The important regulatory roles of circRNA-encoded proteins or peptides in cancer pathogenesis (Review)

LEI ZHANG, HUIJUAN GAO, XIN LI, FEI YU and PEIFENG LI

Institute for Translational Medicine, The Affiliated Hospital of Qingdao University, Qingdao University, Qingdao, Shandong 266021, P.R. China

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Abstract. Circular RNAs (circRNAs) represent a class of RNA molecules characterized by their covalently closed structures. There are three types of circRNAs, namely exonic circRNAs, exon-intron circRNAs and circular intronic RNAs. To date, four distinct mechanisms have been unveiled through which circRNAs exert their functional influence, including serving as microRNA (miRNA) sponges, interacting with RNA binding proteins (RBPs), modulating parental gene transcription and acting as templates for translation. Of note, among these mechanisms, the miRNA/RBP sponge function has been the most investigated one. Recent research has uncovered the presence of various proteins or peptides encoded by circRNA. CircRNAs are translated independent of the 5' cap and 3' polyA tail, which are typical elements for linear RNA translation. Some unique elements, such as internal ribosome entry sites and N-methyladenosine modifications, facilitate the initiation of translation. These circRNA-encoded proteins or peptides participate in diverse signalling pathways and act as important regulators in carcinogenesis by influencing cell proliferation, migration, apoptosis and other key processes. Consequently, circRNA-encoded proteins or peptides have great potential as therapeutic targets for anticancer drugs. The present comprehensive review aimed to systematically summarize the current understanding of circRNA-encoded proteins or peptides and to unveil their roles in carcinogenesis.

Contents

Correspondence to: Dr Lei Zhang or Professor Peifeng Li, Institute for Translational Medicine, The Affiliated Hospital of Qingdao University, Qingdao University, No. 38 Dengzhou Road, Qingdao, Shandong 266021, P.R. China
E-mail: leizhang@qdu.edu.cn
E-mail: peifli@qdu.edu.cn

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1. Introduction

Circular RNAs (circRNAs) are distinctive noncoding RNAs characterized by a covalently closed circular structure that lack the typical translation initiation elements (5' cap and 3' polyA tail) of linear RNAs (1). Originally identified in plant viruses (2), circRNAs were initially presumed to lack functional roles (3-5). Subsequently, circRNAs were found in multiple eukaryotes ranging from yeast to humans (6,7). With advances in technology and experimental methods, previous studies have confirmed the multifunctional roles of circRNAs in various physiological and pathological processes (8-10). CircRNAs are widely involved in different types of coronary artery diseases, such as myocardial infarction and angiogenesis (11,12). They also have pivotal roles in various cancer types, such as non-small cell lung cancer (1,13), gastric cancer (14,15) and glioma (16,17).

CircRNAs can function by sponging microRNAs (miRNAs) or RNA binding proteins (RBPs) and modulating parental gene expression (18). Remarkably, circRNAs can encode proteins or peptides that directly influence relevant signalling pathways (19-21). CircRNAs were first found to have protein-coding ability in viruses and prokaryotes, such as *hepatitis D* virus (22) and *Escherichia coli* (23). Subsequently, additional circRNAs that encode proteins or peptides were identified (24-26). For instance, circ-ZNF609 promotes myoblast proliferation in patients with Duchenne muscular dystrophy and can be translated into a protein in a splicing-dependent manner (27). CircMBL can be translated into a protein that may exert synaptic functions dependent on forkhead box (FOX)O activity (28). CircRNA-encoded proteins or peptides are closely associated with cancer pathogenesis (29-32). The present review offers a succinct summary of the properties and functional mechanisms of circRNAs, with a particular emphasis on the mechanisms underlying circRNA translation. Furthermore, the functions of circRNA-encoded

proteins or peptides in the pathogenesis of various cancer types are explored.

2. Characteristics of circRNAs

There are three types of circRNAs produced by back-splicing: i) Exonic circRNAs (ecRNAs) (33), ii) exon-intron circRNAs (EIciRNAs) (34) and iii) circular intronic RNAs (ciRNAs) (33). CircRNAs are produced via four different mechanisms (35). The lariat-driven circularization model, involving the activities of splice donors and acceptors, exclusively produces ecRNAs (9,36). The intron pairing-driven circularization model relies on RNA base motif pairing (e.g., Alu repeats) in introns, resulting in the generation of ecRNAs or EIciRNAs (9). In the RBP-mediated circularization model, RBPs bridge with pre-mRNAs, leading to the formation of ecRNAs or EIciRNAs. CiRNAs are produced by the binding of C-rich elements near the branch and GU-rich elements close to the 5'splice site of introns (1).

Different types of circRNAs exhibit distinct mechanisms of action (Fig. 1). EcRNAs, mainly localized in the cytoplasm (37,38), can act as miRNAs/RBP sponges to modulate downstream gene expression and encode functional proteins or peptides to influence specific pathways (1,9,39). EIciRNAs and ciRNAs, which are confined to the nucleus due to their intronic sequences (9), have roles in parental gene transcription by binding to RNA polymerase II (Pol II) (34) (Fig. 1A). CiRNAs interact with Pol II to directly enhance parental gene transcription (40). EIciRNAs form a complex with U1 small nuclear ribonucleoproteins and then interact with Pol II (34). EcRNAs containing miRNA response elements (MREs) can interact with miRNAs, exerting a 'sponge effect' that decrease miRNA levels and then upregulate the activities of miRNA targets (37) (Fig. 1B). One ecRNA may contain ≥1 MRE, allowing it to perform different functions. Similarly, ecRNAs can bind to RBPs resembling the sponge effect to decrease the levels of RBP and then increase the activity of RBP targets (41,42) (Fig. 1C). Unlike linear RNAs, circRNAs lack typical translation initiation elements (5' cap and 3' polyadenylated tail). However, they possess unique elements, such as N6-methyladenosine (m^6A) modifications and internal ribosome entry sites (IRESs) that facilitate their unique protein translation (19,43) (Fig. 1D).

3. CircRNA translation mechanisms

Translation initiation is the key step in protein generation. In this step, ribosomes and transfer RNAs interact with mRNAs to form an initiation complex. This intricate process involves the assembly of initiation factors into various complexes, such as the eukaryotic translation initiation factor (eIF)4E complex (comprising eIF4E, eIF4G and eIF4A) and the eIF3 complex (including eIF4G2, eIF4A and eIF4B). These complexes facilitate and ensure an accurate cap-dependent translation (44). In contrast to linear RNAs, circRNAs undergo cap-independent translation. Initiation factors bind to the IRES or m^6A to facilitate the formation of the initiation complex (45) (Fig. 1E and F).

IRES-dependent circRNA translation. The IRES is located in the 5'-untranslated region of an mRNA (46). IRES-mediated mRNA translation initiation occurs only in response to cellular stress conditions, such as hypoxia or heat shock (47). However, this IRES-dependent translation mechanism is ubiquitous across circRNAs (48). IRESs in circRNAs serve as recognition sites for initiation factors such as eIF4G and can be engaged by ribosomes to promote translation initiation (49) (Fig. 1E). Fan *et al* (48) found multiple IRES-like short elements that were abundant in endogenous circRNAs. These IRES-like short elements could drive circRNA translation. Furthermore, numerous trans-acting factors interact with IRES-like elements.

m^6A-dependent circRNA translation. m^6A is an important regulatory modification that promotes mRNA translation (50,51). Previous studies have unveiled that even a single m^6A-modified site can trigger circRNA translation with the help of the m^6A reader YTH domain family protein 3 (YTHDF3) and eIF4G2 (29,52,53). YTHDF3 promotes the m^6A modification of eIF4G2, which subsequently recruits ribosomes to form the translation initiation complex (29,50) (Fig. 1F).

4. Identification and research methodology of circRNA-encoded proteins or peptides

Various bioinformatics tools have been developed to facilitate the identification and exploration of circRNAs with translational potential (Table I). CircBase and CircNet offer comprehensive information, including genome sequences, annotation, expression profile and possible downstream factors of circRNAs (54,55). CircCode, CircPro and CircRNADb can predict and identify circRNAs with coding potential (56-58). CircRNADb additionally provides genome sequences, IRES information and open reading frame (ORF) details (56). ORF Finder searches for possible ORFs and predicts corresponding amino acid (aa) sequences (59). BLASTp assesses the conservation of these aa sequences, providing reference information for functional research. IRESite, IRESbase, DeepM6ASeq and M6APred-EL can predict IRES/m^6A modifications and provide evidence of their existence (60-63).

In addition to bioinformatic tools, experimental evidence is crucial to detect the translation of circRNAs. High-throughput techniques such as ribosome profiling, ribosome immunoprecipitation and ribosome affinity purification can identify circRNAs with encoding function (64). Mass spectrometry offers direct evidence through identifying specific peptides (65). Biochemical molecular techniques, including western blotting, enzyme immunoassays and dual luciferase reporting assays, enable the detection of putative peptides or proteins (66,67), screening of the targeted proteins and evaluation of IRES/m^6A activity (29,47).

5. Functional mechanisms of circRNA-encoded proteins or peptides in cancers

Zhao *et al* (68) reported that circRNA-encoded proteins or peptides may function as baits for functional proteins. In cancer pathogenesis, circRNA-encoded proteins or peptides exert their effects by directly interacting with various proteins, such as transcription factors, regulatory elements and signalling

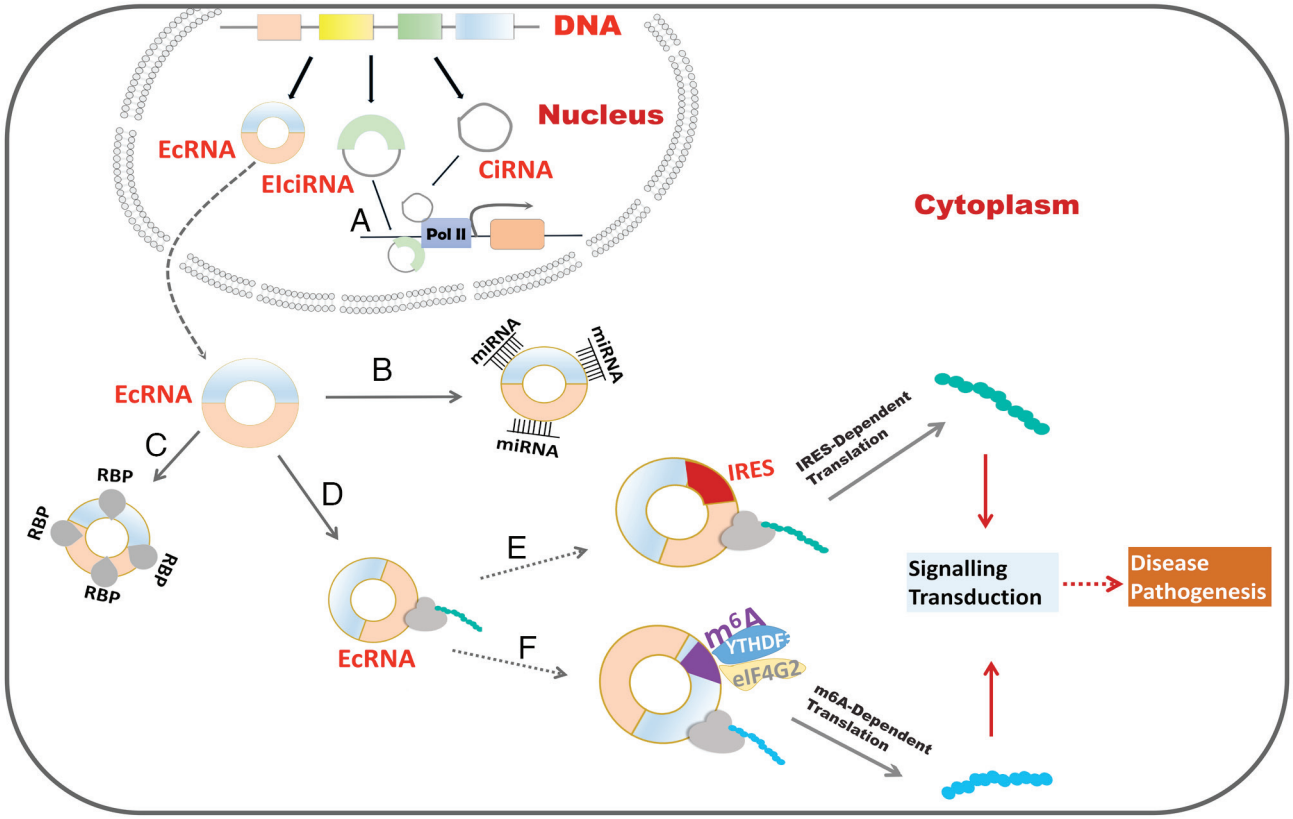

Figure 1. Mechanism of action of circRNAs. There are three types of circRNAs with ecRNAs accounting for the majority. CircRNAs have different action mechanisms, including (A) regulating the transcription of parental genes, (B) sponging miRNAs, (C) interacting with RBPs and (D) encoding proteins. CircRNAs can be translated into proteins in a cap-independent manner that is mediated by (E) IRESs or (F) m^6A modifications. CircRNA, circular RNA; miRNA, microRNA; RBP, RNA binding protein; Pol, polymerase; ecRNA, exonic circRNA; EIciRNA, exon-intron circRNAs; ciRNA, circular intronic RNA; IRES, internal ribosome entry sites; m^6A, N6-methyladenosine; YTHDF3, YTH domain family protein 3; eIF4, eukaryotic translation initiation factor 4.

components (13,16,19,69,70). Their specific roles in different cancer types are presented in Figs. 2-4 and Table II.

Glioma. Glioma, a malignant brain tumour, has a high mortality rate and is categorized into four grades (I, II, III, IV) according to the World Health Organization classification (71), with a higher grade indicating greater malignancy. Glioma frequently recurs after surgery and survival rates are markedly low. Among gliomas, glioblastoma (GBM), classified as a grade IV glioma, represents the most malignant subtype (72,73). GBM develops rapidly; it usually progresses from the initial stage to the late stage within a short period of time (only 3-6 months). CircRNAs have been demonstrated to affect glioma progression by encoding functional proteins or peptides (Fig. 2).

CircRNA F-box and WD repeat domain containing 7 (circFBXW7) generated from exons 3 and 4 of the *FBXW7* gene, was identified by deep RNA sequencing (RNA-seq) of clinical samples from patients with GBM (16). IRES-dependent translation of circFBXW7 generates a 185-aa protein named FBXW7-185aa. FBXW7-185aa overexpression induces cell cycle arrest and represses glioma cell proliferation, whereas knockdown of FBXW7-185aa exacerbates tumour symptoms. FBXW7-185aa competitively interacts with ubiquitin specific peptidase 28 (USP28) to degrade c-Myc via the ubiquitination pathway. The expression levels of circFBXW7 and FBXW7-185aa are both decreased in GBM tissues. High levels of circFBXW7 and FBXW7-185aa are associated with a more favourable prognosis. Altogether, these observations indicate the inhibitory role of the protein encoded by circFBXW7 in glioma progression by destabilization of c-Myc (16).

Long intergenic non-protein-coding RNA p53-induced transcript (LINC-PINT) is a long non-coding RNA with tumor-suppressive properties (74). Zhang *et al* (75) found a circRNA, circPINTexon2, that was generated from exon 2 of LINC-PINT. CircPINTexon2 has an active open reading frame (ORF) and contains an IRES. CircPINTexon2 can be translated to an 87-aa peptide named PINT87aa. Both PINT87aa and circPINTexon2 levels are lower in glioma tissues than in normal tissues. PINT87aa overexpression induces cell cycle arrest and inhibits tumour cell proliferation. Further experiments have revealed that circPINTexon2 acted as a tumor suppressor by encoding PINT87aa. Polymerase-associated factor complex (PAF1) participates in the recruitment of RNA Pol II and modulates the transcriptional elongation of multiple genes (76). PINT87aa directly interacts with PAF1 and suppresses the transcriptional elongation of numerous oncogenes. PINT87aa expression is negatively associated with the clinical prognosis of patients with glioma. Collectively, these results suggest that PINT87aa may function as a tumour suppressor and can serve as a therapeutic target (75).

Zhang *et al* (17) identified a circRNA with significantly decreased expression levels in GBM tissues by RNA-seq. This circRNA is generated from exons 26-29 of the SNF2

Table I. Databases for circRNA research.

Name	URL	Function
CircBase	http://www.circbase.org/	Collects the circRNA information of numerous species, such as humans, mice and *C.elegans*
CircNet	http://circnet.mbc.nctu.edu.tw/	Integrates the following information: Identification of new circRNAs, genome annotations of circRNAs, the expression profiles of circRNAs and the network of circRNA-miRNA-mRNA.
CircCode	https://github.com/PSSUN/CircCode	Predicts translated circRNAs.
CircPro	http://bis.zju.edu.cn/CircPro	Predicts and identifies circRNAs with coding potential.
CircRNADb	http://reprod.njmu.edu.cn/circrnadb	Summarizes IRES and ORF information of circRNAs that encode proteins; contains 32,914 human circRNAs.
ORF Finder	www.ncbi.nlm.nih.gov/gorf/gorf.html	Finds possible ORFs; deduces the translated amino acid sequence.
BLASTp	https://blast.ncbi.nlm.nih.gov/Blast.cgi?PROGRAM=blastp&PAGE_TYPE=BlastSearch&LINK_LOC=blasthome	Finds and compares protein sequences.
IRESbase	http://reprod.njmu.edu.cn/cgi-bin/iresbase/index.php	Summarizes functional IRESs from various species.
RESite	http://www.iresite.org	Presents information about the structures of experimentally studied IRESs.
DeepM6ASeq	https://github.com/rreybeyb/DeepM6ASeq	Predicts the situation of single-base m^6A; obtains the biological characteristics around the m6A site; visualizes the m6A site.
M6APred-EL	http://server.malab.cn/M6APred-EL/	Identifies m6A sites using ensemble learning.

CircRNA, circular RNA; miRNA, microRNA; IRES, internal ribosome entry sites; m^6A, N6-methyladenosine; ORF, open reading frame.

histone linker PHD RING helicase (*SHPRH*) gene and is named circ-SHPRH. Circ-SHPRH has one IRES and encodes a protein known as SHPRH-146aa. Both circ-SHPRH and SHPRH-146aa exhibit reduced levels in GBM cells. SHPRH-146aa upregulation reduces tumour cell proliferation and tumorigenicity. Proliferating cell nuclear antigen (PCNA) promotes cell proliferation (77). Full-length SHPRH protein functions as an E3 ligase that ubiquitinates PCNA for degradation (77). SHPRH-146aa may stabilize the level of full-length SHPRH and then promote the degradation of PCNA, thereby decreasing cell proliferation and tumorigenicity. In general, these findings indicate that circ-SHPRH encodes a protein, namely SHPRH-146aa, which acts as an inhibitor of GBM progression by protecting SHPRH from degradation (17).

Aerobic glycolysis can promote GBM pathogenesis (78). CircRNA HEAT repeat containing 5B (circHEATR5B), derived from exons 19-33 of the *HEATR5B* gene, is expressed at low levels in GBM cells and is capable of suppressing glycolysis in these cells (70). CircHEATR5B encodes an 881-aa protein (HEATR5B-881aa) in an IRES-dependent manner. HEATR5B-881aa overexpression suppresses the glycolytic process in GBM cells, whereas HEATR5B-881aa knockdown increases glucose consumption. Consequently, HEATR5B-881aa inhibits GBM cell proliferation. CircHEATR5B cannot suppress the glycolytic process and cell proliferation in the absence of HEATR5B-881aa, suggesting an essential role for HEATR5B-881aa in mediating the inhibitory effect of circHEATR5B on GBM cell proliferation. Jumonji-C domain-containing protein 5 (JMJD5), a protein that regulates metabolism (79), can interact with HEATR5B-881aa. HEATR5B-881aa phosphorylates JMJD5 to promote its degradation. HEATR5B-881aa upregulation decreases the JMJD5 level, and inhibits GBM cell glycolysis and proliferation. Therefore, circHEATR5B and HEATR5B-881aa function as suppressors in GBM tumorigenesis (70).

The receptor tyrosine kinase/phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K)/protein kinase B (AKT) pathway has a pivotal role in GBM progression (80,81). Circ-AKT3 is significantly downregulated in GBM tissues (82). Circ-AKT3 is an ecRNA originating from exons 3-7 of the *AKT3* gene. Circ-AKT3 has an ORF and an IRES that can initiate the translation of a 174-aa protein named AKT3-174aa. AKT3-174aa upregulation suppresses GBM cell proliferation, radioresistance and tumorigenicity, thus indicating its inhibitory role. The expression level of AKT3-174aa is positively associated with the overall survival rate of patients with GBM. AKT3-174aa interacts with activated (phosphorylated) 3-phosphoinositide-dependent kinase 1 and then inhibits the activation of AKT by reducing its phosphorylation at Thr308. Conclusively, these findings emphasize the antitumour role of AKT3-174aa in GBM pathogenesis by positively modulating the PI3K/AKT signalling pathway (82).

The epidermal growth factor receptor (EGFR) signalling pathway is important for GBM progression (83,84).

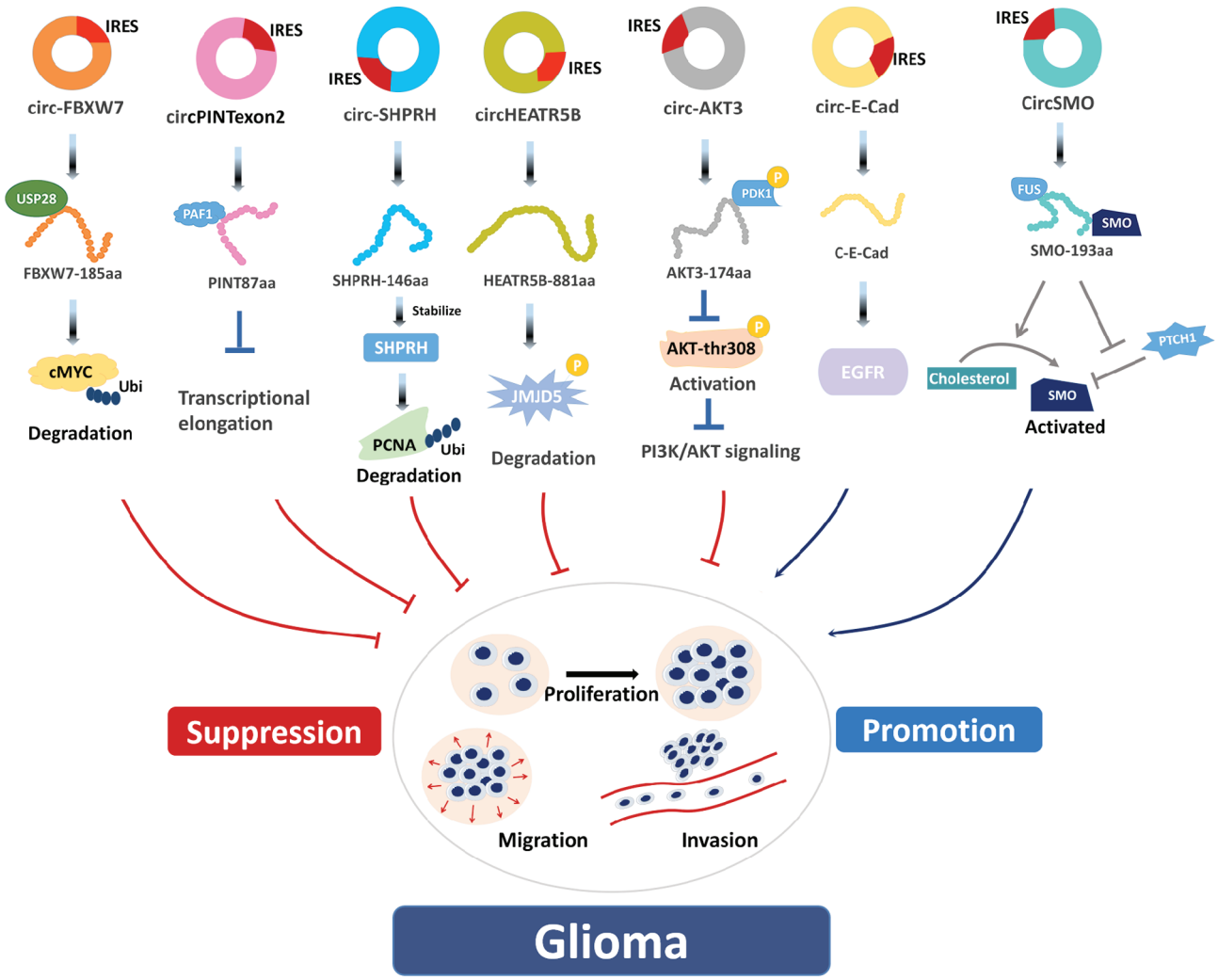

Figure 2. CircRNA-encoded proteins can regulate glioma pathogenesis. CircRNA-encoded proteins may act as targets of various proteins and then participate in glioma through different signalling pathways. CircRNA, circular RNA; IRES, internal ribosome entry sites; FBXW7, F-box and WD repeat domain containing 7; USP28, ubiquitin specific peptidase 28; PINT, p53-induced transcript; PAF1, polymerase-associated factor complex; SHPRH, SNF2 histone linker PHD RING helicase; PCNA, proliferating cell nuclear antigen; HEATR5B, HEAT repeat containing 5B; JMJD5, Jumonji-C domain-containing protein 5; AKT, protein kinase B; PDK1, 3-phosphoinositide-dependent kinase 1; EGFR, epidermal growth factor receptor; SMO, G protein-coupled-like receptor smoothened; PTCH1, patched homolog 1; FUS, fused in sarcoma.

Gao *et al* (85) identified a circRNA capable of encoding a protein that facilitates EGFR signalling pathway activity. By RNA-seq analysis, the authors identified circular E-cadherin (circ-E-Cad) RNA as the most upregulated circRNA. Circ-E-Cad RNA can be translated into a 254-aa protein named circRNA-encoded E-cadherin (C-E-Cad). C-E-Cad is highly expressed in cells and tissues from patients with GBM compared with control subjects. In addition, the C-E-Cad levels are negatively associated with the prognosis of patients with GBM. C-E-Cad worsens the symptoms of malignant GBM. Both C-E-Cad and circ-E-Cad levels are positively correlated with GBM cell stemness. C-E-Cad is soluble and can activate the EGFR signalling pathway by binding to the CR2 domain of EGFR, thereby promoting GBM tumorigenicity. EGFR-targeted treatments for GBM are ineffective, but the removal of C-E-Cad significantly enhances the antitumour activity of conventional anti-EGFR therapeutic strategies in GBM. Taken together, these findings indicate that C-E-Cad has an oncogenic role in GBM pathogenesis by activating the EGFR signalling pathway, thus paving a new way for GBM treatment (85).

The Hedgehog (HH) pathway is closely related to cancer progression (86,87). The G protein-coupled-like receptor smoothened (SMO) and glioma-associated oncoprotein Gli1 are key components of HH signalling (88). Wu *et al* (21) reported that circSMO, generated from exons 3-6 of the *SMO* gene, was highly expressed in GBM tissues. CircSMO contains an IRES and may be translated into a 193-aa protein termed SMO-193a.a. High SMO-193a.a levels may indicate poor prognosis. SMO-193a.a knockdown inhibits the self-renewal and decreases the proliferation and tumorigenicity of brain cancer stem cells, suggesting an oncogenic role of SMO-193a.a. SMO-193a.a knockdown also obviously reduces HH signalling activity. SMO-193a.a directly interacts with SMO to activate it. SMO-193a.a participates in the activation of SMO induced by sonic HH (Shh) through promoting SMO-mediated cholesterol modification and rescuing SMO from inhibition by patched homolog 1, a patched family transmembrane receptor.

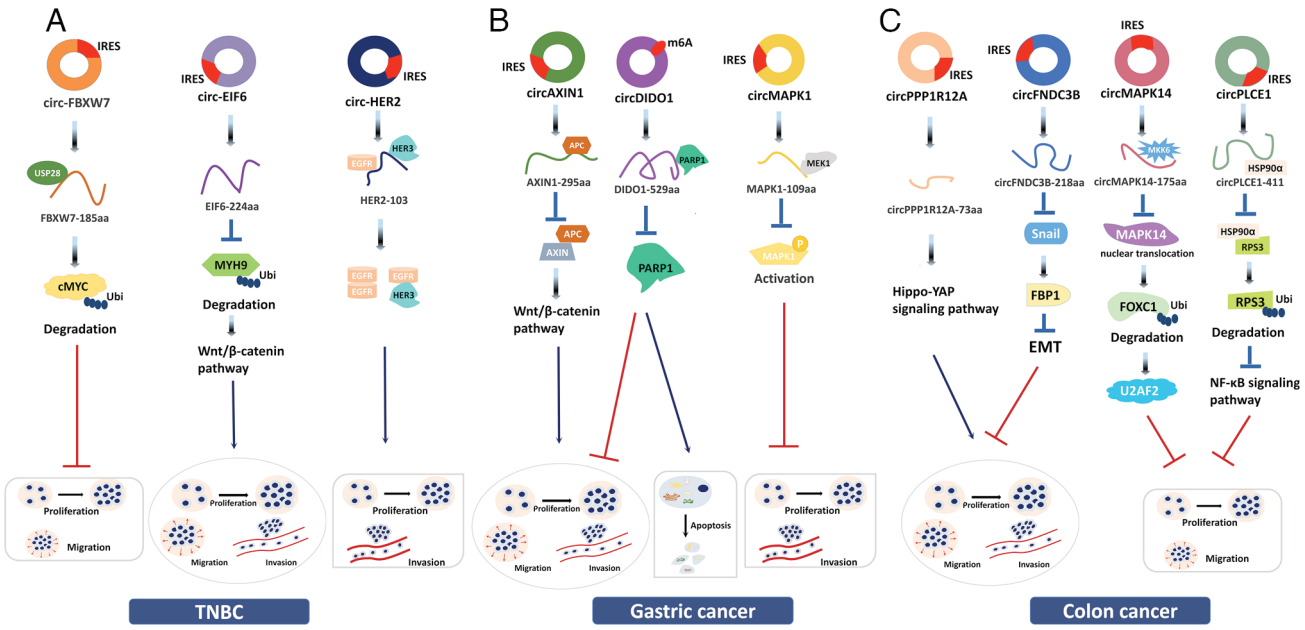

Figure 3. Roles of circRNA-encoded proteins in (A) TNBC, (B) gastric cancer and (C) colon cancer. CircRNA, circular RNA; IRES, internal ribosome entry sites; TNBC, triple-negative breast cancer; m^{6}A, N6-methyladenosine; EMT, epithelial to mesenchymal transition; ubi, ubiquitin; MYH9, myosin 9; HER2, human epidermal growth factor receptor 2; EGFR, epidermal growth factor receptor; APC, adenomatous polyposis coli; DIDO1, the death-inducer obliterator 1; PARP1, poly ADP-ribose polymerase 1; PRDX2, peroxiredoxin-2; MAPK, mitogen-activated protein kinase; MEK1, mitogen-activated protein kinase kinases 1; PPP1R12A, protein phosphatase 1, regulatory subunit 12a; YAP1, Yes-associated protein 1; FNDC3B, fibronectin type III domain-containing protein 3B; EMT, epithelial-mesenchymal transition; FBP1, fructose-1,6-bisphosphatase 1; MKK6, MAPK kinase 6; FOXC1, forkhead box C1 protein; U2AF2, U2 auxiliary factor; PLCE1, phospholipase C epsilon 1; RPS3, ribosomal protein S3; HSP90α, heat-shock protein 90α.

Importantly, SMO-193a.a is a direct target of fused in sarcoma (FUS), which is a direct transcriptional target of Gli1. Taken together, these findings demonstrate that SMO-193a.a. functions as an oncogenic protein and promotes GBM through the HH signalling axis-Shh/Gli1/FUS/SMO-193a.a/SMO (21).

Triple-negative breast cancer (TNBC). Breast carcinomas (BC) are heterogeneous tumours. TNBC is the subtype of BC with the poorest prognosis (89). Studies have shown that circRNAs may be translated into important proteins or peptides that influence TNBC progression (31,66,90) (Fig. 3A).

CircFBXW7 can encode a protein with 185 aa (FBXW7-185aa) via its IRES (16). FBXW7-185aa has been found to suppress gliomagenesis (16). Ye *et al* (31) explored the role of circFBXW7 in TNBC. The levels of circFBXW7 were reduced in patients with TNBC, while overexpression of circFBXW7 inhibited tumour progression. Furthermore, FBXW7-185aa may be produced in TNBC cells. FBXW7-185aa overexpression obviously hindered TNBC cell proliferation and migration (31). FBXW7-185aa upregulation may reverse the oncogenic effect of circFBXW7 downregulation. FBXW7-185aa promoted FBXW7 expression and facilitated c-Myc degradation via ubiquitination. USP28 had the opposite effect to that of FBXW7-185aa. Overall, these findings indicate that circFBXW7 and FBXW7-185aa can suppress TNBC development (31).

Li *et al* (66) identified a circRNA, circ-EIF6, whose expression was associated with poor prognosis in patients with TNBC. Circ-EIF6 can promote TNBC cell proliferation, migration and invasion. Circ-EIF6 encodes a novel peptide with 224 aa (EIF6-224aa) in an IRES-dependent manner. Both TNBC tissues and cell lines exhibit endogenous expression of EIF6-224aa. The oncogenic function of circ-EIF6 is dependent on EIF6-224aa (66). Myosin-9 (MYH9), known for its role in promoting BC pathogenesis, is a direct target of EIF6-224aa. EIF6-224aa participates in the ubiquitin-proteasome pathway, reducing the degradation of MYH9. Upregulation of MYH9 stimulates the Wnt/β-catenin pathway, thereby promoting tumorigenesis. Altogether, these observations show that circ-EIF6 has an oncogenic role in TNBC by encoding EIF6-224aa, which enhances the activity of the MYH9/Wnt/β-catenin signalling pathway (66).

Human epidermal growth factor receptor 2 (HER2) is an important target for TNBC treatment. Li *et al* (90) identified a circular RNA named circ-HER2, which is produced from exons 3-7 of the *HER2* gene by backsplicing. Circ-HER2 has an ORF that can be translated into a 103-aa protein driven by an IRES. This protein is denoted as HER2-103. Circ-HER2 and HER2-103 are expressed in ~30% of TNBC tissues and their levels are negatively correlated with prognostic efficacy. HER2-103 knockout suppresses TNBC cell proliferation, invasion and tumorigenicity. HER2-103 can directly interact with EGFR and HER3 to promote the formation of EGFR/EGFR homodimers or EGFR/HER3 heterodimers. This binding subsequently activates downstream signalling cascades to promote tumorigenesis. The majority of the HER2-103 sequences are identical to the HER2 CR1 domain, which can be targeted by pertuzumab, an antibody against HER2. Addition of pertuzumab reverses the tumour-promoting effect of HER2-103 overexpression, suggesting that HER2-103 is a possible clinical target for TNBC treatment (90).

Gastric cancer (GC). GC is a common malignancy with high morbidity and mortality. The pathological progression of GC

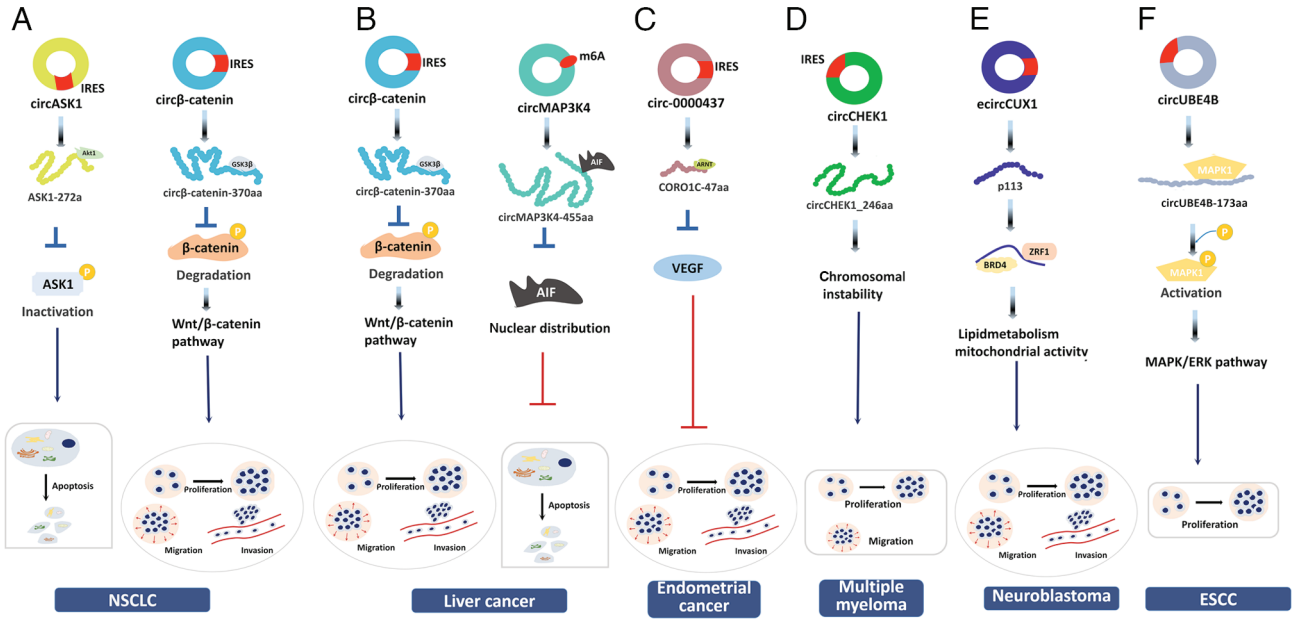

Figure 4. Roles of circRNA-encoded proteins in (A) NSCLC, (B) liver cancer, (C) endometrial cancer, (D) multiple myeloma, (E) neuroblastoma and (F) ESCC. NSCLC, non-small cell lung cancer; circRNA, circular RNA; IRES, internal ribosome entry sites; m6A, N6-methyladenosine; GSK3β, glycogen synthase kinase 3β; ASK1, apoptosis signal-regulating kinase 1; MAP3K4, mitogen-activated protein kinase kinase kinase 4; AIF, apoptosis-inducing factor; ARNT, aryl hydrocarbon receptor nuclear translocator; VEGF, vascular endothelial growth factor; CHEK1, checkpoint kinase 1; CUX1, CUT-like homeobox 1; ZRF1, Zuotin-related factor 1; BRD4, bromodomain protein 4; UBE4B, ubiquitination factor E4B; ERK, extracellular signal-regulated kinase.

is notably slow, often making early detection challenging (91). Therefore, patients with GC are frequently diagnosed at advanced stages, implying a generally poor prognosis. Consequently, the exploration of effective therapeutic targets and regulators is of great importance. Recent studies have shown that circRNAs can encode functional proteins to modulate GC pathogenesis (15,20,42) (Fig. 3B).

Adenomatous polyposis coli (APC)/AXIN is a regulatory complex that inhibits the Wnt/β-catenin signalling pathway (92). AXIN dysfunction results in the abnormal accumulation of β-catenin (92). CircAXIN1 is derived from exon 2 of the *AXIN* gene (20). Peng *et al* (20) found upregulated circAXIN1 expression in GC tissues. CircAXIN1 overexpression promotes GC cell proliferation, migration and invasion, whereas circAXIN1 downregulation suppresses gastric tumorigenesis. CircAXIN1 is able to encode a 295-aa protein (AXIN1-295aa) in a process dependent on an IRES. AXIN1-295aa directly interacts with the APC protein to block the interaction between AXIN1 and APC, thus abolishing the suppressive effect of the AXIN/APC complex on the Wnt/β-catenin pathway. This leads to the activation of the Wnt/β-catenin pathway, which, in turn, promotes gastric tumorigenesis. Therefore, circAXIN1 may promote gastric tumorigenesis via AXIN1-295aa (20).

The death-inducer obliterator 1 (*DIDO1*) gene has a role in apoptosis and regulates tumour development (93). CircDIDO1 is derived from exons 2-6 of the *DIDO1* gene. CircDIDO1 levels are decreased in GC tissues (43). A low circDIDO1 level indicates worse tumour symptoms and poor prognosis, indicating an oncogenic role of circDIDO1. CircDIDO1 can be translated into a 529-aa protein (DIDO1-529aa) with the help of m^6A modification. DIDO1-529aa upregulation suppresses GC cell proliferation, migration and invasion. Co-immunoprecipitation assays revealed an interaction between DIDO1-529aa and poly ADP-ribose polymerase 1 (PARP1), which is an apoptosis inhibitor. DIDO1-529aa upregulation reduces the PARP1 level, ultimately resulting in apoptosis. In addition, circDIDO1 may facilitate GC progression by inducing the ubiquitin-mediated degradation of peroxiredoxin-2 (PRDX2), a protein that promotes tumorigenesis (94,95). Taken together, the findings indicate that circDIDO1 can inhibit gastric tumorigenesis by encoding the DIDO1-529aa protein, which promotes PRDX2 degradation (43).

The mitogen-activated protein kinase (MAPK) signalling pathway is a classical signal transduction pathway that participates in cell proliferation, differentiation, metastasis and other processes (96). CircMAPK1, generated from exons 2-4 of the *MAPK1* gene, is downregulated in GC tissues and cell lines (15). A low circMAPK1 level suggests poor survival in patients with GC. CircMAPK1 may suppress GC cell proliferation and invasion *in vivo* and *in vitro*. With an ORF and an IRES, circMAPK1 can be translated into a 109-aa protein, MAPK1-109aa. MAPK1-109aa competitively interacts with MAPK kinase 1, an upstream kinase in the MAPK signaling pathway, and then inhibits MAPK1 phosphorylation, leading to the inactivation of MAPK1 and the downstream signalling pathway. Altogether, these observations indicate that circMAPK1 has an antitumour role in GC progression via its encoded protein MAPK1-109aa (15).

Colorectal cancer (CRC). CRC is a solid malignancy originating in the large intestine (97). Despite advances in therapeutic techniques, the metastasis and recurrence rates of CRC remain high. CircRNAs and the proteins they encode have emerged as crucial regulators of CRC pathogenesis, offering potential insight into prognosis (26,39,69) (Fig. 3C).

Table II. Functional roles of circRNA-encoded proteins in cancers.

Cancer type	Protein	Effect	Expression	Possible mechanisms	(Refs.)
Glioma	FBXW7-185aa	Suppression	Downregulated	Promotes cMyc degradation by ubiquitination	(16)
	PINT87aa	Suppression	Downregulated	Suppresses the transcriptional elongation of oncogenes	(75)
	SHPRH-146aa	Suppression	Downregulated	Promotes PCNA degradation by ubiquitination	(17)
	HEATR5B-881aa	Suppression	Downregulated	Promotes JMJD5 degradation by phosphorylation	(70)
	AKT3-174aa	Suppression	Downregulated	Suppresses the PI3K/AKT signalling pathway	(82)
	C-E-Cad	Promotion	Upregulated	Promotes EGFR signalling activation	(85)
	SMO-193aa	Promotion	Upregulated	Promotes HH signalling activation	(21)
Triple-negative breast cancer	FBXW7-185aa	Suppression	Downregulated	Promotes FBXW7 expression and c-Myc degradation	(31)
	EIF6-224aa	Promotion	Upregulated	Promotes Wnt/β-catenin pathway activation	(66)
	HER2-103	Promotion	Upregulated	Promotes activation of the EGFR pathway	(90)
Gastric cancer	AXIN1-295aa	Promotion	Upregulated	Promotes Wnt/β-catenin pathway activation	(20)
	DIDO1-529aa	Suppression	Downregulated	Promotes apoptosis and inhibits PRDX2 activity	(43)
	MAPK1-109aa	Suppression	Downregulated	Inhibits MAPK1 phosphorylation, to inactivate the MAPK1 pathway	(15)
Colorectal cancer	circPPP1R12A-73aa	Promotion	Upregulated	Promotes activation of theHippo-YAP signalling pathway	(25)
	circFNDC3B-218aa	Suppression	Downregulated	Suppresses the Snail-FBP-EMT axis	(26)
	circMAPK14-175aa	Suppression	Downregulated	Promotes the degradation of FOXC1 through ubiquitination	(69)
	circPLCE1-411	Suppression	Downregulated	Suppresses NF-κB signalling	(39)
Non-small-cell lung cancer	circβ-catenin-370aa	Promotion	Upregulated	Promotes the β-catenin signalling pathway	(13)
	ASK1-272a	Suppression	Downregulated	Promotes the ASK1 signalling pathway	(108)
Liver cancer	CircMAP3K4-455aa	Promotion	Upregulated	Suppresses nuclear distribution of AIF	(110)
	circβ-catenin-370aa	Promotion	Upregulated	Promotes the β-catenin signalling pathway	(111)
Endometrial cancer	CORO1C-47aa	Suppression	Downregulated	Suppresses VEGF expression	(19)
Multiple myeloma	circCHEK1_246aa	Promotion	Upregulated	Promotes chromosomal instability	(32)
Neuroblastoma	p113	Promotion	Upregulated	Promotes the p113/ZRF1/BRD4 pathway	(118)
Esophageal squamous cell carcinoma	circUBE4B-173aa	Promotion	Upregulated	Activates the MAPK/ERK pathway	(122)

CircRNA, circular RNA; HH, hedgehog; YAP, Yes-associated protein; FBXW7, F-box and WD repeat domain containing 7; PCNA, proliferating cell nuclear antigen; JMJD5, Jumonji-C domain-containing protein 5; PI3K, phosphatidylinositol 3-kinase; AKT, protein kinase B; PDK1, 3-phosphoinositide-dependent kinase 1; EGFR, epidermal growth factor receptor; HH, Hedgehog; HER2, human epidermal growth factor receptor 2; PRDX2, peroxiredoxin-2; MAPK, mitogen-activated protein kinase; YAP1, Yes-associated protein 1; EMT, epithelial-mesenchymal transition; FBP1, fructose-1,6-bisphosphatase 1; FOXC1, forkhead box C1 protein; ASK1, apoptosis signal-regulating kinase 1; AIF, apoptosis-inducing factor; VEGF, vascular endothelial growth factor; ZRF1, zuotin-related factor 1; BRD4, bromodomain protein 4; ERK, extracellular signal-regulated kinase.

Zheng *et al* (25) carried out a circRNA microarray analysis using CRC and control tissues, and identified hsa_circ_0000423 as the most upregulated circRNA. Hsa_circ_0000423 is derived from exons 24 and 25 of the protein phosphatase 1, regulatory subunit 12a (*PPP1R12A)* gene, and is also named circPPP1R12A. CircPPP1R12A expression is significantly increased in CRC tissues and cell lines. CircPPP1R12A encodes a 73-aa protein, named circPPP1R12A-73aa. CircPPP1R12A-73aa enhances CRC cell proliferation and metastasis. Yes-associated protein 1 (YAP1), a transcriptional activator of the Hippo-YAP signalling pathway, is essential for cancer cell proliferation and metastasis (98). CircPPP1R12A-73aa can interact with YAP1 and other proteins in the Hippo-YAP signalling pathway. YAP1 knockdown attenuates the oncogenic effect of circPPP1R12A-73aa on CRC cells, suggesting that circPPP1R12A-73aa promotes CRC tumorigenesis by activating the Hippo-YAP signalling pathway (25).

Fibronectin type III domain-containing protein 3B (FNDC3B) is associated with cell migration (99). CircFNDC3B, generated from exons 5 and 6 of the *FNDC3B* gene, has been implicated in various cancer types (14,100). CircFNDC3B can encode a protein (14), although the specific functions of this protein are still unknown. Pan *et al* (26) reported the role of circFNDC3B as a translation template in CRC development. CircFNDC3B is downregulated in CRC tissues and cell lines. Lower levels of circFNDC3B are associated with poor overall survival. Overexpression of circFNDC3B suppresses CRC cell proliferation, migration and invasion. CircFNDC3B may be translated into a 218-aa protein, called circFNDC3B-218aa, which exerts inhibitory effects on CRC cell proliferation, invasion and migration. Snail is a transcription factor known to induce epithelial-mesenchymal transition (EMT) by reducing fructose-1,6-bisphosphatase 1 (FBP1) expression (24,101). Mechanistic exploration has shown that circFNDC3B-218aa can suppress the expression of the Snail protein, resulting in FBP1 upregulation and EMT inhibition in CRC cells. Overall, these observations suggest that circFNDC3B-218aa may have a tumour-suppressive role in CRC pathogenesis through the Snail-FBP-EMT axis (26).

MAPK14, a key member of the MAPK family, has pivotal roles in CRC (102). CircMAPK14 is generated from exons 4-10 of the *MAPK14* gene. CircMAPK14 levels are markedly reduced in CRC samples (69). Overexpression of circMAPK14 inhibits CRC cell proliferation and migration. CircMAPK14 contains an IRES that drives the translation of a 175-aa protein (circMAPK14-175aa). CircMAPK-175aa abolishes tumorigenicity and blocks the metastasis of CRC cells. CircMAPK14-175aa can interact with MAPK kinase 6 to reduce the nuclear translocation of MAPK14, thus promoting the degradation of FOXC1 protein through ubiquitination. FOXC1 suppresses the transcription of U2 auxiliary factor (U2AF2). U2AF2 can bind to *MAPK14* introns and promote circMAPK14 expression. Thus, a positive feedback loop is formed: CircMAPK14-175aa inhibits FOXC1 activity to upregulate U2AF2. In turn, higher U2AF2 levels promote the formation of circMAPK14 and the translation of circMAPK14-175aa. In summary, these results indicate that circMAPK14 and circMAPK14-175aa suppress CRC progression by regulating FOXC1 and U2AF2 activity (69).

Through RNA-seq analysis, Liang *et al* (39) found that the levels of circRNA phospholipase C epsilon 1 (PLCE1) were significantly lower in CRC tissues than in normal control tissues. Lower circPLCE1 levels are positively associated with poor overall survival in patients with CRC, indicating its potential as a prognostic biomarker. CircPLCE1 overexpression suppresses the proliferation and migration of CRC cells. CircPLCE1 is generated from exon 2 of the *PLCE1* gene and encodes a 411-aa protein whose translation is driven by an IRES. The expression levels of circPLCE1-411 are decreased in most CRC tissues. CircPLCE1-411 can regulate the NF-κB signalling pathway, which is known to promote CRC development and progression (103,104). Ribosomal protein S3 (RPS3) is the most important regulator of the NF-κB pathway. Heat-shock protein (HSP)90α interacts with RPS3 to form the RPS3/HSP90α complex, which inhibits the ubiquitin-dependent degradation of RPS3 (105,106). CircPLCE1-411 binds to HSP90α to mediate the dissociation of the HSP90α/RPS3 complex. The released RPS3 is degraded by ubiquitination. Subsequently, the NF-κB signalling pathway is inhibited, leading to the suppression of colorectal tumorigenesis. Therefore, circPLCE1 serves as a tumour suppressor by encoding the protein circPLCE1-411 to suppress the NF-κB signalling pathway (39).

Lung cancer. Non-small cell lung cancer (NSCLC) is the most prevalent and malignant type of lung cancer, with high mortality and morbidity due to its high metastasis and recurrence rates (107). CircRNAs are important regulators of NSCLC pathogenesis (1). Recent studies have revealed that the proteins or peptides encoded by circRNAs also participate in NSCLC progression (13,108) (Fig. 4A).

Zhao *et al* (13) found that circβ-catenin was involved in NSCLC formation. Circβ-catenin expression is upregulated in NSCLC tissues. Circβ-catenin overexpression promotes NSCLC cell proliferation, migration and invasion. The oncogenic effect of circβ-catenin in NSCLC is mediated through the activation of the Wnt/β-catenin pathway. Circβ-catenin encodes a 370-aa peptide (circβ-catenin-370aa) driven by an IRES. Circβ-catenin-370aa can bind to glycogen synthase kinase (GSK)3β to inhibit the GSK3β-mediated phosphorylation of β-catenin, thus stimulating the Wnt/β-catenin pathway. Therefore, circβ-catenin promotes NSCLC by encoding a peptide that increases the activity of the Wnt/β-catenin signalling pathway (13).

Lung adenocarcinoma (LUAD) is a major histological type of NSCLC (30). Apoptosis signal-regulating kinase 1 (ASK1) induces apoptosis and regulates the stress response by activating the c-Jun N-terminal kinase and p38 signalling pathways (109). Gefitinib is a clinical therapeutic agent used to treat LUAD, but resistance to this drug is an important clinical challenge. CircASK1 and its encoded protein, ASK1-272aa, can participate in acquired gefitinib resistance in LUAD (108). CircASK1 is derived from exons 2-7 of the *ASK1* gene and is markedly downregulated in gefitinib-resistant LUAD cells. Decreased circASK1 expression contributes to gefitinib resistance in LUAD cells. CircASK1 encodes a 272-aa protein, ASK1-272aa, whose sequence is similar to that of the ASK1 protein. ASK1-272aa levels are reduced in gefitinib-resistant LUAD cells. ASK1-272aa upregulation enhances the gefitinib sensitivity of LUAD cells. ASK1-272aa competitively binds to Akt1 to release ASK1 from phosphorylation-mediated inactivation. Activated ASK1 enhances ASK1-mediated apoptosis in LUAD cells and increases the sensitivity of LUAD cells to

gefitinib (108). In general, these observations demonstrate that circASK1 can decrease gefitinib resistance in LUAD cells via ASK1-272aa (108).

Liver cancer. Liver cancer is a devastating cancer type with a poor prognosis. The lack of techniques for early diagnosis, the limited therapeutic options and chemotherapeutic resistance make the treatment of liver cancer difficult. CircRNAs and their encoded proteins or peptides have emerged as important regulators in liver cancer progression (110,111) (Fig. 4B).

Hepatocellular carcinoma (HCC) is a type of primary liver cancer. CircMAP3K4, generated from exon 3 of the MAPK kinase kinase 4 (*MAP3K4*) gene, is upregulated in HCC (110). Higher levels of circMAP3K4 indicate poor overall survival. CircMAP3K4 can be translated into a 455-aa peptide, circMAP3K4-455aa via m^6A modification. CircMAP3K4-455aa promotes HCC development *in vivo* and *in vitro*. Apoptosis-inducing factor (AIF), a regulator of cell survival and death, can interact with circMAP3K4-455aa. Such interaction reduces the nuclear distribution of AIF and suppresses cisplatin-induced HCC cell apoptosis. Therefore, circMAP3K4-455aa enhances HCC progression by influencing AIF activity (110).

Circβ-catenin and its encoded protein circβ-catenin-370aa can promote the progression of liver cancer (111). Circβ-catenin is significantly upregulated in liver cancer tissues. Circβ-catenin-370aa interacts with GSK3β to abolish the GSK3β-mediated degradation of β-catenin, thereby promoting Wnt/β-catenin signalling. Activation of the Wnt/β-catenin signalling pathway enhances liver cancer progression (111).

Endometrial cancer (EC). EC is a common malignant tumour in women that accounts for 1-2% of cancer-associated mortalities (107,112). Li *et al* (19) conducted deep RNA-seq on human EC tissue samples and identified a circRNA (circ-0000437) that was involved in EC progression (Fig. 4C). Circ-0000437 is significantly downregulated in EC samples and does not function as a miRNA sponge. Circ-0000437 encodes a 47-aa peptide (named CORO1C-47aa) in the presence of an IRES. CORO1C-47aa overexpression suppresses angiogenesis in EC through inhibiting the proliferation, migration and differentiation of endothelial cells. CORO1C-47aa interacts with the aryl hydrocarbon receptor nuclear translocator (ARNT) protein, which is related to hypoxia (113). CORO1C-47aa competes with transforming acidic coiled-coil-containing protein 3, a co-activator of the vascular endothelial growth factor (VEGF) promoter, for binding to ARNT to suppress VEGF activation, thereby inhibiting angiogenesis in EC. Thus, CORO1C-47aa has an antitumour role in EC pathogenesis by decreasing VEGF expression (19).

Multiple myeloma (MM). MM originates in the bone marrow. MM is different from solid tumours, as it is a plasma cell malignancy. MM is difficult to cure and the mortality rate is markedly high (114). Checkpoint kinase 1 (CHEK1) facilitates MM development (115,116). CHEK1 overexpression promotes MM cell proliferation and macrophage-osteoclast differentiation, and enhances the drug resistance of MM cells, thus having an oncogenic role (32). CircCHEK1 is derived from the *CHEK1* gene and can be translated into a functional protein called circCHEK1_246aa in an IRES-dependent manner (Fig. 4D). Chromosomal instability is related to cell proliferation. CircCHEK1_246aa overexpression in MM cells results in chromosomal instability, thereby promoting MM cell proliferation. Furthermore, macrophage-osteoclast differentiation is enhanced. Taken together, these findings indicate that CHEK1 and circCHEK1_246aa are promising therapeutic targets in MM (32).

Neuroblastoma (NB). NB is a sympathetic nervous system tumour that originates at the neural crest and is one of the most malignant life-threatening tumours in children. CUT-like homeobox 1 (CUX1) is a homeodomain transcription factor that regulates the pathogenesis of numerous tumours (117). CUX1 can produce a circRNA, termed ecircCUX1 (118) (Fig. 4E). In an IRES-mediated manner, ecircCUX1 is translated into a 113-aa protein (p113) that is upregulated in NB samples. p113 facilitates lipid metabolism, increases mitochondrial activity and promotes NB cell proliferation, migration and metastasis. EcircCUX1 exacerbates NB cell tumour symptoms via p113. p113 functions by directly binding to Zuotin-related factor 1 (ZRF1) and bromodomain protein 4 (BRD4) to form a transcriptional regulatory complex. The activity of the p113/ZRF1/BRD4 complex increases the levels of lipid metabolism-related proteins to induce lipid metabolic reprogramming and mitochondrial complex I activity, thereby increasing the tumorigenesis and aggressiveness of NB cells. Disassociation of the p113-ZRF1 complex attenuates NB pathogenesis. High levels of p113, ZRF1 and BRD4 indicate poor overall survival in patients with NB. Overall, these results indicate that the ecircCUX1-encoded protein has an oncogenic role in NB through the formation of the p113/ZRF1/BRD4 complex (118).

Esophageal squamous cell carcinoma (ESCC). ESCC is one of the invasive malignant cancers with the highest mortality rate (36,119). The 5-year survival rate of patients with ESCC is <50%. Understanding the mechanisms underlying ESCC development and exploring potential biological predictors are of great importance. Emerging evidence implicates circRNAs in ESCC pathogenesis (120,121). In a recent study, Lyu *et al* (122) conducted a microarray analysis and identified a circRNA with protein coding potential, named circUBE4B (Fig. 4F). CircUBE4B is formed from exons 6-9 of the ubiquitination factor E4B (*UBE4B*) gene. CircUBE4B is upregulated in ESCC tissues. High expression of circUBE4B is negatively associated with the overall survival rate of patients with ESCC. CircUBE4B contains an IRES that facilitates the translation of a novel 173-aa protein (circUBE4B-173aa), whose elevated expression in ESCC indicates poor prognosis. Overexpression of circUBE4B-173aa promotes the proliferation of ESCC cells. CircUBE4B-173aa is involved in the MAPK pathway, which functions in tumorigenesis (123). Further investigations reveal that circUBE4B-173aa can bind to MAPK1 to phosphorylate MAPK1, leading to the subsequent activation of the MAPK/extracellular signal-regulated kinase (ERK) pathway. *In vivo* experiments also demonstrate that circUBE4B-173aa overexpression enhances tumor growth. Collectively, all of

these findings indicate that circUBE4B-encoded protein promotes ESCC by interacting with MAPK1 to activate the MAPK/ERK pathway (122).

6. Conclusion and future perspectives

The characteristics of circRNAs, such as their unique conformation and stability, have attracted numerous researchers to develop technologies based on circRNAs (124,125). The high stability and specific expression of circRNAs make them promising candidate diagnostic and prognostic biomarkers. CircRNAs can be employed in the development of circRNA-based aptamers or sensors to modulate various intracellular pathways (126). CircRNAs containing IRESs/m^6A modifications are translatable, implying their potential as expression vectors to initiate the production of diverse proteins. There have been some patents that confirm the roles of circRNAs as effective vectors/carriers for vaccines. In comparison to linear RNA (mRNA) vaccines, circRNA vaccines exhibit higher stability and reduced susceptibility to degradation. Of note, during the COVID-19 pandemic, scientists developed circRNA vaccines aimed at enabling enhanced and more enduring antigen production (127).

CircRNA-encoded proteins/peptides hold significant potential for extensive clinical applications in cancer, such as early diagnosis, drug development, prognosis and treatment. Based on the antigen-antibody interaction principle, a rapid test strip method has been developed for early diagnosis, including early pregnancy, COVID-19 detection and H1N1 detection strips. This method offers non-invasive, fast and convenient (only several drops of urine or nasal mucus are needed) diagnostic options, facilitating a quick preliminary diagnosis at home. The prospect of constructing distinct circRNA-encoded protein/peptide strips for diagnosing various cancer types seems feasible. In the realm of cancer therapy, precise treatment and targeting are crucial. The limited number of effective target drugs is mainly due to low target specificity, which highlights the need for more precise approaches. Compared with nucleotide targets, protein targets are more specific. Developing precision antitumour drugs targeting proteins or peptides translated from circRNAs may yield highly selective and minimally toxic therapeutic effects. Despite their potential, challenges must be addressed before clinical implementation.

First, the rapid degradation of multiple circRNA-encoded proteins or peptides results in low abundance (48). This adds to the difficulty of their clinical application. Second, the understanding of circRNA translation mechanisms is still insufficient. Many underlying mechanisms are unclear and need further exploration. Third, there is a lack of a uniform naming method for proteins or peptides translated from circRNAs, making research findings across different laboratories confusing. Therefore, more efforts should be made to overcome these limitations. Future studies should provide new insight and ideas for clinical applications.

In summary, circRNA-encoded proteins or peptides have crucial roles in numerous signalling pathways and are thus important factors in cancer pathogenesis. The aforementioned findings open up new avenues for cancer diagnosis and therapeutic strategies.

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Authors' contributions

LZ drafted the manuscript. HG and XL edited the manuscript. FY revised the manuscript. LZ and PL conceived the idea of the review and performed the final proofreading. All authors have read and approved the final manuscript. Data authentication is not applicable.

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Competing interests

The authors declare that they have no competing interests.

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