Effects of circulating RNAs on tumor metabolism in lung cancer (Review)

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Received November 19, 2024; Accepted February 13, 2025

DOI: 10.3892/ol.2025.14950

Abstract. During the development and progression of lung cancer, cell metabolism function is altered. Thus, cells rely on aerobic glycolysis and abnormal lipid and amino acid metabolism to obtain energy and nutrients for growth, proliferation and drug resistance. Circular RNAs (circRNAs), a class of non-coding RNAs, serve important biological roles in the growth and development of tumors. Functionally, circRNAs act as molecular sponges that absorb microRNAs (miRNAs) and RNA-binding proteins and as protein scaffolds that regulate gene transcription and translation through the maintenance of mRNA stability. In addition, circRNAs are important regulators of tumor metabolism and promote tumor progression through mediating tumor cell proliferation, metastasis and the induction of chemoresistance. Results of previous studies reveal that circRNAs may serve a key role in regulating tumor metabolic processes in lung cancer, through miRNA sponging and alternative mechanisms. Thus, circRNAs demonstrate potential as therapeutic targets for lung cancer. The present study aimed to review the effects of circRNAs on lung cancer cell metabolism and provide novel insights into the clinical treatment of lung cancer. The present review may also provide a novel theoretical basis for the development of lung cancer drug targets.

Contents

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Key words: circular RNAs, lung cancer, tumor metabolism, therapeutic target

1. Introduction

Lung cancer is one of the most common malignant tumors, with the highest morbidity and mortality rates worldwide. According to the American Cancer Society, ~350 individuals succumb to lung cancer each day (1). In addition, lung cancer is the most common cause of cancer-associated mortality and morbidity and mortality rates are continually increasing (2). Notably, lung cancer is divided into two major histological types; namely, non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) (3), with NSCLC accounting for ~85% of all lung cancer cases (4). NSCLC is characterized by early metastasis, high rates of recurrence and a lack of symptoms in the early stage of disease that leads to late-stage diagnosis in the majority of patients. Although treatment options, including surgery, radiotherapy, chemotherapy, molecular targeted therapy and anti-angiogenic drugs, have improved the survival rates of patients (5), tumor heterogeneity, drug resistance and immune side effects remain challenging, leading to poor clinical outcomes. Thus, further explorations into the mechanisms underlying lung cancer progression may aid in the development of novel, effective therapeutic targets.

Circular RNAs (circRNAs) are a class of endogenous non-coding RNA (6). CircRNAs differ from classical linear RNAs, forming covalently-closed and stable loops through precursor-specific shearing. Notably, these are resistant to nucleic acid exonuclease-mediated digestion (7), leading to higher levels of stability and abundance compared with linear RNAs (8). Previous studies have suggested that circRNAs are products of incorrectly sheared precursor mRNAs. However, improvements in high-throughput technologies have led to the discovery of numerous types of circRNAs that exert regulatory effects on gene expression in eukaryotic organisms and these serve a role in the development of a variety of diseases (9). For instance, research indicates that hsa_circ_0002005 exhibits overexpression in OS tissues and cells, with its downregulation leading to a decrease in cellular proliferation, migration, invasion and metastatic capabilities (10). Moreover, circRNAs

may act as molecular signals that interact with other RNAs or proteins (11), regulating the expression of downstream genes through several mechanisms. CircRNAs may also participate in a variety of oncogenic signaling pathways, which, in turn, are involved in the regulation of gene transcription and protein translation (12). Notably, circRNAs may act as microRNA (miRNA) sponges that compete with miRNAs for binding sites, thus regulating miRNA activity to affect the expression of their target proteins (13). For example, circRNA_000166 inhibits the proliferation and apoptosis of breast cancer cells through the miR-326/ETS transcription factor ELK1 (ELK1) and miR-330-5p/ELK1 pathways (14). In lung cancer, circRNAs regulate apoptosis-associated genes and signaling pathways through various mechanisms, thereby affecting the apoptosis of lung cancer cells. For example, circ_0000620 exerts its effects on lung adenocarcinoma (LUAD) cell apoptosis through the miR-216b-5p/KRAS signaling pathway (15). In addition, circRNA circHIPK3 inhibits the apoptosis of NSCLC cells by regulating the expression of apoptosis-associated protein forkhead box protein M1 (16).

Results of a previous study indicated that circRNAs are closely associated with proliferation, metastasis and drug resistance in tumor cells (17). Overexpression of circRNA_102171 promoted papillary thyroid cancer progression via activation of the catenin β interacting protein 1-dependent Wnt/β-catenin pathway (18). Moreover, results of a previous study revealed that tumor-associated macrophage-induced circMRCKα encodes a peptide that facilitates glycolysis, ultimately accelerating hepatocellular carcinoma progression (19). Therefore, circRNAs may serve a key role in the regulation of cancer progression (20). The aberrant expression of circRNA is associated with the pathophysiology of numerous diseases; thus, current research is focused on the use of circRNAs as potential diagnostic biomarkers and therapeutic targets (21). Research has shown that circKIAA0182 promotes cisplatin resistance and tumor progression in NSCLC both *in vitro* and *in vivo* (22).

Nutrients, energy and biosynthetic activity are required for cell metabolism and function (23). Glucose, lipid and amino acid metabolism are the key metabolic pathways in eukaryotic organisms and these processes are balanced and interconnected to provide nutrients and energy for cell growth and development. However, tumor cells exhibit a loss of function of energy metabolism and undergo reprogramming of glucose, lipid and amino acid metabolism. Through metabolic reprogramming, tumor cells obtain high levels of energy and nutrients that are required for proliferation and growth. Results of a previous study demonstrated that N-acetyltransferase 10/N4-acetylcytidine/forkhead box protein P1 axis may promote the malignant progression and immunosuppression of cervical cancer through reprogramming glycolytic metabolism (24). Thus, metabolic reprogramming may serve a key role in tumor development.

Due to the heterogeneity of tumors, the metabolic requirements of tumor cells in different states change according to the developmental process of NSCLC (25). The metabolic reprogramming of tumor cells creates high levels of energy and nutrients, subsequently impacting tumor growth and cell proliferation (26). Results of a previous study highlight that circRNAs are critical contributors to both cancer progression and metabolic reprogramming (27). The present review aimed to discuss the mechanisms underlying the circRNA-mediated metabolic reprogramming of lung cancer cells and aimed to provide a novel theoretical basis for the clinical treatment of NSCLC.

2. Characterization and function of circRNAs

CircRNAs are covalently-closed non-coding RNAs formed through the reverse shearing of precursor mRNAs. Notably, circRNAs are not affected by the action of nucleic acid exonucleases and are stably expressed in the human body with high tissue specificity. Exonic circRNA is the most common subtype of circRNAs, accounting for ~80% of all identified circRNAs (28). CircRNAs were discovered in *Murine respirovirus* using electron microscopy (29) and were initially considered by-products of incorrect shearing (30). However, developments in bioinformatics and high-throughput sequencing technologies have furthered the understanding of circRNAs and results of a previous study demonstrated that these are widely expressed in eukaryotic organisms (31). CircRNAs are species-conserved, tissue-specific, disease-specific and serve key regulatory roles as epigenetic regulators in a variety of diseases (32).

CircRNAs also act as miRNA molecular sponges that bind miRNAs through competing endogenous (ce)RNA mechanisms to regulate the expression of downstream target genes. CeRNA is not a specific type of RNA, but rather a regulatory mechanism. In this mechanism, different types of RNAs (such as mRNA, lncRNA, circRNA, etc.) can interact through common microRNA (miRNA) response elements (MREs) and competitively bind to the same miRNA, thereby regulating each other's expression levels. In addition, circRNAs act as protein decoys or scaffolds that bind to single proteins or chelate with multiple proteins for the formation of circRNA-protein complexes. Thus, circRNAs may directly or indirectly affect the expression of target proteins. Liang *et al* (33) demonstrate that circDCUN1D4 acts as a scaffold for the formation of the protein ternary complex of circDCUN1D4-human antigen R-thioredoxin interacting protein (TXNIP) RNA, leading to the inhibition of NSCLC metastasis and improved TXNIP mRNA stability (33). Although circRNAs are categorized as a class of non-coding RNA without protein translational capacity, results of a previous study demonstrated that a small proportion of circRNAs may mediate translation in a non-cap-dependent manner. This process involves internal ribosomal entry sites and N6-methyladenosine (m6A) epigenetic modifications (34). Yang *et al* (35) demonstrated that circFBXW7 inhibited the occurrence of glioma through protein encoding. Specifically, circFBXW7 was able to encode a novel protein, FBXW7-185aa. This protein inhibits the development of malignant gliomas by antagonizing USP28-induced c-Myc stability and reducing the half-life of c-Myc. This finding suggests that circFBXW7 and its encoded proteins have important regulatory roles in glioma tumorigenesis and may provide new targets for the treatment of glioma. Collectively, these results demonstrated that circRNAs may impact the progression of numerous diseases, including cancer (Fig. 1). For instance, circRNA_0039480, which is abundant in plasma exosomes, exhibits heightened expression levels in individuals with gestational diabetes mellitus

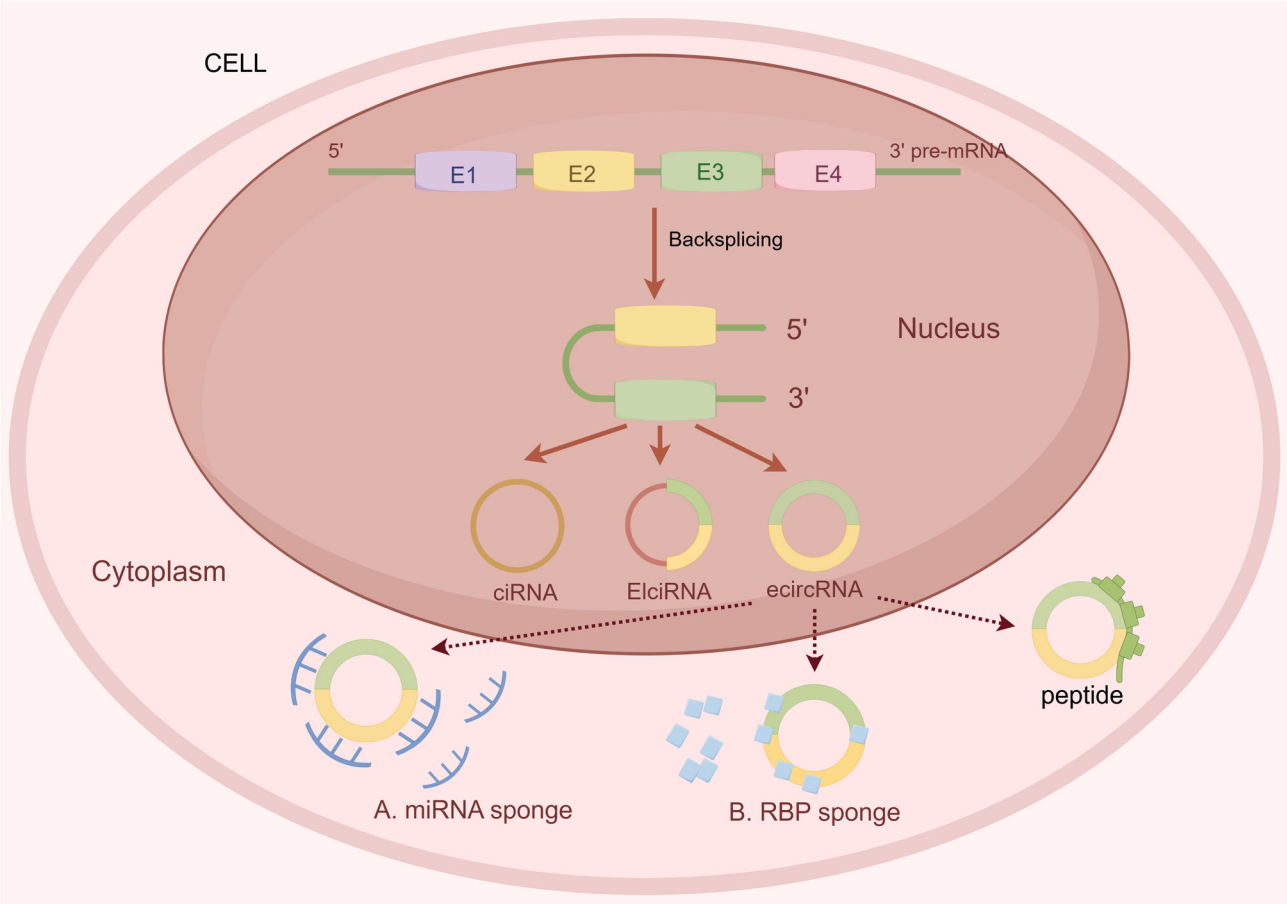

Figure 1. Production and function of circRNA. CircRNA is primarily produced through a process called back-splicing, where the 3' end of an exon invades the upstream intron and forms a lariat intermediate, which is then ligated to generate a circRNA molecule. The functions of circRNAs include miRNA sponging, RBP sponging and coding peptides. CiRNA is a covalently closed RNA molecule that stably exists within cells due to the abnormal failure of intron lariat debranching during precursor RNA splicing. EIciRNA is a circular RNA composed of both exon and intron sequences. EcircRNA is a type of circular RNA composed entirely of exons (single or multiple). It is also an important category of circRNA formed through back-splicing. The figure was created using Figdraw (www.figdraw.com). CircRNA, circular RNA; miRNA, microRNA; ciRNA, circular intronic RNA RBP, RNA-binding protein; EIciRNA, exon-intron circular RNA.

and holds potential as a biomarker for early diagnosis (36). Notably, circRNAs may exhibit potential as diagnostic and prognostic biomarkers in numerous cancer types, due to high levels of stability and specificity in expression (37). Research has demonstrated that the expression levels of circACVR2A and circCCNB1 can serve as a distinguishing marker to differentiate non-small cell lung cancer (NSCLC) between adenocarcinoma and squamous cell carcinoma subtypes (38). Furthermore, CiRS-7/CDR1as has been extensively utilized as a prognostic indicator in various cancers, including colon (39), lung (40) and breast cancer (41). This circular RNA has shown potential in predicting patient outcomes and guiding treatment strategies in these malignancies.

3. Effects of circRNAs on metabolic reprogramming in tumors

Glucose, lipid and amino acid metabolism are altered in tumor cells for the maintenance of uncontrolled cell proliferation and survival under conditions of low nutrients, low PH and a lack of oxygen. Alterations in metabolic pathways are known as metabolic reprogramming. Results of previous studies demonstrated that the metabolic reprogramming of tumors may impact the natural differentiation of tumor stem cells, leading to tumorigenesis and tumor development (42,43). Through metabolic reprogramming, tumor cells acquire high levels of ATP, lipids, proteins and nucleotides, thus promoting tumor cell growth, proliferation and metastasis.

Cancer cells are characterized by abnormalities in glucose metabolism (44) and most of the energy in tumor cells is preferentially synthesized through the glycolytic pathway, even under aerobic conditions. This process is known as the Warburg effect (45). Tumor cells utilize the metabolic pattern of aerobic glycolysis, resulting in high glucose consumption and lactic acid accumulation. The development of a hypoxic and acidic tumor microenvironment facilitates angiogenesis, invasion, metastasis and therapeutic resistance of tumor cells (46,47). Studies have revealed that tumor cells fulfill their energy requirements for rapid proliferation by enhancing glycolysis, a phenomenon known as the Warburg effect. This process not only results in the production of lactic acid but also alters the tumor microenvironment, thereby inhibiting the immune response and facilitating drug resistance (48). During the growth and development of tumors, immunosurveillance

serves a key role in eliminating and controlling malignant cells. However, tumor cells evade immunosurveillance through the increased proliferation and function of effector T-cells in the tumor microenvironment, using lactic acid produced by aerobic glycolysis (49).

Alterations in glucose metabolism also affect tumor cell growth and proliferation. Notably, glycolysis differs to oxidative phosphorylation, in that it does not utilize the tricarboxylic acid cycle pathway, providing ATP to cells in a more efficient manner. Thus, tumor cells obtain energy through glycolysis, leading to higher levels of growth and proliferation compared with healthy cells (50). Moreover, lipid metabolic reprogramming in malignant tumors cells involves fatty acid uptake and biosynthesis, fatty acid β-oxidation and lipid desaturation. In addition, amino acid metabolic reprogramming is required for tumor cell growth and development due to increased levels of amino acids and nutrients. Thus, tumor cells may mediate the activation of amino acid metabolism-associated pathways, leading to amino acid metabolism disorders and the promotion of tumor development (51).

Metabolic reprogramming also impacts glucose transporter proteins (GLUTs), metabolism-associated enzymes, transcription factors and signaling pathways and this serves an important role in sustaining tumorigenesis and progression. Results of a previous study reveal that circITCH inhibits melanoma cancer cell proliferation through the downregulation of glucose uptake via GLUT1 (52). Moreover, circRNF20 upregulated hexokinase 2 expression through the miR-487a/hypoxia-inducible factor (HIF)-1α axis, leading to the promotion of glycolysis and breast cancer development (53). Results of a previous study reveal that circMAT2B promotes glycolysis and the proliferation and invasion of hepatocellular carcinoma cells, through upregulation of pyruvate kinase muscle isozyme M2 (PKM2) by sponging miR-338-3p (54). Moreover, circ_0006677 may inhibit NSCLC progression and glycolysis during NSCLC cell growth and development, by acting as a miR-578 sponge for the regulation of suppressor of cytokine signaling 2 expression (55). Collectively, these results reveal that circRNAs serve an important role in regulating the metabolic reprogramming of tumors, leading to increased tumor cell growth and proliferation.

CircRNAs are conserved due to a specific loop structure that is resistant to nucleic acid exonucleases and are associated with numerous diseases. The metabolic environment of tumors impacts tumor cell survival and previous studies have demonstrated the key regulatory role of circRNAs in the tumor metabolism network. CircRNAs may impact tumorigenesis and disease progression through alterations in tumor metabolism, acting on specific target molecules or proteins. Thus, circRNAs have potential as therapeutic targets in the treatment of cancer. In addition, determining metabolic differences between malignant and healthy cells may lead to the development of targeted therapies for use in clinical practice (Fig. 2).

Effects of circRNAs on glucose metabolism in NSCLC. Even under aerobic conditions, tumor cells favor aerobic glycolysis without the tricarboxylic acid cycle, leading to the evasion of mitochondria-induced oxidative stress damage (56,57). Glucose metabolic reprogramming is a key metabolic adaptation in NSCLC that promotes the growth and proliferation of NSCLC cells, under hypoxic and non-hypoxic conditions.

CircRNAs act as miRNA sponges and bind to proteins to affect mRNA and protein expression. Notably, circRNAs manipulate glucose metabolism-associated enzymes or kinases to regulate the metabolic reprogramming of glucose. Glucose molecules are ingested into the cell via GLUT and a series of glucose metabolic reactions are carried out through the regulation of associated metabolic enzymes. For instance, in tumor cells, the expression of PKM2 is elevated, facilitating glycolysis and biosynthesis (58). Results of previous studies demonstrated that circRNAs affect the growth and proliferation of tumor cells through regulating glucose transporter proteins and key enzymes associated with glucose metabolism. Among the identified 14 GLUT isoforms, GLUT1, GLUT3 and GLUT4 are upregulated in malignant tumor cells (59), suggesting that they may facilitate glucose transport to provide more energy for tumor cell growth (60). In addition, protein expression levels of GLUT1 are decreased in NSCLC cells following circACACA knockdown, leading to the inhibition of tumor growth and proliferation (61). Results of a previous study demonstrate that circENO1 knockdown attenuates glycolysis in LUAD cells through enolase 1 (62). Xiong *et al* (63) report that circMYLK acts as a molecular sponge for miR-195-5p and circMYLK knockdown suppresses the expression levels of GLUT3. NSCLC cells do not favor aerobic glycolysis and inhibit tumor cell growth, proliferation and lactic acid production (63). For instance, it has been discovered that the aconitine alkaloid inhibits aerobic glycolysis and decreases lactate production in NSCLC cells through modulation of the PI3K/Akt-mTOR signaling pathway (64). Aerobic glycolysis promotes the expression of glucose transporter proteins to enhance glucose uptake and glycogen synthesis (65), serving a key role in the regulation of glucose metabolism. Following aerobic glycolysis in NSCLC, a tumor microenvironment with high levels of lactate and hypoxia is established. Notably, activation of glucose metabolism-associated pathways and increased HIF-1 expression may promote the regulation of glycolytic metabolism through PKM2.

In addition, circRNAs regulate multiple signaling pathways, including PI3K/Akt, c-myc and Wnt/β-catenin pathways, which enable tumor cells to obtain the energy required for rapid growth. Results of a previous study demonstrate that circHIPK3 absorbs miR-381-3p to regulate the Akt/mTOR signaling pathway, leading to increased glycolysis and the promotion of tumor cell growth and proliferation (66).

CircRNA-mediated glucose metabolic reprogramming results in a hypoxic tumor environment with a low pH and low levels of nutrients (67). In addition, high levels of lactic acid may aid tumor cell survival and impair the growth and development of healthy cells. Targeting key metabolism-associated pathways and enzymes of the glycolytic pathway may control the growth and proliferation of NSCLC cells, thus exhibiting potential in the treatment of cancer. Collectively, these results demonstrate that circRNAs may be potential targets for the treatment of lung cancer.

Effects of circRNAs on lipid metabolism in NSCLC. In healthy cells, the source of fatty acids is almost entirely dependent on exogenous intake; however, tumor cells require a large amount

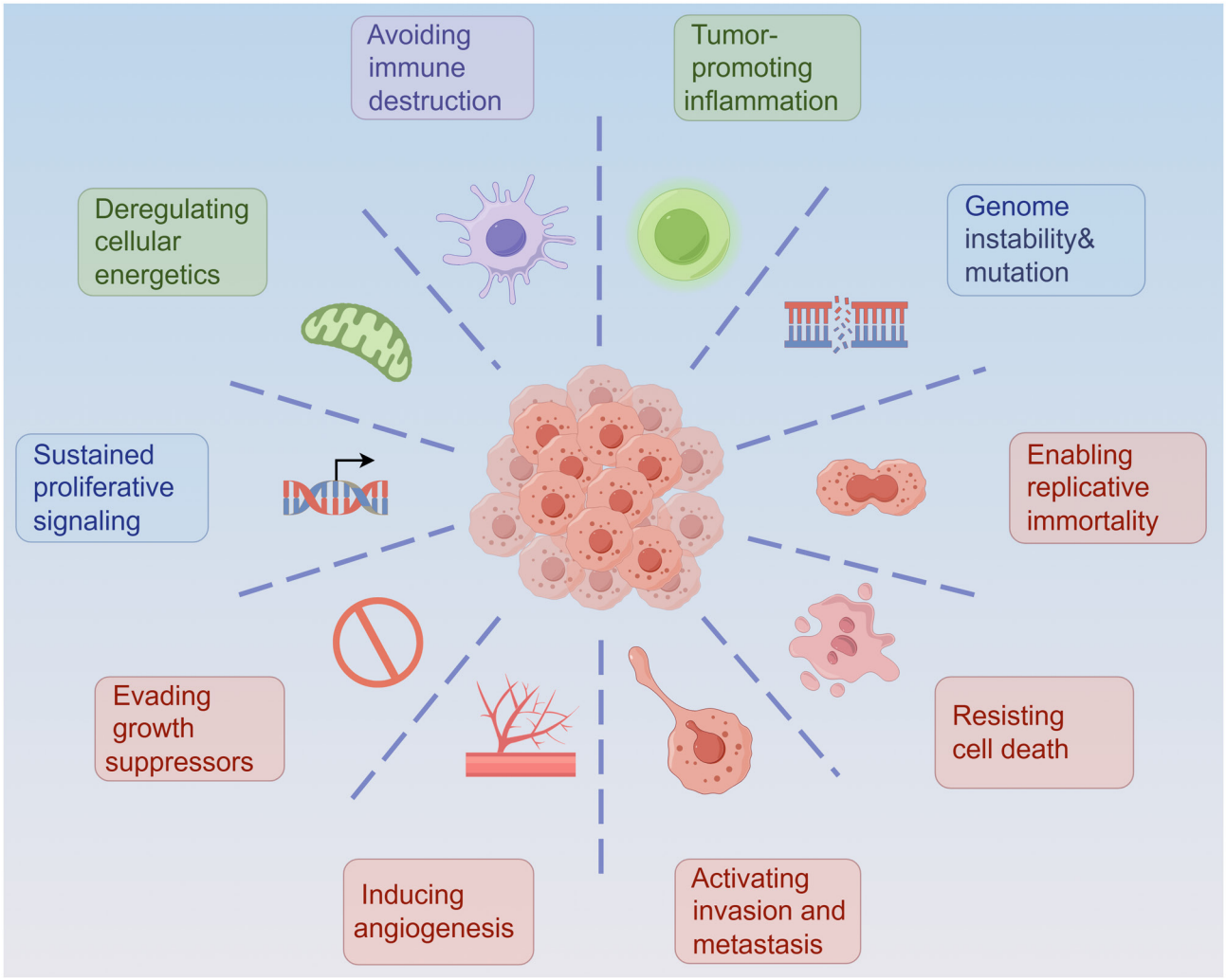

Figure 2. Circular RNA regulates malignant biological behavior of tumors through metabolic reprogramming. The figure was created using Figdraw (www.figdraw.com).

of fatty acids to synthesize cell membranes for rapid growth. Reprogramming of lipid metabolism not only provides raw materials for cell membrane synthesis in tumor cells but also provides energy for cell proliferation through fatty acid oxidation. Notably, products produced through lipid metabolism may also serve as important components of signal transmission. Reprogramming of lipid metabolism in tumor cells promotes tumorigenesis and development via interaction with the tumor microenvironment. Lipid uptake and storage are increased in tumor cells to maintain rapid proliferation. Tumor growth and proliferation are promoted through enhanced lipid synthesis and reduced catabolism (68). Results of a previous study reveal that acute fat reduction may lead to increased tumor malignancy in patients with triple negative breast cancer (69).

Under non-cancerous conditions, lipids are mainly produced in hepatocytes and adipocytes. However, tumor cells may activate lipogenesis in response to high metabolic demands or a lack of serum-derived lipids in the tumor microenvironment (70). Disordered lipid metabolism results in the accumulation of lipid oxides, which, in turn, induces the activation of oncogenic signaling pathways, e.g., the PI3K/AKT/mTOR pathway, the MAPK/ERK pathway and the HIF-1α pathway (71). These pathways promote the malignant phenotype of tumors and impact neighboring healthy cells. For instance, JAG1 exerts an influence on vascular endothelial cells within the tumor microenvironment by stimulating angiogenesis (72). Cheng *et al* (73) reveal that alterations in healthy lipid composition affects the antitumor immunity of T-cells.

Reprogramming of lipid metabolism in tumor cells is mediated through the production of ATP, the biosynthesis of macromolecules and maintenance of an appropriate redox state that supports carcinogenesis, progression, distal metastasis and chemoresistance. For instance, circIPO7 enhances cisplatin resistance in NPC cells by interacting with YBX1, thereby promoting its phosphorylation and nuclear localization, which in turn boosts the cells' DNA damage repair capability (74). Furthermore, circITGB6 stabilizes FGF9 mRNA via IGF2BP2, which facilitates the polarization of M2 macrophages and modulates the tumor immune microenvironment, ultimately promoting ovarian cancer resistance to cisplatin (75). During the reprogramming of lipid metabolism, circRNAs alter the metabolic environment of tumors via regulation of lipid metabolism-associated transcription factors and key enzymes of lipid metabolism pathways. Thus, dysregulation of circRNAs may lead to lipid metabolism disorders, tumor progression and increased drug resistance (76).

Results of a previous study reveal that circFARSA may affect fatty acid biosynthesis in NSCLC cells through binding to miR-330-5p and miR-326. When circFARSA binds to these miRNAs, it alleviates their inhibitory effect on fatty acid synthesis, leading to an enhancement in fatty acid synthesis (77). Furthermore, circRNA_101093 regulated ferroptosis in LUAD through lipid peroxidation. This mechanism holds significant importance in the progression of lung adenocarcinoma, chemotherapy resistance and the regulation of the tumor microenvironment. It offers novel targets and insights for clinical treatment strategies (78). Collectively, these results may provide a novel theoretical basis for targeting lipid metabolism in cancer. However, further investigations are required to determine the specific mechanistic role of circRNAs in regulating lipid metabolism in NSCLC.

Effects of circRNAs on amino acid metabolism in NSCLC. Amino acids are involved in protein, purine and pyrimidine synthesis, bioenergy generation and the maintenance of redox balance. During the rapid growth and proliferation of tumor cells, there is an increased demand for energy, amino acids and nutrients. Tumor cells regulate key pathways of amino acid metabolism and amino acid transport, for increased amino acid synthesis that meets the nutritional demands of rapid cell growth. Moreover, tumor cells may suppress tumor immunity through the depletion of amino acids and nutrient competition in the microenvironment. Thus, the reprogramming of amino acid metabolism may serve an important role in the development and progression of tumors (79).

Glutamate, as the most abundant non-essential amino acid in humans, provides a source of carbon or nitrogen for the synthesis of nucleotides and lipids. In addition, glutamate provides the biological macromolecules and energy required for cell growth. Glutaminase catalyzes glutamate for conversion to glutamine, which participates in the synthesis of glutathione. Notably, this serves an important role in cellular antioxidant stress.

Tumor cells have an increased metabolic demand for glutamine during growth and proliferation and glutamine relies on glutamine carriers on tumor cell membranes for increased entry into cells. Results of a previous study reveal that circ_0000518 may promote NSCLC cell proliferation, invasion and glutamine metabolism through competitive binding with miR-330-3p. Circ_0000518 inhibited the activity of miR-330-3p through competitive binding to it (80). Furthermore, circOXCT1-mediated upregulation of solute carrier family 1 member 5 (SLC1A5) expression promotes glutamine metabolism and malignant progression in NSCLC (81). Results of a previous study demonstrate that IMD-0354 specifically blocks SLC1A5 and reduces glutamine levels (82), thereby inhibiting tumor proliferation. Thus, targeting tumor metabolism may exhibit potential in clinical practice.

In addition, serine/glycine metabolic disorders serve a key role in tumor progression (83). Serine is involved in nucleotide metabolism and the tricarboxylic acid cycle and is converted to glycine to provide carbon units for one-carbon metabolism. However, research focused on circRNA-mediated synthesis and the catabolic metabolism of serine/glycine in NSCLC is currently limited.

Numerous circRNAs have been identified as key regulators of metabolism in NSCLC; however, further investigations are required to determine the specific role of these non-coding RNAs. Determining the metabolic differences between patients with NSCLC and healthy individuals may exhibit potential in the development of novel therapeutic targets for the treatment of NSCLC.

4. Further investigations

CircRNAs serve key regulatory roles in numerous physiological processes in eukaryotic organisms. Research to date has focused on the role of circRNAs in gene expression and the abnormal expression of circRNAs which may be a target for the treatment of several human diseases (84). In addition, research has focused on the effect of circRNAs on tumor cells at the molecular level; however, studies focused on the effect of extracellular factors are limited. Metabolic reprogramming is considered a key hallmark of cancer and circRNA-mediated reprogramming of glucose, lipid and amino acid metabolism provides energy and nutrients for NSCLC cell growth, leading to tumor progression. Thus, oncogenic signals of metabolic reprogramming may exhibit potential as therapeutic targets for the treatment of NSCLC. For instance, studies have shown that inhibiting the PI3K/Akt/mTOR pathway decreases the glycolytic activity of NSCLC cells, subsequently impeding tumor growth (85). Furthermore, it is noteworthy that distinct cancer types exhibit unique metabolic reprogramming characteristics (86). For instance, circMBOAT2 promotes the cytoplasmic export of fatty acid synthase mRNA by stabilizing polypyrimidine tract-binding protein 1, thereby facilitating lipid metabolic reprogramming in intrahepatic cholangiocarcinoma (87). Additionally, studies have shown that GC-MSC-derived circ_0024107 promotes gastric cancer cell lymphatic metastasis via fatty acid oxidation metabolic reprogramming mediated by the miR-5572/6855-5p/carnitine palmitoyltransferase 1A axis (88). Furthermore, the 127-amino acid peptide encoded by circSpdyA has been reported to enhance lipid metabolic reprogramming in breast cancer, contributing to immune suppression in the tumor microenvironment (89). These differences in metabolic reprogramming are probably attributable to the divergent metabolic demands of various cancers, as well as the tumor microenvironment's inherent heterogeneity. Immune cells display considerable heterogeneity within the tumor microenvironment (TME), with tumor-associated macrophages (TAMs) capable of exhibiting either a pro-tumor M2 phenotype or an anti-tumor M1 phenotype (90). Moreover, the variability in the activity of metabolic enzymes across different cancers further contributes to these metabolic discrepancies. Understanding such metabolic differences between tumors is of paramount importance for the development of targeted therapeutic strategies. Further investigations into the expression patterns and functional effects of circRNAs in different tumor types are required.

CircRNAs exhibit distinct gene expression patterns across different tumor stages and cancer types (91) and expression is highly specific in both temporal and tissue contexts (92). Thus, circRNA expression profiles may be associated with the differing biological behavior of tumor cells at different stages

of lung cancer. Notably differentially expressed circRNAs exhibit potential as biomarkers for early diagnosis, prognostic evaluation and monitoring of therapeutic responses. For instance, circ0001785 has demonstrated superior diagnostic accuracy compared to traditional markers like CEA and CA15-3 in detecting breast cancer, and it holds significant prognostic potential in predicting histological grade, TNM stage and the occurrence of distant metastasis during breast cancer progression (93). Furthermore, previous studies have reported both shared and unique circRNA expression patterns between LUAD and lung squamous cell carcinoma (38,94). For example, results of a previous study reveal that circ_0001821 is markedly upregulated in LUAD; however, circ_0077837 is notably downregulated in lung squamous cell carcinoma (95). Thus, the expression patterns of circRNAs may be specific to different lung cancer subtypes and disease stages. CircRNAs may exhibit potential as biomarkers that aid in tumor staging, subtype differentiation and the development of subtype-specific cancer therapies.

CircRNAs exhibit complex functions and diverse types and their functional mechanisms remain to be fully elucidated. CircRNAs exhibit potential in the treatment of cancer due to diversity in their biological functions. Notably, circRNAs are endogenous molecules that exert therapeutic effects through specialized targets. CircRNAs exhibit high levels of stability in expression; thus, they have potential as therapeutic targets or for drug delivery. A previous study discusses the development of circRNA vaccines for coronavirus, with increased use observed in clinical practice (96). In addition, the antitumor effects of circRNA vaccines in a mouse model of advanced malignant melanoma demonstrates the potential of these non-coding RNAs in the treatment of tumors (97). Notably, circRNAs are generated through intronic shearing and therefore exert fewer effects on immunosuppression compared with other RNAs. Therefore, circRNA vaccines are safer and more stable (98). Further investigations into the mechanisms underlying circRNAs in tumor metabolism may aid in the development of novel treatment options and highlight the role of metabolic reprogramming in the treatment of NSCLC.

CircRNA-mediated metabolic reprogramming may be closely associated with the efficacy of immune checkpoint inhibitors (ICIs). Metabolic reprogramming exerts notable effects on immune cell function within the tumor microenvironment (67) and circRNAs may affect the effectiveness of ICIs through the direct or indirect regulation of tumor metabolism and immune modulation pathways (99). Specifically, circRNAs can alter the tumor microenvironment by driving metabolic reprogramming processes, such as enhanced glycolysis, lipid metabolism and glutamine metabolism, resulting in an immunosuppressive environment. These metabolic changes deplete key nutrients (such as glucose and glutamine) and lead to the accumulation of metabolic byproducts (such as lactate), which suppress the function of effector immune cells, such as T cells and natural killer (NK) cells, thereby promoting tumor immune evasion. For example, circSOBP inhibits the progression of glioblastoma by disrupting glycolysis and promoting the quantity and activity of CD8 T and NK cells (100). Additionally, research has demonstrated that circRHBDD1 enhances aerobic glycolysis in hepatocellular carcinoma and limits the efficacy of anti-programmed cell death protein 1 (PD-1) therapy (101).

The combined use of circRNA-targeted interventions and ICI therapy may exhibit potential in improving antitumor immune responses. For example, the use of specific antisense oligonucleotides that target and silence circPIAS1, in combination with PD-1 inhibitors, demonstrated notable tumor inhibition effects in a model of melanoma. CircPIAS1 inhibits the phosphorylation of STAT1 and activates the SLC7A11/GPX4 signaling pathway through the encoding of circPIAS1-108AA, ultimately suppressing immunogenic ferroptosis and impeding the effectiveness of PD-1 inhibitors (102). Prior to the implementation of immunotherapy, analysis of circRNA expression profiles in patients may provide valuable insights into their metabolic state and immune microenvironment, leading to the optimization of personalized ICI treatment strategies.

CircRNAs exhibit potential in vaccine development, gene regulation and adoptive cell therapy (103). However, the development of circRNA-targeted therapies for the treatment of lung cancer remains challenging. The partial sequence overlap between circRNAs and their linear RNA counterparts leads to challenges in the specific targeting of circRNAs, without inadvertently affecting linear RNAs (104). The use of small molecules or RNA interference tools with a high specificity are therefore required to target the unique splice junctions of circRNAs. In addition, effective drug delivery is fundamental for improving treatment outcomes (105). Delivering circRNAs or their corresponding inhibitors to specific cancer sites, while minimizing off-target effects on healthy tissues, remains challenging. Thus, the development of novel targeted delivery systems, such as lipid nanoparticles and exosome-based carriers, are required (106). Furthermore, exogenous circRNAs or their delivery systems may activate immune responses, leading to immune-related side effects (107). Thus, chemical modifications of circRNAs and their delivery vehicles may exhibit potential in reducing immunogenicity. A previous study reported that m6A modifications may aid in controlling circRNA-mediated immune activation (108).

Following additional technological innovation and interdisciplinary collaboration, circRNAs could be a novel therapeutic strategy for the treatment of lung cancer. Notably, lung cancer may metastasize to soft tissues (109). CircRNAs serve a pivotal role in regulating the metabolic reprogramming of lung cancer cells, providing adaptive support for cancer cells within soft tissue metastatic lesions. This regulation enables cancer cells to survive and proliferate in hypoxic or nutrient-deprived environments (33). However, further investigation is required to determine the impact of circRNA-mediated metabolic reprogramming on lung cancer soft tissue metastasis.

The metabolic regulatory network is complex and circRNAs are involved in the regulation of tumor metabolic pathways that involve multiple target pathways. Moreover, circRNA expression may be affected by the negative feedback regulation of tumor metabolites. For instance, in research on gastric cancer (GC), it has been discovered that the RNA-binding protein QKI promotes the onset and progression of the disease by regulating the splicing of genes associated with epithelial-mesenchymal transition (EMT), leading to the formation of circRNAs. Notably, QKI expression is elevated

during EMT, and it establishes a negative feedback loop with miR-200. This loop helps maintain a homeostatic balance in response to signals induced by EMT (110). Thus, the expression profiles of circRNAs in tumor metabolic pathways should be determined using metabolomics and spatial transcriptomics, to identify circRNAs that are co-expressed in tumor metabolism pathways in NSCLC. This may aid in the development of novel therapeutic drugs that exhibit a high level of specificity for tumor metabolism.

5. Conclusions

The present review provides insights into the association between circRNAs and glucose, lipid and amino acid metabolism in lung cancer, leading to a novel theoretical basis for the clinical treatment of lung cancer. CircRNAs exhibit potential as treatment targets for tumors due to their unique structure and wide-ranging effects. Exploring the regulatory mechanisms underlying circRNAs in the metabolic reprogramming of lung cancer cells may further the current understanding of the tumor metabolic regulatory network. CircRNA-mediated interference of the metabolic reprogramming of lung cancer cells may reverse the malignant transformation of NSCLC cells, highlighting the potential of circRNAs in lung cancer treatment. However, the challenge of accurately identifying and detecting circRNAs arises due to their low cellular abundance and the coexistence of linear mRNAs with identical sequences. As a result, there is a pressing need for the development of more precise detection methodologies.

Acknowledgements

Not applicable.

Funding

The present study was supported by the Natural Science and Technology Fund of Guizhou Province [grant nos. Qiankehe Basic-ZK (2022) General 644; Qiankehe Support (2021) General 082].

Availability of data and materials

Not applicable.

Authors' contributions

PZ, ZZ and XZ conceived and designed the review. PZ,ZZ and YS wrote the manuscript. GX, CC and XK critically revised and polished the manuscript. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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