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REVIEW

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Emerging roles of exosomal circRNAs in non-small cell lung cancer

Hongyuan Yin[1,2†], Jiayi Shi[2†], Shaoling Li[1†], Qianhui You[2†], Huici Zhu[2], Chinying Koo[2], Baonian Liu[2*], Likun Hou[1*] and Chunyan Wu[1*]

Abstract

Despite the prevalence of non-small cell lung cancer (NSCLC) is high, the limited early detection and management of these tumors are restricted since there is an absence of reliable and precise diagnostic biomarkers and therapeutic targets. Exosomes transport functional molecules for facilitating intercellular communication, especially in the tumor microenvironment, indicating their potential as cancer biomarkers and therapeutic targets. Circular RNA (circRNA), a type of non-coding RNA possessing a covalently closed loop structure, substantial abundance, and tissue-specific expression patterns, is stably enriched in exosomes. In recent years, significant breakthroughs have been made in research on exosomal circRNA in NSCLC. This review briefly introduces the biogenesis, characterizations, and functions of circRNAs and exosomes, and systematically describes the biological functions and mechanisms of exosomal circRNAs in NSCLC. In addition, this study summarizes their role in the progression of NSCLC and discusses their clinical significance as biomarkers and therapeutic targets for NSCLC.

Keywords Exosomal circRNAs, Non-small cell lung cancer, Exosomes, CircRNAs, Biomarker, Therapeutic target

Background

Lung cancer, one of the most lethal malignancies globally, can be categorized into two primary forms: non-small-cell lung cancer (NSCLC) and small-cell lung cancer. NSCLC accounts for around 85% of all occurrences of lung cancer [1]. NSCLC exhibits a comparatively slower pace of growth and a prolonged disease course, and it typically does not manifest notable symptoms in its infancy, unlike small cell lung cancer [2]. The suboptimal therapeutic efficacy in NSCLC can be attributed to the paucity of reliable tumor markers and the emergence of drug resistance [3, 4]. Therefore, it is crucial to investigate NSCLC-related biomarkers to improve the efficiency of NSCLC diagnosis and treatment [5].

Exosomes, which have sizes ranging between 40 and 160 nm, are extracellular vesicles secreted by multiple kinds of active cells [6–8]. They form a highly heterogeneous population, and this heterogeneity manifests in four main aspects: size, content, function, and origin [9–12]. The content of exosomes influences their size, while the microenvironment of the cell and biological processes occurring within the cell can impact their content. Exosomes transport a substantial quantity of miRNAs, circRNAs, and other nucleic acids, membrane proteins, and small molecules [13, 14]. Upon being released from the cell surface, exosomes merge with the plasmalemma

†Hongyuan Yin, Jiayi Shi, Shaoling Li and Qianhui You contributed equally to this work.

*Correspondence:
Baonian Liu
bnliu15@fudan.edu.cn
Likun Hou
hlk9575@163.com
Chunyan Wu
wuchunyan581@163.com
[1]Department of Pathology, Shanghai Pulmonary Hospital, School of Medicine, Tongji University, Shanghai 200433, China
[2]Department of Anatomy, School of Integrative Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai 201203, China

of recipient cells, promoting the transportation of their content into the cytoplasm [15]. Notably, cancer cells can produce a higher number of exosomes in comparison to non-malignant cells [16–18]. Exosomes can facilitate the occurrence and progression of NSCLC by enhancing cell migration, invasion, proliferation, and immune evasion. The study of exosomes contributes to the understanding of cell communication mechanisms and offers novel insights into the diagnosis and management of malignancies [19, 20]. Furthermore, exosomes can be modified through various methods of engineering and materials science to achieve the targeted delivery of specific drugs, which endows them with significant clinical research value and broad application prospects.

Circular RNAs (circRNAs) are plentiful endogenous RNAs characterized by circular structures created through the covalent closure of the 5' and 3' ends of precursor RNA [21–24]. CircRNAs are a class of highly expressed, stable, diversified and conserved RNA molecules, and the expression of circRNA has tissue specificity and disease specificity, which makes circRNA a potentially perfect biomarker [21, 25, 26]. Research has demonstrated that circRNAs have significant impacts on promoting the advancement of cancer by influencing the expression of critical genes that participate in epithelial-to-mesenchymal transition (EMT), apoptosis, proliferation, migration, and metastasis [27–29]. In addition, circRNAs possess the capacity to be enclosed within exosomes for intercellular transport, which are known as exosomal circRNAs [30–32]. In recent years, research on exosomal circRNA in cancer, such as urinary tumors, gastrointestinal cancer, etc., has received widespread attention [33–45]. However, the latest research progress on exosomal circRNA in NSCLC has not been reviewed yet.

In this review, we offer an in-depth exploration of the latest research progress pertaining to the biogenesis, distinctive features, and functional roles of circRNAs. In addition, we provide a comprehensive summary of the current research progress on the mechanism of circRNA entering exosomes. Finally, we explore the role of exosomal circRNAs in NSCLC and the potential of employing exosomal circRNAs as biomarkers for NSCLC.

Exosomes, circrnas and exosomal circRNAs

Characteristics and biological roles of exosomes

Exosomes, typically measuring 40–160 nm in diameter, are extracellular vesicles derived from endosomes formed through ongoing inward folding of cytomembrane, resulting in the generation of multivesicular bodies. They are able to fuse with another intracellular vesicle or organelle, resulting in the variety and heterogeneity of exosomal components [46–49].

Exosomes contain multifarious substances, including transmembrane proteins, cell adhesion molecules, scaffold proteins, RNA-binding proteins, RNA, DNA, and complex polysaccharides [50]. Exosomal proteins are specifically modificated by a significant biological process named ubiquitination. Several exosomal proteins are nonspecific molecules and can serve as a type of effective biomarkers [51–54], which can be broadly categorized into two types. According to the biological composition, the first kind of biomarker is protein biomarkers, such as tetraspanins (CD9, CD63, CD81), followed by cytoplasmic proteins including Actin and calcium phospholipid binding protein (Annexins), in addition to CEA (carcinoembryonic antigen) apoptosis through gene interactions protein X2 (ALIX), Her2 (human epidermal growth factor receptor-2), tumor susceptibility gene 101 (TSG101) protein, heat shock protein (HSP70 and HSP90), and EpCAM (epithelial cell adhesion molecule). The second type of exosomal biomarker are certain kinds of nucleic acid, such as miR-141, miR-15a-5p, miR-10b, and mutated KRAS DNA [55, 56]. Specific exosomal miRNAs have been confirmed to serve as non-invasive biomarkers for colorectal cancer, indicating information about pathological changes sensitively and accurately [57]. The potential of exosomes to serve as biomarkers has garnered extensive attention and investigation across a spectrum of diseases, including cardiovascular disorders, liver diseases, infectious diseases and cancer. Notably, a recent study elucidated the crucial role of exosomes in osteoporotic effects, identifying that exosomes originated from the plasma of murine models exposed to cold temperature (CT-EXO) sponged miR-25-3p to impact targeted gene SATB2 which ultimately attenuating autophagy in the advancement of osteoporosis [58]. The differences in exosome composition, especially on cell surface proteins impact recipient cells. Distinct cell surface indicators enable the purification of specific subpopulations of exosomes [49, 59] and also endow exosomes with the capacity to play a pivotal role in intercellular communication.

Upon the secretion into the extracellular environment, exosomes may interact with recipient cells through three mechanisms [60–63]. The first is the ligand-receptor interaction [64], which refers to the communication between molecules on the outer layer of exosomes and molecules on the target cytoplasmic membrane. The second is endocytosis [65], where recipient cells can absorb exosomes through grid protein-dependent and grid protein-independent endocytic processes, such as phagocytosis, macropinocytosis, and engulfment. The small membrane-bound structures are enriched with proteins and genetic information originating from the cells from which they are derived. Specifically, exosomes that originate from tumors contain oncogenic proteins and genes [65, 66]. The third is direct membrane fusion [67], where

exosomes fuse directly with plasmalemma, secreting their contents into the cytoplasm of the recipient cell [68, 69]. In the process of direct fusion, these vesicles merge instantaneously with the plasma membrane of recipient cells through membrane fusion, which is facilitated by the interaction with ubiquitous fusion-associated molecules, including SNARE proteins [69].

Moreover, originating from a host-cell lipid membrane, exosomes exhibit organotrophic and tissue tropism modulated by surface molecules, granting them stability and targeted delivery capabilities in intercellular communication. These attributes pave the way for exosomes to play a pivotal role in transmitting cancer cell signals and influencing cancer progression. Exosomes are more abundantly secreted by cancer cells than by their normal counterparts and are capable of exchanging materials with diverse cellular populations. Numerous studies have demonstrated that exosomes either promote or inhibit the activation and metastasis of cancer cells and cause drug resistance of anti-cancer drugs in multiple aspects. Xia et al. found that exosomes derived from HCC cells rich in Smoothened (SMO) can be absorbed by hepatic stellate cells and activate cancer-associated fibroblasts (CAFs) through the Gli1-MIRLET7BHG signaling pathway, thereby influencing the tumor microenvironment [70]. A large number of studies have shown that tumor cell-derived exosomes can accelerate cancer progression by secreting a variety of secretagogues [71]. In the case of cervical squamous cell carcinoma, exosomes express elevated high levels of miR-221-3p, and they transport it to lympho-endothelial cells (LECs). This promotes migration and lymphangiogenesis in vitro by down-regulating vascular hibin-1, a well-established blocker of lymphangiogenesis, and it promotes lymph node (LN) metastasis in mice [72, 73]. Exosomal circGSE1 facilitates immune escape from HCC by promoting the growth of regulatory T cells [74]. An immunosuppressive microenvironment in exosomes is created by circTMEM181 to imbue HCC with anti-PD1 resistance by increasing CD39 expression within macrophages [75, 76]. Intercellular transportation of wild-type EGFR proteins encapsulated in exosomes activates PI3K/AKT and MAPK pathways, triggering osimertinib resistance [77]. Gastric carcinoma cell-derived exosomes induce autophagy in neutrophils and promote cancer activation through HMGB1/TLR4/NF-κB pathway [78]. HucMSC-derived exosome delivers BECN1 to regulate the xCT/GPX4 axis to induce hepatic stele iron death, and it also carries miR-378a-5p to inhibit the NLRP3 inflammasome to alleviate colitis [79, 80].

In addition to being a medium of intercellular communication, exosomes also exert a significant part in regulating immune responses. By modulating the activity of immune cells via diverse mechanisms, including the release of cytokines and bioactive molecules and the expression of immune-inhibitory cell surface markers, exosomes contribute to alleviate inflammation and immune responses [78, 81, 82]. For instance, exosomal lnc-AFTR inhibits staphylococcus aureus-induced cell apoptosis and inflammatory responses by suppressing the activation of the TNF pathway and MAPK pathway [83]. TGF-β1 enriched in MDSCs-Exos weakens NK cells' cytotoxicity and promotes the immunosuppressive properties of MDSCs Exos by inducing Tregs or Th17 cells [84]. Tumour-derived exosomes (TEX) have potential immunogenicity due to their ability to carry tumour antigens. For example, when combined with cytokine IL-23, extracellular vesicles collected from tumor cells overexpressing Rab27a can produce strong and long-lasting anti-tumor immune effects [85]. Platelet-rich plasma-derived exosomes promote nerve repair and regeneration in patients with peripheral nerve damage by stimulating the PI3K/Akt signaling pathway in bone marrow mesenchymal stem cells [86]. In conclusion, exosomes, as crucial messengers of intercellular communication, not only participate in the exchange of substances and information between cells, but also play an important role in immune regulation.

Furthermore, exosomes possess significant characteristics including remarkable stability, high biocompatibility, minimal toxicity, low immunogenicity, the ability to permeate biological barriers and extended circulation in vitro environment, making them ideal vehicles for drug delivery [87–90]. For example, hnRNPK mediates the sorting of miR-4732-3p into exosomes, and exosomes help to form immune escape and promote the progression of NSCLC [91]. They are able to transport multifarious categories of drugs including small molecule chemical drugs, proteins, and peptide drugs, as well as large biomolecule drugs, such as antibodies and enzymes. Exosomes have the ability to actively migrate to diseased tissues and release their cargo into target cells, exerting precise targeted therapeutic effects. Benzo[a]pyrene-induced tumor exosomes can deliver circ_0011496 to activate lung fibroblasts by miR-486-5p/TWF1/MMP9 cascade, promoting HCC metastasis [92]. Additionally, exosomes mediate the link among diverse environmental stressors and negative influences and LC, particularly implicated in processes such as triggering pulmonary fibrosis, altering the tumor microenvironment, promoting apoptosis resistance, and suppressing immune reactions. For example, lung cancer cell-derived exosomes (LCCDEs) can trigger a pro-inflammatory state in mesenchymal stem cells through the NFκB-TLR signaling pathway [93]. Drug formulations based on exosomes can be applied to multiple kinds of diseases including cardiovascular diseases, infectious diseases, neurodegenerative diseases and cancer [94]. Drug delivery systems mediated by extracellular vesicles can inhibit tumor proliferation

and metastasis in gastrointestinal cancer and overcome drug resistance [95].

Biogenesis, characterization, and functions of circRNAs

CircRNA is generated through a reverse splicing mechanism in which the 5' splicing site is linked to the 3' splicing site, resulting in the formation of a closed-loop structure [96–98]. CircRNAs are categorized into three groups based on their composition: Exon-intron circRNAs (EIciRNAs), Exonic circRNAs (EcircRNAs), Circular intronic RNAs (CiRNAs). (1) The majority of ElciRNAs, when located in the nucleus, interact with U1 small nuclear ribonucleoproteins (snRNPs) and positively regulate the transcription of their parent genes in a cis approach [99]. (2) EcircRNAs are identified with the cytoplasm and contain one or more exons, accounting for 80% of the identified circRNAs [100]. (3) CiRNAs are predominantly localized in the nucleus, contain only introns, and possess the ability to transcriptionally promote Pol II within the nucleus [101].

To date, there are four proposed models of circRNA biogenesis: intron pairing-driven circulation, RNA-driven circularization, lariat-driven circularization and circularization intronic RNA, as depicted in Fig. 1. In intron pairing-driven circulation, splicing sites are approached through the complementary base pairing of reverse repeat sequences in introns on both sides of the circular exon. Reverse splicing involves the upstream branching point (BP) attacking, in which BP in turn attacks the upstream SA site, forming EIciRNAs or EcircRNAs [21]. Additionally, RNA binding proteins (RBPs) can bind to specific motifs in flanking introns, promoting RNA-driven circularization [102, 103]. CircRNAs can also be formed through the splicing of intermediates called lariat precursors, which are generated when an exon is skipped during linear splicing or when intronic lariat precursors manage to avoid the debranching process of canonical

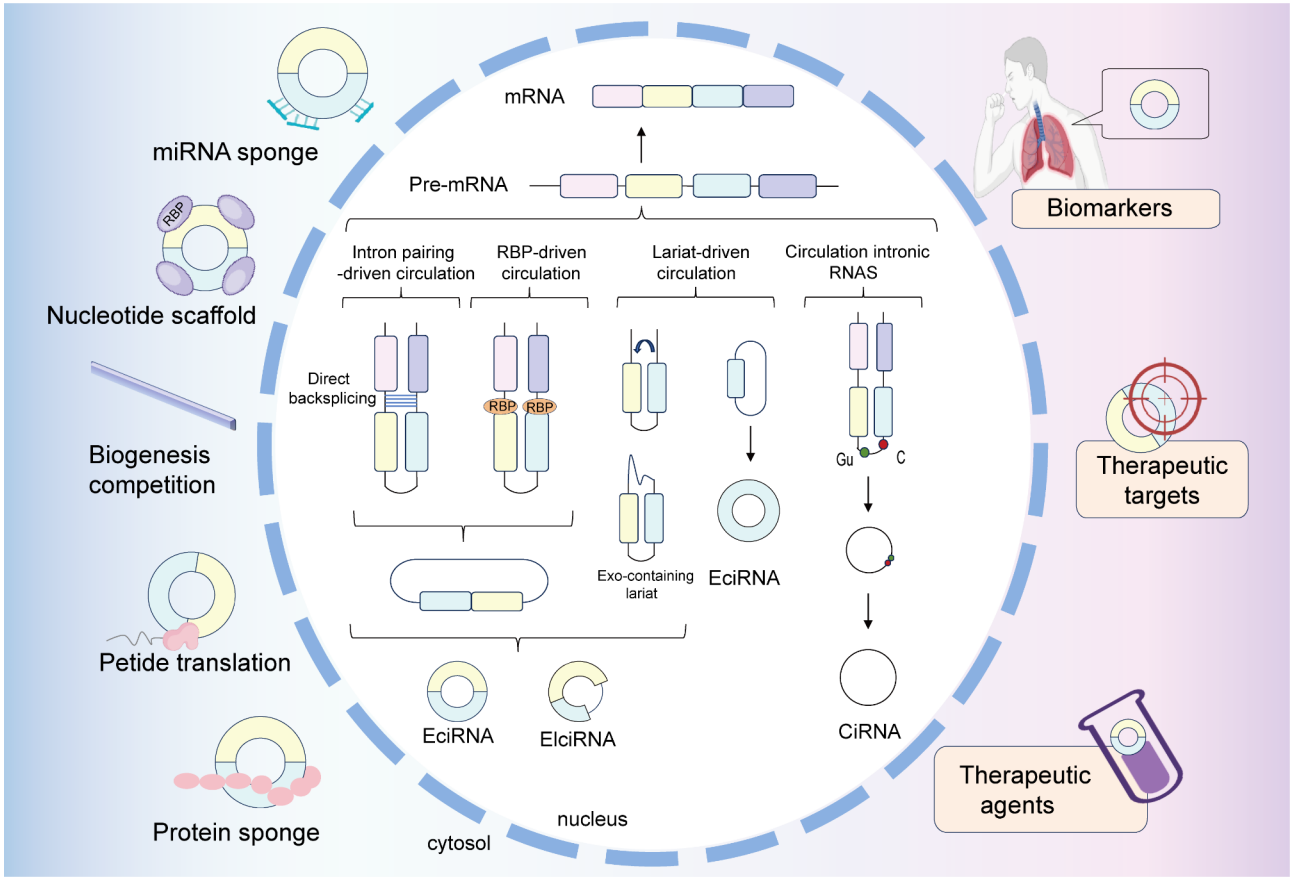

Fig. 1 Biogenesis and functions of circRNAs. CircRNAs form ElciRNAs, EcircRNAs, and CiRNAs through four hypothesized mechanisms: intron pairing-driven circulation, RNA-driven circularization, lariat-driven circularization and circularization intronic RNA. Reverse direct splicing or RNA-binding proteins (RBPs) bind to specific motifs in flanking introns, promoting RNA-driven circularization. Splicing intermediates known as lariat precursors, which result from intronic lariat precursors that elude the debranching stage of canonical linear splicing or from an exon-skipping event during linear splicing, can also produce circRNAs. CiRNAs are generated by the retention of a 7 nt GU-rich element and an 11 nt C-rich element. CircRNAs can be sponges, interact with proteins, regulate gene expression, and translate proteins. They serve as biomarkers, therapeutic targets, and therapeutic agents. Detailed information on circRNAs was sourced from Lingling Chen

linear splicing [104]. In circularization intronic RNA, CiRNAs containing both a 7 nt GU-rich element around the 5′ splice site and an 11 nt C-rich element close to the branch-point site are spared, then CiRNAs appear.

The molecular mechanisms underlying the formation of circRNA are still under continuous exploration, and the latest research has revealed some new molecular mechanisms underlying the generation of circRNAs. For example, ESRP1 (epithelial splicing regulatory protein 1) controls the biosynthesis of circDOCK1 by binding to the repeating GGU motifs in intron 1 and preventing its splicing until Pol II completes its 157 kb journey to exon 27 [105]. Tang et al. found that back-splicing predominantly occurs at m^6A-enriched locations, which are often found near the start and stop codons in linear mRNAs, for a subset of circRNAs [106]. Another study demonstrates a widespread role for NOVA2 in enhancing circRNA biogenesis during neuronal differentiation and YCAY clusters located in flanking introns were found to be responsible for the impairment of NOVA2-mediated back-splicing of circEfnb2 [107]. Liang et al. showed that the steady-state levels of circRNAs are elevated when canonical pre-mRNA processing activities are inhibited or slowed down. This is partially due to the fact that developing RNAs are diverted into other pathways that result in the synthesis of circRNAs [24, 108]. Additionally, studies on viral circRNA biogenesis revealed that they primarily use the alternative 5′ splicing site (A5SS) for variable splicing and exhibit a non-standard reverse splicing signal that is significantly higher than that of mammals and plants [109]. In summary, the molecular mechanism of circRNA generation is complex and further research is needed.

CircRNAs are abundant in eukaryotic cells, and they display characteristics as follows [110]. (1) High stability: CircRNAs are more steady than linear RNAs. CircRNAs are rarely degraded by exonuclease R and niacin phosphatase 5′-terminal exonuclease and have a longer half-life [111]. (2) Evolutionary conservation: CircRNA sequences exhibit evolutionary conservation across various species. One example of conserved circRNAs originates from the human PHF21A locus and the mouse Phf21a locus [111]. (3) High abundance: CircRNAs have higher expression than that of corresponding linear RNAs [112]. In the environment of HEK293 and whole blood specimens, the abundance of circRNA can exceed that of the corresponding linear RNA by at least 30 times [113]. (4) Tissue specificity: CircRNAs also exhibit tissue, disease, and developmental stage-specific expression, endowing them with significant potential as biomarkers. Notably, there is abundant circRNA derived from normal cells and cancer cells in human body fluids, which provides potential for circRNA to be used as a biomarker for forensic body fluid identification [114–117] and clinical liquid biopsy diagnosis of various types of cancers [28, 118, 119]. Importantly, mounting evidence has demonstrated that numerous circRNAs participate in stem cell differentiation, highlighting the role of circRNAs in a wide range of physiopathological processes and the potential as therapeutic targets for stem cell-based therapy [120].

Functionally, circRNAs can be sponges, interact with proteins, regulate gene expression, and protein translation [121–124] (Fig. 1). Circ6834 functions as a molecular sponge for miR-873-5p and increased the expression of the TXNIP gene, leading to the inactivation of the TGF-β/Smad signaling pathway in NSCLC cells [125]. CircRNAs are also capable of regulating tumor cell proliferation, migration, and apoptosis, inducing multidrug resistance, modulating the tumor microenvironment, and facilitating immune evasion through diverse signaling pathways. For instance, lung cancer progression is impeded by o8G-modified circPLCE1 through the mechanism of chaperone-mediated autophagy [126]. Besides, recent studies have revealed that circRNAs can function through novel regulatory mechanisms, including the formation of circR-loops and the interaction with protein kinase R (PKR) to impact innate immune responses. CircRNAs combine with DNA to form an R-loop structure [127], influencing chromatin structure, interacting with other ncRNAs [128, 129], and transcriptionally impacting gene expression [130]. Moreover, for immune regulation, circRNAs form a small stem-loop structure that binds to PKR in normal circumstances. In a Lewis lung carcinoma model, circRNA encoding interleukin-12 (IL-12)) induces a robust immune response to regress lung tumors [131]. Upon viral stimulation, RNase L degrades the circRNAs to release PKR and initiate immune responses [132]. CircRNAs can also influence intracellular activities through phosphorylation processes. The circLIFRSA/miR-1305/PTEN pathway mitigates oncogenic processes in NSCLC through the modulation of AKT phosphorylation [133]. Research on the functions of circRNA is continuously expanding as an emerging field. Recent studies have focused on the impact of circRNA folding structures on their biological functions [134], hinting at future discoveries of additional functions and mechanisms with improved research techniques.

Biogenesis of exosomal circRNAs

Due to the multiple biological functions of exosomal circRNA that are currently being discovered and confirmed, the mechanism of circRNA entering exosomes is of significant research value. Researchers have observed that circRNAs are stably and abundantly expressed in exosomes [135]. In recent years, the process by which circRNAs are transported into exosomes has been extensively studied. Although the specific mechanisms are still

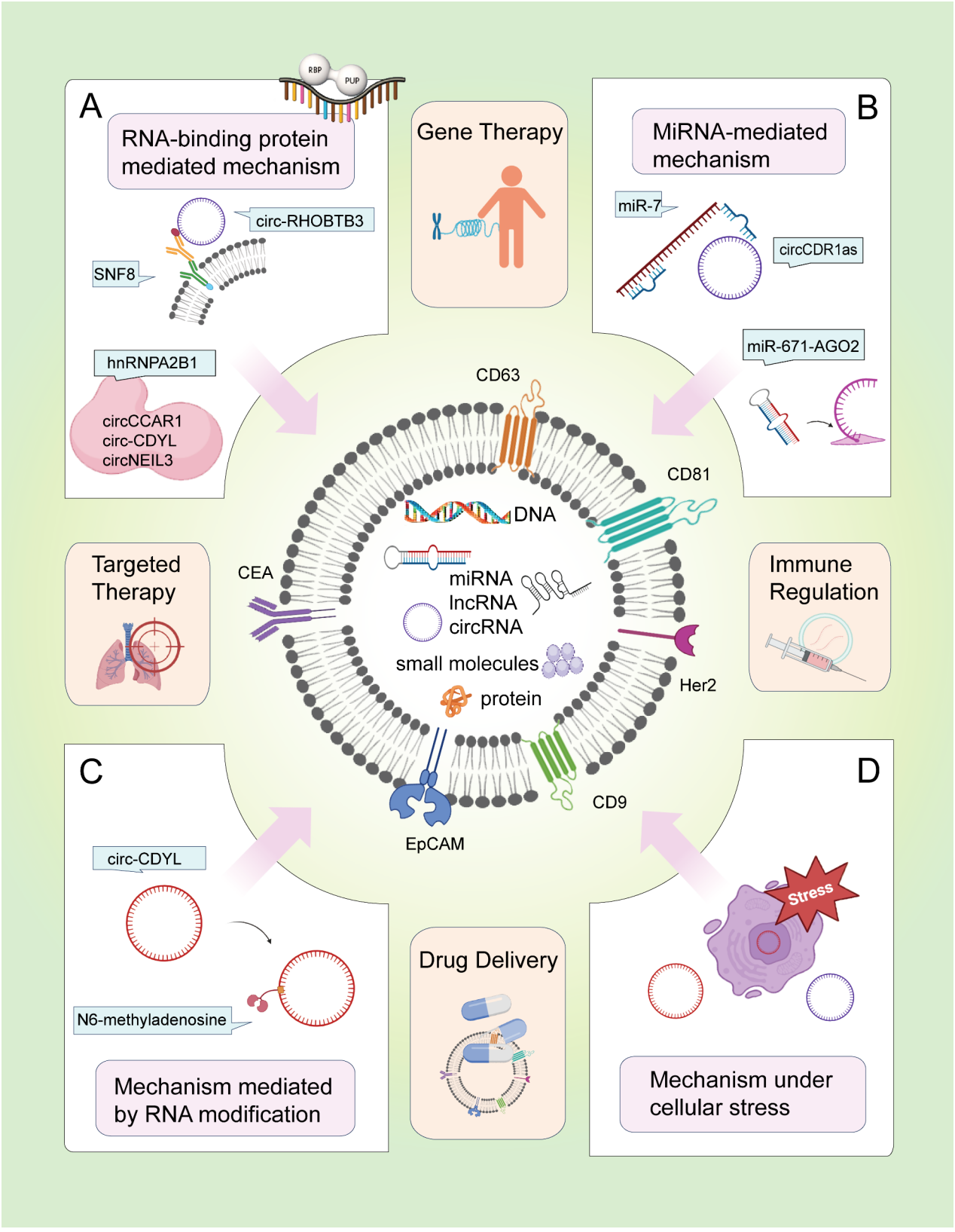

Fig. 2 (See legend on next page.)

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Fig. 2 Bioactive molecules on exosomes, the mechanisms of circRNAs' entry into exosomes, and the therapy strategies of exosomes. Various bioactive molecules on exosomes can be used as biomarkers for disease. They can be roughly divided into two categories: protein biomarkers such as CD9, CD63, CD81, CEA (carcinoembryonic antigen), Her2 (human epidermal growth factor receptor-2), and EpCAM (epithelial cell adhesion molecule); nucleic acid biomarkers. Exosomes play a role in gene therapy, targeted therapy, drug delivery, immune regulation, etc. The mechanisms by which circRNAs enter exosomes include (**A**) RNA-binding protein mediated mechanism, (**B**) miRNA-mediated mechanism, (**C**) mechanisms mediated by RNA modification, and (**D**) mechanisms under cellular stress. In RNA-binding protein-mediated mechanism, circRHOBTB3 can be specifically sorted into exosomes by interacting with SNF8, a member of the ESCRT-II complexes, via its distinctive components. CircCCAR1, circ-CDYL and circNEIL3 can be packaged into exosomes by hnRNPA2B. In miRNA-mediated mechanism, exosomes with miR-7 mimics can effectively decrease the levels of competing endogenous spongy circCDR1as, and miR-671-AGO2 mediates the degradation of circCDR1as in source cells. In mechanism mediated by RNA modification, the structure and function of circRNAs may be affected by RNA modifications. M^6A modification of circ-CDYL can promote the sorting of circ-CDYL into exosomes. In addition, when cells are exposed to external stimuli or stress conditions, the integration of circRNAs into exosomes is also affected. Exosome therapy strategies primarily include drug delivery, targeted therapy, gene therapy, and immune regulation

being explored, there have been some important discoveries and hypotheses (Fig. 2).

RNA-binding protein mediated mechanism

Studies have revealed that RNA-binding proteins (RBPs) extensively participate in RNA transport and regulation within cells and circRNAs can form complexes with RBPs and enter exosomes through interaction [136, 137]. Protein heterogeneous nuclear ribonucleoprotein A2B1 (hnRNPA2B1) is an RBP exerting significant regulatory function in controlling the transport and subcellular localization of specific mRNAs in neurons, thereby influencing neuronal function and development [138]. Moreover, hnRNPA2B1 is essential for the selective packaging of miRNAs and lncARSR into exosomes [139, 140]. CircRNAs are preferentially incorporated into exosomes over linear RNAs, yet the specific sorting mechanism for circRNAs in exosomes is not well understood [141]. For circRNAs, it has been reported that hnRNPA2B1 can facilitate the packaging of circCCAR1, circ-CDYL and circNEIL3 into exosomes [75, 142, 143]. Another study suggested that KHDRBS3 mediates the entry of circ_0088300 into exosomes [144]. Additionally, the mechanism of circRNAs sorted into exosomes may also be influenced by protein complexes in exosomes. For example, circRHOBTB3 has been shown to be specifically sorted into exosomes through the interaction with SNF8, a constituent part of ESCRT-II complex, with its own unique components [141]. CircFAT1 may be transported into exosomes by some specific RNA-binding proteins [145]. Another study found that circRNAs presumably utilize similar transportation procedure as that of linear RNAs, where RBPs specifically selectively identify RNAs that possess matching binding motifs. A study showed that exosomes have the capability to specifically encapsulate circRNAs compromising 5'-GMWGVW-GRAG-3' motifs [146]. However, the molecular mechanism that contributes to the selective entry of circRNA into exosomes still needs further investigation.

MiRNA-mediated mechanism

Some studies suggest that circRNAs can connect to miRNAs, perform as miRNA baits, and inhibit their activities [147]. Studies have shown that the miR-7 simulation of cells may trigger a notable decrease of competitive endogenous spongiform circCDR1as within exosomes, suggesting that the process of selecting of circRNAs into exosomes is partially controlled by alterations in the amounts of associated miRNAs [135, 148, 149]. Furthermore, miRNAs can regulate the intracellular breakdown of circRNAs, leading to decreased expression of circRNAs in exosomes. For instance, miR-671-AGO2 mediates the degradation of circCDR1as in source cells, which may result in decreased circCDR1as expression level in exosomes [150].

Mechanism mediated by RNA modification

RNA modifications play an important regulatory role in many aspects of the RNA post-transcriptional process, including splicing, processing, export, stability, degradation, and translation [151, 152]. In eukaryotic cells, the predominant form of RNA modification is regulated by N6-methyladenosine (m^6A) [153]. M^6A modification exerts a crucial role in enriching and regulating the physiological properties of circRNAs [154]. Research has shown that m^6A modification of circNSUN2 promotes its translocation to the cytoplasm [155]. In addition, RNA modifications may affect the process of circRNAs' entry into exosomes [156]. Of note, it has been reported that m^6A modification of circ-CDYL promoted the exosomal sorting of circ-CDYL [143]. However, the role of RNA modification in the process of circRNA entering exosomes still needs further investigation.

Mechanism under cellular stress

When cells are exposed to external stimuli or stress conditions, the composition and release of exosomes may change, which in turn affects the types and amounts of circRNAs contained in them. This change may be related to the biological response of cells under stress [157]. For example, the characteristics of exosomal circRNAs observed in tumor development, immune response, and

metabolic diseases are different from those under normal conditions, so exosomal cirRNAs can also be employed as diagnostic markers for multiple kinds of diseases [158, 159].

These studies provide some clues for understanding the mechanism of circRNAs' entry into exosomes, but further experimental validation and in-depth research are still needed. With the continuous advancement of technology and a deeper understanding of exosome biology, more mechanisms regarding the entry of circRNAs into exosomes will be revealed.

Exosomal circRNAs in NSCLC

In recent years, the research interest in the exosomal circRNAs in NSCLC has rapidly increased. We conducted a search on the PubMed website for all articles on the research of exosomal circRNA in NSCLC published before August 12, 2024. After manual verification and exclusion of reviews and retracted articles, a total of 30 articles have been identified as target articles to be included in our review.

Exosomal circRNAs and angiogenesis

Angiogenesis is one of the pivotal areas of investigation in oncology due to its crucial role in tumor progression. In particular, angiogenesis plays an integral part in NSCLC, facilitating the growth and metastasis of tumor cells by establishing a robust vascular network that supplies essential nutrients and oxygen. This network supports the sustained proliferation of cancer cells and enables their dissemination throughout the body via the bloodstream. Research has uncovered novel mechanisms underlying NSCLC tumorigenicity, with one study highlighting that cancer-released exosomal circ0008717 promotes angiogenesis in NSCLC progression. The number of formed branches of human umbilical vein endothelial cells (HUVECs) was reduced in the si-circ_0008717 group. Mechanism studies showed that exosomal circ0008717 specifically targeted the miRNA-1287-5p/P21-activated kinase 2 (PAK2) axis to speed up NSCLC advancement [160].

Exosomal circRNAs and lung cancer proliferation, migration, and invasion

Exosomal circRNAs exhibit a substantial impact on proliferation, metastasis, angiogenesis, and apoptosis of NSCLC. Chen et al. reported that the upregulation of NSCLC cell-derived exosomal circFARSA leads to increased metastasis of NSCLC cells, which is prompted by the induction of M2 polarization via the ubiquitylation and degradation of PTEN, ultimately activating the PI3K/AKT pathway [161]. CircSHKBP1 was upregulated in NSCLC tissues and cell lines and was enriched in their exosomes. It was proved that circSHKBP1 within exosomes promotes NSCLC proliferation, migration, invasion, and stemness [162]. Fang et al. proved that serum-derived exosome-mediated circARHGAP10 drives NSCLC cell growth via the miR-638/FAM83F pathway [163]. Additionally, high expression of circ-PLK1 in serum exosomes enhances HMGA1 levels by sponging miR-1294 and promotes the growth of NSCLC [164]. It has shown that the up-regulated expression of has-circ-0002130 in serum exosomes of patients with ocitinib-resistant NSCLC promotes NSCLC progression [165]. Moreover, Ning et al. found that exosomal circ0007385 promotes the NSCLC process by targeting miR-1253 and FAM83A [166]. The abundance of circCD226 was elevated in serum exosomes of NSCLC. Exosomal circCD226 can promote NSCLC advancement via the miR-1224-3p/HMGA2 axis [167]. Furthermore, exosomal circPIP5K1A relies on the miR101/ABCC1 axis, enhancing the proliferation and migration of NSCLC cells [168]. It was found that circCCDC134 highly expressed in the serum exosomes of NSCLC patients. Exosomal circCCDC134 regulates NFAT5 by sponging miR-625-5p and promotes the NSCLC process [169]. Circ_0002476 is transported between cells by exosomes, and it is found that circ-0002476 promotes NSCLC progression and mtDNA damage via the miR-1182/TFAM axis [170]. Zhang et al. observed that circSATB2 was highly upregulated in NSCLC cells and tissues. Databases for circRNA-miRNA binding prediction and FISH (fluorescence in situ hybridization) to detect the sublocalization of circRNAs were utilized. Mechanism studies revealed that circSATB2 positively regulated fascin homolog 1, actin-bundling protein 1 (FSCN1) expression by sponging miR-326, and transits through exosomes to promote NSCLC progression, NSCLC progression, and may stimulate anomalous growth in healthy bronchial epithelial cells [32]. Exosomal ERBB2IP is pivotal in promoting tumor growth in NSCLC by upregulating PSAT1 expression [171]. Additionally, exosomal circ-0008928 inhibits NSCLC development through the miR-488/HK2 axis [172]. Wang et al. proved that a hypoxia-induced exosomal circPLEKHM1 facilitates PABPC1-eIF4G interaction to promote NSCLC cell metastasis by increasing OSMR expression and M2 polarization of macrophages [173]. In the experiment of Liu et al., circPLK1 highly expressed in serum exosomes from NSCLC patients, and it was demonstrated that glycolysis and NSCLC progression can be accelerated through the circFTO/miR-148a-3p/PDK4 axis [174]. These studies demonstrate that exosomal circRNA is involved in multiple aspects of NSCLC progression (Fig. 3; Table 1), suggesting it may be a potential therapeutic target that requires further investigation.

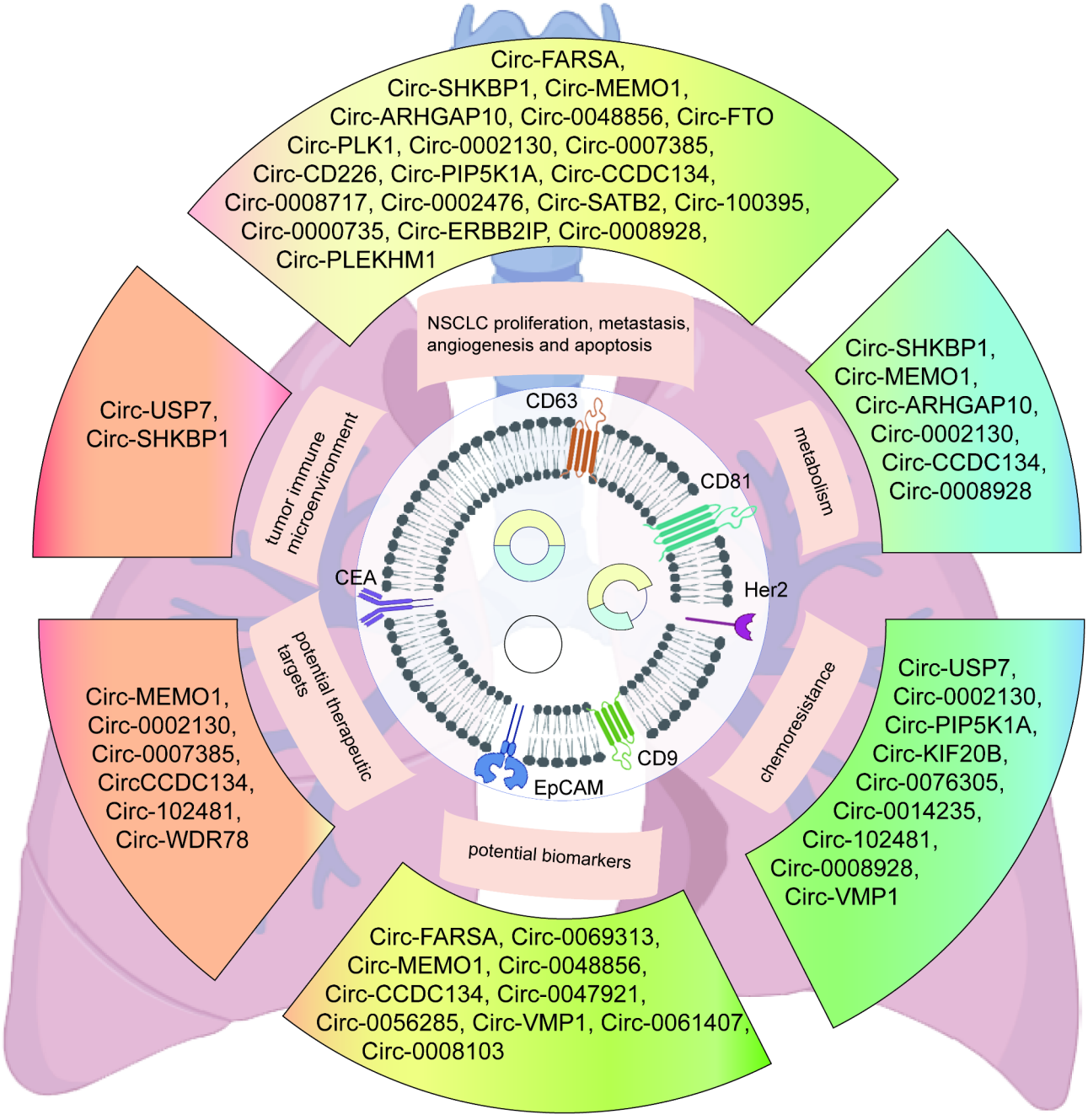

Fig. 3 Diagram of the functions of exosomal circRNAs in various aspects of NSCLC. The functions of exosomal circRNAs in NSCLC include lung cancer proliferation, metastasis, angiogenesis and apoptosis, in addition to playing roles in metabolism, tumor immune microenvironment, and chemoresistance, making exosomal circRNAs potential biomarkers and therapeutic targets

Exosomal circRNAs and metabolism

Altered energy metabolism is a hallmark of malignancies as a result of the necessity to provide the essential nutrients for tumorigenesis and advancement, and the swift growth of cancer cells is dependent on glycolysis [175, 176]. Chen et al. have found that exosomal circSHKBP1 modulates glycolysis with the aid of PKM2 in a HIF-1α-dependent manner, promoting NSCLC progression [162]. Ding et al. have investigated that knocking down serum exosomal circ-MEMO1 inhibits glucose absorption and attenuates lactate synthesis, indicating its role in promoting glycolysis in them [177]. Elevating serum-derived exosome-mediated circARHGAP10 leads to a significant increase in glucose consumption and lactic acid production, contributing to glycolysis in NSCLC cells [163]. Furthermore, exosomal hsa-circ0002130 influences glycolysis in osimertinib-resistant NSCLC cells by conducting as miR-498 sponge and facilitating the modulation of

Table 1 Exosomal circRNAs in non-small cell lung cancer

Research Subjects	Circular RNA	Effects	Targets or pathways	References
Immortalized human bronchial epithelial cells (BEAS-2B), human lung cancer cell lines (A549, H460, H1299, H226, MES-1), NSCLC and matched normal adjacent tissue samples	Circ-SATB2	Progression of NSCLC↑	miR-326↓, FSCN1↑	N.Zhang et al. (2020) [32]
Tumor tissues, adjacent normal tissues, and blood samples, Human NSCLC cell lines (A549 and H1299) and bronchial epithelial cells (BEAS-2B)	Circ-0008717	Cell tumorigenicity and angiogenesis in NSCLC↑	miR-1287-5p↓, PAK2↑	H.Wang et al. (2022) [160]
Human NSCLC cell lines (A549, H1299, H460, H226, PC9), THP-1 cells	Circ-FARSA	NSCLC metastasis↑	M2 macrophage polarization↑ PTEN/PI3K/AKT pathway↑	T.Chen et al. (2021) [161]
The human normal lung epithelial cell line HBE, human lung cancer cell lines (A549, PC9, 1650, and H1299)	Circ-SHKBP1	Proliferation, migration, invasion, stemness of NSCLC cells↑	miR-1294↓, PKM2 expression↑, glycolysis↑	W.Chen et al. (2022) [162]
Patient plasma, Normal lung cell BEAS-2B and NSCLC cell lines A549 and H292	Circ-ARHGAP10	Proliferation, migration, invasion, glycolysis of NSCLC cells↑	miR-638↑, FAM83F↑	K.Fang et al. (2022) [163]
NSCLC tumors and their adjacent normal tissues, CALU3, CALU6, A549, H1229, H1975 cells	Circ-PLK1	Malignant phenotype of NSCLC cells↑, the progression of NSCLC↑	miR-1294↓, HMGA1↑	C.Li et al. (2022) [164]
Patient NSCLC tissues, cell lines HCC827 and H1975	Circ-0002130	Osimertinib-Resistance in NSCLC↑	miR-498↓	J.Ma et al. (2020) [165]
NSCLC tissue samples, NSCLC cells (A549 and H1299), human bronchial epithelial cells (BEAS-2B)	Circ-0007385	NSCLC proliferation and stemness↑	miR-1253↓, FAM83A↑	Z.Ning et al. (2022) [166]
human HCC827, A549, H1755 and H1299, NSCLC cells and bronchial airway epithelial BEAS-2B cells (CRL-9609)	Circ-CD226	NSCLC cell proliferation, migration, invasion, stemness↑	miR-1224-3p↓, HMGA2↑	L.Peng et al. (2022) [167]
NSCLC tissues and blood samples, human normal bronchial epithelial cells (16HBE) and NSCLC cells (A549 and 1299)	Circ-PIP5K1A	Progression of NSCLC cells↓, cisplatin sensitivity↑	miR-101↓, ABCC1↑	N.Shao et al. (2021) [168]
NSCLC tumor tissues, Human NSCLC cells (H1299, HCC827, PC9, and A549) and a normal bronchial epithelial cell line (BEAS-2B)	Circ-CCDC134	NSCLC cell growth, metastasis, glycolysis↑	miR-625-5p↓, NFAT5↑	Z.Tong et al. (2023) [169]
Tumor tissues, Human NSCLC cells (H1299 and A549) and bronchial epithelial cells (16HBE)	Circ-0002476	NSCLC cell growth, invasion↑, mtDNA damage↓	miR-1182↓, PAK2↑	W.Wang et al.(2022) [170]
NSCLC blood samples, NSCLC cells A549 and H1299	Circ-ERBB2IP	Tumor growth in NSCLC↑	miR-5195-3p↓, PSAT1↑	X.Peng et al. (2023) [171]
Human NSCLC cell lines (A549, H1299, H661, and SKMES-1), human normal bronchial epithelial cell line 16HBE, and human embryonic kidney cell line 293T	Circ-0008928	CDDP sensitivity↓, cell proliferation, migration, invasion, glycolysis metabolism↑	miR-488↓, HK2↑	Q.Shi et al. (2023) [172]
Human monocyte/macrophage cell line THP-1, human NSCLC lines A549 and H1299	CircPLEKHM1	NSCLC cell metastasis↑	OSMR expression↑, m2 polarization of macrophages↑	D.Wang et al. (2024) [173]
LC tissues and paracancerous tissues, NSCLC cell lines (HCC1833, A549), male nude mice	CircFTO	Glycolysis and NSCLC progression↑	miR-148a-3p↓, PDK4 expression↑	Q.Liu et al. (2024) [174]
Patient NSCLC tissues, Serum samples, NSCLC cell lines (H1650, PC9, H1299, and A549)	Circ-MEMO1	Proliferation, cell cycle progression, glycolytic metabolism of NSCLC cells↑, the apoptosis of NSCLC cells↓	miR-101-3p↓, KRAS level↓	C.Ding et al. (2020) [177]
Patient NSCLC tissues, Patient plasma, CD8 + T cell, NCI-H460, NCI-H1299, A549, PC9, 95D, HBE	Circ-USP7	IFN-γ, TNF-α, Granzyme-B and Perforin secretion by CD8 + T cells↓; CD8 + T cell function↓; anti-PD1 immunotherapy resistance↑	miR-934↓, SHP2 expression↑	S.Chen et al. (2021) [179]
NSCLC tissues, NSCLC cells (A549 and H1299) and human bronchial epithelial cells (16HBE; non-cancer cells)	Circ-0014235	DDP chemoresistance↓, deteriorates the development of NSCLC	miR-520a-5p↓, CDK4↑	X.Xu et al. (2020) [181]
NSCLC A549/DDP and H1299/DDP cells	Circ-VMP1	NSCLC progression and cisplatin (DDP) resistance↑	miR-524-5p↓, METTL3/SOX2↑	H.Xie et al. (2022) [182]

Table 1 (continued)

Research Subjects	Circular RNA	Effects	Targets or pathways	References
Serum from NSCLC patients, human bronchial epithelial cells (BEAS-2B) and NSCLC cell lines (A549 and H292)	Circ-0076305	Cisplatin (DDP) resistance of NSCLC↑	miR-186-5p8↓, ABCC1↑	X.Wang et al. (2023) [183]
NSCLC and matched normal tissues, PC9GR and HCC827GR (gefitinib-resistant NSCLC cell lines)	Circ-KIF20B	Gefitinib resistance and cell proliferation↓	miR-615-3p↓, MEF2A↑	S.Wei et al. (2023) [184]
NSCLC patients treated with EGFR-TKIs, the gefitinib sensitive cell lines PC9 and the corresponding gefitinib resistant cell lines PC9/GR, the erlotinib sensitive cell lines HCC827 and the corresponding erlotinib resistant cell lines HCC827/ER	Circ-102,481	EGFR-TKIs resistance in NSCLC↑	miR-30a-5p↓, ROR1↑	B.Yang et al. (2021) [185]
NSCLC tissues, A549, H1650, H460, H1299 from the NSCLC cell line along with 16 HBE-T from a cell line of human bronchial epithelial cell	Circ-100,395	Malignant Transformation of NSCLC↓, epithelial mesenchymal transition↓	miR-141-3p↓, LATS2 ↑	C.Zhang et al. (2021) [186]
NSCLC cells (A549 and H1299) and normal bronchial epithelial cells (BEAS-2B)	Circ-000735	Non-small lung cancer malignant progression↑, epithelial mesenchymal transition↓	miR-345-5p↓, ADAM19↑	S.Liu et al. (2023) [187]
Patient plasma, Serum exosome isolation	Circ-0069313, Circ-0063526, Circ-0010522, Circ-0048677, Circ-0001946	Hsa-circ-0069313 have the potential to discriminate NSCLC	None	Y.Chen et al. (2022) [188]
Patients' blood samples	Circ-0048856	NSCLC development↑	miR-1287–5p↓	Y.He et al. (2022) [189]
NSCLC patient plasma, serum exosome isolation	Circ-0047921, Circ-0056285, Circ-0007761	Circ-0047921 could distinguish NSCLC cases from COPD controls, circ-0056285 and circ-007761 combination could distinguish NSCLC cases from tuberculosis controls	None	J.Xian et al. (2020) [190]
Patient plasma, NSCLC cell line (NCI-H1299, A549, SPC-A-1, LTEP-A2, and Beas-2B)	Circ_0061407, Circ_0008103	Proliferation, migration, invasion capabilities of NSCLC cells↓	None	Z.Chen et al. (2024) [191]
A549 and H2170 cell lines, Tanreqing	Circ-WDR78	Proliferation and migration of NSCLC↓	HIF1α↓	W.Hong et al. (2023) [193]

GLUT1, HK2, and LDHA, which are key factors involved in glycolysis [165]. Exosomal circCCDC134 contributes to NSCLC development by suppressing the glucose utilization, lactate generation, and ATP levels of PC9 and A549 cells to hinder glycolysis [169]. It is shown that exosomal circ-0008928 inhibits the glycolytic metabolism of NSCLC via the miR-488/HK2 axis [172] (Fig. 3; Table 1).

Exosomal circRNAs and tumor immune microenvironment

The tumor immune microenvironment is a dynamic ecosystem in which cancer cells interact with stromal components, immune cells, and various soluble factors in complex ways. In this microenvironment, exosomes have gained attention due to their potential dual role as drivers of tumor development and regulators of immune responses [8]. Research has revealed that exosomal circRNAs function as innovative genetic information molecules which can facilitate the interaction between malignant cells and microenvironmental cells [35, 178]. Chen and colleagues have demonstrated that exosomal circUSP7 suppresses the activities of CD8 + T cells by increasing the levels of Src homology region 2 (SH2)-containing protein tyrosine phosphatase 2 (SHP2) through sequestering miR-934 [179] (Fig. 3; Table 1). These studies indicate that exosomal circRNAs affect NSCLC by regulating specific components in the tumor immune microenvironment. However, as a complex and dynamically changing microenvironment, the exact regulatory role of exosomal circRNA in the tightly interconnected microenvironment of various components may not yet be fully explored when based on one or several cell lines cultured in vitro. Therefore, further research is required in this regard. (Fig. 3; Table 1).

Exosomal circRNAs and chemoresistance

More and more evidence indicates that exosomal circRNAs play an essential role in tumor chemotherapy resistance [39, 180]. Chen et al. elucidated the role of exosomal circUSP7 in anti-PD1 therapy resistance in NSCLC. ExoQuick Exosome Precipitation Solution kit

was utilized to isolate exosomes from patients' plasma. Transmission electronic microscopy (TEM), NanoSight, and western blotting were employed to characterize exosomes. CircRNA precipitation (circRIP) and luciferase reporter revealed that exosomal circUSP7 blocked CD8 + T cell function by enhancing the expression of Src homology region 2 (SH2)-containing protein tyrosine phosphatase 2 (SHP2) through sponging miR-934, inducing CD8 + T cell dysfunction and diminishing the efficacy of anti-PD1 therapy in NSCLC [179]. Exosomal circ_PIP5K1A decreases the sensitivity of NSCLC to cisplatin therapy by sponging miR-101 [168], and overexpression of circ_0014235 in NSCLC serum-derived exosomes increases the resistance of A549 and H1299 cells to cisplatin (DDP) [181]. In addition, expression of circ_0008928 increased in serum exosomes of CDDP-resistant NSCLC patients promotes CDDP resistance in NSCLC [172], and serum exosomal circVMP1 knockdown exhibits inhibitory effects on resistance to cisplatin (DDP) [182]. Furthermore, circ_0076305 increased in NSCLC cell-derived exosomes can promote DDP resistance within NSCLC cells by modulating ABCC1 via miR-186-5p [183]. Increasing exosome-derived circKIF20B restores gefitinib sensitivity by modulating the cell cycle, accelerating apoptosis, and reducing mitochondrial oxidative phosphorylation [184]. A recent study showed that exosomal circRNA_102481 derived from tumor cells exerts a significant function in the advancement of resistance to EGFR-TKIs (epidermal growth factor receptor tyrosine kinase inhibitors) in NSCLC mediated through the miR-30a-5p/ROR1 axis [185]. (Fig. 3; Table 1).

Exosomal circRNAs and apoptosis

Apoptosis is a fundamental mechanism in tumor biology that ensures cellular homeostasis and eliminates potentially oncogenic cells. In NSCLC, apoptosis functions as a crucial checkpoint, curbing the uncontrolled proliferation of cancer cells and thereby influencing disease progression and therapeutic responsiveness. Ding et al. have shown that the silencing of exosomal circMEMO1 potently induces apoptosis in NSCLC cells, whereas its overexpression significantly dampens the apoptotic rate. Further mechanism exploration revealed that the downregulation of exosomal circ-MEMO1 inhibits NSCLC tumor growth by decreasing KRAS protein expression and elevating miR-101-3p levels [177].

Exosomal circRNAs and epithelial mesenchymal transition

Epithelial-mesenchymal transition (EMT) plays a crucial role in the progression of non-small cell lung cancer (NSCLC) by enhancing cancer cell mobility and invasiveness, which is characterized by the downregulated expression of the epithelial cadherin (E-cadherin) and upregulated expression of the mesenchymal cadherin (N-cadherin and Vimentin). Zhang et al. demonstrated that overexpression of exosomal circ_100395 hampered the EMT of H1650 cells and the Hippo/YAP pathway, thereby inhibiting NSCLC advancement [186]. Liu et al. observed that downregulated expression of exosomal circ_0000735 enhanced E-cadherin expression and decreased the expression of N-cadherin and Vimentin, indicating the potential of exosomal circ_0000735 to induce EMT in NSCLC [187]. These findings highlight the potential of exosomal circ_100395, and circ_0000735 in regulating NSCLC progression through its influence on EMT.

Therapy potential of Exosomal circRNAs in NSCLC

Exosomal circRNAs are widely involved in various physiological and pathological processes, and their roles as biomarkers, therapeutic targets, and therapeutic agents are being extensively investigated. In non-small cell lung cancer, current research primarily focuses on the exploration and validation of diagnostic biomarkers and therapeutic targets.

Regarding clinical biomarkers, exosomal circRNAs present potential as diagnostic biomarkers for NSCLC. It has been shown that exosomal circFARSA can facilitate communication between macrophages and NSCLC cells via the PTEN/PI3K/AKT pathway, highlighting its potential as a promising biomarker for the diagnosis of NSCLC [161]. Serum exosomal hsa_circ_0069313 can differentiate benign lung tumors from NSCLC with AUC values of 0.803 and 0.749, respectively [188]. Moreover, serum exo-circ-MEMO1 [177], exo-circ_0048856 [189], and exosomal circCCDC134 [169] also show diagnostic potential for NSCLC. Xian et al. reported that in serum exosomes, circ0047921 exhibits the ability to distinguish between NSCLC cases and COPD controls, and the combination of circ0056285 and circ-0007761 shows potential in distinguishing NSCLC cases [190]. In addition, Chen et al. demonstrated that encapsulated within exosomes, circ_0061407 and circ_0008103 are transported to recipient cells, having good diagnostic value for NSCLC [191]. Also, the expression of serum exosomal circVMP1 is significantly upregulated in DDP-resistant NSCLC patients, which shows its diagnostic value [182] (Fig. 3; Table 1).

In recent years, targeted therapy has become a therapeutic tool in oncological therapy, replacing chemotherapy, which is prone to side effects and drug resistance [166, 192]. CircRNAs with anticancer properties, which are facilitated by extracellular vesicles, have the ability to enter tumor cells or hinder their production, so they hold promise as therapeutic targets and the basis for developing circRNA-based therapies [175]. Has-circ-0002130 was upregulated in serum exosomes from osimertinib-resistant NSCLC patients. Hsa-circ-0002130 knockdown suppresses cancer development in vivo, making it a potential therapeutic target for osimertinib-resistant

NSCLC. It also significantly promotes the advancement of oxitinib-resistant NSCLC [165]. Similarly, the suppression of exosomal circ-0007385 inhibited the advancement of NSCLC by modulating the expression of miR-1253 and FAM83A [166]. Additionally, the inhibition of exosomal circCCDC134 effectively suppresses the growth, metastasis, and glycolysis of NSCLC [169]. Exosomes secreted by Tanreqing-treated NSCLC cells deliver circ-WDR78 to untreated NSCLC cells, thereby curbing the malignancy of the recipient tumor cells [193]. These all indicate the great potential of exosomal circRNAs as potential therapeutic targets for NSCLC treatment (Fig. 3; Table 1). However, further investigation is required to determine their specific physiopathology activities and underlying mechanisms in NSCLC.

However, regarding therapeutic agents based on exosomal circRNAs, relevant research in NSCLC is still in its infancy. Despite the promising results obtained from studies on diagnostic biomarkers and therapeutic targets, the development of circRNA-based therapeutic agents requires further investigation. Future efforts should be directed towards exploring the specific physiopathology activities and underlying mechanisms of exosomal circRNAs in NSCLC, as well as optimizing their therapeutic potential.

Conclusions and perspectives

Extracellular vesicle-derived circRNA is closely associated with the occurrence and progression of NSCLC. It participates in various mechanisms involved in NSCLC development, including promoting tumor proliferation, metastasis, angiogenesis, and apoptosis. It can also suppress anti-tumor immune response, regulate NSCLC immune evasion, and induce chemotherapy resistance. Furthermore, an increasing number of extracellular vesicle-derived circRNAs have been identified as potential early diagnostic markers and therapeutic targets for NSCLC, such as circ0047921, circFARSA, circ0069313, and circCCDC134.

In recent years, some clinical trials and applications on exosomes, exosomal RNA and NSCLC have begun to be implemented. Clinical trials have been registered to predict the immunotherapeutic effects, efficacy, and adverse reactions of anlotinib in the treatment of advanced NSCLC using exosome detection (NCT04427475, NCT05218759) [194, 195]. However, exosomal circRNAs have not yet been applied in clinical settings. This may be due to technical challenges in detecting specific circRNAs in exosomes, as circRNAs have common exonic sequences with their corresponding linear counterparts. Furthermore, the obstacles of exosome purification and circRNA extraction also limit the clinical validation of the reliability of exosomal circRNAs as diagnostic markers and therapeutic targets [36]. However, the rapidly developed sequencing technology and droplet digital PCR (ddPCR) with high specificity and sensitivity are increasingly being used in liquid biopsies, which are more suitable for testing with a limited size of patient cohorts. Moreover, machine learning combined with ddPCR is being utilized to upgrade the accuracy of clinical applications [196]. Moreover, novel modalities for exosomal circRNA detection depended on electrochemistry, rolling circle amplification and biosensors are gradually emerging [197, 198]. Excitingly, various engineering materials science methods are widely used to study noncoding RNAs and exosomes, which significantly expands their application scenarios [64, 199, 200]. In recent years, engineered exosomes designed with additional surface features and medicinal compounds within their structure, such as antitumor drugs and siRNA, have attracted increasing attention, particularly in the field of cancer, due to their temporal and spatial targeting capability [66, 94, 201, 202]. However, despite the increasing reports on exosome engineering strategies, there is still a lack of ideal targeting molecules that can guide exosomes to tumor sites to prevent them from being absorbed by normal cells. Notably, the anticancer potential of circRNAs is currently under extensive investigation. Consequently, engineered exosomes carrying these circRNAs may exhibit heightened anticancer efficacy and reduced side effects. Moreover, significant progress has been made in the synthesis of circRNA with biological functions in vitro, which increases the clinical value of circRNA with low expression levels but high anti-cancer activity. However, artificially synthesizing circRNAs still faces the problems of standardization and immunogenicity [203]. In addition, the size of circRNA molecules may affect their efficiency in loading into exosome. More and more evidence show that the nanoparticle-based circRNA delivery system could also be a highly valuable therapeutic strategy. Research shows that a lipid nanoparticle system for delivering circRNA can activate the adaptive immune response and demonstrate excellent anti-tumor effects in various murine maligancy models, providing novel prospects for the advancement of tumor circRNA vaccines.

Excitingly, in addition to the mentioned techniques of exosome engineering and artificial synthesis of circRNA, 3D bioprinting has gained extensive attention in recent years and demonstrated tremendous potential in the field of tumor research due to its significant advantages in closely simulating in vivo conditions. Research has shown that 3D bioprinting can simulate various tumor microenvironments [204–207], thereby providing strong support for studying the cancer biology and enhancing medical intervention of tumors. As an important component of the tumor microenvironment, exosomes play a crucial role in the intercellular communication between various cells within the tumor microenvironment. Clearly elucidating the role and precise

molecular mechanisms by which exosomes mediate intercellular communication in tumor microenvironment holds great potential for both treating cancer and achieving personalized therapy. It is worth noting that exosomes will receive significant technical support in exploring their biological role in tumor progression through 3D bioprinting. Most essentially, 3D bioprinting provides high submicron scale resolution and precise spatiotemporal control, which can be utilized to incorporate and direct the gradient release of exosomes, including engineered and natural exosomes. Furthermore, screening for synthetic circRNA with ideal biological functions is crucial for its clinical translation. Compared to traditional 2D cell culture-based screening, 3D bioprinting will provide a more physiologically relevant environment for circRNA screening and overcome many limitations of in vivo experiments. Therefore, 3D bioprinting will inevitably promote the clinical translation of exosome and circRNA. In the future, people will witness the clinical applications of 3D bioprinting in facilitating the targeted gradient release of engineered exosomes carrying artificially synthesized circRNAs to exert biological functions in specific diseases. Moreover, hydrogels are confirmed to possess substantial adjustability, biocompatibility, degradability, and physical characteristics akin to tissues. The synergistic combination of exosomes and hydrogels promotes the efficiency of exosomes' activities, which holds enormous potential for future application.

Intriguingly, the research on plant or food exosomes in drug delivery has gained widespread attention due to their advantages of a lower cost, broader availability, and easy accessibility [208, 209]. Exosome-like nanovesicles generated from Yam possess a capability to promote the biogenesis of osteoblasts and protect against osteoporosis [210]. Bovine milk-derived exosomes show cross-species tolerance in drug delivery without adverse immune and inflammatory responses [208]. Nevertheless, natural exosomes exhibit certain limitations, such as their heterogeneity, which may diminish their anti-cancer efficacy and even promote tumor progression.

Future studies delving into exosomal circRNAs across various biological settings and diseases such as cancer will continue to unravel the enigma surrounding exosomal circRNAs and benefit humankind.

Abbreviations

NSCLC	Non-small cell lung cancer
circRNA	Circular RNA
EMT	Epithelial-to-mesenchymal transition
LC	Lung cancer
LCCDEs	Lung cancer cell-derived exosomes
EIciRNAs	Exon-intron circRNAs
EcircRNAs	Exonic circRNAs
CiRNAs	Circular intronic RNAs
BP	Branching point
RBPs	RNA binding proteins
ESRP1	Epithelial splicing regulatory protein1
A5SS	Alternative 5′ splicing site
m^6A	N6-methyladenosine
PAK2	P21-activated kinase 2
EGFR-TKIs	Epidermal growth factor receptor tyrosine kinase inhibitors
ddPCR	Droplet digital PCR

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Author contributions
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Data availability
All data generated or analyzed during this study are included in this article.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
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Competing interests
The authors declare that they have no competing interests.

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