Metabolic remodeling by circular RNAs in gastric tumorigenesis: From mechanisms to biomarker discovery (Review)

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Abstract. Gastric cancer (GC), which primarily originates from gastric mucosal epithelium, is driven by factors such as *Helicobacter pylori* infection, genetic susceptibility and lifestyle. GC poses a serious threat to patient survival and quality of life. Metabolic reprogramming, a hallmark of tumorigenesis and progression, enables cancer cells to continuously adapt their energy metabolism to support proliferation, invasion, metastasis and drug resistance. Circular RNAs (circRNAs) are a class of non-coding RNAs characterized by a covalently closed circular structure, which confers high stability. They are differentially expressed in tumor cells and facilitate tumor proliferation and metastasis through multiple mechanisms such as microRNA sponging, protein binding, short peptide translation and N^6-methyladenosine modification. Furthermore, circRNAs contribute to tumor metabolic remodeling, meeting the energy demands of tumor cells by regulating key enzymes and transporters involved in metabolic pathways, thereby modulating the synthesis or degradation of metabolites. The present review summarizes the mechanisms by which circRNAs mediate different metabolic modes during the initiation and progression of GC as well as discusses their potential as biomarkers for GC. By systematically elucidating the intricate interactions between circRNAs and metabolic reprogramming in GC, the present study aims to provide a theoretical foundation for the development of innovative therapeutic strategies against GC.

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1. Introduction

According to a 2024 report by The International Agency for Research on Cancer, gastric cancer (GC) ranked as the fifth most commonly diagnosed malignancy globally in 2022, accounting for ~968,000 new cases (4.9% of total cancer cases) and 660,000 deaths (6.8% of total cancer mortality) (1,2). This positions GC as a major public health challenge requiring urgent attention worldwide. Although improvements in healthcare and social development have contributed to a gradual reduction in the overall burden of GC, countries with large populations such as China and India continue to experience a high incidence of early-stage GC (1,2). The incidence of GC exhibits distinct geographical variation, with age-standardized rates in Asia, Latin America and Europe being notably higher than those in other regions (3), indicating substantial disease risk. The high morbidity and mortality rates associated with GC are largely attributed to limitations in early diagnosis, with the majority of patients diagnosed at locally advanced or metastatic stages, posing a severe threat to both survival and quality of life (4). In recent years, the emergence of novel targeted agents and immunotherapies has partially enhanced clinical management strategies. However, their efficacy is influenced by factors including patient pathology, disease stage, clinical symptoms and performance status (5). The tumor microenvironment (TME), comprising cellular components such as cancer-associated fibroblasts and endothelial cells, as well as non-cellular components including cytokines, chemokines and the extracellular matrix (ECM),

plays a pivotal role in tumor progression; it promotes ECM remodeling, epithelial-mesenchymal transition and sustained tumor proliferation, while also fostering an immunosuppressive milieu. Consequently, a considerable proportion of patients exhibit a poor response to immunotherapy and are prone to developing treatment resistance (6). Therefore, enhancing GC prevention and treatment capabilities, along with continuously refining clinical strategies, represents a critical and pressing challenge in the fields of gastroenterology and oncology worldwide.

Tumor tissues exhibit metabolic pathways distinct from those in normal tissues. Normal cells in the quiescent phase maintain basal metabolic activity with limited uptake of nutrients such as glucose and amino acids to support essential life activities, and during proliferation moderately upregulate nutrient transporters to facilitate orderly synthesis of genetic materials in a tightly regulated manner. However, tumor cells display markedly enhanced nutrient uptake to sustain their high energy and biosynthetic demands (7). This metabolic reprogramming in the TME is characterized by dysregulated metabolic fluxes and serves as a critical basis for tumor proliferation, metastasis, invasion and therapy resistance, particularly in digestive system cancer types (8). In the 1920s, Professor Otto Warburg observed that under aerobic conditions, the ATP yield relative to oxygen consumption in oxidative phosphorylation (OXPHOS) is ~1:7. By contrast, tumor cells exhibit notable metabolic plasticity during proliferation and metastasis. They activate cytokines and metabolism-related signaling pathways, adapt their metabolic routes, induce mitochondrial abnormalities and remodel the entire metabolic network. These alterations enhance energy production efficiency, facilitate immune evasion, acidify the TME and collectively promote rapid tumor growth and dissemination (9,10). Despite these insights, current understanding of tumor metabolic reprogramming remains insufficient to meet the precision requirements for GC prevention and treatment. Recent advances in microarray and high-throughput sequencing technologies have accelerated the recognition of epigenetic modifications (11), initially conceptualized by Professor Conrad Waddington. These heritable yet reversible chemical modifications, affecting DNA, histones or RNA, regulate gene expression without altering the DNA sequence and thereby influence cellular phenotypes (11).

Over the past two decades, non-coding RNAs (ncRNAs), once considered transcriptional 'noise', have been demonstrated to participate in the development and progression of multiple cancer types through their regulatory modifications (12). ncRNAs represent a diverse class of RNAs that lack open reading frames and do not encode proteins. Notably, up to 98% of RNAs in numerous organisms are non-coding, highlighting their crucial functional roles at the RNA level within the transcriptome (13). Among these, circular RNAs (circRNAs) have emerged as key regulatory ncRNA molecules. They influence the expression of metabolic enzymes and transporters, encode short peptides in certain cases and regulate gene expression at transcriptional and post-transcriptional levels, thereby participating in various metabolic processes in GC (14). The present review focuses on circRNAs as potential key regulatory nodes in metabolic reprogramming, which may reflect tumor metabolic activity and drug sensitivity. By integrating circRNAs into the metabolic remodeling network of GC, the present review aims to contribute to the development of precise targeted therapies for GC.

2. Biological characteristics of circRNA

Linear RNAs are processed by splicing out introns, connecting exons and adding a 5' cap and a 3' poly(A) tail (Fig. 1A). By contrast, circRNAs are generated from pre-mRNAs through back-splicing mediated by cis-acting elements and specific trans-acting factors, resulting in exonic circRNAs or exon-intron circRNAs when introns are retained. circular intronic RNA are derived from intronic lariats that escape debranching and undergo cyclization (15) (Fig. 1B-D). circRNAs lack a 5' m^7GpppN cap and a 3' poly(A) tail, possess a covalently closed non-linear structure, are resistant to exonuclease digestion and have a longer half-life in blood, making them more stable for detection in tissues and body fluids (16). Efficient identification and enrichment of circRNAs can be achieved through two principal strategies: i) Enzymatic digestion of linear RNAs using RNase R, followed by high-throughput sequencing of the resistant circRNA fraction; and ii) immunoprecipitation or affinity-based depletion of linear RNAs using antibodies against the 5' cap (such as anti-m^7G) or oligo(dT) probes targeting the poly(A) tail (17,18). Notably, certain circRNAs exhibit higher abundance than their linear mRNA counterparts derived from the same parental gene (19).

The biogenesis of circRNAs is facilitated by structural motifs in pre-mRNA introns. Alu repeat elements, which are enriched in intronic regions, contain inverted complementary sequences that enable the formation of intramolecular double-stranded RNA (dsRNA) structures. These structures bring distal splice sites into spatial proximity, creating a favorable configuration for the spliceosome to perform backsplicing (20,21). Additionally, specific RNA-binding proteins (RBPs) recognize cis-elements in pre-mRNAs and promote circRNA circularization (22). Quaking (QKI), a member of the STAR family of KH domain-containing proteins, dynamically regulates ~1/3 of all circRNAs (23). The N-terminal Qua1 domain of QKI mediates dimerization, enabling the protein to recognize and bind specific Quaking response elements within introns. This facilitates the alignment of a downstream 5' splice site with an upstream 3' splice site, driving efficient and specific circRNA biogenesis via backsplicing (24).

Adenosine deaminase acting on RNA 1 (ADAR1), which catalyzes adenosine-to-inosine editing, also plays a critical role in circRNA formation, particularly near regions with inverted complementary matches (25). Notably, ADAR1 knockdown in 293 cells leads to upregulation of circRNA levels (26). This phenomenon may be attributed to ADAR1-mediated destabilization of intramolecular dsRNA structures. In the absence of editing, stable dsRNA bridges bring the upstream 3' and downstream 5' splice sites into proximity, facilitating backsplicing. ADAR1 expression disrupts these dsRNA interactions, preventing spliceosome recognition and efficient circRNA production.

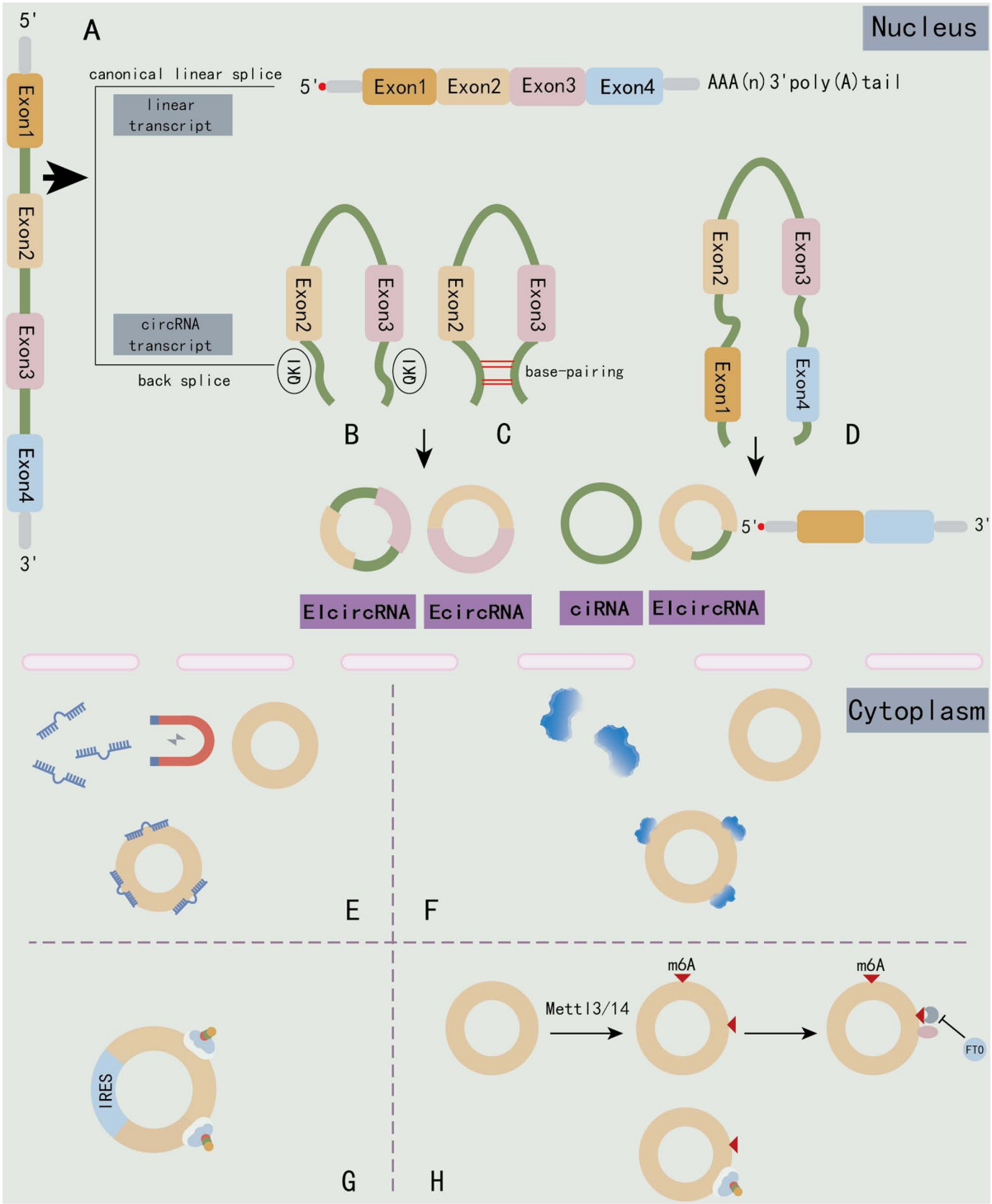

Figure 1. Schematic illustration of circRNA biogenesis and functions in the nucleus and cytoplasm. (A) Canonical linear splicing of precursor mRNA produces a linear transcript containing a 5' cap and 3' poly(A) tail, whereas back-splicing generates circRNA molecules. (B) EIciRNAs: Formed when back-splicing retains an intron between the circularizing exons, mediated by QKI and facilitated by base-pairing interactions. (C) EcircRNAs: Formed by back-splicing of exons (such as Exon2 and Exon3) with the introns removed. This results in a circular molecule composed entirely of exons. (D) ciRNAs: Generated from introns that escape debranching and form a circle (shown here as Exon1-derived ciRNA). The diagram also illustrates an EIciRNA variant comprising Exon1 directly spliced to Exon3/4. circRNAs (E) acting as miRNA sponges, (F) interacting with RBPs, (G) serving as templates for cap-independent translation via IRESs and (H) undergoing m^{6}A-dependent translation mediated by Mettl3/14 and eIF4G2. circRNA, circular RNA; EIcircRNAs, exon-intron circRNAs; EcircRNAs, exonic circRNAs; ciRNAs, intronic circRNAs; RBPs, RNA-binding proteins; IRESs, internal ribosome entry sites; m^{6}A, N6-methyladenosine; Mettl, methyltransferase-like; QKI, quaking; FTO, complex and fat mass and obesity-associated protein. Created in Adobe Illustrator.

circRNAs can participate in metabolic regulation by sponging microRNAs (miRNAs/miRs) (Fig. 1E), interacting with RBPs (Fig. 1F) and driving cap-independent translation through internal ribosome entry sites (IRESs) (Fig. 1G) or N6-methyladenosine (m^{6}A) modification co-regulated by the methyltransferase-like (Mettl)3)/Mettl14 complex and fat mass and obesity-associated protein (FTO) (Fig. 1H).

3. Metabolic reprogramming in GC

Glycolysis. Under oxygen-sufficient conditions, normal cells primarily satisfy their energy requirements through the sequential biological processes of 'glucose uptake → glycolysis → pyruvate entry into the tricarboxylic acid (TCA) cycle → OXPHOS'. By contrast, tumor cells preferentially utilize aerobic glycolysis, consuming large amounts of glucose and converting pyruvate into lactate, yielding a net gain of only two ATP molecules per glucose molecule (27). This metabolic shift is partly driven by mitochondrial reprogramming, wherein tumor cells maintain TCA cycle activity to support biosynthetic precursor synthesis, partially compensating for the reduced ATP yield from OXPHOS (28).

Glycolytic reprogramming occurs predominantly within the cytosol. In highly migratory tumor cells, glycolytic enzymes are recruited to the cell cortex, where they propagate as self-organizing waves along the membrane/cortex and interact with actin filaments (29). Key regulatory enzymes, including hexokinase (HK), pyruvate dehydrogenase kinase (PDK), phosphofructokinase-1 (PFK1) and the pyruvate kinase M2 (PKM2) isoform, orchestrate a series of catalytic reactions (30). These protein-protein interactions among metabolic enzymes lead to altered levels of glucose-metabolizing proteins and glycolytic intermediates such as fructose, glyceraldehyde and pyruvate. Most pyruvate is subsequently converted into lactate, which is exported extracellularly via monocarboxylate transporters (MCTs). Extracellular lactate accumulation further drives histone lysine lactylation, influencing transcriptional regulation, post-transcriptional modifications and post-translational processes in tumor cells (31). By accelerating glycolytic flux, tumor cells rapidly generate energy, thereby promoting proliferation, invasion, metastasis and therapy resistance, a mechanism critically involved in GC pathogenesis (32,33). Consequently, targeting key glycolytic enzymes represents a promising strategy to suppress the Warburg effect and impede GC progression (Fig. 2A).

The HK family comprises four isoforms (HK1-4), each encoded by distinct genes and exhibiting unique functional and distribution profiles. Among these, HK2 is upregulated in most tumor cells, including GC cells, and serves as the key rate-limiting enzyme catalyzing the first committed step of glycolysis (34). HK2 transfers a phosphate group from ATP to glucose, generating glucose-6-phosphate (G6P), which provides a critical metabolic intermediate for downstream reactions (35). PFK1, a major regulatory node in the glycolytic pathway, acts as another essential rate-limiting enzyme that directs G6P flux into glycolysis; it catalyzes the conversion of fructose-6-phosphate to fructose-1,6-bisphosphate. Under conditions of high energy demand or hypoxia, PFK1 activity is enhanced, accelerating G6P consumption and favoring glycolytic ATP production (36). The PDK family also consists of four isoforms (PDK1-4). Elevated expression of PDK isoforms in GC cells promotes S-phase entry and serves as an independent prognostic factor in patients with GC (37). PDK plays a decisive role in directing pyruvate metabolism, where it phosphorylates and inactivates pyruvate dehydrogenase, thereby preventing the conversion of pyruvate to acetyl-CoA and entry into the TCA cycle. This suppression of mitochondrial OXPHOS shifts metabolism toward anaerobic glycolysis, leading to lactate accumulation. Concomitantly, altered histone acetylation patterns and suppressed programmed cell death-ligand 1 (PD-L1) expression contribute to immune evasion, further enhancing the pro-tumorigenic effects in GC (38). Pyruvate kinase, the terminal rate-limiting enzyme of glycolysis, transfers a high-energy phosphate group from phosphoenolpyruvate to ADP, generating pyruvate. The metabolic fate of pyruvate is closely linked to the oligomeric state of the predominant tumor isoform PKM2. In its tetrameric form, PKM2 exhibits high catalytic activity, facilitating pyruvate conversion to acetyl-CoA and supporting sustained energy production via OXPHOS. By contrast, the dimeric form of PKM2 displays reduced activity, leading to the accumulation of glycolytic intermediates such as phosphoribosyl pyrophosphate and 3-phosphoglycerate. This metabolic configuration prioritizes biosynthetic precursor supply, thereby supporting rapid tumor proliferation and metastasis (39,40).

Lipid metabolism. Fatty acids (FAs), essential components of various cellular structures, play critical roles in biological processes such as membrane biogenesis and energy provision (41). Mitochondrial β-oxidation serves as the core pathway for FA breakdown and energy production. However, long-chain FAs cannot freely traverse the mitochondrial membrane. Instead, they are first converted to acyl-CoA in the cytosol and then transported into the mitochondrial matrix via the carnitine palmitoyltransferase (CPT) system located on the inner mitochondrial membrane (42). Subsequently, through repeated cycles of dehydrogenation, hydration and thiolysis, FAs are degraded to generate acetyl-CoA, NADH and NADPH, which enter the TCA cycle to produce ATP (42). To rapidly adapt to hypoxic and nutrient-deprived microenvironments, tumor cells reprogram lipid metabolism by modulating FA uptake, synthesis, storage and β-oxidation. They utilize lipids for membrane construction, to support progression, and upregulate factors such as CD36 in regulatory T cells and $CD8^+$ T cells. This enhances lipid uptake and alters immune cell recruitment, activation and function, thereby facilitating immune evasion and accelerating tumor proliferation and metastasis (43,44) (Fig. 2B).

The transport of long-chain FAs into cells is a critical step in lipid metabolic reprogramming, primarily mediated by transport proteins. The transmembrane glycoprotein CD36, expressed on various cells within the TME, including endothelial, stromal and immune cells, facilitates long-chain FA uptake via endocytosis (45). Internalized FAs can be directed to lipid droplets for storage or undergo β-oxidation. This process involves activation of the Lck/Yes novel tyrosine kinase, which phosphorylates and inactivates zinc finger DHHC-type palmitoyltransferase 5 at tyrosine 91. Subsequently, acyl-protein thioesterase 1 mediates CD36 depalmitoylation, initiating a new cycle of CD36-mediated endocytosis and FA transport. This dynamic palmitoylation-depalmitoylation cycle of CD36 forms a closed loop crucial for remodeling the tumor lipidome and generating oncogenic lipid species, thereby promoting tumor growth and progression (46). Furthermore, FAs can upregulate *O*-GlcNAcylation, which in turn modifies CD36 and enhances its transcriptional expression. This positive feedback loop increases FA uptake in GC cells, accelerates metastasis and is closely associated with poor prognosis in

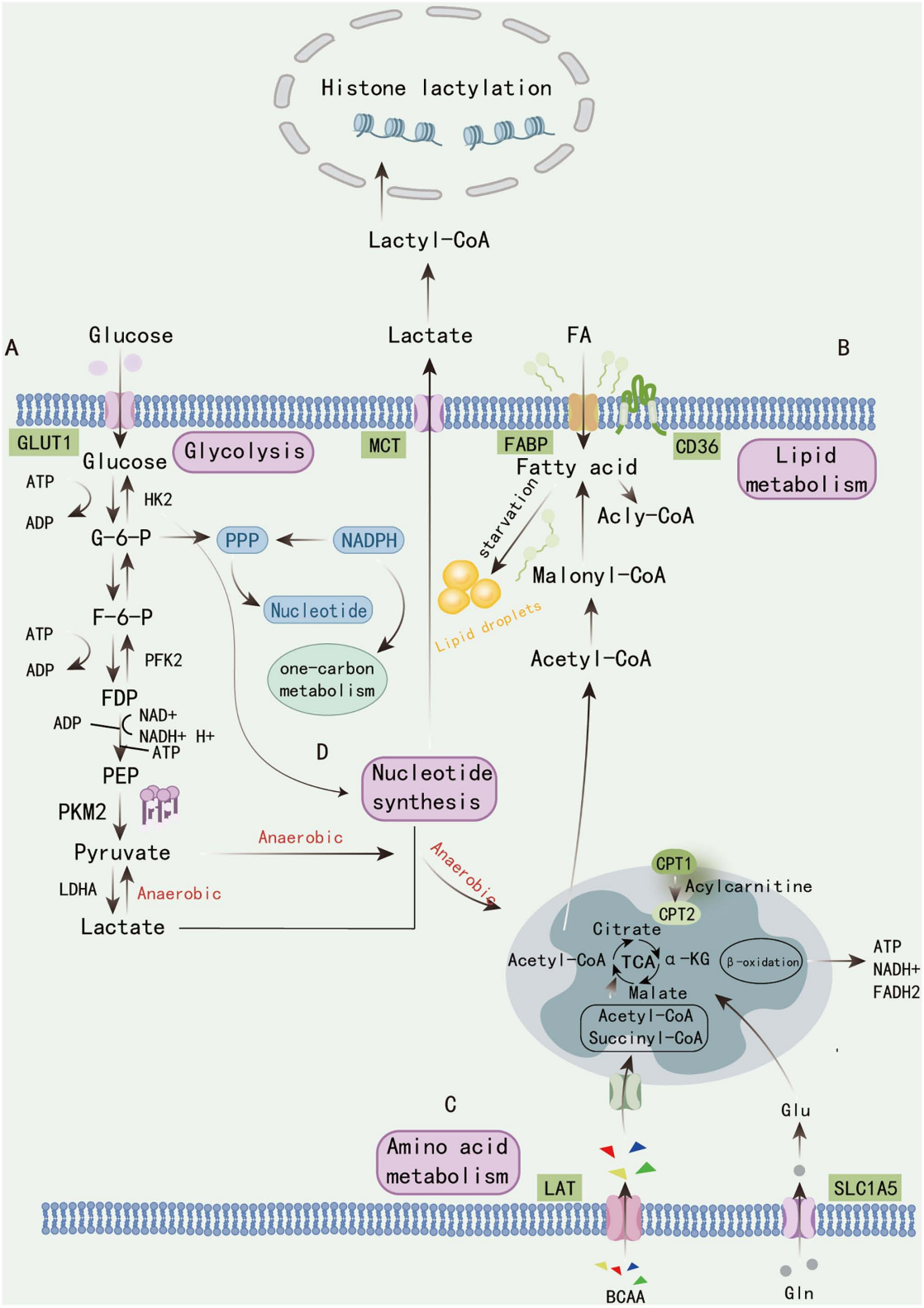

Figure 2. Overview of the metabolic pathways linking glycolysis, lipid metabolism, amino acid metabolism and nucleotide metabolism. (A) Glucose uptake via GLUT1 triggers glycolysis, producing pyruvate and lactate through the sequential actions of HK2, PFK2, PKM2 and LDHA. Under anaerobic conditions, lactate is exported and can re-enter cells via MCTs, serving as a substrate for lactyl-CoA formation that drives histone lactylation. (B) FAs imported through CD36 and FABP undergo activation to acyl-CoA, conversion to malonyl-CoA and oxidation via mitochondrial CPT1/2, producing ATP, NADH and $FADH_2$ through the TCA cycle. Lipid droplets act as energy reservoirs during starvation. (C) Amino acids, including BCAAs and glutamine transported by LAT and SLC1A5, feed into the TCA cycle to replenish intermediates such as α-KG. (D) Parallel to glycolysis, the PPP generates NADPH and ribose intermediates to support nucleotide synthesis and one-carbon metabolism. Together, these integrated metabolic routes coordinate carbon flux and epigenetic regulation through lactate-derived histone modifications. HK2, hexokinase 2; PFK2, phosphofructokinase-2; PKM2, pyruvate kinase M2; MCTs, monocarboxylate transporters; FA, fatty acid; CPT, carnitine palmitoyltransferase; TCA, tricarboxylic acid; PPP, pentose phosphate pathway; LAT, L-type amino acid transporter; SLC1A5, solute carrier family 1 member 5; α-KG, α-ketoglutarate; GLUT1, glucose transporter 1; LDHA, lactate dehydrogenase A; FABP, fatty acid-binding protein; BCAAs, branched-chain amino acids; G-6-P, glucose-6-phosphate; F-6-P, fructose-6-phosphate; FDP, fructose-1,6-bisphosphate; PEP, phosphoenolpyruvate; Glu, glutamate; Gln, glutamine. Created in Adobe Illustrator.

patients with GC (47). While transporter-dependent pathways are important, they are not the sole mechanism for long-chain FA uptake. The acidic TME can neutralize negatively charged FAs, promoting their protonation and passive diffusion into cells. This alternative pathway further drives FA accumulation and lipid droplet formation, supporting cancer cell metabolism and rapid proliferation (48).

The CPT system, a key regulator of FA β-oxidation, is central to lipid metabolic reprogramming. It consists of two isoforms: i) CPT1, located on the outer mitochondrial membrane and serving as the primary rate-limiting enzyme for FA translocation into mitochondria (49); and ii) CPT2, residing on the inner mitochondrial membrane, which facilitates the entry of FAs into the mitochondrial matrix for β-oxidation (50). In GC, CPT1A is highly expressed and interacts with S100A10, promoting its succinylation at lysine 47 (51). CPT1A expression also correlates with CD44, a key regulator of cancer metastasis. CD44 activates intercellular signaling pathways that target CPT1A to modulate FA oxidation (FAO), thereby enhancing the invasive and metastatic potential of GC cells (51,52). Similarly, CPT2 is notably upregulated in GC cells (53). Nuclear factor of activated T cells c3, a member of the NFAT transcription factor family, can be activated by reactive oxygen species (ROS) and translocate to the nucleus. There, it binds to the CPT2 promoter to enhance its transcription, elevating β-oxidation levels. This increase in FA catabolism raises the $NADPH/NADP^+$ ratio, protecting GC cells from ROS-induced damage and maintaining cellular homeostasis (53).

Amino acid metabolism. Through metabolic reprogramming of amino acid networks, tumor cells continuously adapt to survival pressures. Glutamine (Gln), the most abundant free amino acid in systemic circulation, plays a particularly critical role. As tumor cells are unable to synthesize Gln *de novo*, they compete with normal cells for exogenous Gln, developing a metabolic dependency to sustain proliferation and metastasis (54). Given its hydrophilic nature, Gln requires specific solute carriers, such as solute carrier family 1 member 5 (SLC1A5; also known as ASCT2), to traverse the plasma membrane. Once intracellular, Gln is sequentially deamidated by glutaminase (GLS) and glutamate dehydrogenase to produce glutamate (Glu), which is further converted to α-ketoglutarate (α-KG). This metabolite replenishes the TCA cycle, provides biosynthetic precursors, enhances mitochondrial activity and ultimately fuels cancer proliferation (55-57).

Due to their rapid energy consumption, tumor cells frequently face glucose starvation in the TME. To address this, they reconfigure intrinsic metabolic pathways to maintain NADPH homeostasis, thereby meeting the high energy demands and preserving the $NADPH/NADP^+$ balance (58). In GC, upregulation of malic enzyme 1 (ME1) helps replenish intracellular NADPH pools and maintain redox homeostasis. Conversely, ME1 knockdown depletes NADPH, lowers the glutathione (GSH)/GSH disulfide ratio, elevates ROS, exacerbates oxidative stress and promotes GC cell death (58,59). A portion of the Glu generated from Gln in mitochondria is transported back to the cytosol, where it serves as a substrate for GSH synthesis. Glu-cysteine ligase catalyzes the conjugation of Glu and cysteine to form γ-glutamylcysteine, which is subsequently combined with glycine by GSH synthase to produce GSH. This pathway assists tumor cells in countering oxidative stress (60-62) and modulates host immune surveillance and suppression. When Gln is extensively depleted by tumors, impaired GSH synthesis triggers Fas/CD95-mediated apoptosis. However, concurrent upregulation of PD-L1 expression can suppress $CD8^+$ T cell antitumor activity. Thus, simultaneously targeting Gln deprivation and PD-L1 activity, by blocking PD-L1/PD-1 interactions, presents a promising clinical strategy to alleviate immunosuppression in the TME (63). The oncogenic transcription factor c-Myc further supports Gln metabolism by binding to E-box sequences in target gene promoters. This upregulates GLS expression, enhances Gln uptake and catabolism, supplies TCA cycle intermediates, promotes nucleotide synthesis and sustains the malignant proliferative phenotype of tumors (64,65) (Fig. 2C).

In addition to Gln, other amino acids contribute to metabolic remodeling in GC, enabling tumor cells to compete for energy resources and support disease progression. Branched-chain amino acids (BCAAs), such as leucine, isoleucine and valine, are non-polar aliphatic amino acids characterized by carboxyl groups, amino groups and isopropyl side chains. They can be directly incorporated into proteins or catabolized into various metabolites to fuel related metabolic pathways (66). BCAAs enter cells via L-type amino acid transporters (LATs) and are shuttled into mitochondria by SLC25A44. Within mitochondria, they are transaminated to branched-chain α-keto acids (BCKAs), which subsequently transfer amino groups to α-KG. BCKAs are further metabolized to acetyl-CoA and succinyl-CoA, while generating Glu. The resulting metabolites ultimately enter the TCA cycle to support energy production (67).

In addition, an inter-amino acid compensatory mechanism exists. Under Gln-deficient conditions, elevated expression of the PPM1K protein promotes BCAA catabolism to sustain tumor cell survival (68). Previous studies suggest that elevated circulating BCAA levels may be associated with several human cancer types (69,70). However, a large-scale prospective cohort study by Yu *et al* (71) reached a contrasting conclusion, indicating that higher BCAA levels correlate with a reduced risk of GC, particularly among elderly populations. Given this dual role of BCAAs in tumor development, further investigation is needed to determine whether these context-dependent effects stem from distinct components within BCAA catabolic pathways.

Nucleotide metabolism. Nucleotides, composed of a nucleoside and a phosphate group, are essential for DNA and RNA synthesis, enzyme regulation, substrate activation and various metabolic processes in cells. Their synthesis is energy-intensive and requires carbon and nitrogen donors for support (72). This process relies on the cytosolic one-carbon (1C) metabolic pathway. To meet the demands of proliferation and metastasis, tumor cells upregulate the expression of enzymes related to 1C metabolism, altering their metabolic patterns to support the *de novo* synthesis of purines and pyrimidines (73). Pyrimidines and purines are the core structural components of nucleotides, and nucleotide synthesis involves two pathways: i) *De novo* synthesis; and ii) salvage pathways (74). In the *de novo* synthesis process, precursor molecules generated

by various metabolic pathways are utilized. For example, Gln is deaminated by GLS to produce Glu, which is then converted by glutamate dehydrogenase, releasing ammonia in the process. In glucose metabolism, the pentose phosphate pathway produces G6P, which then undergoes dehydrogenation, decarboxylation and isomerization reactions to form ribose-5-phosphate. Together, these intermediates provide essential raw materials for nucleotide synthesis.

The salvage pathway allows cells to rapidly generate nucleoside monophosphates from free nucleobases or nucleosides through phosphorylation or phosphoribosyl transfer reactions. This process avoids base wastage, is relatively energy-efficient and helps replenish the nucleotide pool (75). Normal cells primarily rely on the salvage pathway for nucleotide synthesis. However, the aggressive behavior of tumor cells depends on higher nucleotide synthesis and metabolic activity, requiring faster and greater acquisition of nucleotides to support rapid proliferation, drug resistance, immune evasion and metastasis. Therefore, tumor cells mainly utilize the *de novo* synthesis pathway for nucleotide production (76). U2AF homology motif kinase 1 (UHMK1) is a nuclear-localized serine/threonine kinase and acts as an effective oncogenic factor. In GC, UHMK1 expression is upregulated; it can phosphorylate nuclear receptor coactivator 3 at serine 1062 and threonine 1067, promoting its interaction with activating transcription factor 4 (ATF4) and inducing the nuclear translocation of ATF4. This activates transcriptional activity, mediates oligomeric nucleotide synthesis pathways and simultaneously enhances the *de novo* purine synthesis pathway, providing a material basis for GC cell proliferation and driving GC progression (77,78) (Fig. 2D).

Cells can secrete nucleotides and nucleosides to initiate paracrine and autocrine signaling, thereby driving cellular metabolic networks, regulating immune responses and influencing the development and progression of tumor cells (79). Due to genomic mutations, the expression level of major histocompatibility complex (MHC) class I polypeptide-related sequence A (MICA) increases in tumors. MICA binds to the natural killer group 2 member D receptor, thereby triggering NK cell-mediated immune surveillance. This process is associated with the high levels of nucleotide metabolism observed in tumor cells (80,81). A study found that certain nucleotide metabolism-related genes are associated with levels of immune cell infiltration (82). Patients with GC exhibiting high nucleotide metabolism have poorer overall survival, disease-specific survival, disease-free interval and progression-free interval. Additionally, these patients show increased expression of immunosuppressive factors and MHC molecules (82).

Adenosine can receive a phosphate group under the catalysis of adenosine kinase, which is an important pathway for nucleotide synthesis. Conversely, nucleotides can be dephosphorylated by phosphatases to generate adenosine; this bidirectional conversion is a key node in intracellular purine metabolism (83). Adenosine receptors are present on the surface of various cell types including human dendritic cells (DCs), which mainly express A1 and A3 receptors (84). Adenosine can mediate the migration of DCs to lymphoid organs, promote antigen presentation and T cell activation, thereby driving immune regulation (85,86). Additionally, regulatory B cells can regulate their own function through adenosine signaling derived from ATP enzymatic degradation, maintaining an immunosuppressive cell phenotype and inhibiting T cell activation, thus participating in the regulation of adaptive immunity. Excessive adenosine signaling can impede immune surveillance and thereby promote tumor progression (84).

4. Core mechanisms of circRNA in regulating metabolic reprogramming in GC

Non-coding mechanism: Acting as a 'molecular sponge' to competitively bind miRNA. Early transcriptome studies mainly focused on the competing endogenous RNA (ceRNA) interactions between mRNA and long ncRNA. With advances in high-throughput sequencing and RNA interaction analysis technologies, it was discovered that circRNAs retain only the circularized regions of exons, introns or exon-intron sequences, and naturally lack a 5' cap and 3' poly(A) tail. This makes them more stable within the ceRNA network and enables them to have specific regulatory functions (87). circRNAs can bind to miRNA through sequence-complementary miRNA response elements, competitively inhibiting the degradation or translational repression of target mRNAs by miRNAs. Therefore, circRNAs regulate the expression level of target gene transcripts and are extensively involved in various cellular biological processes (88).

circDNMT1 can act as a molecular sponge for miR-576-3p, thereby relieving its inhibitory effect on the hypoxia-inducible factor 1-α (HIF-1α) 3' untranslated region (3'UTR). This accelerates glucose uptake in GC cells, increases lactate production, suppresses pyruvate and ATP generation and promotes tumor progression (89). Similarly, inhibition of circSLAMF6 can enhance the targeted regulation of myosin heavy chain 9 (MYH9) by miR-204-5p, thereby weakening the glycolytic capacity of GC cells under hypoxia and further suppressing tumor metastasis and invasion (90). As shown in Table I, numerous circRNAs have been reported to participate in GC glycolysis via the ceRNA network in previous years. The majority of circRNAs linked to GC are upregulated and act as miRNA sponges to abolish the inhibition of key glycolytic enzymes or transcription factors, consequently enhancing glucose uptake and lactate production as well as promoting GC proliferation, migration and invasion.

GC cells can recruit mesenchymal stem cells (MSCs) by secreting microvesicles. Under the combined induction of immune cells and *Helicobacter pylori*, these MSCs are transformed into GC-MSCs, which retain mesenchymal lineage and stem cell properties, possess multipotent differentiation potential and strongly promote GC cell proliferation, migration and angiogenesis (91). circ_0024107 derived from GC-MSCs can act as a molecular sponge for miR-5572 and miR-6855-5p, negatively regulating their expression, upregulating CPT1A mRNA and protein expression, participating in FA transport and activating FAO, thus promoting GC proliferation and metastasis (92). Additionally, circRNAs can enhance the expression of amino acid metabolism-related transporters by sponging miRNAs through sequence complementarity. A study has shown that circAKT3 targets miR-515-5p, relieving its suppression of SLC1A5 by binding to the SLC1A5 3'UTR, thereby increasing the expression of the SLC1A5 transporter

Table I. The potential mechanism of circRNA in regulating metabolic reprogramming of gastric cancer.

A, ceRNA

Authors, year	circRNAs	Expression	Target	Metabolic mechanism	Effect	Function	(Refs.)
Zhou *et al*, 2022	circ_0006089	Up	miR-361-3p/TGFB1	Glycolysis	Glucose absorption↑, lactate↑, ATP↑, HK2↑	Proliferation, migration	(175)
Jiang *et al*, 2022	circ_0067514	Down	miR-654-3p/LATS2	Glycolysis	Glucose absorption↑, lactate↑, ATP↑, HK2↑, LDHA↑	Proliferation, invasion	(176)
Shen *et al*, 2022	circZNF131	Up	miR-186-5p/PFKFB2	Glycolysis	Glucose absorption↑, lactate↑, HK2↑, GLUT1↑	Migration, invasion	(177)
Qian *et al*, 2025	circ_0001756	Up	miR-185-3p/PGK1	Glycolysis	Glucose absorption↑, lactate↑, HK2↑, LDHA↑, GLUT1↑	Proliferation, migration, invasion	(100)
Yang *et al*, 2024	circFLNA	Up	miR-1200/SOX5	Glycolysis	Glucose absorption↑, lactate↑, HK2↑	Proliferation	(178)
Wang *et al*, 2021	circBFAR	Up	miR-513a-3p/HK2	Glycolysis	Lactate↑, ECAR↑, OCR↓, HK2↑	Proliferation	(179)
Zheng *et al*, 2023	circRPS19	Up	miR-125a-5p/USP7	Glycolysis	Glucose absorption↑, lactate↑, ECAR↑, OCR↓, HK2↑	Proliferation	(180)
Chen *et al*, 2020	circ_0032821	Up	miR-1236-3p/HMGB1	Glycolysis	Glucose absorption↑, lactate↑, ATP↑, ECAR↑, OCR↓	Proliferation, migration, invasion	(181)
Liu *et al*, 2022	circ_0009910	Up	miR-361-3p/SNRPA	Glycolysis	Glucose absorption↑, lactate↑, HK2↑, PKM2↑	Proliferation, migration, invasion	(182)
Liu *et al*, 2020	circ-NRIP1	Up	miR-186-5p/MYH9	Glycolysis	Glucose absorption↑, lactate↑, ATP↑, HK2↑, PKM2↑	Proliferation, migration	(169)
Zheng *et al*, 2024	circKIAA1797	Up	miR-4429/PBX3	Glycolysis	Glucose absorption↑, lactate↑,	Proliferation, migration, invasion	(183)
Zhao *et al*, 2021	circATP2B1	Up	miR-326-3p/ miR-330-5p/PKM2	Glycolysis	Glucose absorption↑, lactate↑, ATP↑, GLUT1↑, GLUT3↑, LDHA↑, PKM2↑	Proliferation	(184)
Chen *et al*, 2021	circC6orf132	Up	miR-873-5p/PRKAA1	Glycolysis	Glucose absorption↑, lactate↑, ATP↑, HK2↑, GLUT1↑	Proliferation, migration, invasion	(185)
Yang *et al*, 2021	circUBE2Q2	Up	miR-370-3p/STAT3	Glycolysis	Glucose absorption↑, lactate↑, ATP↑, ECAR↑, HK2↑, PFK↑	Proliferation, migration, invasion	(186)
Liu *et al*, 2020	circ-MAT2B	Up	miR-515-5p/HIF-1α	Glycolysis	Glucose absorption↑, lactate↑, HIF-1α↑	Proliferation	(187)

Table I. Continued.

A, ceRNA

Authors, year	circRNAs	Expression	Target	Metabolic mechanism	Effect	Function	(Refs.)
Fang *et al*, 2020	circSLAMF6	Up	miR-204-5p/MYH9	Glycolysis	Glucose absorption↑, lactate↑, HK2↑	Migration, invasion	(90)
Ou *et al*, 2025	circ_0043256	Up	miR-593-5p/RRM2	Glycolysis	Glucose absorption↑, lactate↑, ATP↑, HIF-1α↑, HK2↑, ENO1↑, LDHA↑, GLUT1↑, PKM2↑	Proliferation, migration	(188)
Lu *et al*, 2021	circVPS33B	Up	miR-873-5p/ HNRNPK	Glycolysis	Glucose absorption↑, lactate↑, ECAR↑, OCR↓	Proliferation, migration, invasion	(189)
Qu *et al*, 2020	circFLNA	Up	miR-646/PFKFB2	Glycolysis	Glucose absorption↑, lactate↑, ATP↑, PFKFB2↑	Proliferation, migration	(190)
Lan *et al*, 2024	circPRDM5	Down	miR-485-3p/GCNT4	Glycolysis	ECAR↑, HK2↑	Proliferation, migration, invasion	(191)
Li *et al*, 2022	circDNMT1	Up	miR-576-3p/HIF-1α	Glycolysis	Glucose absorption↑, lactate↑, ATP↑, ECAR↑, OCR↓	Proliferation, migration, invasion	(89)
Lu *et al*, 2023	circ_0000419	Down	miR-300/RGMB	Glycolysis	Glucose absorption↑, lactate↑, HK2↑, GLUT1↑	Migration, invasion	(192)
Wu *et al*, 2021	circ-RNF111	Up	miR-876-3p/KLF12	Glycolysis	Glucose absorption↑, lactate↑, HK2↑	Migration, invasion	(193)
Ji *et al*, 2022	circ_000059	Up	miR-1179/ANXA4	Glycolysis	Glucose absorption↑, lactate↑, HK2↑	Proliferation, migration, invasion	(194)
Xu *et al*, 2020	circNRIP1	Up	miR-138-5p/HIF-1α	Glycolysis	Glucose absorption↑, lactate↑, G6P↑, HIF-1α↑	5-FU resistance	(170)
Pu *et al*, 2020	circCUL3	Up	miR-515-5p/STAT3/ HK2	Glycolysis	Glucose absorption↑, lactate↑, ATP↑, ECAR↑	Proliferation	(195)
Wang *et al*, 2023	circ_0024107	Up	miR-5572/6855-5p/ CPT1A	Lipid metabolism	CPT1A↑, β oxidation rate↑	Migration, invasion	(92)
Ye *et al*, 2020	circB3GNTL1	Up	miR-598	Amino acid metabolism	Gln↑, Glu↑, α-KG↑	Proliferation	(94)
Li *et al*, 2022	circAKT3	Up	miR-515-5p/SLC1A5	Amino acid metabolism	Gln↑, SLC1A5↑	Proliferation, survival	(93)
Li *et al*, 2020	circSFMBT2	Up	miR-665	Amino acid metabolism	Gln↑, Glu↑, α-KG↑	Migration, invasion	(95)

Table I. Continued.

Authors, year	circRNAs	Expression	Target	Metabolic mechanism	Effect	Function	(Refs.)
B, Encoding peptide							
Jiang *et al*, 2024	circ_0008035	Up	EXT1/PKM2	Glycolysis	PKM2↑	Proliferation	(113)
Lu *et al*, 2025	circUBE2G1	Down	ENO1	Glycolysis	Glucose absorption↑, lactate↑, ATP↑, pyruvate↑, ENO1↑	Proliferation, migration, invasion	(114)
C, RBP							
Qian *et al*, 2025	circ_0001756	Up	PTBP1/PGK1	Glycolysis	Glucose absorption↑, lactate↑, HK2↑, LDHA↑, GLUT1↑	Proliferation, migration	(100)
Lin *et al*, 2025	circTFRC	Up	SCD1	Lipid metabolism	SCD1↑	Proliferation, migration	(102)
Lin *et al*, 2024	circ-CDK13	Up	EIF4A3	Amino acid metabolism	Methionine↑	DDP resistance	(105)
D, m^6A modification							
Wu *et al*, 2024	circFAM192A	Up	FTO	Amino acid metabolism	FTO↑, SLC7A5↑	Proliferation	(128)

circRNA, circular RNA; ceRNA, competing endogenous RNA; TGFB1, transforming growth factor β1; ATP, adenosine triphosphate; HK2, hexokinase 2; LATS2, large tumor suppressor kinase 2; LDHA, lactate dehydrogenase A; PFKFB2, 6-phosphofructo-2-kinase/fructose-2, 6-bisphosphatase 2; GLUT1, glucose transporter 1; PGK1, phosphoglycerate kinase 1; SOX5, SRY-box transcription factor 5; ECAR, extracellular acidification rate; OCR, oxygen consumption rate; USP7, ubiquitin-specific processing protease 7; HMGB1, high mobility group box 1; SNRPA, small nuclear ribonucleoprotein polypeptide A; PKM2, pyruvate kinase M2; MYH9, myosin heavy chain 9; PBX3, pre-leukemia transcription factor 3; PRKAA1, protein kinase AMP-activated α1 catalytic subunit; STAT3, signal transduction and activator of transcription 3; PFK, phosphofructokinase; HIF-1, hypoxia-inducible factor 1; RRM2, ribonucleotide reductase M2; ENO1, enolase 1; HNRNPK; heterogeneous nuclear ribonucleoprotein K; GCNT4, glucosaminyl (*N*-acetyl) transferase 4; RGMB, repulsive guidance molecule B; KLF12, kruppel-like factor 12; ANXA4, annexin A4; G6P, glucose-6-phosphate; CPT1A, carnitine palmitoyltransferase 1A; Gln, glutamine; Glu, glutamic acid; α-KG, α-ketoglutarate; SLC1A5, solute carrier family 1 member 5; SCD1, stearoyl-CoA desaturase 1; EIF4A3, eukaryotic initiation factor 4A3; FTO, fat mass and obesity-associated protein; SLC7A5, solute carrier family 7 member 5; 5-FU, 5-fluorouracil; DDP, cisplatin.

and enhancing Gln uptake in GC cells, which in turn promotes malignant proliferation (93). circB3GNTL1 and circSFMBT2 can also participate in amino acid metabolism in GC by sponging miR-598 and miR-665, respectively (94,95). Although direct research focusing on circRNA-mediated regulation of nucleotide metabolic reprogramming in GC via the ceRNA network is limited, a study has found that hsa_circ_0008434 in GC can sponge miR-6838-5p, relieving its inhibition of ubiquitin-specific peptidase 9X (USP9X), resulting in USP9X protein accumulation and promoting GC cell proliferation, migration and invasion (96). USP9X, through multiple synergistic mechanisms, regulates the stability of Gln synthetase, increases nucleotide availability, supports nucleotide synthesis and stemness maintenance in tumor cells, and participates in tumor growth and proliferation (97).

Non-coding mechanism: Acting as a 'protein decoy' by binding to the functional domains of proteins. The binding of circRNAs to RBPs relies on the complementary pairing or spatial recognition between specific binding sites within circRNA sequences and the RNA-binding domains of RBPs. This interaction forms distinct circRNA-RBP complexes, which regulate the activity, conformational changes and subcellular localization of target proteins, thereby modulating circRNA functions in tumor cells (98). Additionally, circRNAs can regulate the expression of key metabolic dependency enzymes or transporters and participate in multiple signaling pathways to directly or indirectly influence metabolic reprogramming in GC cells.

Polypyrimidine tract-binding protein 1 (PTBP1), a shuttling protein between the cytoplasm and nucleus with distinct functions in each compartment, is involved in tumor proliferation and invasion (99). circ_0001756 binds to PTBP1, facilitating its interaction with phosphoglycerate kinase 1 (PGK1) via the RRM1 domain. This interaction enhances the stability of PGK1 mRNA, promotes its cytoplasmic expression and participates in the first step of ATP production through the glycolytic pathway, thereby contributing to GC initiation and progression (100). Stearoyl-CoA desaturase 1 (SCD1), a key rate-limiting enzyme that desaturates saturated FAs to produce monounsaturated FAs, controls lipid metabolic flux. Aberrant transcriptional regulation and epigenetic modifications of SCD1 induce abnormal lipid accumulation, driving tumor progression (101). circTFRC directly binds to SCD1 mRNA, recruits ELAV-like RNA binding protein 1 and interacts with the 3'UTR of SCD1 mRNA. This protects SCD1 from nuclease degradation, enhances its stability and sustains SCD1 mRNA translation. Consequently, this promotes oncogenic lipid metabolic remodeling, thereby accelerating GC progression (102).

Rapidly dividing tumor cells exhibit methionine (Met) dependence due to their high demand for Met in processes such as histone modification, nuclear division and GSH synthesis (103,104). Met deprivation induces DNA damage in tumor cells, leading to proliferation arrest. A study has shown that eukaryotic initiation factor 4A3 (EIF4A3) binds to and interacts with the flanking sequences downstream of circ-CDK13. Met degradation downregulates EIF4A3 expression, restricting circ-CDK13 circularization, inhibiting GC cell proliferative activity, increasing intracellular cisplatin concentrations and enhancing chemosensitivity (105). The oncogenic transcription factor myelocytomatosis oncogene (MYC) has been extensively studied in metabolic contexts, with its expression consistently elevated across all stages of intestinal-type GC development (106,107). MYC provides sugar backbones for purine and pyrimidine biosynthesis and activates phosphoribosyl pyrophosphate synthetase 2 (PRPS2) via eukaryotic translation initiation factor 4E. Through specific cis-regulatory elements within its 5'UTR, PRPS2 couples protein and nucleotide biosynthesis (108), enabling tumor cells to reprogram nucleotide metabolic pathways to adapt to nutrient-deprived environments. Research has confirmed that circ-TNPO3 binds to the KH domain at the C-terminus of insulin-like growth factor 2 mRNA-binding protein 3 (IGF2BP3), impairing IGF2BP3-mediated stabilization of MYC mRNA and thereby inhibiting GC proliferation and metastasis (109). Additionally, circ-hnRNPU can also directly bind to non-POU domain-containing octamer-binding protein (NONO), inducing the cytoplasmic accumulation of NONO, thereby abolishing the activating effect of nuclear NONO on c-Myc and downregulating c-Myc expression (110). c-Myc is well established as a transcriptional activator of PRPS2, a rate-limiting enzyme in *de novo* purine and pyrimidine synthesis (108). Whether circ-hnRNPU-mediated c-Myc downregulation translates into altered nucleotide metabolic flux in GC cells, however, has not been investigated. Direct evidence linking circ-hnRNPU to changes in nucleotide synthesis rates, PRPS2 activity, or intracellular metabolite levels is currently absent, and this putative relationship awaits experimental validation.

Coding mechanism: Encoding peptide. Conventional translation initiation typically involves the recognition of the 5' cap by the small ribosomal subunit and its associated initiation factors. However, circRNAs lack this structure and cannot initiate translation through the canonical pathway. IRESs, which are structured RNA elements capable of directly recruiting the small ribosomal subunit and initiation factors, enable a subset of circRNAs to undergo cap-independent translation, yielding functional short peptides (111).

Emerging evidence indicates that peptides encoded by endogenous circRNAs play potential roles in tumorigenesis (112). For example, circ_0008035 encodes a novel peptide, EXT1-219aa, which suppresses EXT1 phosphorylation. This promotes the nuclear localization of PKM2 and reduces its EXT1-dependent glycosylation, thereby enhancing pyruvate metabolism and accelerating glycolysis in GC cells (113). By contrast, circUBE2G1 can encode circ_UBE2G1-99aa, which binds to enolase 1, thereby promoting glycolysis in GC (114). Similarly, circFNDC3B may encode a 267-amino-acid peptide that facilitates c-Myc protein degradation via the proteasomal pathway, inhibiting GC cell proliferation and migration (115). These findings underscore the importance of c-Myc in amino acid metabolic remodeling and suggest that circFNDC3B may participate in GC progression through this metabolic axis. c-Myc serves as a key transcriptional driver of PRPS2 in the *de novo* synthesis pathways of purines and pyrimidines (108). Whether the negative regulatory mechanism of FNDC3B-267aa on c-Myc (115) establishes a link between this peptide and nucleotide metabolism remains to be determined, as direct

evidence demonstrating that FNDC3B-267aa alters PRPS2 activity, nucleotide precursor levels or pyrimidine/purine pools in GC cells is currently lacking.

To date, studies on circRNA-encoded micropeptides regulating metabolic reprogramming in GC remain relatively limited, with most focusing on glycolytic pathways. However, research on other solid tumors, such as glioblastoma and colorectal cancer, has revealed that circRNA-derived micropeptides influence malignant progression by modulating key processes such as nucleotide metabolism and FAO (112,116). Given the high conservation of these metabolic pathways in cancer, it is plausible that GC proliferation similarly depends on such mechanisms. For example, a novel 127-amino-acid micropeptide encoded by circSpdyA binds to the ER catalytic domain of FA synthase, activating *de novo* FA synthesis, enhancing FAO and upregulating CPT1A activity. This promotes the uptake of accumulated FAs to supply membrane biosynthesis and support tumor cell proliferation and metastasis in breast cancer (117). Another micropeptide, E2F1-99aa, is encoded by circE2F1, which contains an IRES and a 297-nucleotide open reading frame. E2F1-99aa mimics the DP-binding domain of E2F1, interacts with SPIB and competitively inhibits E2F1-SPIB binding. This intervention downregulates nucleotide biosynthetic gene expression, reduces purine and pyrimidine synthesis and consequently suppresses neuroblastoma progression (118). Future research should focus on identifying GC-specific circRNA-encoded micropeptides and validating whether their functions align with these conserved metabolic pathways.

Non-coding and coding mechanisms: m^{6}A modification. m^{6}A modification of circRNAs is regulated by methyltransferases, demethylases and reader proteins, primarily occurring at the N^6 position of adenine residues (119). The covalently closed circular structure of circRNAs restricts the spatial distribution of modification sites, facilitating the formation of an 'aggregation effect' of m^{6}A modifications. This effect enhances the recruitment efficiency of binding proteins and results in a more concentrated distribution of modification sites within the exonic sequences of circularized regions (120). Notably, m^{6}A modification of circRNAs primarily reinforces and expands their non-coding functional repertoire; it enables the subcellular trafficking and localization of circRNAs between the nucleus and cytoplasm and regulates processes such as RNA processing, degradation, nuclear export and translation (121). By modulating the abundance and functional duration of circRNAs, m^{6}A modification serves as one of the critical pathways mediating circRNA degradation (122), thereby further interfering with the metabolic homeostasis of tumor cells and contributing to tumor progression (123). However, in rare, specialized contexts, m^{6}A modification can endow circRNAs with coding potential, whereby the m^{6}A reader protein YTHDF3 recognizes m^{6}A-modified circRNAs, recruits the translation initiation factor eIF4G2, and mediates ribosome assembly on circRNAs. By providing an IRES, this process drives the translation of circRNAs into short peptides (124). Notably, a single m^{6}A modification is sufficient to initiate circRNA translation (125). In such cases, certain circRNA molecules temporarily acquire coding capacity upon m^{6}A modification, which contributes to the complex regulatory networks underlying tumor initiation and progression.

Abnormal glycolytic flux is a key hallmark of bioenergetic metabolism in GC. circRNAs can regulate glycolytic pathways through epigenetic remodeling, while dynamic m^{6}A epitranscriptomic modifications modulate the expression of glycolytic enzymes via methyltransferase/demethylase-mediated RNA methylation cycles. These interconnected mechanisms collectively maintain the metabolic plasticity of GC cells (126). FTO, an RNA demethylase with specific m^{6}A demethylation activity (127), binds to circFAM192A at specific sites and removes its m^{6}A modifications to prevent degradation. Subsequently, circFAM192A interacts with the membrane-localized leucine transporter SLC7A5 to enhance its stability, increasing the membrane localization of SLC7A5 for leucine transport. Elevated leucine uptake thereby promotes GC cell proliferation (128). FTO can also specifically remove the m^{6}A modification of circ_0112136 to maintain its stability, thereby activating the PI3K/AKT/mTOR pathway. Notably, mTORC1 is a critical signaling molecule that activates the rate-limiting enzyme of pyrimidine synthesis (129,130). It should be emphasized that whether the FTO/circ_0112136 axis regulates pyrimidine biosynthesis, carbamoyl-phosphate synthetase 2, aspartate transcarbamylase and dihydroorotase (CAD) activity or nucleotide levels in GC cells via the mTORC1 signaling pathway warrants further investigation. This speculation is derived solely from the established function of mTORC1 in nucleotide metabolism.

Although the most abundant epitranscriptomic modification of RNA, direct evidence for m^{6}A-modified circRNAs regulating metabolic remodeling pathways in GC remains limited. However, findings from other tumor types provide valuable insights. For example, in hepatocellular carcinoma, m^{6}A-modified circRAPGEF1 competitively binds to IGF2BP3 via its KH domain, leading to the degradation of certain enzymes in aspartate metabolism. Aspartate activates CAD, the rate-limiting enzyme in *de novo* pyrimidine synthesis, thereby enhancing tumor cell stemness (131). The 'm^{6}A-circRNA-metabolic reprogramming' axis represents a conserved regulatory module across tumors, which strengthens the credibility of a similar mechanism operating in GC. Table I systematically summarizes the molecular mechanisms of circRNAs in the metabolic reprogramming of GC.

5. Evidence for circRNAs as potential biomarkers

Patients with early-stage GC typically present with no specific clinical manifestations, but may exhibit non-specific symptoms such as mild epigastric pain, abdominal distension and acid reflux (132,133). These symptoms are often overlooked, leading to diagnostic delays. Consequently, most patients are diagnosed at an advanced stage when they first seek medical attention, which notably increases the difficulty of treatment. Therefore, early diagnosis is a critical strategy to improve patient survival rates. In certain high-incidence countries, screening and intervention measures have alleviated part of the disease burden. However, challenges such as low early diagnosis rates, limited treatment options due to high tumor heterogeneity and insufficient sensitivity of disease monitoring indicators still persist (1). Thus, the identification of

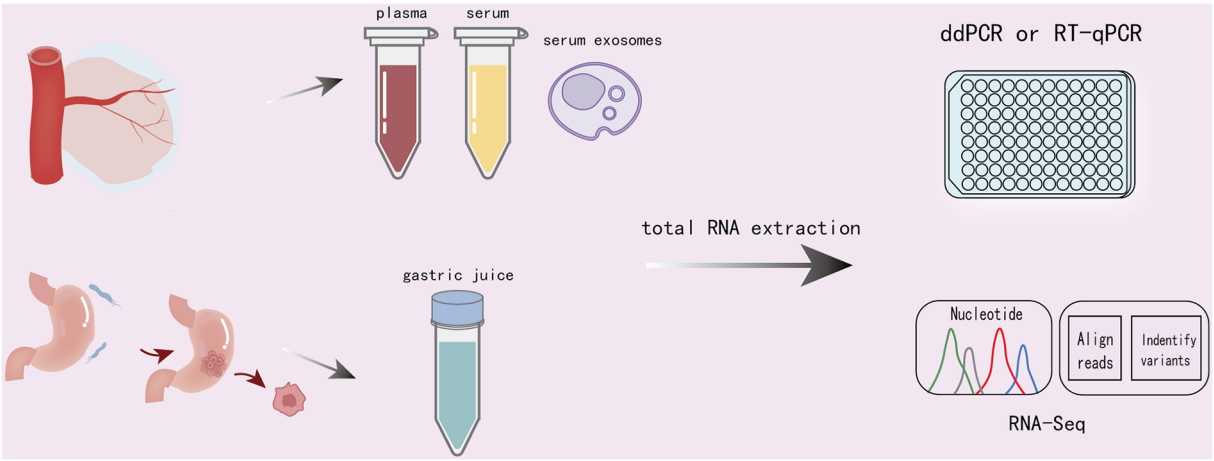

Figure 3. Workflow for the detection and analysis of circRNAs in the body fluids of patients with gastric cancer. Schematic overview illustrating sample sources and analytical procedures for circRNA profiling. Plasma, serum, serum-derived exosomes and gastric juice are collected from patients and subjected to total RNA extraction. Extracted RNA is subsequently analyzed by ddPCR or RT-qPCR for quantification and by RNA sequencing for transcriptomic profiling. circRNA, circular RNA; ddPCR, droplet digital PCR; RT-qPCR, reverse transcription-quantitative PCR. Created in Adobe Illustrator.

novel biomarkers, development of reproducible detection methods, detection of preclinical disease and implementation of large-scale population screening are crucial for early diagnosis and improving clinical outcomes (134).

At present, endoscopic biopsy combined with histopathological examination is the gold standard for the diagnosis of GC, with endoscopic ultrasonography providing specificity for tumor staging (135). However, these methods have certain limitations, including being highly invasive, having poor patient compliance and relatively high operational costs. Conventional tumor markers such as carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) are not specific to GC and have insufficient sensitivity and specificity (136). Therefore, developing non-invasive biomarkers with high sensitivity and accuracy that can dynamically reflect disease activity has become a key focus in GC clinical research (137). Due to their covalently closed circular structure, circRNAs are highly stable in body fluids (such as serum, plasma and gastric juice), exhibit high tissue specificity and show expression patterns correlated with tumor progression. They are also closely related to tumor metabolic reprogramming and have been recognized as novel biomarkers (138). Currently, techniques such as droplet digital polymerase chain reaction, reverse transcription quantitative PCR or RNA sequencing (RNA-seq) are commonly used for detection (Fig. 3). A study has confirmed that circRNAs in the body fluids of patients with GC display differential expression, which may be associated with the anatomical location of the tumor (139). These findings provide a molecular 'yardstick' for the clinical diagnosis, screening and treatment of GC. Table II summarizes the potential diagnostic value of circRNAs from different sample sources.

Plasma and serum. Plasma and serum are clinically accessible body fluid samples, and research on circRNA biomarkers in these fluids is relatively advanced. On the one hand, plasma circRNAs can be used for early detection and to distinguish between healthy individuals and patients with GC. For example, the combined detection of circulating hsa_circ_0001017 and hsa_circ_0061276 is closely associated with major clinicopathological factors of GC, showing a sensitivity and specificity of 84.7 and 96.6%, respectively, which demonstrates notable clinical value for GC diagnosis and prognosis assessment (140). On the other hand, plasma circRNAs can differentiate between different clinical stages of patients with GC. For instance, the expression level of plasma exosomal circLPAR1 in patients with GC is notably decreased in the advanced stages (stages IIb and III), while it is elevated in the early and intermediate stages (stages I and IIa) or after surgery. Moreover, the diagnostic performance of plasma exosomal circLPAR1 is superior to that of CEA and CA19-9, with notably improved diagnostic efficiency, demonstrating good sensitivity and specificity, making it a potential biomarker for GC diagnosis and staging (141). Additionally, studies have isolated exosomes from the plasma of patients with GC and healthy individuals and used high-throughput RNA-seq to analyze circRNA expression in circulating exosomes. The authors found that hsa_circ_0093425, hsa_circ_0007247 and hsa_circ_0029780 were significantly upregulated, while hsa_circ_0139983, hsa_circ_0001989, hsa_circ_0011115 and hsa_circ_0019618 were significantly downregulated in patients with GC, indicating that plasma exosomal circRNAs exhibit differential expression in GC (142). In addition, plasma-derived hsa_circ_0000745 (143), hsa_circ_0000190 (144), hsa_circ_0000181 (145), hsa_circ_0003195 (146), circPTPN22 (147), hsa_circ_0005927 (148) and hsa_circ_0065149 (149), as well as serum-derived hsa_circ_0001649 (150), hsa_circ_0000231 (151), circHAS2 (152), hsa_circ_0000702 (153), hsa_circ_0050547 (154) and hsa_circ_000200 (155), also play important roles in the screening, diagnosis and prognosis of GC.

Gastric juice. Gastric juice is directly secreted by gastric cells and more accurately reflects local gastric lesions compared with serum and plasma; it is not cleared by the liver and, in theory, may lack ribonucleoprotein and lipoprotein complexes, thereby reducing the risk of ncRNA degradation by nucleases, proteases and the acidic environment of gastric juice. This makes gastric juice a potentially ideal source of biomarkers

Table II. Research on circRNAs from different sample sources as clinical diagnostic biomarkers.

First author, year	circRNAs	Samples	Expression alteration	AUC	SEN (%), SPE (%)	Function	(Refs.)
Li *et al*, 2018	hsa_circ_0001017	Plasma	Down	0.871	79.4, 81.1	Diagnosis, prognosis	(140)
Li *et al*, 2018	hsa_circ_0061276	Plasma	Down	0.764	90.3, 51.7	Diagnosis, prognosis	(140)
Huang *et al*, 2017	hsa_circ_0000745	Plasma	Down	0.683	85.5, 45	Diagnosis, tumor differentiation	(143)
Chen *et al*, 2017	hsa_circ_0000190	Plasma	Down	0.60	41.4, 87.5	Screening	(144)
Zhao *et al*, 2018	hsa_circ_0000181	Plasma	Down	0.582	99.0, 20.6	Tumor differentiation	(145)
Ma *et al*, 2022	hsa_circ_0003195	Plasma	Down	0.695	46.9, 94.6	Screening, prognosis	(146)
Ma *et al*, 2021	circPTPN22	Plasma	Up	0.857	78, 84	Diagnosis	(147)
Li *et al*, 2017	hsa_circ_0001649	Serum	Down	0.834	71.1, 81.6	Screening	(150)
Fang *et al*, 2024	hsa_circ_0000231	Serum	Down	0.781	86.73, 57.81	Diagnosis monitoring, prognosis	(151)
Ma *et al*, 2024	circHAS2	Serum	Up	0.845	74, 83	Screening, prognosis	(152)
Yuan *et al*, 2023	hsa_circ_0000702	Serum	Down	0.745	82.69, 48.44	Diagnosis, monitoring	(153)
Zang *et al*, 2024	hsa_circ_0050547	Serum exosomes	Up	0.90	68.42, 100	Diagnosis	(154)
Huang *et al*, 2023	hsa_circ_000200	Serum exosomes	Up	0.7092	98, 44	Diagnosis	(155)
Shao *et al*, 2017	hsa_circ_0014717	Gastric juice	ns	/	/	Screening	(157)
Shao *et al*, 2024	hsa_circ_0005927	Plasma	Up	0.623	52.38, 76.19	Screening	(148)
Shao *et al*, 2024	hsa_circ_0005927	Gastric juice	ns	/	/	/	(148)
Shao *et al*, 2020	hsa_circ_0065149	Plasma	Down	0.640	48.7, 90.2	Screening, prognosis	(149)
Shao *et al*, 2020	hsa_circ_0065149	Gastric juice	ns	/	/	/	(149)

circRNA, circular RNA; AUC, area under the curve; SEN, sensitivity; SPE, specificity; ns, not significant.

for the dynamic monitoring of GC screening, diagnosis, treatment efficacy and recurrence (156). Shao *et al* (157) studied circRNA expression changes in gastric juice and confirmed that hsa_circ_0014717 can stably exist in human gastric juice. By comparing healthy individuals, patients with gastric ulcer, patients with chronic atrophic gastritis and patients with GC, they found that hsa_circ_0014717 expression was significantly downregulated in the chronic atrophic gastritis group, but increased in the GC group, a trend similar to that observed for hsa_circ_0005927 in gastric juice (148). This suggests a possible link to tumor cell secretion mechanisms and changes in the TME. Additionally, hsa_circ_0065149 was shown to stably exist in gastric juice, but its expression did not notably differ among the four groups. Furthermore, the expression trend of hsa_circ_0065149 in gastric juice was not consistent with that in GC tissues or plasma exosomes, suggesting that this may be related to small sample size or selective changes in circRNA sources (149). Therefore, gastric juice circRNA holds unique value for early evaluation of GC treatment efficacy and is especially suitable for patients unable to tolerate repeated endoscopic examinations.

6. Challenges in circRNA and metabolic reprogramming research

Current research on circRNA biomarkers predominantly focuses on tissue samples, with a smaller number of studies investigating their presence in body fluids such as serum, plasma and exosomes. The majority of these are single-center, retrospective studies with limited statistical power, which currently precludes their translation into routine clinical testing (158). Some scholars have performed independent validation using serum samples from both training and validation sets, including patients with GC and control subjects (159). However, the cut-off value was mainly determined based on the training set, lacking real-world prospective cohort studies. Furthermore, the diagnostic efficacy of a single circRNA is limited, requiring evaluation using multi-molecule panels (160). In addition, the individual physiological status of the patient is associated with circRNA expression levels in body fluids, which may lead to fluctuations in the accuracy and sensitivity of circRNAs as biomarkers (161). Although circRNA-based biomarker prediction systems remain in the exploratory stage, multiple hospitals have completed the clinical registration of prospective, multicenter studies investigating circRNA, indicating that this field is advancing. Efforts are being made to overcome the 'noise' caused by individual heterogeneity through technical optimization, multicenter validation and large-sample verification.

There is also a lack of uniform standards for the identification and validation of circRNAs. The back-splice site is critical for circRNA identification. However, variations exist among research teams in raw materials such as cell types and platforms, as well as in analytical pipelines and methods including RNA isolation, linear RNA depletion and library preparation (162). Furthermore, circRNA abundance in body fluids is affected by multiple pre-analytical factors, including centrifugation time and temperature, freeze-thaw cycles and serum clotting time (163). In addition, the detection and analysis of circRNAs require specialized high-precision instruments to generate millions of sequencing reads, making it difficult to extend to routine clinical settings in the short term (164).

Meanwhile, cell lines used in laboratory studies differ metabolically and functionally from their *in vivo* counterparts. Animal models, while useful, are limited by species-specific differences and cannot fully recapitulate human disease pathology. Therefore, validating circRNA findings in human cohorts is essential to strengthen their clinical relevance (165).

Research on metabolic reprogramming has often lacked visual evidence directly linking it to clinical disease manifestations. However, the emergence of ^{18}F-FDG PET/CT imaging has repositioned metabolic reprogramming at the forefront of oncology research. This technique assesses tumor metabolic activity by measuring the accumulation of ^{18}F-FDG, a glucose analog, within key molecules involved in the metabolic reprogramming of cancer cells (166). A growing body of evidence indicates that aberrantly expressed circRNAs contribute to GC progression by modulating the activity and expression of metabolic enzymes, thereby driving metabolic remodeling. This influence on cellular energy supply and biosynthetic capacity positions circRNAs as critical regulators of GC proliferation, invasion, metastasis, drug resistance and immune evasion. While studies focusing on the glycolytic axis are relatively abundant, further investigation is needed to elucidate the roles of circRNAs in other metabolic pathways, such as amino acid and nucleotide metabolism, within the context of GC metabolic reprogramming. Such an imbalance in research focus not only reflects that glycolytic indicators are relatively easy to observe but also reveals that current findings are largely limited to easily verifiable stages, which does not allow the inference that circRNAs participate in the regulation of the entire metabolic network in GC.

Moreover, studies investigating circRNA-mediated regulation of nucleotide synthesis or catabolism in GC are characterized by substantial limitations, most notably the absence of direct quantification of nucleotide intermediates, *de novo* purine/pyrimidine synthesis flux or the activities of rate-limiting enzymes. By contrast to the conventional assay kit approaches widely employed in glycolysis research, methodologies for nucleotide metabolic analysis are technically demanding and lack accessible phenotypic endpoints. These challenges likely represent major contributing factors to the current dearth of research in this field.

The mechanisms by which circRNAs regulate metabolic reprogramming in GC are not limited to linear pathways. Recent studies have demonstrated that circRNAs influence GC remodeling through multiple strategies, including direct interaction with metabolic enzymes (114), modulation of epigenetic modifications (167) and participation in various signaling pathways (168). For example, a single circRNA can regulate multiple signaling circuits. circ-NRIP1 competitively sequesters miR-186-5p, thereby relieving its suppression of MYH9 and promoting GC cell proliferation, migration and glycolysis (169). Independently, it also acts as a sponge for miR-138-5p, modulating HIF-1α-dependent glycolysis and sensitizing GC cells to hypoxia-induced 5-fluorouracil resistance (170). This suggests that the circRNA regulatory network is context-dependent, yet the mechanisms underlying the functional allocation of circRNAs across distinct

signaling pathways under specific cellular backgrounds or microenvironmental conditions remain elusive.

Furthermore, metabolic reprogramming in GC exhibits notable heterogeneity. Different cellular subpopulations within the same tumor, such as cancer stem cells and differentiated tumor cells, utilize distinct metabolic pathways, which dynamically evolve during disease progression (171). There are substantial differences between model cell lines and human tumors. Nutrient composition, oxygen tension and cell-cell interactions in *in vitro* culture systems tend to exaggerate specific metabolic phenotypes; meanwhile, animal models are limited by interspecies differences. Current research predominantly relies on bulk RNA-seq of mixed cell populations, which provides averaged gene expression profiles, or single-cell RNA-seq of individual cell lines, which may be subject to limited genetic drift and fail to fully represent intratumoral diversity (172,173). Both approaches face challenges in comprehensively capturing this metabolic heterogeneity. Although notable hurdles remain in elucidating circRNA-mediated metabolic reprogramming, spanning mechanistic validation, technological limitations and clinical translation, the field is poised for advancement. The deepening integration of multi-omics technologies, the initiation of multi-center prospective clinical studies and continued optimization of targeted delivery systems (such as antisense oligonucleotides, small interfering RNAs and CRISPR/Cas systems) collectively strengthen the potential of circRNAs to provide critical insights for GC screening, diagnosis, therapeutic monitoring and detection of recurrence (174).

7. Conclusion

GC exhibits high heterogeneity and its pathogenesis involves complex metabolic remodeling networks. circRNAs, as stable, conserved and functionally versatile members of the ncRNA family, are no longer regarded as biological 'dark matter'. Instead, they have emerged as key regulators of metabolic reprogramming in GC. Through diverse coding and non-coding mechanisms, circRNAs indirectly modulate target genes involved in glucose, lipid, amino acid and nucleotide metabolism. These findings highlight the interplay between epigenetic regulation and metabolic phenotypes, underscoring the potential of circRNAs as biomarkers and therapeutic targets. However, the pronounced heterogeneity of GC poses notable challenges for clinical management. The expression profiles of circRNAs and their selective roles in metabolic regulation across different molecular subtypes, such as HER2-positive, EBV-positive and microsatellite instability-high GC remain poorly characterized. Moreover, current research has largely focused on the impact of circRNAs on individual metabolic pathways, such as glycolysis, while systematic investigations into the mechanisms by which circRNAs coordinately regulate interconnected metabolic processes in GC are still lacking. Integrative analysis using metabolomics and single-cell sequencing remains limited, making it difficult to capture the spatiotemporal dynamics of circRNA expression and metabolite concentrations in GC. This gap hinders the identification of critical regulatory networks. Future studies should prioritize multi-omics approaches to construct comprehensive molecular maps of circRNA-mediated metabolic reprogramming, thereby providing a theoretical foundation and technical support for precision metabolic therapy in GC. In summary, targeting circRNA-regulated metabolic reprogramming holds substantial promise for advancing both basic research and clinical applications in GC.

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Authors' contributions

XL conceived and designed the review. TW wrote the first draft. JM, SZ, WG, YY and XZ participated in writing the manuscript. HL edited, reviewed and supervised the manuscript and acquired funding. All authors contributed to the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

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Competing interests

The authors declare that they have no competing interests.

References

1. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I and Jemal A: Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 74: 229-263, 2024.
2. Li X, Wang J, Ma Y, Wang S, Yu X, Niu K, Yan P, Wu D, Song J, Kou Y, *et al*: Burden and trends of early-onset gastric cancer in the 11 BRICS countries (2025 expansion): 1990-2021 with projections to 2035. BMC Cancer 25: 1478, 2025.
3. Luzko I, Moreira L and Bornschein J: Screening for and surveillance of premalignant conditions of the stomach. Best Pract Res Clin Gastroenterol 75: 101978, 2025.
4. Ko MT, Fung A, Kumar A, McArdle A and Alexandre L: Post-endoscopy upper gastrointestinal cancer: Emerging data and opportunities to improve early detection. Best Pract Res Clin Gastroenterol 75: 102003, 2025.
5. Luo D, Zhou J, Ruan S, Zhang B, Zhu H, Que Y, Ying S, Li X, Hu Y and Song Z: Overcoming immunotherapy resistance in gastric cancer: insights into mechanisms and emerging strategies. Cell Death Dis 16: 75, 2025.
6. Sun Q, Li S, Lou J, Wang X and Xu X: Recent advances in tumour microenvironment impact immunotherapy resistance in gastric cancer. Crit Rev Oncol Hematol 215: 104837, 2025.

7. Vander Heiden MG, Cantley LC and hompson CB: Understanding the Warburg effect: The metabolic requirements of cell proliferation. Science 324: 1029-1033, 2009.
8. Schiliro C and Firestein BL: Mechanisms of metabolic reprogramming in cancer cells supporting enhanced growth and proliferation. Cells 10: 1056, 2021.
9. Warburg O: On the origin of cancer cells. Science 123: 309-314, 1956.
10. Cai H, Zhang F, Xu F and Yang C: Metabolic reprogramming and therapeutic targeting in non-small cell lung cancer: Emerging insights beyond the Warburg effect. Front Oncol 15: 1564226, 2025.
11. Marei HE: Epigenetic regulators in cancer therapy and progression. NPJ Precis Oncol 9: 206, 2025.
12. Toden S, Zumwalt TJ and Goel A: Non-coding RNAs and potential therapeutic targeting in cancer. Biochim Biophys Acta Rev Cancer 1875: 188491, 2021.
13. Saw PE, Xu X, Chen J and Song E: Non-coding RNAs: The new central dogma of cancer biology. Sci China Life Sci 64: 22-50, 2021.
14. Xie S, Chang Y, Jin H, Yang F, Xu Y, Yan X, Lin A, Shu Q and Zhou T: Non-coding RNAs in gastric cancer. Cancer Lett 493: 55-70, 2020.
15. Li J, Sun D, Pu W, Wang J and Peng Y: Circular RNAs in cancer: Biogenesis, function, and clinical significance. Trends Cancer 6: 319-336, 2020.
16. Xia L, Song M, Sun M, Wang F and Yang C: Circular RNAs as biomarkers for cancer. Adv Exp Med Biol 1087: 171-187, 2018.
17. Pandey PR, Munk R, Kundu G, De S, Abdelmohsen K and Gorospe M: Methods for analysis of circular RNAs. Wiley Interdiscip Rev RNA 11: e1566, 2020.
18. Memczak S, Jens M, Elefsinioti A, Torti F, Krueger J, Rybak A, Maier L, Mackowiak SD, Gregersen LH, Munschauer M, *et al*: Circular RNAs are a large class of animal RNAs with regulatory potency. Nature 495: 333-338, 2013.
19. He AT, Liu J, Li F and Yang BB: Targeting circular RNAs as a therapeutic approach: Current strategies and challenges. Signal Transduct Target Ther 6: 185, 2021.
20. Lee K, Ku J, Ku D and Kim Y: Inverted Alu repeats: Friends or foes in the human transcriptome. Exp Mol Med 56: 1250-1262, 2024.
21. Jeck WR, Sorrentino JA, Wang K, Slevin MK, Burd CE, Liu J, Marzluff WF and Sharpless NE: Circular RNAs are abundant, conserved, and associated with ALU repeats. RNA 19: 141-157, 2013.
22. Wang S, Sun Z, Lei Z and Zhang H: RNA-binding proteins and cancer metastasis. Semin Cancer Biol 86: 748-768, 2022.
23. Galarneau A and Richard S: Target RNA motif and target mRNAs of the Quaking STAR protein. Nat Struct Mol Biol 12: 691-698, 2005.
24. Conn SJ, Pillman KA, Toubia J, Conn VM, Salmanidis M, Phillips CA, Roslan S, Schreiber AW, Gregory PA and Goodall GJ: The RNA binding protein quaking regulates formation of circRNAs. Cell 160: 1125-1134, 2015.
25. Hong H, An O, Chan THM, Ng VHE, Kwok HS, Lin JS, Qi L, Han J, Tay DJT, Tang SJ, *et al*: Bidirectional regulation of adenosine-to-inosine (A-to-I) RNA editing by DEAH box helicase 9 (DHX9) in cancer. Nucleic Acids Res 46: 7953-7969, 2018.
26. Ivanov A, Memczak S, Wyler E, Torti F, Porath HT, Orejuela MR, Piechotta M, Levanon EY, Landthaler M, Dieterich C and Rajewsky N: Analysis of intron sequences reveals hallmarks of circular RNA biogenesis in animals. Cell Rep 10: 170-177, 2015.
27. Warburg O: On respiratory impairment in cancer cells. Science 124: 269-270, 1956.
28. Ciccarone F and Ciriolo MR: Reprogrammed mitochondria: A central hub of cancer cell metabolism. Biochem Soc Trans 52: 1305-1315, 2024.
29. Zhan H, Pal DS, Borleis J, Deng Y, Long Y, Janetopoulos C, Huang CH and Devreotes PN: Self-organizing glycolytic waves tune cellular metabolic states and fuel cancer progression. Nat Commun 16: 5563, 2025.
30. Zhang H, Liu S, Fu S, Zhao Q, Wang Y, Yuan Y and Zhang C: Novel insight into the Warburg effect: Sweet temptation. Crit Rev Oncol Hematol 214: 104844, 2025.
31. Qu J, Li P and Sun Z: Histone lactylation regulates cancer progression by reshaping the tumor microenvironment. Front Immunol 14: 1284344, 2023.
32. Pavlova NN, Zhu J and Thompson CB: The hallmarks of cancer metabolism: Still emerging. Cell Metab 34: 355-377, 2022.
33. Barba I, Carrillo-Bosch L and Seoane J: Targeting the Warburg effect in cancer: Where do we stand? Int J Mol Sci 25: 3142, 2024.
34. Wang Q, Li M, Chen C, Xu L, Fu Y, Xu J, Shu C, Wang B, Wang Z, Chen C, *et al*: Glucose homeostasis controls N-acetyltransferase 10-mediated ac4C modification of HK2 to drive gastric tumorigenesis. Theranostics 15: 2428-2450, 2025.
35. Bian X, Jiang H, Meng Y, Li YP, Fang J and Lu Z: Regulation of gene expression by glycolytic and gluconeogenic enzymes. Trends Cell Biol 32: 786-799, 2022.
36. Campos M and Albrecht LV: Hitting the sweet spot: How glucose metabolism is orchestrated in space and time by phosphofructokinase-1. Cancers (Basel) 16: 16, 2023.
37. Zhang Z, Han S, Ouyang S, Zeng Z, Liu Z, Sun J and Kang W: PDK4 constitutes a novel prognostic biomarker and therapeutic target in gastric cancer. Diagnostics (Basel) 12: 1101, 2022.
38. Zhang R, Mao G, Tang Y, Li C, Gao Y, Nie W, Song T, Liu S, Zhang P, Tao K and Li W: Inhibition of glycolysis enhances the efficacy of immunotherapy via PDK-mediated upregulation of PD-L1. Cancer Immunol Immunother 73: 151, 2024.
39. Zhu S, Guo Y, Zhang X, Liu H, Yin M, Chen X and Peng C: Pyruvate kinase M2 (PKM2) in cancer and cancer therapeutics. Cancer Lett 503: 240-248, 2021.
40. Zhang Z, Deng X, Liu Y, Liu Y, Sun L and Chen F: PKM2, function and expression and regulation. Cell Biosci 9: 52, 2019.
41. Röhrig F and Schulze A: The multifaceted roles of fatty acid synthesis in cancer. Nat Rev Cancer 16: 732-749, 2016.
42. Houten SM and Wanders RJ: A general introduction to the biochemistry of mitochondrial fatty acid β-oxidation. J Inherit Metab Dis 33: 469-477, 2010.
43. Jin HR, Wang J, Wang ZJ, Xi MJ, Xia BH, Deng K and Yang JL: Lipid metabolic reprogramming in tumor microenvironment: From mechanisms to therapeutics. J Hematol Oncol 16: 103, 2023.
44. Li C, Zhang L, Qiu Z, Deng W and Wang W: Key molecules of fatty acid metabolism in gastric cancer. Biomolecules 12: 706, 2022.
45. Guerrero-Rodríguez SL, Mata-Cruz C, Pérez-Tapia SM and Velasco-Velázquez MA: Role of CD36 in cancer progression, stemness, and targeting. Front Cell Dev Biol 10: 1079076, 2022.
46. Hao J, Wang J, Guo H, Zhao Y, Sun H, Li Y, Lai X, Zhao N, Wang X, Xie C, *et al*: CD36 facilitates fatty acid uptake by dynamic palmitoylation-regulated endocytosis. Nat Commun 11: 4765, 2020.
47. Jiang M, Wu N, Xu B, Chu Y, Li X, Su S, Chen D, Li W, Shi Y, Gao X, *et al*: Fatty acid-induced CD36 expression via O-GlcNAcylation drives gastric cancer metastasis. Theranostics 9: 5359-5373, 2019.
48. Severin M, Hansen RK, Rolver MG, Hels T, Maeda K, Pardo LA and Pedersen SF: Tumor acidosis supports cancer cell lipid uptake via a rapid transporter-independent mechanism. J Cell Sci 138: jcs263688, 2025.
49. Schlaepfer IR and Joshi M: CPT1A-mediated fat oxidation, mechanisms, and therapeutic potential. Endocrinology 161: bqz046, 2020.
50. Pereyra AS, Rajan A, Ferreira CR and Ellis JM: Loss of muscle carnitine palmitoyltransferase 2 prevents diet-induced obesity and insulin resistance despite long-chain acylcarnitine accumulation. Cell Rep 33: 108374, 2020.
51. Wang C, Zhang C, Li X, Shen J, Xu Y, Shi H, Mu X, Pan J, Zhao T, Li M, *et al*: CPT1A-mediated succinylation of S100A10 increases human gastric cancer invasion. J Cell Mol Med 23: 293-305, 2019.
52. Wang M, Yu W, Cao X, Gu H, Huang J, Wu C, Wang L, Sha X, Shen B, Wang T, *et al*: Exosomal CD44 transmits lymph node metastatic capacity between gastric cancer cells via YAP-CPT1A-mediated FAO reprogramming. Front Oncol 12: 860175, 2022.
53. Wang Y, Lu JH, Wang F, Wang YN, He MM, Wu QN, Lu YX, Yu HE, Chen ZH, Zhao Q, *et al*: Inhibition of fatty acid catabolism augments the efficacy of oxaliplatin-based chemotherapy in gastrointestinal cancers. Cancer Lett 473: 74-89, 2020.
54. Ma G, Zhang Z, Li P, Zhang Z, Zeng M, Liang Z, Li D, Wang L, Chen Y, Liang Y and Niu H: Reprogramming of glutamine metabolism and its impact on immune response in the tumor microenvironment. Cell Commun Signal 20: 114, 2022.
55. Lieu EL, Nguyen T, Rhyne S and Kim J: Amino acids in cancer. Exp Mol Med 52: 15-30, 2020.
56. Wang B, Pei J, Xu S, Liu J and Yu J: A glutamine tug-of-war between cancer and immune cells: Recent advances in unraveling the ongoing battle. J Exp Clin Cancer Res 43: 74, 2024.

57. Zou W, Han Z, Wang Z and Liu Q: Targeting glutamine metabolism as a potential target for cancer treatment. J Exp Clin Cancer Res 44: 180, 2025.
58. Ying M, You D, Zhu X, Cai L, Zeng S and Hu X: Lactate and glutamine support NADPH generation in cancer cells under glucose deprived conditions. Redox Biol 46: 102065, 2021.
59. Lu YX, Ju HQ, Liu ZX, Chen DL, Wang Y, Zhao Q, Wu QN, Zeng ZL, Qiu HB, Hu PS, *et al*: ME1 regulates NADPH homeostasis to promote gastric cancer growth and metastasis. Cancer Res 78: 1972-1985, 2018.
60. Yu JC, Jiang ZM and Li DM: Glutamine: A precursor of glutathione and its effect on liver. World J Gastroenterol 5: 143-146, 1999.
61. Jiang B, Zhang J, Zhao G, Liu M, Hu J, Lin F, Wang J, Zhao W, Ma H, Zhang C, *et al*: Filamentous GLS1 promotes ROS-induced apoptosis upon glutamine deprivation via insufficient asparagine synthesis. Mol Cell 82: 1821-1835.e6, 2022.
62. Jaune-Pons E and Vasseur S: Role of amino acids in regulation of ROS balance in cancer. Arch Biochem Biophys 689: 108438, 2020.
63. Byun JK, Park M, Lee S, Yun JW, Lee J, Kim JS, Cho SJ, Jeon HJ, Lee IK, Choi YK and Park KG: Inhibition of glutamine utilization synergizes with immune checkpoint inhibitor to promote antitumor immunity. Mol Cell 80: 592-606.e8, 2020.
64. Caforio M, Sorino C, Iacovelli S, Fanciulli M, Locatelli F and Folgiero V: Recent advances in searching c-Myc transcriptional cofactors during tumorigenesis. J Exp Clin Cancer Res 37: 239, 2018.
65. Gao P, Tchernyshyov I, Chang TC, Lee YS, Kita K, Ochi T, Zeller KI, De Marzo AM, Van Eyk JE, Mendell JT and Dang CV: c-Myc suppression of miR-23a/b enhances mitochondrial glutaminase expression and glutamine metabolism. Nature 458: 762-765, 2009.
66. Xu E, Ji B, Jin K and Chen Y: Branched-chain amino acids catabolism and cancer progression: Focus on therapeutic interventions. Front Oncol 13: 1220638, 2023.
67. Peng H, Wang Y and Luo W: Multifaceted role of branched-chain amino acid metabolism in cancer. Oncogene 39: 6747-6756, 2020.
68. Yang D, Liu H, Cai Y, Lu K, Zhong X, Xing S, Song W, Zhang Y, Ye L, Zhu X, *et al*: Branched-chain amino acid catabolism breaks glutamine addiction to sustain hepatocellular carcinoma progression. Cell Rep 41: 111691, 2022.
69. Zhang L and Han J: Branched-chain amino acid transaminase 1 (BCAT1) promotes the growth of breast cancer cells through improving mTOR-mediated mitochondrial biogenesis and function. Biochem Biophys Res Commun 486: 224-231, 2017.
70. Kami K, Fujimori T, Sato H, Sato M, Yamamoto H, Ohashi Y, Sugiyama N, Ishihama Y, Onozuka H, Ochiai A, *et al*: Metabolomic profiling of lung and prostate tumor tissues by capillary electrophoresis time-of-flight mass spectrometry. Metabolomics 9: 444-453, 2013.
71. Yu L, Bao S, Zhu F, Xu Y, Liu Y, Jiang R, Yang C, Cao F, Chen W and Li P: Association between branched-chain amino acid levels and gastric cancer risk: Large-scale prospective cohort study. Front Nutr 11: 1479800, 2024.
72. Lane AN and Fan TWM: Regulation of mammalian nucleotide metabolism and biosynthesis. Nucleic Acids Res 43: 2466-2485, 2015.
73. Feng Q, Zhang W, Peng Y, Zhao C, Ren J and Qu X: Precise targeting one-carbon metabolism for potent cancer therapy and metastasis suppression. Small 21: e04631, 2025.
74. Malvi P, Bugide S, Dutta R, Reddi KK, Edwards YJK, Singh K, Gupta R and Wajapeyee N: PDE7A inhibition suppresses triple-negative breast cancer by attenuating de novo pyrimidine biosynthesis. Cell Rep Med 6: 102356, 2025.
75. Mullen NJ and Singh PK: Nucleotide metabolism: A pan-cancer metabolic dependency. Nat Rev Cancer 23: 275-294, 2023.
76. Tran DH, Kim D, Kesavan R, Brown H, Dey T, Soflaee MH, Vu HS, Tasdogan A, Guo J, Bezwada D, *et al*: De novo and salvage purine synthesis pathways across tissues and tumors. Cell 187: 3602-3618.e20, 2024.
77. Yoon BK, Kim H, Oh TG, Oh SK, Jo S, Kim M, Chun KH, Hwang N, Lee S, Jin S, *et al*: PHGDH preserves one-carbon cycle to confer metabolic plasticity in chemoresistant gastric cancer during nutrient stress. Proc Natl Acad Sci USA 120: e2217826120, 2023.
78. Feng X, Ma D, Zhao J, Song Y, Zhu Y, Zhou Q, Ma F, Liu X, Zhong M, Liu Y, *et al*: UHMK1 promotes gastric cancer progression through reprogramming nucleotide metabolism. EMBO J 39: e102541, 2020.
79. Shi DD, Savani MR, Abdullah KG and McBrayer SK: Emerging roles of nucleotide metabolism in cancer. Trends Cancer 9: 624-635, 2023.
80. Møller SH, Mellergaard M, Madsen M, Bermejo AV, Jepsen SD, Hansen MH, Høgh RI, Aldana BI, Desler C, Rasmussen LJ, *et al*: Cytoplasmic citrate flux modulates the immune stimulatory NKG2D ligand MICA in cancer cells. Front Immunol 11: 1968, 2020.
81. Ferrari de Andrade L, Tay RE, Pan D, Luoma AM, Ito Y, Badrinath S, Tsoucas D, Franz B, May KF Jr, Harvey CJ, *et al*: Antibody-mediated inhibition of MICA and MICB shedding promotes NK cell-driven tumor immunity. Science 359: 1537-1542, 2018.
82. Chen S and Wang Z: Integration of mult-omics and nucleotide metabolism reprogramming signature analysis reveals gastric cancer immunological and prognostic features. Cancer Cell Int 24: 212, 2024.
83. Losenkova K, Zuccarini M, Karikoski M, Laurila J, Boison D, Jalkanen S and Yegutkin GG: Compartmentalization of adenosine metabolism in cancer cells and its modulation during acute hypoxia. J Cell Sci 133: jcs241463, 2020.
84. Antonioli L, Fornai M, Blandizzi C, Pacher P and Haskó G: Adenosine signaling and the immune system: When a lot could be too much. Immunol Lett 205: 9-15, 2019.
85. Haskó G, Linden J, Cronstein B and Pacher P: Adenosine receptors: Therapeutic aspects for inflammatory and immune diseases. Nat Rev Drug Discov 7: 759-770, 2008.
86. Wang M, Zhao X, Hou S, Wu Z and Yin HY. Purinergic receptors in dendritic cells. J Inflamm Res 18: 13423-13432, 2025.
87. Pisignano G, Michael DC, Visal TH, Pirlog R, Ladomery M and Calin GA: Going circular: History, present, and future of circRNAs in cancer. Oncogene 42: 2783-2800, 2023.
88. Shahpari M, Hashemi M, Younesirad T, Hasanzadeh A, Mosanne MM and Ahmadifard M: The functional roles of competitive endogenous RNA (ceRNA) networks in apoptosis in human cancers: The circRNA/miRNA/mRNA regulatory axis and cell signaling pathways. Heliyon 10: e37089, 2024.
89. Li H, Cao B, Zhao R, Li T, Xu X, Cui H, Deng H, Gao J and Wei B: circDNMT1 promotes malignant progression of gastric cancer through targeting miR-576-3p/hypoxia inducible factor-1 alpha axis. Front Oncol 12: 817192, 2022.
90. Fang X, Bai Y, Zhang L and Ding S: Silencing circSLAMF6 represses cell glycolysis, migration, and invasion by regulating the miR-204-5p/MYH9 axis in gastric cancer under hypoxia. Biosci Rep 40: BSR20201275, 2020.
91. Shen J and Zhu W: Research advances in the role of gastric cancer-derived mesenchymal stem cells in tumor progression (review). Int J Mol Med 47: 455-462, 2021.
92. Wang L, Wu C, Xu J, Gong Z, Cao X, Huang J, Dong H, Zhu W, Huang F, Zhou C and Wang M: GC-MSC-derived circ_0024107 promotes gastric cancer cell lymphatic metastasis via fatty acid oxidation metabolic reprogramming mediated by the miR-5572/6855-5p/CPT1A axis. Oncol Rep 50: 138, 2023.
93. Li F, Zhang L and Sun Q: CircAKT3 promotes cell proliferation, survival and glutamine metabolism of gastric cancer by activating SLC1A5 expression via targeting miR-515-5p. Histol Histopathol 37: 227-241, 2022.
94. Ye B, Yu S, Wang J and Ren Y: CircB3GNTL1 and miR-598 regulation effects on proliferation, apoptosis, and glutaminolysis in gastric cancer cells. Cell Mol Biol (Noisy-le-grand) 66: 18-23, 2020.
95. Li J, Zhang G and Wu G: Effect of paeonol on proliferation, apoptosis, migration, invasion and glutamine of gastric cancer cells via circSFMBT2/miR-665 axis. Cell Mol Biol (Noisy-le-grand) 66: 33-40, 2020.
96. Xu X, Wang S, Wang H, Pan C, Yang W and Yu J: Hsa_circ_0008434 regulates USP9X expression by sponging miR-6838-5p to promote gastric cancer growth, migration and invasion. BMC Cancer 21: 1289, 2021.
97. Kim GW, Cha M, Ong HTM, Yoo J, Jeon YH, Lee SW, Oh SY, Kang MJ, Kim Y and Kwon SH: HDAC6 and USP9X control glutamine metabolism by stabilizing GS to promote glioblastoma tumorigenesis. Adv Sci (Weinh) 12: e2501553, 2025.
98. Li L, Wei C, Xie Y, Su Y, Liu C, Qiu G, Liu W, Liang Y, Zhao X, Huang D and Wu D: Expanded insights into the mechanisms of RNA-binding protein regulation of circRNA generation and function in cancer biology and therapy. Genes Dis 12: 101383, 2024.
99. Ji C, Zhu J, Hou X, Zhou C, Zhao J, Zheng X and Tang Y: PTBP1 and cancer: From RNA regulation to therapeutic potential. J Cell Mol Med 29: e70675, 2025.

100. Qian L, Wang L, Chen H, Wang S, Hou Y, Xu L, Xia Y, Xu M and Huang X: Hsa_circ_0001756 drives gastric cancer glycolysis by increasing the expression and stability of PGK1 mRNA. Front Immunol 16: 1511247, 2025.
101. Sun Q, Xing X, Wang H, Wan K, Fan R, Liu C, Wang Y, Wu W, Wang Y and Wang R: SCD1 is the critical signaling hub to mediate metabolic diseases: Mechanism and the development of its inhibitors. Biomed Pharmacother 170: 115586, 2024.
102. Lin Z, Zhong C, Shi M, Long Q, Jing L, Yu Y, Chou J, Chen M, Lan M and Long F: Circular RNA TFRC/SCD1 mRNA interaction regulates ferroptosis and metastasis in gastric cancer. Cell Death Dis 16: 436, 2025.
103. Cellarier E, Durando X, Vasson MP, Farges MC, Demiden A, Maurizis JC, Madelmont JC and Chollet P: Methionine dependency and cancer treatment. Cancer Treat Rev 29: 489-499, 2003.
104. Li F, Liu P, Mi W, Li L, Anderson NM, Lesner NP, Burrows M, Plesset J, Majer A, Wang G, *et al*: Blocking methionine catabolism induces senescence and confers vulnerability to GSK3 inhibition in liver cancer. Nat Cancer 5: 131-146, 2024.
105. Xin L, Zou YH, Liu CX, Lu H, Fan LJ, Xu HS, Zhou Q, Liu J, Yue ZQ and Gan JH: Methionine restriction promotes cisplatin sensitivity of gastric cancer resistant cells by down-regulating circ-CDK13 level. Exp Cell Res 443: 114315, 2024.
106. Xu AG, Li SG, Liu JH and Gan AH: Function of apoptosis and expression of the proteins Bcl-2, p53 and C-myc in the development of gastric cancer. World J Gastroenterol 7: 403-406, 2001.
107. Calcagno DQ, Leal MF, Assumpcao PP, Smith MAC and Burbano RR: MYC and gastric adenocarcinoma carcinogenesis. World J Gastroenterol 14: 5962-5968, 2008.
108. Cunningham JT, Moreno MV, Lodi A, Ronen SM and Ruggero D: Protein and nucleotide biosynthesis are coupled by a single rate-limiting enzyme, PRPS2, to drive cancer. Cell 157: 1088-1103, 2014.
109. Yu T, Ran L, Zhao H, Yin P, Li W, Lin J, Mao H, Cai D, Ma Q, Pan X, *et al*: Circular RNA circ-TNPO3 suppresses metastasis of GC by acting as a protein decoy for IGF2BP3 to regulate the expression of MYC and SNAIL. Mol Ther Nucleic Acids 26: 649-664, 2021.
110. Li H, Jiao W, Song J, Wang J, Chen G, Li D, Wang X, Bao B, Du X, Cheng Y, *et al*: circ-hnRNPU inhibits NONO-mediated c-Myc transactivation and mRNA stabilization essential for glycosylation and cancer progression. J Exp Clin Cancer Res 42: 313, 2023.
111. Lei M, Zheng G, Ning Q, Zheng J and Dong D: Translation and functional roles of circular RNAs in human cancer. Mol Cancer 19: 30, 2020.
112. Zhang M, Zhao K, Xu X, Yang Y, Yan S, Wei P, Liu H, Xu J, Xiao F, Zhou H, *et al*: A peptide encoded by circular form of LINC-PINT suppresses oncogenic transcriptional elongation in glioblastoma. Nat Commun 9: 4475, 2018.
113. Jiang R, Li P, Meng E, Cheng X, Wu X and Wu H: Hsa_Circ_0008035 drives immune evasion of gastric cancer via promoting EXT1-mediated nuclear translocation of PKM2. Transl Oncol 48: 102004, 2024.
114. Lu L, Guo G, Guo J, Li H, Chen K, Chen Y, Li Q, Li Q, Diao Y, Sun M, *et al*: A novel protein encoded by circUBE2G1 suppresses glycolysis in gastric cancer through binding to ENO1. Cell Death Discov 11: 350, 2025.
115. Liu YY, Zhang YY, Ran LY, Huang B, Ren JW, Ma Q, Pan XJ, Yang FF, Liang C, Wang XL, *et al*: A novel protein FNDC3B-267aa encoded by circ0003692 inhibits gastric cancer metastasis via promoting proteasomal degradation of c-Myc. J Transl Med 22: 507, 2024.
116. Xiong L, Liu HS, Zhou C, Yang X, Huang L, Jie HQ, Zeng ZW, Zheng XB, Li WX, Liu ZZ, *et al*: A novel protein encoded by circINSIG1 reprograms cholesterol metabolism by promoting the ubiquitin-dependent degradation of INSIG1 in colorectal cancer. Mol Cancer 22: 72, 2023.
117. Gao X, Sun Z, Liu X, Luo J, Liang X, Wang H, Zhou J, Yang C, Wang T and Li J: 127aa encoded by circSpdyA promotes FA synthesis and NK cell repression in breast cancers. Cell Death Differ 32: 416-433, 2025.
118. Wang J, Wang X, Yang C, Li Q, Li D, Du X, Cheng Y, Tian M, Zheng L and Tong Q: circE2F1-encoded peptide inhibits circadian machinery essential for nucleotide biosynthesis and tumor progression via repressing SPIB/E2F1 axis. Int J Biol Macromol 280: 135698, 2024.
119. Hu H, Tang J, Wang H, Guo X, Tu C and Li Z: The crosstalk between alternative splicing and circular RNA in cancer: Pathogenic insights and therapeutic implications. Cell Mol Biol Lett 29: 142, 2024.
120. Zhou C, Molinie B, Daneshvar K, Pondick JV, Wang J, Van Wittenberghe N, Xing Y, Giallourakis CC and Mullen AC: Genome-wide maps of m6A circRNAs identify widespread and cell-type-specific methylation patterns that are distinct from mRNAs. Cell Rep 20: 2262-2276, 2017.
121. Yi Q, Liao Y, Sun W, Li J, Yang D, Shang H and Sun W: m6A modification of non-coding RNA: Mechanisms, functions and potential values in human diseases (review). Int J Mol Med 56: 164, 2025.
122. An Y and Duan H: The role of m6A RNA methylation in cancer metabolism. Mol Cancer 21: 14, 2022.
123. Wang T, Kong S, Tao M and Ju S: The potential role of RNA N6-methyladenosine in cancer progression. Mol Cancer 19: 88, 2020.
124. Yang Y, Fan X, Mao M, Song X, Wu P, Zhang Y, Jin Y, Yang Y, Chen LL, Wang Y, *et al*: Extensive translation of circular RNAs driven by N^6-methyladenosine. Cell Res 27: 626-641, 2017.
125. Zeng K, Peng J, Xing Y, Zhang L, Zeng P, Li W, Zhang W, Pan Z, Zhou C and Lin J: A positive feedback circuit driven by m^6A-modified circular RNA facilitates colorectal cancer liver metastasis. Mol Cancer 22: 202, 2023.
126. Shan Z and Liu Y: Harnessing glycolysis in gastric cancer: Molecular targets, therapeutic strategies, and clinical horizons. Front Immunol 16: 1628937, 2025.
127. Jia G, Fu Y, Zhao X, Dai Q, Zheng G, Yang Y, Yi C, Lindahl T, Pan T, Yang YG and He C: N6-methyladenosine in nuclear RNA is a major substrate of the obesity-associated FTO. Nat Chem Biol 7: 885-887, 2011.
128. Wu X, Fang Y, Gu Y, Shen H, Xu Y, Xu T, Shi R, Xu D, Zhang J, Leng K, *et al*: Fat mass and obesity-associated protein (FTO) mediated m^6A modification of circFAM192A promoted gastric cancer proliferation by suppressing SLC7A5 decay. Mol Biomed 5: 11, 2024.
129. Liu J and Fang X: Regulation of hsa_circ_0112136 by m6A demethylase FTO can enhance the malignancy of gastric cancer via the regulation of the PI3K/AKT/mTOR pathway. Biotechnol Appl Biochem 71: 1316-1328, 2024.
130. Villa E, Ali ES, Sahu U and Ben-Sahra I: Cancer cells tune the signaling pathways to empower de novo synthesis of nucleotides. Cancers (Basel) 11: 688, 2019.
131. Shi J, Mui S, Yan Y, Liu S, Wen K, He C, Li H, Liao H, Tao M, Wen J, *et al*: m^6A-modified circRAPGEF1 interaction with IGF2BP3 promotes hepatocellular carcinoma progression via reprogramming aspartate metabolism. Adv Sci (Weinh) 12: e03851, 2025.
132. Necula L, Matei L, Dragu D, Neagu AI, Mambet C, Nedeianu S, Bleotu C, Diaconu CC and Chivu-Economescu M: Recent advances in gastric cancer early diagnosis. World J Gastroenterol 25: 2029-2044, 2019.
133. Ott JJ, Ullrich A and Miller AB: The importance of early symptom recognition in the context of early detection and cancer survival. Eur J Cancer 45: 2743-2748, 2009.
134. Hazelton WD and Luebeck EG: Biomarker-based early cancer detection: Is it achievable? Sci Transl Med 3: 109fs9, 2011.
135. Jacobson BC, Bhatt A, Greer KB, Lee LS, Park WG, Sauer BG and Shami VM: ACG clinical guideline: Diagnosis and management of gastrointestinal subepithelial lesions. Am J Gastroenterol 118: 46-58, 2023.
136. Feng F, Tian Y, Xu G, Liu Z, Liu S, Zheng G, Guo M, Lian X, Fan D and Zhang H: Diagnostic and prognostic value of CEA, CA19-9, AFP and CA125 for early gastric cancer. BMC Cancer 17: 737, 2017.
137. Smyth EC, Nilsson M, Grabsch HI, van Grieken NC and Lordick F: Gastric cancer. Lancet 396: 635-648, 2020.
138. Zhang HD, Jiang LH, Sun DW, Hou JC and Ji ZL: CircRNA: A novel type of biomarker for cancer. Breast Cancer 25: 1-7, 2018.
139. Reis-das-Mercês L, Vinasco-Sandoval T, Pompeu R, Ramos AC, Anaissi AKM, Demachki S, de Assumpção PP, Vidal AF, Ribeiro-Dos-Santos Â and Magalhães L: CircRNAs as potential blood biomarkers and key elements in regulatory networks in gastric cancer. Int J Mol Sci 23: 650, 2022.
140. Li T, Shao Y, Fu L, Xie Y, Zhu L, Sun W, Yu R, Xiao B and Guo J: Plasma circular RNA profiling of patients with gastric cancer and their droplet digital RT-PCR detection. J Mol Med (Berl) 96: 85-96, 2018.
141. Yang X, Xia J, Peng C and Cai W: Expression of plasma exosomal circLPAR1 in patients with gastric cancer and its clinical application value. Am J Cancer Res 13: 4269-4276, 2023.
142. Rao M, Zhu Y, Qi L, Hu F and Gao P: Circular RNA profiling in plasma exosomes from patients with gastric cancer. Oncol Lett 20: 2199-2208, 2020.

143. Huang M, He YR, Liang LC, Huang Q and Zhu ZQ: Circular RNA hsa_circ_0000745 may serve as a diagnostic marker for gastric cancer. World J Gastroenterol 23: 6330-6338, 2017.
144. Chen S, Li T, Zhao Q, Xiao B and Guo J: Using circular RNA hsa_circ_0000190 as a new biomarker in the diagnosis of gastric cancer. Clin Chim Acta 466: 167-171, 2017.
145. Zhao Q, Chen S, Li T, Xiao B and Zhang X: Clinical values of circular RNA 0000181 in the screening of gastric cancer. J Clin Lab Anal 32: e22333, 2018.
146. Ma Y, Li Z, Ma D, Guo J and Sun W: Hsa_circ_0003195 as a biomarker for diagnosis and prognosis of gastric cancer. Int J Clin Oncol 27: 354-361, 2022.
147. Ma S, Kong S, Gu X, Xu Y, Tao M, Shen L, Shen X and Ju S: As a biomarker for gastric cancer, circPTPN22 regulates the progression of gastric cancer through the EMT pathway. Cancer Cell Int 21: 44, 2021.
148. Shao Y, Yu X, Hu M, Yan J, Miao M, Ye G and Guo J: Acting mechanism and clinical significance of hsa_circ_0005927 in the invasion and metastasis of gastric cancer. J Cancer 15: 4081-4094, 2024.
149. Shao Y, Tao X, Lu R, Zhang H, Ge J, Xiao B, Ye G and Guo J: Hsa_circ_0065149 is an indicator for early gastric cancer screening and prognosis prediction. Pathol Oncol Res 26: 1475-1482, 2020.
150. Li WH, Song YC, Zhang H, Zhou ZJ, Xie X, Zeng QN, Guo K, Wang T, Xia P and Chang DM: Decreased expression of Hsa_circ_00001649 in gastric cancer and its clinical significance. Dis Markers 2017: 4587698, 2017.
151. Fang R, Yuan W, Mao C, Cao J, Chen H, Shi X and Cong H: Human circular RNA hsa_circ_0000231 clinical diagnostic effectiveness as a new tumor marker in gastric cancer. Cancer Rep (Hoboken) 7: e2081, 2024.
152. Ma S, Yao Y, Xu Y, Zou M, Zhou M, Abudushalamu G, Chen Y, Cai S, Zhang C and Wu G: Comprehensive evaluation of serum circHAS2 as a novel diagnostic and prognostic biomarker for gastric cancer. Mol Carcinog 63: 94-105, 2024.
153. Yuan W, Fang R, Mao C, Chen H, Tai B and Cong H: Serum circular RNA hsa_circ_0000702 as a novel biomarker for diagnosis of gastric cancer. J Clin Lab Anal 37: e24842, 2023.
154. Zang X, Wang R, Wang Z, Qiu S, Zhang F, Zhou L, Shen Y, Qian H, Xu W and Jiang J: Exosomal circ50547 as a potential marker and promotor of gastric cancer progression via miR-217/HNF1B axis. Transl Oncol 45: 101969, 2024.
155. Huang XJ, Wang Y, Wang HT, Liang ZF, Ji C, Li XX, Zhang LL, Ji RB, Xu WR, Jin JH and Qian H: Exosomal hsa_circ_000200 as a potential biomarker and metastasis enhancer of gastric cancer via miR-4659a/b-3p/HBEGF axis. Cancer Cell Int 23: 151, 2023.
156. Gareev I, Ahmad A, Wang J, Beilerli A, Ilyasova T, Sufianov A and Beylerli O: Gastric juice non-coding RNAs as potential biomarkers for gastric cancer. Front Physiol 14: 1179582, 2023.
157. Shao Y, Li J, Lu R, Li T, Yang Y, Xiao B and Guo J: Global circular RNA expression profile of human gastric cancer and its clinical significance. Cancer Med 6: 1173-1180, 2017.
158. Arnaiz E, Sole C, Manterola L, Iparraguirre L, Otaegui D and Lawrie CH: CircRNAs and cancer: Biomarkers and master regulators. Semin Cancer Biol 58: 90-99, 2019.
159. Roy S, Kanda M, Nomura S, Zhu Z, Toiyama Y, Taketomi A, Goldenring J, Baba H, Kodera Y and Goel A: Diagnostic efficacy of circular RNAs as noninvasive, liquid biopsy biomarkers for early detection of gastric cancer. Mol Cancer 21: 42, 2022.
160. Xu J, Liu Y, Zhang J, Yang S, Li T, Huang H, Liu Q, Wang H, Cao L, An Z, *et al*: Single-droplet dual-target quantification of circRNA biomarkers for colorectal cancer screening. Adv Sci (Weinh) 12: e06159, 2025.
161. Yang L, Wilusz JE and Chen LL: Biogenesis and regulatory roles of circular RNAs. Annu Rev Cell Dev Biol 38: 263-289, 2022.
162. Szabo L and Salzman J: Detecting circular RNAs: Bioinformatic and experimental challenges. Nat Rev Genet 17: 679-692, 2016.
163. Porwal O, Visht S and Muhammed RA: Circular RNAs as biomarkers and targets in ovarian cancer. Clin Chim Acta 582: 120802, 2026.
164. Guria A, Sharma P, Srikakulam N, Baby A, Natesan S and Pandi G: Cost-effective transcriptome-wide profiling of circular RNAs by the improved-tdMDA-NGS method. Front Mol Biosci 9: 886366, 2022.
165. Saadh MJ, Ahmed HH, Kareem RA, Bishoyi AK, Roopashree R, Shit D, Arya R, Joshi KK, Sameer HN, Yaseen A, *et al*: The hidden messengers: Tumor microenvironment-derived exosomal ceRNAs in gastric cancer progression. Pathol Res Pract 269: 155905, 2025.
166. Ferda J, Ferdová E, Vítovec M, Glanc D and Mírka H: The imaging of the hypoxic microenvironment in tumorous tissue using PET/CT and PET/MRI. Eur J Radiol 154: 110458, 2022.
167. Zandieh MA, Farahani MH, Rajabi R, Avval ST, Karimi K, Rahmanian P, Razzazan M, Javanshir S, Mirzaei S, Paskeh MDA, *et al*: Epigenetic regulation of autophagy by non-coding RNAs in gastrointestinal tumors: Biological functions and therapeutic perspectives. Pharmacol Res 187: 106582, 2023.
168. Barati T, Mirzaei Z, Abarghooi Kahaki F and Afkhami H: Regulatory roles of ncRNAs in gastric cancer progression: A comprehensive insight into key signaling pathways. Med Oncol 42: 309, 2025.
169. Liu Y, Jiang Y, Xu L, Qu C, Zhang L, Xiao X, Chen W, Li K, Liang Q and Wu H: circ-NRIP1 promotes glycolysis and tumor progression by regulating miR-186-5p/MYH9 axis in gastric cancer. Cancer Manag Res 12: 5945-5956, 2020.
170. Xu G, Li M, Wu J, Qin C, Tao Y and He H: Circular RNA circNRIP1 sponges microRNA-138-5p to maintain hypoxia-induced resistance to 5-fluorouracil through HIF-1α-dependent glucose metabolism in gastric carcinoma. Cancer Manag Res 12: 2789-2802, 2020.
171. Cordani M, Dando I, Ambrosini G and González-Menéndez P: Signaling, cancer cell plasticity, and intratumor heterogeneity. Cell Commun Signal 22: 255, 2024.
172. Golestanifar A, Zakeri M, Gohari-Lasaki S, Khedri H and Saberiyan M: Combined bulk and single-cell transcriptomic analysis reveals cell-type-specific inflammatory crosstalk in pancreatic cancer. Clin Exp Med 25: 263, 2025.
173. Li Y, Xu Q, Wu D and Chen G: Exploring additional valuable information from single-cell RNA-Seq data. Front Cell Dev Biol 8: 593007, 2020.
174. Aquino-Jarquin G: CircRNA knockdown based on antisense strategies. Drug Discov Today 29: 104066, 2024.
175. Zhou Y, Zhang Q, Liao B, Qiu X, Hu S and Xu Q: circ_0006089 promotes gastric cancer growth, metastasis, glycolysis, and angiogenesis by regulating miR-361-3p/TGFB1. Cancer Sci 113: 2044-2055, 2022.
176. Jiang SF and Li RR: hsa_circ_0067514 suppresses gastric cancer progression and glycolysis via miR-654-3p/LATS2 axis. Neoplasma 69: 1079-1091, 2022.
177. Shen X, Zhu X, Hu P, Ji T, Qin Y and Zhu J: Knockdown circZNF131 inhibits cell progression and glycolysis in gastric cancer through miR-186-5p/PFKFB2 axis. Biochem Genet 60: 1567-1584, 2022.
178. Yang X, Li D, Sun Y, Yi L, Chen Q and Lai Y: CircFLNA facilitates gastric cancer cell proliferation and glycolysis via regulating SOX5 by sponging miR-1200. Arab J Gastroenterol 25: 369-377, 2024.
179. Wang Y, Cao B, Zhao R, Li H, Wei B and Dai G: Knockdown of circBFAR inhibits proliferation and glycolysis in gastric cancer by sponging miR-513a-3p/hexokinase 2 axis. Biochem Biophys Res Commun 560: 80-86, 2021.
180. Zheng X, Shao J, Qian J and Liu S: circRPS19 affects HK2-mediated aerobic glycolysis and cell viability via the miR-125a-5p/USP7 pathway in gastric cancer. Int J Oncol 63: 98, 2023.
181. Chen L, Chi K, Xiang H and Yang Y: Circ_0032821 facilitates gastric cancer cell proliferation, migration, invasion and glycolysis by regulating MiR-1236-3p/HMGB1 axis. Cancer Manag Res 12: 9965-9976, 2020.
182. Liu J, Li J, Su Y, Ma Z, Yu S and He Y: Circ_0009910 serves as miR-361-3p sponge to promote the proliferation, metastasis, and glycolysis of gastric cancer via regulating SNRPA. Biochem Genet 60: 1809-1824, 2022.
183. Zheng X, Xiao H, Liu X, Huang T and Deng C: Exosomal circKIAA1797 regulates cell progression and glycolysis by targeting miR-4429/PBX3 pathway in gastric cancer. Biochem Genet 62: 1762-1778, 2024.
184. Zhao X, Tian Z and Liu L: circATP2B1 promotes aerobic glycolysis in gastric cancer cells through regulation of the miR-326 gene cluster. Front Oncol 11: 628624, 2021.
185. Chen W and Ji Y: CircC6orf132 facilitates proliferation, migration, invasion, and glycolysis of gastric cancer cells under hypoxia by acting on the miR-873-5p/PRKAA1 axis. Front Genet 12: 636392, 2021.

186. Yang J, Zhang X, Cao J, Xu P, Chen Z, Wang S, Li B, Zhang L, Xie L, Fang L and Xu Z: Circular RNA UBE2Q2 promotes malignant progression of gastric cancer by regulating signal transducer and activator of transcription 3-mediated autophagy and glycolysis. Cell Death Dis 12: 910, 2021.
187. Liu J, Liu H, Zeng Q, Xu P, Liu M and Yang N: Circular RNA circ-MAT2B facilitates glycolysis and growth of gastric cancer through regulating the miR-515-5p/HIF-1α axis. Cancer Cell Int 20: 171, 2020.
188. Ou W, Tan R, Zhai J, Sun L, Quan Z, Huang X, Xu F, Xu Q and Zhou C: Silencing circ_0043256 inhibited CoCl2-induced proliferation, migration, and aerobic glycolysis in gastric cancer cells. Sci Rep 15: 171, 2025.
189. Lu Y, Cheng J, Cai W, Zhuo H, Wu G and Cai J: Inhibition of circRNA circVPS33B reduces warburg effect and tumor growth through regulating the miR-873-5p/HNRNPK axis in infiltrative gastric cancer. Onco Targets Ther 14: 3095-3108, 2021.
190. Qu J, Yang J, Chen M, Wei R and Tian J: CircFLNA acts as a sponge of miR-646 to facilitate the proliferation, metastasis, glycolysis, and apoptosis inhibition of gastric cancer by targeting PFKFB2. Cancer Manag Res 12: 8093-8103, 2020.
191. Lan ZZ, Sun FH, Chen C, Niu L, Shi JD and Zhang WY: CircPRDM5 inhibits the proliferation, migration, invasion, and glucose metabolism of gastric cancer cells by reducing GCNT4 expression in a miR-485-3p-dependent manner. Kaohsiung J Med Sci 40: 231-243, 2024.
192. Lu J, Zhou Y, Chen Z, Jiang H, Li J and Dou G: Circ_0000419 acts as a tumor suppressor in gastric cancer development via regulating miR-300/RGMB axis. Int J Clin Oncol 28: 1475-1485, 2023.
193. Wu G, Zhang A, Yang Y and Wu D: Circ-RNF111 aggravates the malignancy of gastric cancer through miR-876-3p-dependent regulation of KLF12. World J Surg Oncol 19: 259, 2021.
194. Ji Z, Diao W and Shang J: Circular RNA circ_0000592 elevates ANXA4 expression via sponging miR-1179 to facilitate tumor progression in gastric cancer. Anticancer Drugs 33: e644-e654, 2022.
195. Pu Z, Xu M, Yuan X, Xie H and Zhao J: Circular RNA circCUL3 accelerates the warburg effect progression of gastric cancer through regulating the STAT3/HK2 axis. Mol Ther Nucleic Acids 22: 310-318, 2020.