Circular RNAs (circRNAs), covalently closed noncoding RNAs, are widely expressed in eukaryotes and viruses. They can function by regulating target gene expression, linear RNA transcription and protein generation. The phosphoinositide 3-kinase (PI3K)/AKT signaling pathway plays key roles in many biological and cellular processes, such as cell proliferation, growth, invasion, migration, and angiogenesis. It also plays a pivotal role in cancer progression. Emerging data suggest that the circRNA/PI3K/AKT axis modulates the expression of cancer-associated genes and thus regulates tumor progression. Aberrant regulation of the expression of circRNAs in the circRNA/PI3K/AKT axis is significantly associated with clinicopathological characteristics and plays an important role in the regulation of biological functions. In this review, we summarized the expression and biological functions of PI3K-AKT-related circRNAs in vitro and in vivo and assessed their associations with clinicopathological characteristics. We also further discussed the important role of circRNAs in the diagnosis, prognostication, and treatment of cancers.

INTRODUCTION

The complexity of cancer and the variability of its clinical features are derived from its complex etiology, involving DNA, RNA, protein, and other factors.1–3 Cancer has become an important public health concern affecting people’s lives.4–6 In the past 10 years, the number of studies on cancer has increased rapidly, providing many novel clues for the treatment of cancer.7,8 The emergence of targeted therapy and immunotherapy has greatly improved the survival rate of cancer patients.9,10 However, cancer treatment remains a major scientific challenge.

CircRNAs are mainly formed by pre-mRNA a back-splicing and are widely expressed in eukaryotes and viruses.14,15 The regulatory role of circRNAs in physiological processes is still not very clear.16 However, accumulating evidence indicates that circRNAs are significantly associated with many diseases and play an important role in the occurrence and development of cancer. A common circRNA-mediated mechanism is that circRNAs act as competitive endogenous RNAs (ceRNAs) of microRNAs (miRNAs) in tumor progression. Circ101237 facilitates the expression of MAPK1 to interact with the PI3K/AKT pathway to regulate cancer progression. Importantly, circRNAs related to the PI3K/AKT pathway have become potential targets in the treatment of cancer. In this review, we summarized the current studies of the role of circRNAs in the circRNA/PI3K/AKT axis is significantly associated with clinicopathological characteristics and plays an important role in the regulation of biological functions. In this review, we summarized the expression and biological functions of PI3K-AKT-related circRNAs in vitro and in vivo and assessed their associations with clinicopathological characteristics. We also further discussed the important role of circRNAs in the diagnosis, prognostication, and treatment of cancers.

THE PI3K/AKT SIGNALING PATHWAY IN TUMORIGENESIS

PI3K

Phosphoinositide 3-kinase (PI3K), a member of the lipid kinase family,7,28 was first identified 3 decades ago.29 It can be divided into 3 types (class I–III) in mammals.19,30,31 Class I PI3Ks have gained much attention in the cancer-related field. PI3K is composed of one catalytic (p110) domain and one regulatory (p85) domain.32,33 p85, which contains the Src homology 2 (SH2) and SH3 protein-binding domains,34,35 can interact with target proteins with corresponding binding sites. The activation of PI3K mainly involves the binding of the substrate near the inner side of the plasma membrane.19 PI3K can be activated in two ways. One is that PI3K interacts with connexin or growth factor receptors with phosphorylated tyrosine residues, and then induces a conformational change of dimer.38–40 It also can be activated by the direct binding of p110 and Ras.41–43
PI3K can be activated by multiple growth factors and signaling complexes, such as G-protein coupled receptors, B-cell receptors, vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), insulin and receptor tyrosine kinases (RTKs) (Fig. 2).\textsuperscript{20,44–48} These factors induce autophosphorylation through the activation of RTKs and then activate PI3K.\textsuperscript{49} The p85 subunit provides docking sites for autophosphorylation. In some cases, this process is mediated by the recruitment of adapter proteins. For example, the insulin receptor activates PI3K via insulin receptor substrate-1 (IRS-1).\textsuperscript{50,51} Activated PI3K increases the conversion of PIP2 to PIP3,
which activates PDK1 and AKT. However, AKT is not the only target molecule of PI3K. PI3K regulates multiple signaling pathways by interacting with BTK, PDK1, and Rac.

AKT
AKT, also called protein kinase B (PKB), is the cellular homolog of the oncogene v-Akt. AKT is a serine/threonine kinase that belongs to the AGC kinase family. There are three different AKT isoforms (AKT1, AKT2, and AKT3), which are widely expressed in most human tissues. AKT can link the interaction between receptors and PI3K to cellular anabolic pathways. AKT acts as a central regulator of cellular metabolism downstream of insulin signaling that is responsible for the regulation of glucose metabolism. In vivo experiments support that AKT2 plays a key role in the regulation of glucose metabolism. Researchers have found that germline mutations of AKT occur during the tumorigenesis and progression of some cancers.

AKT plays a key role in multiple cellular processes, such as cell survival, proliferation, migration, apoptosis, and angiogenesis. AKT prevents TSC1/TSC2 complex formation and activates mTOR pathway, thereby regulating cell growth. It also regulates the expression of cyclin D1 and p53 to affect the cell cycle or the transmission of downstream signaling pathways by inhibiting AKT activity. AKT boosts cell survival via inhibition of apoptosis by regulating specific pathways in gliomas.

Maintenance of AKT activity is required for the survival of tumor cells. AKT regulates the TGFβ signaling by activating or inhibiting downstream target proteins, such as Bad, Caspase9, NF-κB, GSK-3, FKHR, p21, and p27. AKT boosts cell survival via phosphorylation of several proteins including p21 and p27. AKT boosts cell survival via inactivating the pro-apoptotic factors Bad and the transcription factor of the Forkhead (FKHR) family. The expression levels of GABA receptors and ataxin-1 are also regulated by AKT. Some studies have observed that AKT regulates the TGFβ signaling pathway by binding with Smad. The present findings show that AKT is an important target for the treatment of cancer, diabetes, stroke, and neurodegenerative diseases.

The activation of PI3K/AKT pathway
The PI3K/AKT signaling pathway plays a key role in many biological and cellular functions. We have already elaborated on the activation of PI3K when introducing PI3K. The inositol ring of PI3K has five potential phosphorylation sites. PI3K activation could catalyze the phosphorylation of phosphatidylinositols (PI) at the 3'-position of the inositol ring. The phosphorylated products have a critical influence on cellular functions. PI3K can enhance cell migration, and PI3,4-bisphosphate regulates cell activation and insulin sensitivity. AKT and PDK1, which contain PH domains can bind to PI3K. PI3K activates PDK1, and then PDK1 phosphorylates AKT at Thr308 and Ser473. AKT can be also phosphorylated and activated by AKT2 at Ser473. Activated AKT regulates cell proliferation, differentiation, migration, and apoptosis by activating or inhibiting downstream target proteins, such as Bad, Caspase9, Caspase9, NF-kB, GSK-3, FKHR, p21, p53, and FOXO1. Aberrant activation of PI3K/AKT pathway has been found in a variety of cancers. It is widely distributed throughout the nucleus. Intron-derived circRNAs can interact with RNA polymerase II to enhance the transcription of its target genes. The expression of circZKSCAN1 attenuates HCC cell stemness by targeting RBP fragile X mental retardation protein. Moreover, some circRNAs containing the AUG start codon can control gene expression at the translational level. However, this effect has not yet been fully elucidated in cancer.

THE CIRCRNA/PI3K/AKT AXIS IN CANCER
CircRNA plays a critical role in the initiation and development of human cancer. Studies on circRNA are changing our view of cancer genesis, progress, and treatment. CircRNAs alone may be insufficient for driving cancer progression. Similarly, traditional signaling pathways or signaling molecules alone may also be ineffective. Interestingly, studies have found that circRNAs are often interconnected with the PI3K/AKT signaling pathway. The PI3K/AKT signaling pathway plays key roles in many biological and cellular functions, such as cell proliferation, growth, invasion, migration, and angiogenesis. It also plays a pivotal role in the progression of cancer. Recently, a great deal of research regarding the interaction of circRNA with PI3K/AKT signaling pathways has attracted significant research interest. CircRNAs regulate cellular functions and control the occurrence and development of cancer via interactions with the PI3K/AKT pathway. Based on the current study, the mechanism/pattern of interaction between circRNA and PI3K/AKT pathway is primarily the ceRNA mechanism, which involves the activation or repression of downstream pathways by sponging miRNA. Research on the circRNA/PI3K/AKT axis is still in its infancy. With the deepening of research about the structure and function of circRNAs, the mechanism will add clarity regarding the circRNA/PI3K/AKT axis.
| Category                      | Type                        | CircRNA       | Role          | Function                             | Related genes; in vivo | Refs |
|-------------------------------|-----------------------------|---------------|---------------|--------------------------------------|-------------------------|------|
| Digestive system neoplasms    | Esophageal cancer           | circLPAR3     | Oncogene      | Cell migration and invasion          | miR-198, MET, RAS, MAPK, PI3K, and AKT | 171  |
|                               | Esophageal cancer           | cZNF292       |               | Cell viability, migration, invasion, and apoptosis | miR-206, AMPK, PI3K, and AKT | 174  |
|                               | Esophageal cancer           | circVRK1      | Tumor suppressor | Cell proliferation, migration, EMT, and radiosensitivity | miR-624-3p, PTEN, PI3K, and AKT | 172  |
|                               | Esophageal cancer           | circLARP4     | Tumor suppressor | Cell proliferation, migration, and apoptosis | miR-1323, PTEN, PI3K, and AKT | 173  |
|                               | Gastric cancer              | circPIPSK1A   | Oncogene      | Cell proliferation, migration, invasion, and EMT | miR-671-5p, KRT80, PI3K, and AKT | 175  |
|                               | Gastric cancer              | circ0010882   | Oncogene      | Cell proliferation, migration, invasion, and apoptosis | PBK, Akt, and mTOR      | 176  |
|                               | Gastric cancer              | circ0023409   | Oncogene      | Cell viability, proliferation, migration, invasion, and apoptosis | miR-542-3p, IRS4, PI3K, and AKT | 177  |
|                               | Gastric cancer              | cirS-7        | Oncogene      | Cell viability, cell survival, migration, and apoptosis | miR-7, PTEN, PI3K, and AKT | 178  |
|                               | Gastric cancer              | circMAN2B2    | Oncogene      | Cell viability, cell survival, migration, and apoptosis | miR-145, PI3K, AKT, and JNK | 179  |
|                               | Gastric cancer              | circPVT1      | Oncogene      | Cell viability, proliferation, apoptosis, and cisplatin sensitivity | miR-152-3p, HDGF, PI3K, and AKT | 180  |
|                               | Colorectal cancer           | circ001313    | Oncogene      | Cell proliferation and apoptosis      | miR-510-5p, PI3K, and AKT2 | 181  |
|                               | Colorectal cancer           | circCDYL      | Tumor suppressor | Cell viability, migration, invasion, and apoptosis | miR-105-5p, PTEN, PI3K, AKT, JAK2, and STATS | 182  |
|                               | Colorectal cancer           | circ0008285   | Tumor suppressor | Cell viability, cell survival, migration, and apoptosis | miR-382-5p, PTEN, PI3K, and AKT | 183  |
|                               | Liver cancer                | circCDK13     | Tumor suppressor | Cell migration, invasion, and cell cycle | JAK, STAT, PI3K, and AKT; tumor progression | 184  |
|                               | Liver cancer                | circGF1R      | Oncogene      | Cell proliferation, apoptosis, and cell cycle | PBK, and AKT | 185  |
|                               | Liver cancer                | circ0072309   | Tumor suppressor | Cell viability, colony formation, invasion, and migration | miR-665, PI3K, AKT, Wnt, and β-catenin | 186  |
|                               | Liver cancer                | circ0079299   | Tumor suppressor | Tumor growth, cell cycle               | PBK, AKT, and mTOR; tumor size and tumor weight | 187  |
|                               | Liver cancer                | circ0004001   | Oncogene      | Cell proliferation, apoptosis, and cell cycle | miRNAs, VEGF, VEGFR, PI3K, AKT, mTOR, and Wnt | 188  |
|                               | Liver cancer                | circ0004123   | Oncogene      | Cell proliferation, apoptosis, and cell cycle | miRNAs, VEGF, VEGFR, PI3K, AKT, mTOR, and Wnt | 188  |
|                               | Liver cancer                | circ0007592   | Oncogene      | Cell proliferation, apoptosis, and cell cycle | miRNAs, VEGF, VEGFR, PI3K, AKT, mTOR, and Wnt | 188  |
|                               | Liver cancer                | cirEphB4      | Tumor suppressor | Cell viability, apoptosis, migration, and invasion | HIF-1α, PI3K-AKT, and ZEB1; tumor weight, tumor size, and metastasis foci | 189  |
|                               | Liver cancer                | circDYL       | Oncogene      | Cell proliferation, apoptosis, and cell cycle | mir-892a, mir-328-3p, HDGF, HIF1AN, NCL, PI3K, AKT, NOTCH2, C-MYC, and Survivin | 190  |
|                               | Hepatoblastoma              | cirHMGC51     | Oncogene      | Cell proliferation, apoptosis, and glutaminolysis  | miR-503-5p, IGF2, IGF1R, PI3K, and AKT | 191  |
| Category                  | Type            | CircRNA | Role               | Function                                                                 | Refs. |
|--------------------------|-----------------|---------|--------------------|--------------------------------------------------------------------------|-------|
| Pancreatic cancer        | Tumor suppressor | circNFIB1 | Oncogene           | miR-486-5p, PK3R1, and VEGF-C; in vivo                                   | 194   |
| Pancreatic cancer        | Oncogene        | circEIF6 | Cell proliferation, migration, invasion, and apoptosis          | miR-486-5p, PIK3R1, and VEGF-C; in vivo                                   | 196   |
| Pancreatic cancer        | Oncogene        | circBFA1R | Cell proliferation, apoptosis                                   | miR-486-5p, PIK3R1, and VEGF-C; in vivo                                   | 198   |
| Glioma                   | Oncogene        | circ0014359 | Cell viability, migration, invasion, and apoptosis            | miR-153, PIK3R1, and VEGF-C; in vivo                                   | 197   |
| Glioma                   | Oncogene        | circDICER1 | Cell proliferation, invasion, apoptosis, and angiogenesis      | miR-153, PIK3R1, and VEGF-C; in vivo                                   | 198   |
| Glioma                   | Oncogene        | circHIPK3 | Cell proliferation, metastasis, apoptosis, and sensitivity      | miR-153, PIK3R1, and VEGF-C; in vivo                                   | 199   |
| Glioma                   | Oncogene        | circPIP5K1A | Cell proliferation, invasion, apoptosis, and EMT              | miR-153, PIK3R1, and VEGF-C; in vivo                                   | 200   |
| Glioma                   | Oncogene        | circ104075 | Cell proliferation, apoptosis, and autophagy                  | miR-153, PIK3R1, and VEGF-C; in vivo                                   | 201   |
| Glioma                   | Oncogene        | circ0000215 | Cell proliferation, invasion, apoptosis, and EMT              | miR-153, PIK3R1, and VEGF-C; in vivo                                   | 202   |
| Glioblastoma             | Tumor suppressor | circAKT3  | Cell proliferation, migration, invasion, and resistance       | miR-153, PIK3R1, and VEGF-C; in vivo                                   | 203   |
| Glioblastoma             | Oncogene        | circ0067934 | Cell proliferation, metastasis, apoptosis, and sensitivity      | miR-153, PIK3R1, and VEGF-C; in vivo                                   | 204   |
| Glioblastoma             | Oncogene        | circPVT1  | Cell viability, migration, apoptosis, and EMT                 | miR-153, PIK3R1, and VEGF-C; in vivo                                   | 205   |
| Neuroblastoma            | Oncogene        | circ0002343 | Cell proliferation, migration, invasion, and oncogenicity      | miR-153, PIK3R1, and VEGF-C; in vivo                                   | 206   |
| Kidney cancer            | Tumor suppressor | circ0072309 | Cell proliferation, migration, invasion, and apoptosis       | miR-153, PIK3R1, and VEGF-C; in vivo                                   | 207   |
| Bladder cancer           | Oncogene        | circZNF139 | Cell proliferation, migration, invasion, and cell clones       | miR-153, PIK3R1, and VEGF-C; in vivo                                   | 208   |
| Prostate cancer          | Oncogene        | circ0001085 | Cell proliferation, migration, invasion, and EMT              | miR-153, PIK3R1, and VEGF-C; in vivo                                   | 209   |
| Prostate cancer          | Oncogene        | circMBOAT2 | Cell proliferation, migration, invasion, and EMT              | miR-153, PIK3R1, and VEGF-C; in vivo                                   | 210   |
| Prostate cancer          | Oncogene        | circITCH  | Cell proliferation, migration, invasion, and resistance       | miR-153, PIK3R1, and VEGF-C; in vivo                                   | 211   |
| Prostate cancer          | Oncogene        | circNOLC1  | Cell proliferation, migration, invasion, and EMT              | miR-153, PIK3R1, and VEGF-C; in vivo                                   | 212   |
| Ovarian cancer           | Tumor suppressor | circRHOBTB3 | Cell proliferation, migration, invasion, and EMT              | miR-153, PIK3R1, and VEGF-C; in vivo                                   | 213   |
| Endometrial cancer       | Oncogene        | circ0002577 | Cell proliferation, migration, invasion, and metastasis       | miR-153, PIK3R1, and VEGF-C; in vivo                                   | 214   |
| Cervical cancer          | Oncogene        | circCSPP1  | Cell proliferation, migration, invasion, and resistance       | miR-153, PIK3R1, and VEGF-C; in vivo                                   | 215   |

Crosstalk between circRNAs and the PI3K/AKT signaling pathway in cancer...
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| Category                        | Type                  | CircRNA   | Role             | Function                                  | Related genes; in vivo            | Refs |
|--------------------------------|-----------------------|-----------|------------------|-------------------------------------------|----------------------------------|------|
| Tumors of the endocrine system | Thyroid cancer        | circ0067934 | Oncogene         | Cell proliferation, migration, invasion, apoptosis, and EMT | PI3K and AKT                      | 238  |
|                                | Thyroid cancer        | circ0007694 | Tumor suppressor | Cell proliferation, migration, invasion, and apoptosis | PI3K, AKT, mTOR, and Wnt tumor growth | 239  |
|                                | Thyroid cancer        | circpsd3   | Oncogene         | Cell proliferation, metastasis, apoptosis, and cell cycle | mir-637, HEMGN, PI3K, and AKT     | 240  |
| Tumors of the respiratory system | Lung cancer           | circGFRA1  | Oncogene         | Cell proliferation and apoptosis           | miR-188-3p, PI3K, and AKT; cell proliferation | 245  |
|                                | Lung cancer           | circ100826 | Oncogene         | Cell proliferation and apoptosis           | miR-635, RET, PI3K, and AKT       | 247  |
|                                | Lung cancer           | circ1018912 | Oncogene         | Cell proliferation, invasion, apoptosis, and EMT | mir-767-3p, Nidogen 1(NID1), PI3K, and AKT | 246  |
| Tumors of the musculoskeletal system | Osteosarcoma         | circ0001785 | Oncogene         | Cell proliferation and apoptosis           | miR-1200, HOX82, PI3K, AKT, and Bcl-2 | 250  |
|                                | Osteosarcoma          | circ0001785 | Oncogene         | Cell proliferation, migration, and invasion | miR-218, PI3K, and AKT            | 251  |
|                                | Osteosarcoma          | circTFCH   | Tumor suppressor | Cell viability, proliferation, migration, invasion, and apoptosis | miR-22, PTEN, SP-1, PI3K, and AKT | 252  |
|                                | Osteosarcoma          | circ0005909 | Oncogene         | Cell viability and cell clones             | miR-338-3p, HMGA1, MAPK-ERK, PI3K, and AKT | 253  |
| Tumors of other systems        | Oral squamous cell carcinoma | circ043621 | Oncogene         | Cell proliferation, apoptosis, and cell cycle | MAPK, PI3K, AKT, and Bcl-2        | 257  |
|                                | Oral squamous cell carcinoma | circ102459 | Tumor suppressor | Cell proliferation, apoptosis, and cell cycle | MAPK, PI3K, AKT, and Bcl-2        | 257  |
|                                | Multiple myeloma      | circ0007841 | Oncogene         | Cell proliferation, apoptosis, and cell cycle | miR-338-3p, BRD4, PI3K, and AKT    | 261  |
|                                | Breast cancer         | circ013809  | Oncogene         | Cell proliferation, apoptosis, and cell cycle | PI3K and AKT                      | 262  |
|                                | Breast cancer         | circPRMTS   | Oncogene         | Cell proliferation, apoptosis, and angiogenesis | mir-509-3p, TCF7L2, PI3K, and AKT | 263  |
|                                | Breast cancer         | circHIPK3   | Oncogene         | Cell viability, proliferation, migration, and invasion | mir-193a, HMG81, PI3K, and AKT     | 264  |
|                                | Breast cancer         | circ000442  | Tumor suppressor | Cell viability, colony formation, and cell cycle | mir-148b-3p, PTEN, PI3K, and AKT | 265  |
|                                | Breast cancer         | circ001569  | Oncogene         | Cell growth and metastasis                 | PI3K and AKT                      | 266  |
|                                | Breast cancer         | circ0000199 | Oncogene         | Cell proliferation, migration, invasion, chemo-sensitivity, and autophagy | mir-206, mir-613, PI3K, AKT, and mTOR | 267  |
in the initiation and progression of several types of cancer. Current studies may lay the foundation for further research on the mechanisms of cancer progression and provide insights into circRNA-based clinical applications. In this section, we will summarize the expression, biological functions in vitro (Table 1), and associations with clinicopathological characteristics of circRNAs related to the PI3K/AKT signaling pathway (Table 2).

**DIGESTIVE SYSTEM NEOPLASMS**

Esophageal cancer

The expression of circVRK1 and circLARP4 is significantly downregulated and circLARP3 levels are increased in esophageal squamous cell carcinoma (ESCC).\(^{171,173}\) Low circVRK1 expression predicts poor overall survival in patients with ESCC.\(^{172}\) Elevated circLARP3 levels are markedly associated with lymph node metastasis (LNM) and advanced TNM stage.\(^{171}\) In addition, researchers have also observed alterations in biological functions of the circRNA/PI3K/AKT axis by in vitro functional assays. Silencing of the circRNA cZNF292 inhibits the activity of tumor cells and promotes cell apoptosis in ESCC.\(^{174}\) Upregulation of circVRK1 suppresses cell proliferation, increases the radiosensitivity of ESCC cells, and attenuates epithelial–mesenchymal transition (EMT).\(^{175}\) CircLARP4 inhibits cell apoptosis and promotes cell proliferation in ESCC.\(^{175}\) Furthermore, cZNF292, circVRK1, and circLARP4 all inhibit ESCC cell migration. Contrary to the aforementioned investigations, circLARP3 functions as a tumor oncogene and enhances the malignant phenotype of ESCC tumors.\(^{171}\) Mechanistically, circLARP3 increases the expression of the MET gene to enhance the RAS/MAPK and PI3K/Akt pathways by sponging miR-198 in ESCC. Knockdown of cZNF292 induces inactivation of the PI3K/AKT pathway and upregulation of AMPK signaling to exert effects in ESCC.\(^{176}\) CircVRK1 functions as a tumor suppressor gene by upregulating PTEN and inhibiting the PI3K/AKT axis.\(^{172}\) Similarly, circLARP4 promotes the expression of PTEN and inactivates the PI3K/AKT pathway to suppress the progression of ESCC.\(^{173}\)

**Gastric cancer**

PI3K/AKT pathway-related circRNAs (circP5K1A, circ0010882, circ0023409, cirS-7, circMAM2B2, and circPV1) are all obviously upregulated in gastric cancer.\(^{175–180}\) The levels of circ0010882 and circ0023409 are positively associated with tumor size and histological grade in gastric cancer patients.\(^{176,177}\) In addition, higher expression of circ0010882 or cirS-7 is associated with shorter overall survival. Circ0023409 promotes LNM in gastric cancer. In terms of biological function, increased circP5K1A, circ0010882, and circ0023409 expression reduces gastric cancer cell proliferation, migration, and invasion.\(^{175–177}\) High expression of circPV1 may enhance the sensitivity of gastric cancer cells to cisplatin (DDP).\(^{180}\) We also found that circMAM2B2 upregulates cell viability and the surviving cell fraction by cell transfection experiments.\(^{178}\) Silencing of circ0010882 attenuated gastric cancer cell growth and motility in vitro.\(^{176}\) In terms of the mechanism, circP5K1A sponges miR-671-5p to facilitate tumor progression by upregulating the KRT80 and PI3K/AKT pathways in gastric cancer.\(^{175}\) Circ0010882 regulates biological functions by promoting PI3K/AKT/mTOR signaling.\(^{176}\) Further studies have

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**Table 2. Relationship between circRNA/PI3K/AKT axis and clinical features in cancer**

| Cancer type                      | CircRNA          | Expression     | Related features                                                                 | Refs. |
|----------------------------------|------------------|----------------|----------------------------------------------------------------------------------|-------|
| Bladder cancer                   | circZNF139       | Upregulated    | Disease-free survival                                                            | 220   |
| Liver cancer                     | circGFI1         | Upregulated    | Tumor size                                                                       | 185   |
| Liver cancer                     | circRNA0072309   | Downregulated  | 5-year survival                                                                  | 186   |
| Liver cancer                     | circ0004001, circ0004123, and circ00075792 | Upregulated | TNM stage, and tumor size                                                         | 188   |
| Thyroid cancer                   | circ0067934      | Upregulated    | Survival period and AJCC stage                                                    | 238   |
| Glioma                           | circP5K1A        | Upregulated    | Survival time, tumor volume, and tumor stage                                     | 200   |
| Glioblastoma                     | circ0067934      | Upregulated    | Disease-free survival and overall survival                                       | 206   |
| Colorectal cancer                | circ0008285      | Downregulated  | Lymph node metastasis, TNM stage, and tumor size                                 | 183   |
| Oral squamous cell carcinoma     | circ043621       | Upregulated    | Clinical stage, lymph node metastasis, and differentiation degree                | 257   |
| Oral squamous cell carcinoma     | circ02459        | Downregulated  | Clinical stage, lymph node metastasis, and differentiation degree                | 257   |
| Prostate cancer                  | circMBOAT2       | Upregulated    | Gleason score, pathological T stage, and disease-free survival                   | 227   |
| Breast cancer                    | circPRMT5        | Upregulated    | Overall survival                                                                  | 263   |
| Breast cancer                    | circCHIP3        | Upregulated    | Overall survival                                                                  | 264   |
| Breast cancer                    | circ001569       | Upregulated    | Lymph node metastasis, pathological stage, and overall survival                  | 266   |
| Breast cancer                    | circ0001099      | Upregulated    | Tumor size, TNM stage, ki-67 level, and 3-year survival                          | 267   |
| Esophageal cancer                | circLARP3        | Downregulated  | Overall survival                                                                  | 172   |
| Esophageal cancer                | circVRK1         | Downregulated  | Lymph node metastasis and TNM stage                                              | 172   |
| Gastric cancer                   | circ0010882      | Upregulated    | Tumor size, histological grade, and overall survival                             | 176   |
| Gastric cancer                   | circ0023409      | Upregulated    | Tumor size, histological grade, and lymph nodes metastasis                       | 177   |
| Gastric cancer                   | cirS-7           | Upregulated    | Overall survival                                                                  | 178   |
| Pancreatic cancer                | circNF181        | Downregulated  | Lymph node metastasis                                                            | 194   |
| Pancreatic cancer                | circBFAR         | Upregulated    | TNM stage, overall survival, and disease-free survival                           | 196   |
| Endometrical cancer              | circ0002577      | Upregulated    | Overall survival, histological grade, lymph node metastasis, and lymph vascular   | 232   |

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demonstrated that circ0023409, ciRS-7, circMAN2B2, and circPVT1 regulate the PI3K/AKT pathway by acting as sponges of miRNAs in gastric cancer. For example, circ0023409 activates the PI3K/AKT pathway by sponging miR-542-3p to increase IRS4 levels. In addition, researchers have established in vivo xenograft nude mouse models to further explore the relationship between gastric cancer and the circRNA/PI3K/AKT axis. The expression of circPIP5K1A facilitates tumor growth in gastric cancer in vivo. 

Colorectal cancer (CRC)

The expression level of circ0001313 is dramatically upregulated while the levels of circCDYL and circ0008285 are decreased in CRC. Circ0008285 expression is positively associated with LNM, tumor-node-metastasis (TNM) stage, and tumor size in patients with CRC. Functionally, circCDYL inhibits CRC cell migration and invasion. Circ0001313 and circCDYL significantly reduce cell apoptosis in CRC. Silencing the expression of circ0008285 enhances cell proliferation and migration in CRC. The expression of circ0001313 increases the level of AKT2, thus contributing to CRC progression by downregulating miR-510-5p expression. CircCDYL inactivates PI3K/AKT and JAK/STAT signaling by decreasing miR-150-5p levels in colon cancer. Circ0001313 and circCDYL significantly reduce cell apoptosis in CRC. Circ0008285 expression reduces migration and proliferation via regulation of the miR-382-5p/PTEN/PI3K/AKT axis in CRC.

Liver cancer

A series of circRNAs related to the circRNA/PI3K/AKT axis has been found to be closely related to the occurrence and progression of hepatocellular carcinoma (HCC). These circRNAs with aberrant expression are listed in Table 1. Tumor size positively correlates with the expression of circGF1R, circ0004001, circ0004123, and circ0075792 in HCC. High expression of circ0072309 is related to better 5-year survival in patients with HCC. Decreased circCDK13 levels enhance cell motility while low levels of circGF1R inhibit cell growth in HCC. High expression of circ0072309 impairs cell growth and motility, affecting cell viability, colony formation, invasion, and migration. Mechanistically, circCDK13 inhibits HCC progression by regulating the PI3K/AKT and JAK/STAT pathways (Table 1). Circ0072309 functions as a sponge of miR-665 to negatively regulate the PI3K/AKT and Wnt/β-catenin pathways in the pathophysiologic processes of HCC. The expression of circEPHB4 impedes HCC progression by negatively regulating the HIF-1α/PI3K/AKT axis and HIF-1α/VEGF-C signaling. Hepatoblastoma is the most common primary malignant hepatic tumor in children. The expression of circHMGCS1 is significantly upregulated in hepatoblastoma cell lines compared to normal hepatocyte cells and HCC cells. circHMGCS1 also promotes cell proliferation and inhibits apoptosis in hepatoblastoma cell lines. CircHMGCS1 markedly upregulates the IGF2/IGF1R/PI3K/AKT axis to regulate proliferation by sponging miR-503-5p. The expression of circEPHB4 was negatively associated with tumor weight, size, and metastatic foci in vivo. A higher level of circ0079929 predicted decreased tumor size and weight in nude mouse models. CircCDK13 is an important negative regulator in the development and progression of HCC.

Pancreatic cancer

The level of circNFIB1 is markedly decreased while circEIF6 and circBFAR expression levels are elevated in pancreatic cancer. High expression of circNFIB1 restrains lymphatic metastasis of pancreatic cancer. Uregulated levels of circBFAR predict high TNM stage and poor prognosis. Functionally, we found that the expression of circEIF6 promotes cell proliferation, increases cell migration and invasion, and inhibits cell apoptosis by performing siRNA-mediated knockdown experiments in pancreatic cancer cells. Mechanistically, circNFIB1 induces VEGF-C inhibition and attenuates LNM by sponging miR-486-5p and inhibiting the PI3K/AKT signaling pathway.
AKT pathway in pancreatic ductal adenocarcinoma. CircEIF6 regulates biological functions by upregulating miR-557 expression, downregulating SLC7A11 levels, and inactivating the PI3K/AKT pathway in pancreatic cancer. CircBFAR facilitates mesenchymal–epithelial transition by sponging miR-34b-5p and upregulating the MET/PI3K/AKT axis in pancreatic ductal adenocarcinoma. In vivo experiments showed that downregulation of circBFAR or circEIF6 expression can lead to lower tumor weight and volume in pancreatic ductal adenocarcinoma.

NERVOUS SYSTEM NEOPLASMS

Glioma
PI3K/AKT axis-associated circRNAs are significantly upregulated in glioma (Table 1). Elevated circPIP5K1A expression is positively correlated with shorter survival time, larger tumor volume, and higher tumor stage in patients with glioma. CircHIPK3, circPIP5K1A, circ104075, and circ0000215 increase glioma cell proliferation in vitro. CircHIPK3, circPIP5K1A, and circ0000215 facilitate cell motility in glioma. Furthermore, circDICER1 markedly attenuates the angiogenesis of glioma-exposed endothelial cells. Downregulated expression of circHIPK3 induces a significant upregulation of temozolomide sensitivity in glioma. Mechanistic studies have revealed that circ0014359 exerts its effects by inhibiting the level of miR-153 and regulating the PI3K axis in glioma. CircDICER1 in combination with MOV10 plays a critical role in glioma angiogenesis via regulation of miR-103a-3p (miR-382-5p)/ZIC4. CircHIPK3 regulates biological functions to improve sensitivity to temozolomide through suppression of the miR-524-5p/KIF2A-mediated PI3K/AKT pathway. A series of studies have shown that circRNAs can facilitate glioma tumorigenesis and progression by regulating the circPIP5K1A/miR-515-5p/TCF12/PI3K/AKT and circ0000215/miR-495-3p/CXCR2/PI3K/AKT pathways.

Glioblastoma (GBM) is the most malignant glioma and has an extremely poor prognosis. CircAKT3 is overexpressed while circ0067934 and circPVT1 expression are significantly downregulated in GBM. A higher level of circ0067934 portends shorter disease-free survival and decreased overall survival rates in GBM. Inhibition of circ0067934 expression may be a promising strategy for improving GBM prognosis. The upregulation of circAKT3 suppresses GBM cell proliferation and increases sensitivity to radiation. The expression of circ0067934 facilitates cell proliferation and metastasis and inhibits cell apoptosis in GBM by upregulating the PI3K-AKT pathway.

Neuroblastoma (NB) and pituitary tumor
NB is the most common extracranial solid tumor in childhood. The expression of circ0002343 was found to be involved in the regulation of EMT in NB. Elevated circ0002343 significantly affects EMT by regulating the RAC1/PI3K/AKT/mTOR axis. Pituitary tumors are some of the most common benign neoplasms of the central nervous system. The levels of circ0054722, circ0012346, and circ0007362 are significantly increased while the expression of some circRNAs (circ0062222, circ0016403, circ0033349, and circ0049730) is downregulated in invasive nonfunctioning pituitary adenomas compared with the levels in noninvasive nonfunctioning pituitary adenomas.

Genitourinary tumors
Kidney cancer and bladder cancer. Kidney cancer is not a single disease but comprises different types of cancer that occur in the kidney. Renal carcinoma-associated transcripts (circ0072309 and circC3P1) are significantly downregulated in renal carcinoma tissues compared to corresponding normal tissues. These circRNAs significantly suppresses cell proliferation, migration, and invasion and promote cell apoptosis in kidney cancer. Circ-0072309 sponges miR-100 to inhibit the PI3K/AKT and mTOR pathways.
pathways in kidney cancer. CircC3P1 exerts diverse biological functions by inhibiting the PI3K/AKT and NF-κB pathways by regulating the miR-21/PTEN axis (Fig. 4a). The overexpression of circZNF139 is markedly associated with disease-free survival in bladder cancer. circZNF139 overexpression also attenuates bladder cancer cell proliferation, colony formation, migration, and invasion by regulating the PI3K/AKT pathway.

Prostate cancer (PCa). PCa is a major cause of male cancer-related mortality worldwide. The level of circNOLC1 is increased while circITCH expression is obviously downregulated in PCa. CircMBOAT2 is overexpressed in PCa and contributes to poor prognosis. Moreover, increased circMBOAT2 levels are positively correlated with Gleason score and pathological T stage. Functionally, circNOLC1, circITCH, and circMBOAT2 govern multiple cellular processes, such as cell proliferation, migration, and invasion, via the circRNA/PI3K/AKT axis in PCa. Circ0001085 induces EMT in PCa cells in vitro. Circ0001085 regulates PCa progression through the PI3K/AKT pathway by sponging miR-196b-5p and miR-451a (Fig. 4b). CircMBOAT2 clearly promotes tumorigenesis and metastasis in PCa in vivo.

Female reproductive system cancers. Ovarian, endometrial, and cervical cancer are three major malignant tumors causing a severe threat to women’s health. The downregulation of circRHOBTB3 not only attenuates cell proliferation and metastasis but also inhibits glycolysis by suppressing the PI3K/AKT pathway in ovarian cancer. Circ0002577 expression is markedly increased while circITCH expression is obviously downregulated in endometrial cancer. Circ0002577 expression is positively correlated with the histological grade of the tumor, LNM, and lymph vascular space invasion. Studies have revealed that patients with high expression of circ0002577 have a poor prognosis. The overexpression of circ0002577 enhances the IGF1R/PI3K/AKT axis to increase the migration, invasion, and proliferation of endometrial cancer cells (Fig. 4c). Silencing of circ0002577 expression significantly inhibits the growth and metastasis of tumors in nude mouse models of endometrial cancer. The expression of circCSPP1 is markedly upregulated in cervical cancer tissues. CircCSPP1 expression inhibits cervical cancer cell apoptosis and promotes cell proliferation and migration via the miR-361-5p/ITGB1/PI3K/AKT axis in cervical cancer (Fig. 4d).

TUMORS OF THE ENDOCRINE SYSTEM
Thyroid cancer is the most common malignancy occurring in the endocrine system. The expression of circ0067934 and circpsd3 is upregulated whereas circ0007694 expression is downregulated in thyroid tumors. High circ0067934 expression is associated with a shorter survival period of thyroid cancer patients. The expression of circ0067934 and circ0007694 affects diverse cell biological functions, such as cell proliferation, migration, invasion, and apoptosis, in thyroid cancer via the PI3K/AKT signaling pathway. During the regulation of different cellular biological processes, circ0067934 acts as an oncogene, but circ0007694 may function as a tumor suppressor gene in the progression of thyroid cancer. Increased circ0007694 expression effectively suppresses the growth of papillary thyroid carcinoma in vivo.

TUMORS OF THE RESPIRATORY AND MUSCULOSKELETAL SYSTEMS
Lung cancer
Lung cancer is one of the leading causes of cancer-related death worldwide, with NSCLC accounting for 85% of all lung cancers. The expression of circGFRA1 and circ0018818 is significantly upregulated in NSCLC tissues compared to normal counterparts. Silencing of circ0018818 expression inhibits proliferation, invasion, and EMT and promotes cell apoptosis. In addition, circGFRA1 activates the PI3K/AKT pathway by downregulating the expression of miR-188-3p in lung cancer. Knockdown of circ100876 reduces cell proliferation, migration, invasion and facilitates NSCLC cell apoptosis by regulating the miR-636/RET axis and PI3K/AKT signaling. The circ0018818/miR-767-3p/NID1/PI3K/AKT axis also plays a key role in the progression of lung cancer (Fig. 5).

Osteosarcoma (OS). OS is the most common primary malignant bone tumor in children and adolescents. The expression of circRNAs associated with the PI3K/AKT axis is listed in Table 1.
The expression of circEIF4G2 and circITCH affects cellular biological functions, such as cell proliferation, migration, and invasion, in OC.252,253 Silencing of circ0005909 obviously decreases cell viability and cell clone capacity in OS cell lines.253 Decreased expression of circ0001785 reduces cell proliferation and facilitates cell apoptosis in OC.250 Mechanistically, the expression of circ-ITCH attenuates cellular biological functions because circ-ITCH acts as a competing endogenous RNA (ceRNA) for miR-22 to inactivate the PTEN/Pi3K/AKT and SP-1 pathways in OS.252 Circ0005909 expression enhances OS malignant progression by upregulating the MAPK-ERK and Pi3K-Akt signaling pathways by sponging miR-338-3p to inhibit the level of HGMA1.254

Tumors of other systems

Oral squamous cell carcinoma (OSCC) is a malignant type of head and neck squamous cell carcinoma.254-256 Circ043621 expression is remarkably elevated and circ102459 levels are dramatically decreased in OSCC tissues.256 CircPARD3 and circ043621 expression levels are relatively associated with clinical stage, LNM, and differentiation degree in OSCC. In vitro assays have revealed that increased circ043621 levels and decreased circ102459 expression can induce arrest in the G0 and/or G1 phase, apoptosis, and inhibition of cell proliferation by activating the MAPK and PI3K/AKT pathways.257 Multiple myeloma (MM) is a plasma cell malignant.258 The expression of circ0007841 is significantly upregulated in MM cell lines and bone marrow-derived cells.258 High circ0007841 expression enhances the malignant behaviors of MM through suppression of cell viability and cell cycle arrest at the G1 phase and decreases colony formation in breast cancer.262-267 (Table 1). The overexpression of circ0000199 is significantly associated with tumor size, TNM stage, and Ki-67 level in patients with breast cancer.267 Higher levels of circPMT5, circHIPK3, circ001569, and circ0000199 predict poor prognosis in breast cancer.263,264,265,266,267 Circ0000199 can affect tumor cell tolerance of chemotherapy via suppression of the Pi3K/AKT/mTOR pathway and activation of the miR-206/miR-613 axis.268,269 Circ0000199 also enhances cell proliferation, migration, and invasion in breast cancer. Silencing of circPMT5 expression attenuates angiogenesis and proliferation and induces apoptosis.263 CircPMT5 contributes to malignant phenotypes by activating the Pi3K/AKT/mTOR axis via regulation of the miR-509-3p/TCF7L2 pathway. High expression of circHIPK3 significantly promotes cell migration, invasion, viability, and proliferation by targeting the miR-193a/HMG1/Pi3K/AKT axis.265 High circ0000442 expression induces suppression of cell viability and cell cycle arrest at the G1 phase and decreases colony formation in breast cancer.265 Circ0000442 knockdown experiments have further confirmed this result. circ0000442 acts as a sponge of miR-148b-3p to downregulate the PTEN/Pi3K/AKT pathway to impede tumor progression. Moreover, the knockdown of circHIPK3 attenuates breast cancer growth in vivo.264

CircRNAs related to the Pi3K/AKT pathway as biomarkers

In recent years, researchers have focused on identifying effective molecular biomarkers to improve the early detection, monitoring, and prediction of therapy response in cancer patients.280 CircRNAs can positively or negatively modulate biological functions and cancer progression through multiple signaling pathways. CircLARP4 promotes the expression of PTEN and inactivates the Pi3K/AKT pathway to suppress the progression of ESCC.175 CircP5K1A sponges mir-671-5p to facilitate tumor progression by upregulating KRT80 and the Pi3K/AKT pathway in gastric cancer.175 Circ0067934 facilitates cell proliferation and metastasis and inhibits cell apoptosis in GBM by upregulating the Pi3K/AKT pathway.206 CircEPHB4 impedes HCC progression by negatively regulating the HIF-1α/Pi3K/AKT axis and the HIF-1α/ZEB1 pathway in HCC.189 Upregulating or downregulating the expression of circRNAs may be a feasible way to regulate tumor progression. Silencing of circ0010882 attenuates gastric cancer cell growth and motility in vitro.176 Knockdown of circ0021097 reduces cell proliferation, migration, and invasion and facilitates NSCLC cell apoptosis.247 In addition, a mir-671-5p inhibitor was able to significantly reduce the level of circP5K1A to inhibit the progression of gastric cancer.175 Rapamycin, an mTOR inhibitor, blocks the circMOAT2/Pi3K/AKT/mTOR pathway to suppress Pca progression.272 CircHIPK3 regulates biological functions to improve sensitivity to temozolamide through suppression of the miR-524-5p/KIF2A-mediated Pi3K/AKT pathway in glioma.179 Circ000199 can make tumor cells sensitive to chemotherapy via suppression of the Pi3K/AKT/mTOR pathway and activation of the miR-206/miR-613 axis in breast cancer.267 High expression of circPVT1 enhances the sensitivity of gastric cancer cells to cisplatin.
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ADDITIONAL INFORMATION
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