNA_100876 might be a promising prognostic biomarker and therapeutic target for NSCLC.[168] Moreover, the expression of circ_0001649 is closely correlated with some pathological features of NSCLC, including TNM stage, positive lymph node metastasis, and unfavorable prognosis. The overexpression of circ_0001649 significantly suppresses the growth and metastasis of NSCLC both *in vitro* and *in vivo*. circ_0001649 can be regarded as a new prognostic biomarker and potential therapeutic target of NSCLC.[171]

In a recent study by Fu et al., they showed that hsa_circRNA_012515 is increased in NSCLC tissues, NSCLC cells, and gefitinib-resistant cells. Clinically, NSCLC patients with a high expression of hsa_circRNA_012515 show lower OS and shorter PFS compared with patients with a low expression of hsa_circRNA_012515. Moreover, hsa_circRNA_012515 expression is closely associated with the prognosis of NSCLC patients. hsa_circRNA_012515 shows great potential to be a diagnostic and prognostic biomarker for NSCLC.[173] In addition, Peng et al. revealed that F-circEA produced from the *EML4-ALK* fusion gene specifically exists in the plasma of NSCLC patients with the *EML4-ALK* translocation. The overexpression of F-circEA contributes to NSCLC progression by promoting cell migration and invasion. The data from Peng's study suggest that F-circEA possesses great diagnostic value as a "liquid biopsy" biomarker for EML4-ALK-positive NSCLC patients and guides EML4-ALK-targeted NSCLC therapy.[188] These basic studies strongly suggest that circRNAs possess great potential to serve as promising biomarkers for the diagnosis and prognosis of NSCLC. However, the translational process from basic research to clinical application is very long, and more studies are required to overcome the limitations of circRNAs in clinics.

Therapeutic potential of circRNAs in NSCLC

A growing amount of evidence has highlighted the oncogenic or anti-tumoral function of circRNAs in NSCLC progression,[4,58,101] suggesting their great potential as effective therapeutic targets or therapeutic vectors for NSCLC treatment. In addition, circRNAs have longer length and better stability than miRNAs, which provides a greater possibility for designing and screening drugs targeted at circRNAs. The techniques of gene silencing or overexpression targeting circRNAs may provide us with new insights into the development of NSCLC therapeutic strategies. For oncogenic circRNAs, RNAi targeting the back-splicing process can knock out specific circRNAs and avoid interference in their homologous linear mRNA expression.[189] For instance, the high expression of hsa_circ_0062389 is reported to be positively associated with advanced TNM stage and lymph node metastasis. The silencing of hsa_circ_0062389 by siRNA has been shown to decrease the proliferation of NSCLC cells and cause cell-cycle arrest in the G0/G1 phase.[86] Moreover, the CRISPR-Cas9 genome-editing technique is also an effective tool to treat NSCLC, as it can knock out specific genes with low off-target impacts.[190] Li et al. found that circRNAs FECR1, -2, -3, -4, -5, and -6 are generated from the region of the *FLI1* gene that the Cas9 guide RNAs (gRNAs) target. The knockout of *FLI1* by the CRISPR-Cas9 system downregulates the expression of these circRNAs in NSCLC cells.[191] In addition, screening or synthesizing new chemical drugs targeting circRNAs may provide new insights into NSCLC treatment. For anti-tumoral circRNAs, the exogenous introduction of circRNAs may serve as a therapeutic vector to play a role in the regulation of NSCLC progression. For instance, the overexpression of circNDUFB2 suppresses the growth and metastasis of NSCLC cells by enhancing the interaction of TRIM25 with IGF2BPs to promote IGF2BP degradation, indicating the potential therapeutic role of circNDUFB2 by blocking NSCLC progression.[58] In addition, synthetic circRNAs containing miRNA binding sites may represent a simple, fast, and effective strategy for treating NSCLC. To summarize, using circRNAs as novel targets or drugs broadens our insight into NSCLC therapeutic strategies. However, challenges that limit their clinical application still exist, such as safety, off-target effects, and modes of targeted delivery, and further studies are required to resolve these issues.

CONCLUSION AND PERSPECTIVE

NSCLC is the most common malignant tumor type in the respiratory system, with high morbidity and mortality. Its pathogenesis is very complex and still unclear. Understanding the regulation mechanism of NSCLC progression may provide us with new insights into the development of NSCLC therapeutic strategies. circRNAs are recognized as crucial regulators in a variety of physiological and pathological processes due to their multiple functions, including miRNA sponging, protein interaction, gene expression regulation, and protein coding. With the rapid development of high-throughput sequencing techniques, a growing number of circRNAs have been found to be aberrantly expressed in NSCLC tissues. Most of them facilitate NSCLC progression, with only a few circRNAs exhibiting an anti-tumoral role, such as circ_0078767 and hsa_circ_0014130.[85,143] circRNAs participate in the regulation of NSCLC progression by regulating the network of tumor gene expression and/or targeting key signaling pathways.

Early diagnosis and prognosis evaluation are important directions for the effective treatment of NSCLC. Therefore, identifying novel diagnostic and prognostic biomarkers, as well as therapeutic targets, will bring great benefits to the precise treatment of NSCLC patients. Due to the crucial role of circRNAs in NSCLC

progression, they are considered to be valuable diagnostic and prognostic biomarkers for NSCLC. In addition, circRNAs also exhibit great therapeutic potential for NSCLC patients. In recent years, therapeutic strategies based on circRNAs, such as RNAi, CRISPR-Cas9, and synthetic circRNAs, have been developed. However, circRNA research is in its infancy, and some challenges that limited the clinical application of circRNAs in NSCLC treatment still exist, such as safety, off-target effects, and modes of targeted delivery. Future studies should focus on elucidation of the exact mechanism of circRNAs in the regulation of NSCLC progression using large-scale clinical trials.

In conclusion, recent studies have demonstrated that circRNAs possess great potential to be valuable diagnostic and prognostic biomarkers, as well as therapeutic targets, in NSCLC treatment. However, the translational process from basic research to clinical application is very long. We believe that, through the continuous efforts of researchers, circRNAs will become a powerful tool that can be widely used in a variety of aspects of NSCLC treatment.

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AUTHOR CONTRIBUTIONS

Y.L., X.A., W.Y., and Y.Z. collected the related papers. Y.L. drafted and wrote the manuscript. Y.L., X.A., and J.W. revised the manuscript. All authors read and approved the final manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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