The roles and mechanisms of circular RNAs related to mTOR in cancers

Chunli Cao1,2 | Yao Wang1,3 | Xinxin Wu1,3 | Zhe Li3 | Junming Guo1,3,4 | Weiliang Sun2

1Department of Biochemistry and Molecular Biology and Zhejiang Key Laboratory of Pathophysiology, Medical School of Ningbo University, Ningbo, China
2The Affiliated People's Hospital, Ningbo University, Ningbo, China
3Department of Gastroenterology, The Affiliated Hospital of Medical School, Ningbo University, Ningbo, China
4Institute of Digestive Diseases of Ningbo University, Ningbo, China

Correspondence
Junming Guo, Department of Biochemistry and Molecular Biology, School of Medicine, Ningbo University, Ningbo 315211, China.
Email: guojunming@nbu.edu.cn
Weiliang Sun, The Affiliated People's Hospital, Ningbo University, Ningbo 315040, China.
Email: msfsyk@163.com

Abstract
Background: Circular RNAs (circRNAs) are stable molecules with covalently closed structures that have an irreplaceable role in the occurrence, progression, and even treatment of plenty of cancers. Mammalian/mechanistic target of rapamycin (mTOR) is a key regulator in cancers and plays several biological functions, such as proliferation, migration, invasion, autophagy, and apoptosis.

Methods: All data were collected through PubMed and CNKI, using terms including "circRNA," "mTOR," "cancer," "signaling pathway," "biomarker," "diagnosis," "treatment." Articles published in Chinese and English were included.

Results: In this review, the expression, function, and mechanism of circRNA-associated mTOR in cancers were described. CircRNA-associated-mTOR can regulate the progression and therapy of a variety of cancers in multiple signaling pathways, such as phosphatidylinositol-3-kinase (PI3K)/protein kinase B (Akt)/mTOR, mitogen-activated protein kinase (MAPK)/mTOR, and AMP-activated protein kinase (AMPK)/mTOR axis. These cancers including esophageal carcinoma (circLPAR3, ciRS-7), gastric cancer (circNRIP1, hsa_circ_0010882, hsa_circ_0000117, hsa_circ_0072309, and circST3GAL6), colorectal cancer (hsa_circ_0000392, hsa_circ_0084927, hsa_circ_0004001, hsa_circ_0075792, hsa_circ_0079299, and hsa_circ_0002130), pancreatic cancer (circ-IARS and circRHOBTB3), renal carcinoma (ciRS-7), bladder cancer (circUBE2K), prostate cancer (circMBOAT2 and circ-ITCH), ovarian cancer (circEEF2, circRAB11FIP1, circMYLK, and circTPCN), endometrial cancer (hsa_circ_0002577 and circWHSC1), lung cancer (circHIPK3, hsa_circ_0001666), thyroid cancer (hsa_circ_0007694 and hsa_circ_0008274), glioma (circGFRA1, circ-MAPK4, circPCMTD1, and hsa_circ_0037251), osteosarcoma (circTFC25), leukemia (circ-PRKDC), and breast cancer (hsa_circ_0000199, circUBAP2, and circWHSC1).

KEYWORDS
cancer, circRNA, function, mechanism, mTOR
1 | INTRODUCTION

Cancer has become a major public health event that threatens human health, with increasing incidence and mortality worldwide. The main treatments for cancers include surgical resection, radiation therapy, chemotherapy, immunotherapy, and targeted therapy. Due to lack of early effective diagnostic markers and risk of tumor recurrence, cancer patients often have poor prognosis.

Circular RNAs (circRNAs) are biomolecules with closed ring-like structures linked by covalent bonds. In recent years, with the rapid development of high-throughput sequencing technologies and bioinformatics, the structure and function of circRNAs have been continuously explored. Most importantly, circRNAs are found closely related to the occurrence of cancer through regulating mammalian/mechanistic target of rapamycin (mTOR). mTOR is a protein kinase with regulatory effects on cell growth, proliferation, metabolism, autophagy, and apoptosis. More important, it has been demonstrated that circRNAs can influence the occurrence and development of cancers by regulating the activation of mTOR. This article reviews the effects and mechanism of circRNAs on cancers by regulating mTOR signaling pathway.

2 | THE STRUCTURE AND FUNCTION OF CIRCRNAS

connected by the splice-acceptor site of upstream exons and splice-donor site of downstream exons. CircRNAs are produced by back-splicing, which is covalently co. Although circRNAs are less abundant than linear RNAs, the special structure makes them resistant to the digestion degradation of nucleases and have high stability. In addition, the characteristics of circRNAs to accumulate in a time-dependent manner and to be expressed in specific tissues and cells were explored. At present, studies have shown that the formation methods of circRNAs can be divided into two types, intron paired-driven circularization and lariat-driven circularization (Figure 1A). CircRNAs can be divided into three types: exonic circular RNAs (ecircRNAs), exon-intron circular RNAs (EicircRNAs), and intronic circular RNAs (ciRNAs). EicircRNAs are mainly located in the nucleus and may promote transcription of parent genes by connecting with U1 small nuclear ribonucleoprotein (snRNP) and RNA polymerase II (Pol II) at parental gene promoters (Figure 1B). However, the vast majority of circRNAs are transported into the cytoplasm and regulate mRNA expression by acting as sponges of microRNAs (miRNAs), which playing an important role in competitive endogenous RNA (ceRNA) networks (Figure 1C). ciRS-7, also widely known as CDR1as, is present in human brain and mainly acts as sponge for miR-7 with more than 70 miRNA target sites. Moreover, circRNAs can combine with proteins to play the role of protein scaffolds. It has been uncovered three modes of interactions between circRNAs and proteins (Figure 1D). First, circRNAs can bind to two different proteins and further enhance their interconnection. Second, the binding of circRNA to protein A can enhance the connection of circRNA and protein B. In addition, circRNA binds to protein A and protein B which originally combine with each other and then disrupts their interaction. In addition, circRNAs can bind to a protein which is binding to DNA, RNA or proteins and then change its activity. For example, circHuR inhibits the malignant phenotype of gastric cancer (GC) via interacting with CCHC-type zinc finger nucleic acid-binding protein (CNBP) from a human antigen R (HuR) promoter. CircRNAs are not all non-coding RNAs (ncRNAs) and some of them have the ability to translate into peptides or proteins (Figure 1E). For example, CircFBXW7 has been confirmed to encode 185 amino acids termed FBXW7-aa in gliomas mediated by internal ribosome entry site (IRES) and positively correlated with the prognosis of patients. Besides, circRNAs may regulate transcription. For example, circ-SEP3 formed an RNA–DNA hybrid or R-loop by binding to host DNA sites, resulting in the cessation of transcriptional extension or the recruitment of splicing factor. Studies have shown that circRNAs acting as sponge of miRNAs regulate the mTOR signaling pathway in cancers. In addition, the high activity of mTOR can promote the adaptability, proliferation, metabolism, and chemoradiotherapy resistance of cancer cells. Consequently, the significant impact of circRNAs related to mTOR cannot be ignored in the progression and treatment of cancer.

3 | THE STRUCTURE AND FUNCTION OF mTOR

mTOR exists in two complexes in the form of a catalytic subunit, mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2), which function and regulate in different ways. The structure of mTORC1 consists of five components, including mTOR, regulatory-associated protein of mTOR (Rapor), mammalian lethal with sec-13 protein 8 (mLST8), proline-rich substrate of 40kDa (PRAS40), and DEP domain-containing mTOR-interacting protein (Depor) (Figure 2A). In addition to mTOR, Depor, and mLST8, mTORC2 includes three other components, rapamycin-insensitive companion of mTOR (Rictor), mammalian stress-activated protein kinase-interacting protein (mSIN1), and protein observed with Rictor1/2 (Protor1/2) (Figure 2B). mTORC1 primarily regulates cell growth and is sensitive to acute rapamycin. mTORC2, which regulates cell survival, proliferation, metabolism, and cytoskeleton reorganization, is insensitive to rapamycin. However, prolonged rapamycin therapy can inhibit the function of mTORC2. mTOR is a core factor in controlling cell growth, the dysregulation of which can lead to the progression of cancer by the overgrowth of cancer cells. mTORC1 mainly promotes the synthesis of proteins, lipids, and nucleotides, as well as the occurrence of glycolysis to provide energy and inhibits the occurrence of autophagy. mTORC1 promotes protein synthesis primarily through activation of p7056 kinase 1 (S6K1) and eukaryotic initiation factor 4E-binding protein 4 (4E-BPs). Lipids are essential nutrients for the life activities of cells and organisms and the synthesis of which are mainly promoted by mTORC1 through phosphorylated sterol reaction element binding proteins (SREBPs).
In addition, mTORC1 increases the expression of mitochondrial tetrahydrofolate cycle enzyme methylenetetrahydrofolate dehydrogenase 2 (MTHFD2), which is an essential component for the formation of nucleotides. Glycolysis provides energy for cell growth and mTORC1 increases the translation of the regulator hypoxia-inducible factor (HIF)-1α, thereby driving the expression of glycolytic enzymes such as fructosekinase phosphate (PFK). In addition to promoting above-mentioned nutrient synthesis and glucose metabolism processes, mTORC1 can inhibit catabolism such as autophagy by inactivating unc-51-like autophagy-activating kinase 1 (ULK1), an early effector in the induction of autophagy. Conversely, AMPK not only indirectly promotes autophagy by inhibiting mTORC1 expression but also directly functions by activating ULK1 via phosphorylation of Ser 317 and Ser 777.

The regulation modes of mTORC2 are different from mTORC1 (Figure 2B). mTORC2 activates protein kinase C alpha (PKCα), promoting cytoskeletal reorganization and cell migration. The oncoprotein, which can be activated by mTORC2, inhibits apoptosis and promotes glucose metabolism by activating glycogen synthase kinase 3β (GSK3β).

mTOR can function as the primarily downstream signaling molecule of AMPK pathway, MAPK pathway, and PI3K/Akt pathway and is a striking molecule that can promote cancer progression after activation (Figure 3). A variety of growth factors such as insulin and insulin-like growth factor (IGF) can activate PI3K, which can promote the transition from Phosphatidylinositol (4,5)-bisphosphate (PIP2) to phosphatidylinositol (3,4,5)-triphosphate (PIP3), which can then be reversed by phosphatase and tensin homolog (PTEN). Downstream target molecule of PI3K, directly activates the expression of mTORC1 and mTORC2 or indirectly activates mTORC1 by activating the mTORC1 forward regulator ras homolog protein enriched in brain (Rheb) through inhibiting the function of tuberous sclerosis complex 1/2 (TSC1/2). Similarly, rat sarcoma (Ras)-MAPK can inhibit the TSC1/2 complex and induce Rheb-mediated mTORC1 activation. In addition to the strong relationship between growth factors and the activation of mTORC1, nutrients and energy substances, such as ATP, glucose, and some amino acids, play critical roles in cells. High AMP level activates AMPK expression, an inhibitor of mTORC1 that works by promoting the formation of the TSC1/2 complex or directly inhibiting the activation of mTORC1.
The proliferative effects of growth factors can be antagonized by the low energy state in the body.\textsuperscript{30} The regulatory mechanisms of mTORC1 and mTORC2 are intricate and require further exploration of the relevant mechanisms.

### 4 | CIRCRNAS REGULATING MTOR IN CANCERS

Recently, a number of researchers have discovered that circRNAs are of importance for multiple cancers by regulating mTOR pathway (Table 1).

### 5 | DIGESTIVE SYSTEM

#### 5.1 | Esophageal carcinoma

The early symptoms of esophageal carcinoma (EC) are not obvious, therefore, advanced patients characterized by distant metastases account for the majority.\textsuperscript{34} Studies have shown that circRNAs can be used as diagnostic biomarkers and therapeutic targets for EC.\textsuperscript{35} One study investigated circLPAR3 overexpressed in EC tissues and cells, promoted cell migration, invasion, and metastasis through activating the Ras/MAPK and the PI3K/Akt pathway by upregulating the expression of hepatocyte growth factor receptor gene.\textsuperscript{36} Another study explored that overexpression of ciRS-7 can further relieve the inhibition of miR-1299 on the downstream target gene epidermal growth factor receptor (EGFR), which promotes mTOR activation through the EGFR/Akt/mTOR signaling pathway and ultimately inhibit the autophagy and promote the proliferation of cancer cells.\textsuperscript{37} The task significantly explained the progression of EC can be suppressed by regulating the expression of circRNAs related to mTOR and suggested circRNAs are promising therapeutic targets.

#### 5.2 | Gastric cancer

Although the incidence of gastric cancer (GC) has decreased and the diversity and effectiveness of treatment methods have increased compared with the previous period, the 5-year survival rate is <30%, which is proved to be a huge burden in cancer treatment.\textsuperscript{9} Studies have shown that the progression can be modulated by circRNAs via modulating the activation of mTOR in GC.\textsuperscript{9,38–41} CircNRP1, hsa_circ_0010882, and hsa_circ_0000117 are highly expressed in GC tissues and cells compared with normal adjacent tissues and cell lines.\textsuperscript{9,40,41} The investigation found that levels of phosphorylated-PI3K (p-PI3K), phosphorylated-Akt (p-Akt) and phosphorylated-mTOR (p-mTOR) changed synchronously with the expression of hsa_circ_0010882, and bioinformatics findings also showed that hsa_circ_0010882 promotes the progression of GC through the activating PI3K/Akt/mTOR signaling pathway.\textsuperscript{40} When hsa_circ_0010882 was reduced, the proliferation ability of GC cells
was weakened and the apoptosis was significantly enhanced, indicating that it is an independent prognostic factor for GC patients. Another study has explored that hsa_circ_0000117, sponging miR-337-3p, exerted the role of ceRNA, and accelerated the progression of GC by inhibiting the function of tuberous sclerosis complex 1/2 (TSC1/2). MAPK signaling pathway can also inhibit the TSC1/2 complex and in turn induce Rheb-mediated mTORC1 activation. High-AMP levels inhibit mTORC1 by promoting AMPK. CircRNAs regulate cancer progression by regulating mTOR expression. CircWHSC1, hsa_circ_0008274, circLPAR3, circ-0104631, hsa_circ_0072309, circ-ITCH, hsa_circ_0010882, circC16orf62, circRHOBTB3, and circST3GAL6 exert carcinogenic or anti-cancer effects by regulating the mTOR pathway.

**5.3 Colorectal cancer**

Colorectal cancer (CRC) is the second leading cause of death among common cancers worldwide. Metastasis occurs in 20% of patients at the time of diagnosis. Chemoradiation combined with targeted therapy is a common treatment modality in advanced patients, but drug resistance makes clinical treatment less effective, with a 5-year survival rate of <20%. Therefore, it is urgent to explore the biomarkers of diagnosis and therapeutic targets in CRC. Recently, many studies proved that CRC was closely related to abnormal expression of circRNAs associated with mTOR. Compared with healthy control groups, the hsa_circ_0000392, hsa_circ_0084927, and hsa_circ_0072309 were markedly increased in CRC. A study showed that hsa_circ_0104631 were upregulated in CRC tissues and cells, promoting the growth, and migration of cancer cells by activating the Akt/mTOR axis by inhibiting the expression of PTEN. CircRNAs can also inhibit the activation and function of mTOR to participate in cancer suppressive effects. Studies have revealed that circRNA FBXW7 not only had the effect of inhibiting the occurrence of cancer metastasis but also had the potential of being used as a diagnostic marker.
| Cancer type         | CircRNA  | Regulation of mTOR | Function                                               | Associated signaling pathways                                      | Reference |
|---------------------|----------|--------------------|-------------------------------------------------------|---------------------------------------------------------------------|-----------|
| Esophageal carcinoma| circLPAR3| Activation         | Promoting migration, invasion, and metastasis         | Activating Ras/ MAPK and PI3K/ Akt                                  | 36        |
|                     | ciRS-7   | Activation         | Inhibiting autophagy                                   | Activating EGFR/ Akt/mTOR                                          | 37        |
| Gastric cancer      | hsa_circ_0072309 | Inactivation     | Inhibiting proliferation, invasion, and migration     | Inhibiting PI3K/Akt/mTOR                                          | 38        |
|                     | circNRIP1 | Activation         | Promoting proliferation, migration, and invasion      | Activating AKT1/ mTOR                                              | 8         |
|                     | circST3GAL6 | Inactivation      | Inhibiting proliferation, growth, and metastasis, promoting apoptosis and autophagy | Inactivating MET/ Akt/mTOR                                        | 39        |
|                     | hsa_circ_0010882 | Activation    | Promoting proliferation, invasion, and migration; Inhibiting apoptosis | Activating PI3K/ Akt/mTOR                                        | 40        |
|                     | hsa_circ_0000117 | Activation     | Promoting proliferation and invasion                  | Activating AKT1/ mTOR                                              | 41        |
| Colorectal cancer   | circRNA_0000392 | Activation     | Promoting proliferation, invasion, and growth         | Activating PIK3R3/ Akt/mTOR                                       | 45        |
|                     | hsa_circ_0084927 | Activation     | Promoting migration and invasion                      | Activating Akt/ mTOR                                               | 47        |
|                     | circ-FBXW7 | Inactivation      | Inhibiting proliferation, migration, invasion, and growth | Inhibiting expression of mTOR                                   | 49        |
|                     | hsa_circ_0104631 | Activation     | Promoting proliferation and invasion                  | Activating PTEN/ Akt/mTOR                                         | 48        |
| Liver cancer        | circC16orf62 | Activation     | Promoting proliferation, invasion, and glycolysis     | Activating Akt/ mTOR                                               | 50        |
|                     | hsa_circ_100,338 | Activation     | Promoting proliferation                               | Activating expression of mTOR                                    | 54        |
|                     | hsa_circ_0079299 | Inactivation    | Inhibiting growth                                     | Inhibiting PI3K/Akt/mTOR                                          | 56        |
|                     | hsa_circ_0002130 | Inactivation    | Inhibiting growth                                     | Inhibiting expression of mTOR                                    | 57        |
| Pancreatic cancer   | circRHOBTB3 | Inactivation     | Promoting proliferation and autophagy                 | Inhibiting NACCI/ Akt/mTOR                                        | 61        |
| Renal carcinoma     | ciRS-7   | Activation         | Promoting proliferation, invasion, growth, and metastasis | Activating TAGLN/ PI3K/Akt/mTOR                                   | 64        |
| Bladder cancer      | circUBE2K | Activation         | Promoting the proliferation, migration, and EMT       | Activating TGF-β and PI3K/Akt/mTOR                                 | 65        |
| Prostate cancer     | circMBOAT2 | Activation         | Promoting proliferation, migration, invasion, and metastasis | Activating PI3K/ Akt/mTOR                                        | 67        |
|                     | cir-ITCH  | Inactivation       | Inhibiting activity, proliferation, and migration      | Inhibiting Wnt/β-catenin and PI3K/Akt/mTOR                         | 68        |
| Cervical cancer     | circHIAT1 | Inactivation       | Inhibiting growth, cycle, promoting apoptosis         | Inhibiting Akt/ mTOR                                               | 70        |
|                     | circMYLK  | Activation         | Promoting viability and proliferation                  | Activating RHEB/ Akt/mTOR                                         | 74        |
|                     | circTPCN  | Activation         | Promoting proliferation, migration, and invasion; Inhibiting apoptosis | Promoting expression of mTOR                                     | 75        |
and progression of gliomas but also participated in the malignant progression of CRC and GC by inhibiting the expression of mTOR through activating PTEN.49

5.4 | Liver cancer

Hepatocarcinoma (HCC) is the most common pathological type of liver cancer, accounting for 90% of the total and the mortality rate is among the top five cancers worldwide.42,50 With the development of a variety of technologies, the methods of prevention and treatment of liver cancer are increasing, including image-guided radiofrequency ablation, chemotherapy embolization, targeted therapy, which includes first-line targeted therapies such as sorafenib, levatinib, and regrafenib, are all gospel for patients with advanced liver cancer.51 Nevertheless, drug resistance and distant metastasis are remarkable obstacles to liver cancer treatment. Multiple studies have shown that circRNAs are associated with the development and treatment of liver cancer.53 Moreover, the activation of mTOR is considered to be an important event in the development of liver cancer.53 CircC16orf62, hsa_circ_0002577, hsa_circ_0001666, hsa_circ_0008274, hsa_circ_0007694, and hsa_circ_0004123 possess differential expression in HCC tissues and cells compared with adjacent normal tissues and cells and play the significant role of oncogenes when overexpressed in liver cancer.50,54,55 CircC16orf62 upregulation promotes the proliferation and migration of HCC.50 The molecular mechanism is circC16orf62 binds to miR-138-5p, which inhibits the expression of the oncogene protein tyrosine kinase 2 (PTK2) and increases the expression of p-mTOR by activating the Akt/mTOR signaling pathway. Surprisingly, researchers observed that upregulated hsa_circ_0079299 and hsa_circ_0002130 can inhibit the progression of liver cancer by
inactivating the PI3K/Akt/mTOR axis and activating glutamate-oxaloacetate transaminase 2 (GOT2), respectively. Therefore, deeper research is needed on the roles and specific mechanisms of circRNAs related to mTOR activity to provide more reference value for the diagnosis and treatment of cancers.

5.5 | Pancreatic cancer

Known as the “king of cancer,” pancreatic cancer (PC) is known for its high metastaticity and poor prognosis, with most patients diagnosed at an advanced stage and 5-year survival rate of <5%. Therefore, the demand to detect early diagnostic biomarkers is urgent. Knocking down circRNA1 inhibited the production of blood vessels and lymphatic vessels and the transfer of lymph nodes in pancreatic ductal adenocarcinoma (PDAC) via inhibiting the PI3K/Akt/vascular endothelial growth factor (VEGF) signaling by upregulating the expression of phosphoinositide-3-kinase regulatory subunit 1 (PIK3R1). Moreover, circ-IARS promotes vascular infiltration and lymph node metastasis of cancer and is positively correlated with poor prognosis through upregulating ras homolog family member A (RhoA) and RhoA-guanosine triphosphate (GTP) levels. Circ-RHOB1B3 associated with mTOR plays a variety of biological functions in PC, such as promoting cell proliferation, survival, autophagy, and chemotherapy drug resistance. The mechanism is that circ-RHOB1B3 can function as a carcinogen, facilitating the activation of mTOR through nuclear accumbent-associated 1 (NACC1)/Akt/mTOR signaling pathway via acting as a decoy for miR-600. Another has revealed that the circRNAs associated with mTOR can accelerate the development of resistance to chemotherapy drugs through activating MAPK/mTOR axis. These studies provide vital references for targeted therapies based on circRNAs.

6 | UROGENITAL SYSTEM

6.1 | Renal carcinoma

Renal cell carcinoma (RCC) is the largest proportion in renal cancer, and the main clinical symptoms are hematuria, pain, and a palpable renal lump, but many patients have inconspicuous clinical symptoms, and the early clinical diagnosis rate is feeble. ciRS-7 has been found to be highly expressed not only in EC but also in RCC, compared with healthy parts. ciRS-7 overexpression significantly enhances the activity, migration, and invasion ability of RCC cells, promotes tumor weight and lung metastasis in vivo and is negatively correlated with the overall survival of RCC patients. Mechanistically, ciRS-7, acting as sponge of miR-139-3p and ceRNA of the target gene transgelin (TAGLN), activates the expression of the mTOR. Therefore, circRNAs related to mTOR can be used as indispensable biomarkers and targets of targeted therapy for RC patients.

6.2 | Bladder cancer

The incidence and mortality of bladder cancer is the highest among urological tumors worldwide. Cystoscopy and pathological tissue biopsy are gold standard for the diagnosis of bladder cancer, which is lack of specific noninvasive tumor markers that are used for screening and detection. Studies have shown that the proliferation, migration, and epithelial-mesenchymal transition (EMT) of bladder cancer cells in vitro was inhibited, and the size, weight, and lung metastasis in vivo was attenuated by downregulation of circUBE2K through inactivation of mTOR. The importance of circRNAs associated with mTOR is indicated in the judgment of prognosis and treatment in bladder cancer.

6.3 | Prostate cancer

Considering the insidious symptoms, high incidence, and easy metastasis of prostate cancer (PCa), noninvasive testing with diagnostic and prognostic monitoring functions is urgent. circMBOAT2 expression is ascended while circ-ITCH is downregulated in PCa tissues compared with the corresponding healthy tissues. Expression of circMBOAT2 was positively correlated with high Gleason score, high T staging of advanced pathology and poor prognosis. The study demonstrated that knocking down circMBOAT2 restrains malignant behaviors of cancer cells by suppressing the expression of mTOR, mTORC1 substrates phospho-S6K (p-S6K), and mTORC2 substrates p-Rapamycin, a mTOR inhibitor, can reverse the pro-cancer effect of circMBOAT2 and the mechanism of cancer suppressor therapy is still being explored. Oppositely, when circ-ITCH is overexpressed, it has the effect of inhibiting the activity, proliferation, and migration of cancer cells, especially in metastatic castration-resistant prostate cancer (mCRPC), which is resistant to conventional castration drugs and surgical treatment. Mechanistically, circ-ITCH reduces β-catenin, p-Akt, and p-mTOR through suppressing the wingless and int-1 (Wnt)/β-Catenin and PI3K/Akt/mTOR pathways through sponging miR-17.

7 | FEMALE REPRODUCTIVE SYSTEM

Among the events that threaten women's health, ovarian cancer (OC), cervical cancer (CC), and endometrial cancer (EC) are cancers with excessive behaviors of malignancy. With the rapid development of RNA high-throughput sequencing and bioinformatics, the relationship between mTOR-associated circRNAs and cancer is constantly being explored and can serve as new diagnostic biomarkers and promising therapeutic targets. Studies have reported that circEEF2 and circIAB1FIP1 were highly expressed in ovarian cancer tissues and cell lines compared with the normal control group. CircEEF2 accelerates the proliferation, invasion, and autophagy of ovarian cancer. The molecular mechanism is that the expression
of target genes autophagy-related 5 (ATG5) and autophagy-related 7 (ATG7) can be upregulated by miR-129 when circEEF2 is overexpressed, another pathway is that circEEF2 binds directly to annexin A2 (ANXA2) to promote the occurrence of autophagy by inhibiting the activation of mTOR. The upregulation of circMYLK and circTPCN can enhance the growth and inhibit the apoptosis of CC cells through promoting the activation of mTOR by miR-1301-3p/Rheb/mTOR and miR-634/mTOR, respectively.84,85 Recently, studies have revealed that the circRNAs associated with mTOR are important regulators of tumorigenesis and progression of endometrial cancer (EC), for example, hsa_circ_0002577 and CircWHSC1 are highly expressed in tissues and cell lines of EC, promote the malignant phenotype of cancer cells by regulating the activity of mTOR.71,76 CircRNAs associated with the PI3K/Akt/mTOR axis are the basis for targeted therapy, which has been shown by these studies.

of target genes autophagy-related 5 (ATG5) and autophagy-related 7 (ATG7) can be upregulated by miR-129 when circEEF2 is overexpressed, another pathway is that circEEF2 binds directly to annexin A2 (ANXA2) to promote the occurrence of autophagy by inhibiting the activation of mTOR. The upregulation of circMYLK and circTPCN can enhance the growth and inhibit the apoptosis of CC cells through promoting the activation of mTOR by miR-1301-3p/Rheb/mTOR and miR-634/mTOR, respectively.84,85 Recently, studies have revealed that the circRNAs associated with mTOR are important regulators of tumorigenesis and progression of endometrial cancer (EC), for example, hsa_circ_0002577 and CircWHSC1 are highly expressed in tissues and cell lines of EC, promote the malignant phenotype of cancer cells by regulating the activity of mTOR.71,76 CircRNAs associated with the PI3K/Akt/mTOR axis are the basis for targeted therapy, which has been shown by these studies.

Incidence of lung cancer now ranks second in the world and is the leading cause of human mortality.62 Non-small cell lung cancer (NSCLC) accounts for 85% of all and has poor prognosis.77 Therefore, it is necessary to understand the specific mechanism of occurrence of lung cancer in order to explore effective treatments. CircHIPK3 and hsa_circ_0001666, circRNAs associated with lung cancer, are highly expressed in lung cancer tissues and cells compared with healthy controls.78,79 Hsa_circ_0001666 affects pathological grading, lymph node metastasis and is negatively correlated with the overall survival in lung cancer.78 Biological functions of hsa_circ_0001666 are diverse, promoting proliferation, invasion migration, and inhibiting apoptosis of lung cancer cells by activating the argonaute 1 (AGO1)/PI3K/Akt/mTOR axis. Targeted knockdown of cancer-causing circRNAs associated with mTOR activation would be a major breakthrough in tumor therapy.

Papillary thyroid carcinoma (PTC) is the most common subtype and accounts for 85% approximately of total thyroid cancers.80 Although thyroid cancer is less metastatic and has a better prognosis than other malignant cancers, it has a poor prognosis in aggressive thyroid cancer, with a recurrence rate of 10% within 10 years.81 The close association between circRNAs and thyroid cancer is of vital importance. The expression of hsa_circ_0007694 is downregulated compared with healthy controls; however, hsa_circ_0008274 is upregulated.80,82 The malignant progression of PTC, such as proliferation and invasive ability, is reduced by hsa_circ_0008274 downregulation.80 Experiments on the mechanism have verified that the hsa_circ_0008274 increased phosphorylated-AMPK (p-AMPK) and decreased p-mTOR after downregulation, which revealed that the specific mechanism is hsa_circ_0008274 exert carcinogenic effects by activating mTOR via inhibiting AMPK. New references have been provided for the diagnosis and treatment by the specific molecular mechanism of circRNA related to mTOR in thyroid cancer.

10 | NERVOUS SYSTEM

10.1 | Glioma

Gliomas account for 1%–3% of systemic primary malignancies and the prognosis is strikingly poor.63 CircRNAs related to mTOR have regulatory effects on the tumorigenesis and progression of gliomas. It is found that circRNAs have pro-cancer effects, such as circGFRA1, circ-MAPK4, circPCMTD1, and hsa_circ_0037251.84–87 Experiments have explored the upregulation of circGFRA1 and circ-MAPK4 promoted glioma proliferation, migration, and inhibited apoptosis by heighten the expression of p-mTOR through Akt/mTOR and MAPK/mTOR pathways, respectively.84,85 Our knowledge of the roles and mechanisms underlying circRNAs, which is related to mTOR in human glioma, was improved.

11 | MOTION SYSTEM

11.1 | Osteosarcoma

Metastasis and recurrence of osteosarcoma (OS), which mainly occurs in adolescent populations, are the most important factors affecting the overall prognosis of patients.88 Previous studies have demonstrated that circTFC25 overexpression promoted the occurrence and progression of BC and recently, in vivo and in vitro experiments have found that it has critical regulatory role in OS.89 Upregulation of circTFC25 enhances the viability, proliferation, migration, invasion, and other cell phenotypes of glioma cells by increasing the expression of mTOR through activating the mitogen-activated protein kinase (MEK)/extracellular signal-regulated kinase (ERK)/mTOR and Akt/mTOR axis by inhibiting the expression of miR-206.

12 | BLOOD SYSTEM

12.1 | Leukemia

Leukemia is a fluid tumor that differs from solid tumors and has its own unique characteristics, such as the ability to invade and migrate.60 High recurrence rates and drug resistance remain major challenges to treatment.90 The experiment validated that circ-PRKDC overexpression enhanced the proliferation of acute lymphoblastic leukemia (ALL) cells and attenuate autophagy and apoptosis
by activating the PI3K/Akt/mTOR axis. Not only does it play a role in the progression of leukemia but also circRNA regulates the resistance of chemotherapy drugs through activating mTOR.

13 | OTHER CANCERS

Up to date, there have been growing concerns about circRNAs associated with multiple regulators in signaling pathways of cancers. According to GLOBOCAN’s 2020 Global Cancer Statistics, breast cancer (BC) has surpassed lung cancer to become the most common cancer. Hsa_circ_0000199 and circUBAP2 not only have pro-cancer effects on triple-negative breast cancer (TNBC) but also promote the resistance of cisplatin (DDP) by activating the PI3K/Akt/mTOR pathway. CircWHSC1 upregulation not only plays a role in EC but also accelerates malignant cell phenotype of cells in BC. The molecular mechanism is CircWHSC1 regulates the fatty acid synthase (FASN)/AMPK/mTOR Axis through sponging miR-195-5p in BC. Therefore, these circRNAs provide cancer patients with potential prognosis judgment and therapeutic targets.

14 | TREATMENT

mTOR inhibitors have gradually emerged in the study of cancer treatment. Some studies detected that cancer cells are sensitive to mTOR inhibitors under most circumstances. In clinical treatment, the mTOR inhibitors, everolimus, plays an anti-cancer role in patients with advanced gastric cancer and resistant to chemotherapy drugs, but these inhibitors have also shown some promise in preclinical and early clinical trial data and have raised concerns over excessive toxicity and side effects. Targeted therapy for circRNAs or combined with mTOR inhibitors therapy may works better. Therefore, these circRNAs related to mTOR may become promising therapeutic targets for cancer.

15 | CONCLUSIONS AND FUTURE PERSPECTIVES

A growing number of experiments have confirmed that circRNAs are closely related to the progression and treatment of cancer. The role of circRNAs via modulating mTOR in a variety of signaling pathways has a profound impact. Recently, the dawn to the treatment of cancer patients has been brought by the development and application of mTOR inhibitors, although their efficacy still needs to be further verified. These all demonstrate that the circRNAs associated with mTOR expression have potential to become biomarkers and new therapeutic targets for cancers. If targeted therapy for cancer-associated circRNAs and mTOR inhibitors work together, the treatment effect of cancer patients can be improved, and the occurrence of drug resistance can be reduced. Nevertheless, a various of issues still urgently need to be addressed. First, research on the regulatory role of circRNAs and mTOR are scanty in cancer; moreover, the functions and corresponding mechanisms need to be explored further presently. In addition, there are debates about whether autophagy has a pro-cancer or anti-cancer effect on cancer cells and further studies of the specific mechanism of autophagy in various situations is required. Last but not least, these circRNAs function as biomarkers for clinical diagnosis and prognosis, and new therapeutic targets still demand a great deal of sample to validate.

AUTHOR CONTRIBUTIONS

J. G. and C. C. designed the study. C.C. and J.G. wrote the article. Y. W., X. W., and Z. L. contributed to collect literature. All authors revised the article. All authors read and approved the final article.

ACKNOWLEDGMENTS

The authors thank for the assistance of Figdraw (www.figdraw.com) in the pattern drawing.

FUNDING INFORMATION

This study was supported by grants from the National Natural Science Foundation of China (no. 81772279), Ningbo Municipal Bureau of Science and Technology (no. 2021Z133, 2022Z130), Health Commission of Zhejiang Province (no. 2023XY029), and the K.C. Wong Magna Fund in Ningbo University.

CONFLICT OF INTEREST

The authors declare no conflicting interest.

DATA AVAILABILITY STATEMENT

The datasets are available from the corresponding author.

ORCID

Junning Guo https://orcid.org/0000-0003-2026-1075
Weiliang Sun https://orcid.org/0000-0003-0364-4867

REFERENCES

1. Zhao W, Shan B, He D, et al. Recent Progress in characterizing Long noncoding RNAs in cancer drug resistance. J Cancer. 2019;10(26):6693-6702.
2. Yin H, Xue W, Anderson DG. CRISPR-Cas: a tool for cancer research and therapies. Nat Rev Clin Oncol. 2019;16(5):281-295.
3. Tao X, Shao Y, Yan J, et al. Biological roles and potential clinical values of circular RNAs in gastrointestinal malignancies. Cancer Biol Med. 2021;18(2):437-457.
4. Ma YMD, Guo J. Circular RNA: new star in the diagnosis and treatment of gastric cancer. Prog Biochem Biophys. 2022;49(4):714-724.
5. Li R, Jiang J, Shi H, Qian H, Zhang X, Xu W. CircRNA: a rising star in gastric cancer. Cellular and Molecular Life Sciences: CMLS. 2020;77(9):1661-1680.
6. Murugan AK. mTOR: role in cancer, metastasis and drug resistance. Semin Cancer Biol. 2019;59:92-111.
7. Shams R, Ito Y, Miyatake H. Mapping of mTOR drug targets: featured platforms for anti-cancer drug discovery. Pharmacol Ther. 2022;232:108012.
8. Mossmann D, Park S, Hall MN. mTOR signalling and cellular metabolism are mutual determinants in cancer. Nat Rev Cancer. 2018;18(12):744-757.
9. Zhang X, Wang S, Wang H, et al. Circular RNA circNRIP1 acts as a microRNA-149-5p sponge to promote gastric cancer progression via the AKT1/mTOR pathway. Mol Cancer. 2019;18(1):20.

10. Ashwal-Fluss R, Meyerson M, Pamudurti NR, et al. circRNA biogenesis competes with pre-mRNA splicing. Mol Cell. 2014;56(1):55-66.

11. Jeck WR, Sharpless NE. Detecting and characterizing circular RNAs. Nat Biotechnol. 2014;32(5):453-461.

12. Li Z, Huang C, Bao C, et al. Exon-intron circular RNAs regulate transcription in the nucleus. Nat Struct Mol Biol. 2015;22(3):256-264.

13. Long G, Ma S, Shi R, et al. Circular RNAs and drug resistance in genitourinary cancers: a literature review. Cancer. 2022;14(4):866.

14. Hansen TB, Jensen TI, Clausen BH, et al. Natural RNA circles function as efficient microRNA sponges. Nature. 2013;495(7441):384-388.

15. Zhou WY, Cai ZR, Liu J, Wang DS, Ju HQ, Xu RH. Circular RNA: metabolism, functions and interactions with proteins. Mol Med. 2020;19(1):172.

16. Yang F, Hu A, Li D, et al. Circ-HuR suppresses HuR expression and gastric cancer progression by inhibiting CNBP transactivation. Mol Cancer. 2019;18(1):158.

17. Lu Y, Li Z, Lin C, Zhang J, Shen Z. Translation role of circRNAs in cancers. J Clin Anal. 2021;35(7):e23866.

18. Yang Y, Gao X, Zhang M, et al. Novel role of FBXW7 circular RNA in repressing glioma tumorigenesis. J Natl Cancer Inst. 2018;110(3):304-315.

19. Conn VM, Hugouvieux V, Nayak A, et al. A circRNA from SEPALATA3 regulates splicing of its cognate mRNA through R-loop formation. Nature Plants. 2017;3:17053.

20. Alqurashi N, Hashimi SM, Wei MQ. Chemical inhibitors and microRNAs (miRNA) targeting the mammalian target of rapamycin (mTOR) pathway: potential for novel anticancer therapeutics. Int J Mol Sci. 2013;14(2):3874-3900.

21. Li Y, Wang J, Li J, et al. SREBP activity is regulated by mTORC1 and contributes to Akt-dependent cell growth. Mol Cancer. 2021;20(1):26.

22. Biller LH, Schrag D. Diagnosis and treatment of metastatic colorectal cancer: a review. JAMA. 2021;325(7):669-685.

23. di Pietro M, Canto MI, Fitzgerald RC. Endoscopic Management of Early Adenocarcinoma and Squamous Cell Carcinoma of the esophagus: screening, diagnosis, and therapy. Gastroenterology. 2018;154(2):421-436.

24. Inoki K, Zhu T, Guan KL. TSC2 mediates cellular energy response to control cell growth and survival. Cell. 2003;115(5):577-590.

25. Forner A, Reig M, Bruix J. Hepatocellular carcinoma. Lancet (London, England). 2018;391(10127):1301-1314.

26. Xu H, Liu Y, Cheng P, et al. CircRNA_hsa_circ_0000392 promotes colorectal cancer progression through the PI3K/Akt/mTOR signaling pathway. Mol Cancer. 2020;19(1):172.

27. Duchateau L, Collet C, Nemicheva S, et al. CircRNAs in cancer. Adv Exp Med Biol. 2016;895:204-213.

28. Xu H, Liu Y, Cheng P, et al. circRNA_0000392 promotes colorectal cancer progression through the PI3K/Akt/mTOR signaling pathway. Mol Cancer. 2020;19(1):172.

29. Okugawa Y, Grady WM, Goel A. Epigenetic alterations in colorectal cancer: emerging biomarkers. Gastroenterology. 2015;149(5):1204-1225.e12.

30. Li N, Wu J, Hu B, et al. Upregulation of hsa_circ_000977 participates in esophageal squamous cancer progression by sponging miR-874-3p. J Clin Lab Anal. 2022;36(6):e24458.

31. Meng L, Liu S, Ding P, Chang S, Sang M. Circular RNA circR7-7 inhibits its autophagy by functioning as miR-1299 sponge to target EGF signaling. J Cell Biochem. 2020;121(2):1039-1049.

32. Zhou WY, Cai ZR, Liu J, Wang DS, Ju HQ, Xu RH. Circular RNA: metabolism, functions and interactions with proteins. Mol Med. 2020;19(1):172.
53. Khemlina G, Ikeda S, Kurzrock R. The biology of hepatocellular carcinoma: implications for genomic and immune therapies. Mol Cancer. 2017;16(1):149.

54. Huang XY, Huang ZL, Zhang PB, et al. CircRNA-100338 is associated with mTOR signaling pathway and poor prognosis in hepatocellular carcinoma. Front Oncol. 2019;9:392.

55. Sun XH, Wang YT, Li GF, Zhang N, Fan L. Serum-derived three-circRNA signature as a diagnostic biomarker for hepatocellular carcinoma. Cancer Cell Int. 2020;20:226.

56. Zheng H, Chen T, Li C, et al. A circular RNA hsa_circ_0079929 inhibits tumor growth in hepatocellular carcinoma. Cancer Management and Research. 2019;11:443-454.

57. Huang ZL, Huang XY, Huang J, et al. Multiple omics integration reveals key circular RNAs in hepatocellular carcinoma. Front Oncol. 2021;11:621353.

58. Xu C, Yu Y, Ding F. Microarray analysis of circular RNA expression profiles associated with gemcitabine resistance in pancreatic cancer cells. Oncol Rep. 2018;40(1):395-404.

59. Kong Y, Li Y, Luo Y, et al. circFN1BI1 inhibits lymphangiogenesis and lymphatic metastasis via the miR-486-5p/PIK3R1/VEGFC axis in pancreatic cancer. Mol Cancer. 2020;19(1):82.

60. Li J, Li Z, Jiang P, et al. Circular RNA IARs (circ-IARS) secreted by pancreatic cancer cells and located within exosomes regulates endothelial monolayer permeability to promote tumor metastasis. Journal of Experimental & Clinical Cancer Research: CR. 2018;37(1):177.

61. Yang T, Shen P, Chen Q, et al. FUS-induced circRHOBTB3 facilitates cell proliferation via miR-600/NAC1 mediated autophagy response in pancreatic ductal adenocarcinoma. Journal of Experimental & Clinical Cancer Research: CR. 2021;40(1):261.

62. Jin X, Pan Y, Wang L, et al. Fructose-1,6-bisphosphatase inhibits ERK activation and bypasses gemcitabine resistance in pancreatic cancer by blocking IQGAP1-MAPK interaction. Cancer Res. 2017;77(16):4328-4341.

63. Agrawal A, Sahni S, Iftikhar A, Talwar A. Pulmonary manifestations of renal cell carcinoma. Respir Med. 2015;109(12):1505-1508.

64. Mao W, Wang K, Xu B, et al. cIR-S-7 is a prognostic biomarker and potential gene therapy target for renal cell carcinoma. Mol Cancer. 2021;20(1):142.

65. Yang C, Mou Z, Wu S, et al. High-throughput sequencing identified circular RNA circUBE2K mediating RhoA associated bladder cancer phenotype via regulation of miR-516b-5p/ARHGAP5 axis. Cell Death Dis. 2021;12(8):719.

66. Skoloyar E, Zhao Q, Mach KE, et al. Bladder cancer risk stratification using a urinary mRNA biomarker panel-a path towards cystoscopy triaging. Urol Oncol. 2021;39(8):497.e497-497.e415.

67. Shi J, Liu C, Chen C, et al. Circular RNA circMOAT2 promotes prostate cancer progression via a miR-1271-5p/mTOR axis. Aging. 2020;12(13):13255-13280.

68. Li S, Yu C, Zhang Y, et al. Circular RNA cir-ITCH is a potential therapeutic target for the treatment of castration-resistant prostate cancer. Biomed Res Int. 2020;2020:7586521.

69. Shi Y, He R, Yang Y, et al. Circular RNAs: novel biomarkers for cervical, ovarian and endometrial cancer (review). Oncol Rep. 2020;44(5):1787-1798.

70. Hu J, Wang R, Liu Y, Zhou J, Shen K, Dai Y. Bicaulin represses cervical cancer cell growth, cell cycle progression and promotes apoptosis via blocking AKT/mTOR pathway by the regulation of circHIAT1/miR-19a-3p Axis. Oncos Targets Ther. 2021;14:905-916.

71. Wang Y, Yin L, Sun X. CircRNA hsa_circ_0002577 accelerates endometrial cancer progression through activating IGFIR/PI3K/Akt pathway. Journal of Experimental & Clinical Cancer Research: CR. 2020;39(1):169.

72. Zhang Z, Zhu H, Hu J. CircRAB11FIP1 promoted autophagy flux of ovarian cancer through DSC1 and miR-129. Cell Death Dis. 2021;12(2):219.

73. Yong M, Hu J, Zhu H, et al. Circ-EEF2 facilitated autophagy via interaction with mir-6881-3p and ANXA2 in EOC. Am J Cancer Res. 2020;10(11):3737-3751.

74. Chen R, Mao L, Shi R, Wang W, Cheng J. circRNA MYLK accelerates cervical cancer via up-regulation of RHEB and activation of mTOR signaling. Cancer Management and Research. 2020;12:3611-3621.

75. Tian-Zhao D, Yang Y, Xing-Xuan W, Yu-Xin C, Xue-Lian W. Profiling of circular RNAs and circTFPCN/miR-634/mTOR regulatory pathway in cervical cancer. Genomics. 2021;113(4):2253-2263.

76. Liu Y, Chen S, Zong ZH, Guan X, Zhao Y. CircRNA WHSC1 targets the miR-646/NPM1 pathway to promote the development of endometrial cancer. J Cell Mol Med. 2020;24(12):6898-6907.

77. Zhang N, Nan A, Chen L, et al. Circular RNA circSATB2 promotes progression of non-small lung cancer cells. Mol Cancer. 2020;19(1):101.

78. Wang X, Li R, Feng L, et al. Hsa_circ_0001666 promotes non-small lung cancer migration and invasion through miR-1184/miR-548I/AGO1 axis. Molecular Therapy Oncolytics. 2022;24:579-611.

79. Gu F, Zhang J, Yan L, Li D. CircHIPK3/miR-381-3p axis modulates proliferation, migration, and glycolysis of lung cancer cells by regulating the AKT/mTOR signaling pathway. Open Life Sciences. 2020;15(1):683-695.

80. Zhou GK, Zhang CY, Yuan ZN, Pei R, Liu DM. Hsa_circ_0008274 promotes cell proliferation and invasion involving AMPK/mTOR signaling pathway in papillary thyroid carcinoma. Eur Rev Med Pharmacol Sci. 2018;22(24):8772-8780.

81. Paschke R, Lincke T, Müller SP, et al. The treatment of well-differentiated thyroid carcinoma. Deutsches Arzteblatt International. 2015;112(26):452-458.

82. Long MY, Chen JW, Zhu Y, et al. Comprehensive circular RNA profiling reveals the regulatory role of circRNA_0007694 in papillary thyroid carcinoma. American Journal of Translational Research. 2020;12(4):1362-1378.

83. Xu X, Li L, Luo L, et al. Opportunities and challenges of glioma organoids. Cell Communication and Signaling: CCS. 2021;19(1):102.

84. Cao Q, Zhang J, Zhang Z, Feng Y, Wang Z. Knockdown circular RNA circGFRA1 inhibits glioma cell proliferation and migration by upregulating microRNA-99a. Neuroreport. 2021;32(9):748-756.

85. He J, Huang Z, He M, et al. Circular RNA MAPK4 (circ-MAPK4) inhibits cell apoptosis via MAPK signaling pathway by sponging miR-125a-3p in gliomas. Mol Cancer. 2020;19(1):17.

86. Zheng SQ, Qi Y, Wu J, et al. CircPCMTD1 acts as the sponge of miR-224-5p to promote glioma progression. Front Oncol. 2019;9:398.

87. Cao Q, Shi Y, Wang X, et al. Circular METRN RNA hsa_circ_0037251 promotes glioma progression by sponging miR-1229-3p and regulating mTOR expression. Sci Rep. 2019;9(1):19791.

88. Meltzer PS, Helman LJ. New horizons in the treatment of osteosarcoma. N Engl J Med. 2021;385(22):2066-2076.

89. Wang Y, Shi S, Zhang Q, et al. MicroRNA-206 upregulation relieves circTCF25-induced osteosarcoma cell proliferation and migration. J Cell Physiol. 2020;doi:10.1002/jcp.29570. Online ahead of print.

90. Whiteley AE, Price TT, Cantilini G, Sipkins DA. Leukaemia: a model metastatic disease. Nat Rev Cancer. 2021;21(7):461-475.

91. Ling Z, Fang ZG, Wu JY, Liu JJ. The depletion of Circ-PRKDC enhances autophagy and apoptosis in T-cell acute lymphoblastic leukemia via microRNA-653-5p/Reelin mediation of the PI3K/AKT/mTOR signaling pathway. Onco Targets Ther. 2021;14:932-401.

92. Li M, Meng F, Lu Q. Expression profile screening and bioinformatics analysis of circRNA, LncRNA, and mRNA in acute myeloid leukemia drug-resistant cells. Turkish Journal of Haematology: Official Journal of Turkish Society of Haematology. 2020;37(2):104-110.

93. Wang C, Ren M, Zhao X, Wang A, Wang J. Emerging roles of circular RNAs in osteosarcoma. Medical Science Monitor: International Medical Journal of Experimental and Clinical Research. 2018;24:7043-7050.
94. Li H, Xu W, Xia Z, et al. Hsa_circ_0000199 facilitates chemotherapeutic tolerance of triple-negative breast cancer by interfering with miR-206/613-led PI3K/Akt/mTOR signaling. *Aging*. 2021;13(3):4522-4551.

95. Wang L, Yang X, Zhou F, Sun X, Li S. Circular RNA UBAP2 facilitates the cisplatin resistance of triple-negative breast cancer via microRNA-300/anti-silencing function 1B histone chaperone/PI3K/AKT/mTOR axis. *Bioengineered*. 2022;13(3):7197-7208.

96. Chen Q, Yang Z, Ding H, Li H, Wang W, Pan Z. CircWHSC1 promotes breast cancer progression by regulating the FASN/AMPK/mTOR Axis through sponging miR-195-5p. *Front Oncol*. 2021;11:649242.

97. O’Donnell JS, Massi D, Teng MWL, et al. PI3K-AKT-mTOR inhibition in cancer immunotherapy, redux. *Semin Cancer Biol*. 2018;48:91-103.

98. Fruman DA, Rommel C. PI3K and cancer: lessons, challenges and opportunities. *Nat Rev Drug Discov*. 2014;13(2):140-156.

99. Al-Batran SE, Dureux M, Ohtsu A. mTOR as a therapeutic target in patients with gastric cancer. *Int J Cancer*. 2012;130(3):491-496.

*How to cite this article:* Cao C, Wang Y, Wu X, Li Z, Guo J, Sun W. The roles and mechanisms of circular RNAs related to mTOR in cancers. *J Clin Lab Anal*. 2022;36:e24783. doi:10.1002/jcla.24783