Role of circular RNA as competing endogenous RNA in ovarian cancer (Review)

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Abstract. Circular RNA (circRNA), a type of non-coding RNA, plays a regulatory role in biological processes. The special loop structure of circRNA makes it highly stable and specific in diseased tissues and cells, especially in tumors. Competing endogenous RNAs (ceRNAs) compete for the binding of microRNA (miRNA) at specific binding sites and thus regulate gene expression. ceRNAs play an important role in various diseases and are currently recognized as the most prominent mechanism of action of circRNAs. circRNAs can modulate the proliferation, migration, invasion and apoptosis of tumor cells through the ceRNA mechanism. With further research, circRNAs may serve as novel markers and therapeutic targets for ovarian cancer (OC). In the present review, the research progress of circRNAs as ceRNAs in OC was summarized, focusing on the effects of the circRNA/miRNA/mRNA axis on the biological functions of OC cells through mediating pivotal signaling pathways. The role of circRNAs in the diagnosis, prognostic assessment and treatment of OC was also discussed in the present review.

Contents

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1. Introduction

Ovarian cancer (OC) is the most lethal tumor of the female genital system, and caused an estimated 13,270 deaths in the USA in 2023 (1). The poor prognosis of OC is largely attributed to the insidious onset of the disease leading to a delayed diagnosis. Furthermore, the pathogenesis of OC has not been well characterized. The known risk factors of OC include genetic, hormonal, reproductive and lifestyle-related factors (2). At present, surgery and chemotherapy are the standard treatment modalities for OC (3). Chemotherapy is the first-choice treatment for advanced and recurrent OC, which includes conventional platinum-based drugs and paclitaxel, targeted anti-angiogenic drugs, poly (ADP-ribose) polymerase inhibitors and immunotherapy (4). Despite the efficacy of these drugs, the 5-year survival rate of patients with OC remains low, which is 50% in USA (1). Therefore, the identification of novel therapeutic targets for OC is imperative.

Circular RNAs (circRNAs) are highly conserved and stable structures that may serve as novel diagnostic and prognostic biomarkers, as well as chemotherapeutic targets, in the context of tumors (5). The proposed concept of competing endogenous RNA (ceRNA) illustrates a new mechanism of post-transcriptional gene regulation. The phenomenon wherein non-coding RNA (ncRNA) sequester microRNAs (miRNAs) and remove the inhibition of their targets was initially observed in both plant and animal cells (6,7). This phenomenon is the core mechanism of ceRNAs. circRNAs can act as ceRNAs (8), and certain studies have identified numerous circRNAs as potential prognostic biomarkers and therapeutic targets for OC (9,10). The present review aims to discuss current knowledge on the molecular mechanisms by which circRNAs, through miRNA sponging, influence the pathobiology of OC. Furthermore, the present review highlights the clinical applicability of circRNAs as predictive markers and therapeutic targets in OC.

2. circRNA

ncRNAs refer to the RNA molecules that do not encode proteins transcribed from the genome (11). circRNAs belong to the class of regulatory ncRNAs and have both the commonality of ncRNAs and a unique structure and function. circRNAs were first found in viroids by Sanger *et al* (12) over 40 years ago and were shown to have a covalently closed

loop structure, initially thought to be the aberrant product of mis-splicing (13). The loop structure formed by the reversed splicing of circRNA results in the absence of a 5' cap or 3' poly A tail (14). This confers high stability to the molecular structure of circRNA. circRNAs can exist and accumulate in specific cells for long periods due to their ability to avoid digestion by RNA enzymes (15). Most circRNAs are located in the cytoplasm. circRNAs are significantly enriched in the brain, human platelets, during epithelial-mesenchymal transition (EMT) and during the differentiation of hematopoietic progenitor cells into lymphoid and myeloid cells (16).

circRNAs can be categorized based on the composition of exons and introns as follows: Exonic circRNA (ecircRNA), intronic circRNA and exon-intron circRNA (17). ecircRNAs are reported to function in the circRNA sponging of miRNA (18). There are four main mechanisms of circRNAs: i) Sponging miRNA (19); ii) binding to diverse RNA binding proteins (20) or acting as a protein sponge; iii) regulating transcription (21); and iv) participating in the translation progress (22). The generation and mechanism of circRNAs is presented in Fig. 1. The ability of circRNAs to act as ceRNAs has been verified in a number of diseases such as neurological diseases, cardiovascular diseases and tumors, as well as in the context of the immune response (such as the antivirus and antitumor response) (23-26). Functionally, circRNAs have been observed to exert oncogenic or tumor-suppressive effects. At the cellular level, they are instrumental in modulating processes such as proliferation, migration, invasion, apoptosis and chemoresistance (27). *In vivo* studies, particularly those utilizing animal models, have demonstrated that circRNAs influence tumor growth and metastasis (28,29). Moreover, akin to other ncRNAs such as miRNAs (30,31), circRNAs are emerging as vital prognostic and diagnostic biomarkers for a multitude of diseases such as neurologic diseases (32), diabetic complications (33) and tumors (34).

3. ceRNA

ceRNA mechanism. The ceRNA hypothesis has been proposed to describe the mechanism by which ncRNAs that harbor miRNA response elements (MREs) can sequester miRNAs from other targets that share the same MREs, thereby regulating their expression (35). Specifically, ncRNAs competitively bind to miRNAs to reduce the inhibition of mRNA and regulate the corresponding gene expression. Long ncRNAs (lncRNAs), mRNAs, pseudogenic RNAs and circRNAs can act as ceRNAs, among which circRNAs have the strongest binding ability to miRNA, and therefore may be the main type of ncRNAs participating in observed oncogenic effects.

Interaction of circRNAs and miRNAs. The resulting effect of an interaction between circRNAs and miRNAs depends on the number of binding sites among them (36). The higher the number of competitive binding sites, the greater the potential of a circRNA to act as a ceRNA. ciRS-7 is the most well-known ceRNA, has >70 conserved miR-7 binding sites and has high levels of stable expression in the brain (37). Generally, circRNAs that act as ceRNAs negatively regulate miRNA. This implies that when the expression of circRNAs, which act as ceRNAs, increases, the expression of miRNA is reduced (38) and vice versa. The presence of miRNA binding sites on a circRNA does not necessarily imply that it will inhibit miRNA, as whether a circRNA negatively or positively regulates miRNA is related to the stoichiometric relationship between the MREs in the potential sponge and the target mRNA (39).

ceRNA network and tumors. A number of studies have demonstrated the role of circRNAs in respiratory system (40), digestive system (41,42) and female reproductive system tumors (43,44). circRNAs can be upregulated or downregulated in tumors, which regulates mRNA expression in tumor cells by regulating miRNA. ceRNAs of malignant tumors competitively bind to miRNAs in the MREs of the 3' untranslated region (UTR) (35). 3'UTR shortening caused by the reduction of MREs alters the ability of ceRNAs to compete for miRNAs and function as ceRNAs. In a study by Sang *et al* (45), hsa_circ_0025202 was found to act as a ceRNA in breast cancer by sponging miR-182-5p, further regulating the expression and activity of FOXO3a. Moreover, functional studies demonstrated that hsa_circ_0025202 suppresses tumorigenesis and improves sensitivity to tamoxifen via the miR-182-5p/FOXO3a axis. In a study by Wang *et al* (46), has-circRNA-002178 was found to enhance programmed death-ligand 1 expression in lung cancer cells by sponging miR-34, which induced T cell failure. In addition, hsa_circRNA_104348 may act as a ceRNA to promote the progression of hepatocellular carcinoma by targeting the miR-187-3p/rhotekin2 axis and activating the Wnt/β-catenin pathway (47). In conclusion, circRNAs play important roles as ceRNAs in tumors and influence the biological activity of tumor cells.

4. Biological functions of circRNAs as ceRNAs in OC

Cell proliferation. Cell growth is a critical factor in the proliferation of tumors and sustained growth is one of the key attributes of malignant tumors. Proliferation of normal cells in the human body is closely regulated; however, tumor cells evade this regulation and achieve sustained proliferation through four mechanisms: i) Autocrine growth signals; ii) stimulation of normal cells to secrete growth signals; iii) increase in receptor expression and therefore amplification of growth signals; and iv) altered receptor structure, resulting in receptor activation (48). The studies described below demonstrate that circRNAs can act as ceRNAs, sponging miRNAs as well as targeting mRNAs to affect cell proliferation (Fig. 2A).

The cell cycle, which spans from the conclusion of one cell division to the completion of the next, is a critical phase during which circRNAs can exert influence. circ-BNC2 can inhibit the transition of OC cells from the G0/G1 phase into the G2/M phase through the miR-223-3p/F-box/WD repeat-containing protein 7 axis (49). The circUBAP2/miR-382-5p/pre-mRNA-processing-splicing factor 8 axis is another regulatory pathway inducing G0/G1 phase arrest (50). Additionally, circPVT1 promotes OC cell viability through the miR-149-5p/forkhead box protein M1 (FOXM1) pathway (51). Furthermore, circ_0013958, found to be upregulated in OC, targets plexin-B2 (PLXNB2) via miR-637 sponging, promoting OC proliferation (52). PLXNB2 mediates intracellular RNA processing and contributes to cell proliferation and survival (53).

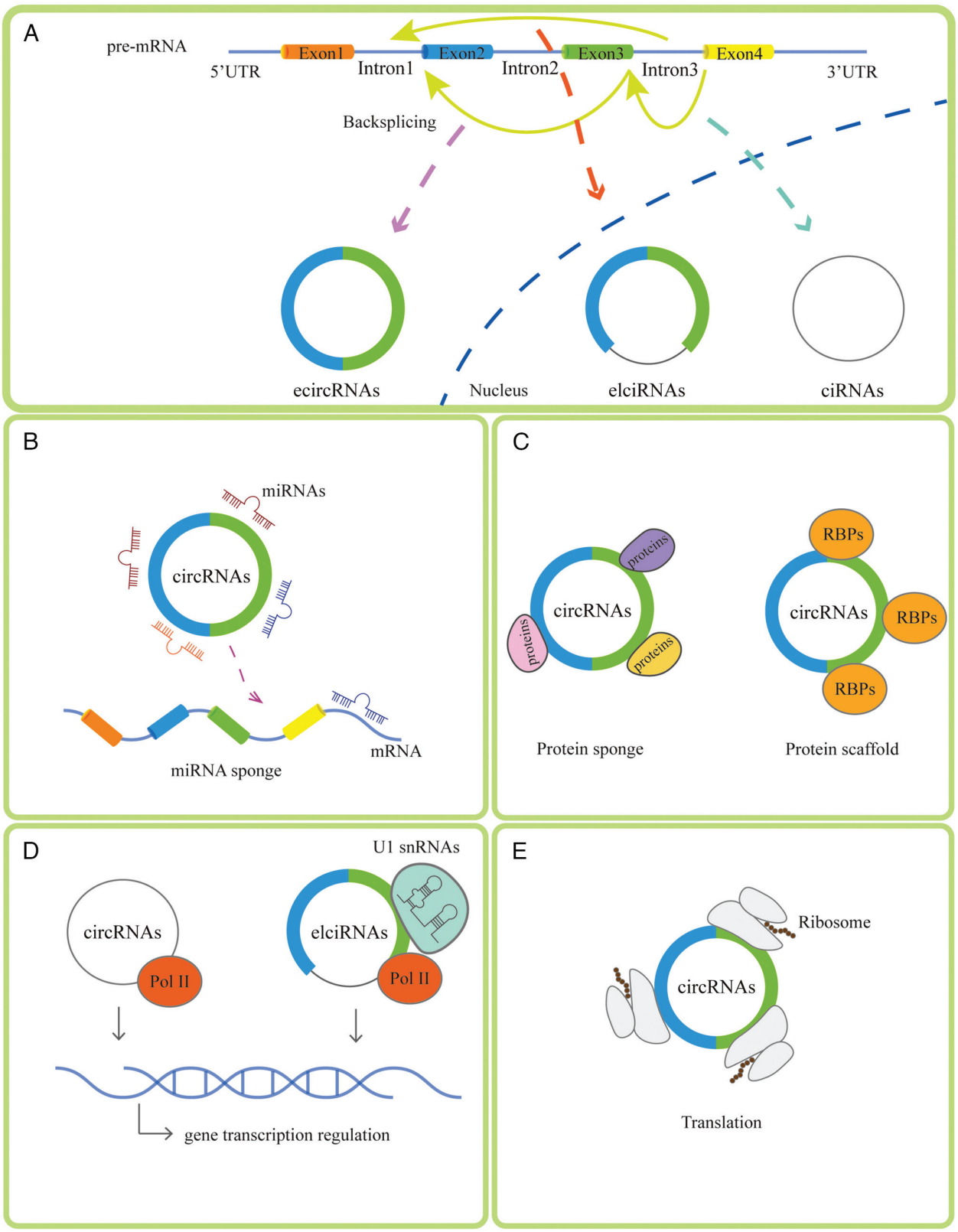

Figure 1. Formation and mechanism of circRNA. (A) circRNA formation and classification. (B) circRNA sponges miRNA to regulate the targeted mRNA. (C) circRNA interacts with protein as a protein sponge (left) or a protein scaffold (right). (D) circRNA is involved in transcription regulation. (E) circRNA is involved in translation. circRNA, circular RNA; ecircRNA, exonic circRNA; elciRNA, exon-intron circRNA; miRNA, microRNA; RBPs, RNA binding proteins; snRNA, small nuclear RNA; UTR, untranslated region.

Autophagy. Autophagy is an evolutionarily conserved, self-degrading, normal cellular metabolic process. Cells can degrade harmful intracellular components to ensure normal cell growth and operation via autophagy. As such, autophagy is a mechanism with a dual role in both the apoptosis and survival of cells. Autophagic levels can be assessed in studies by

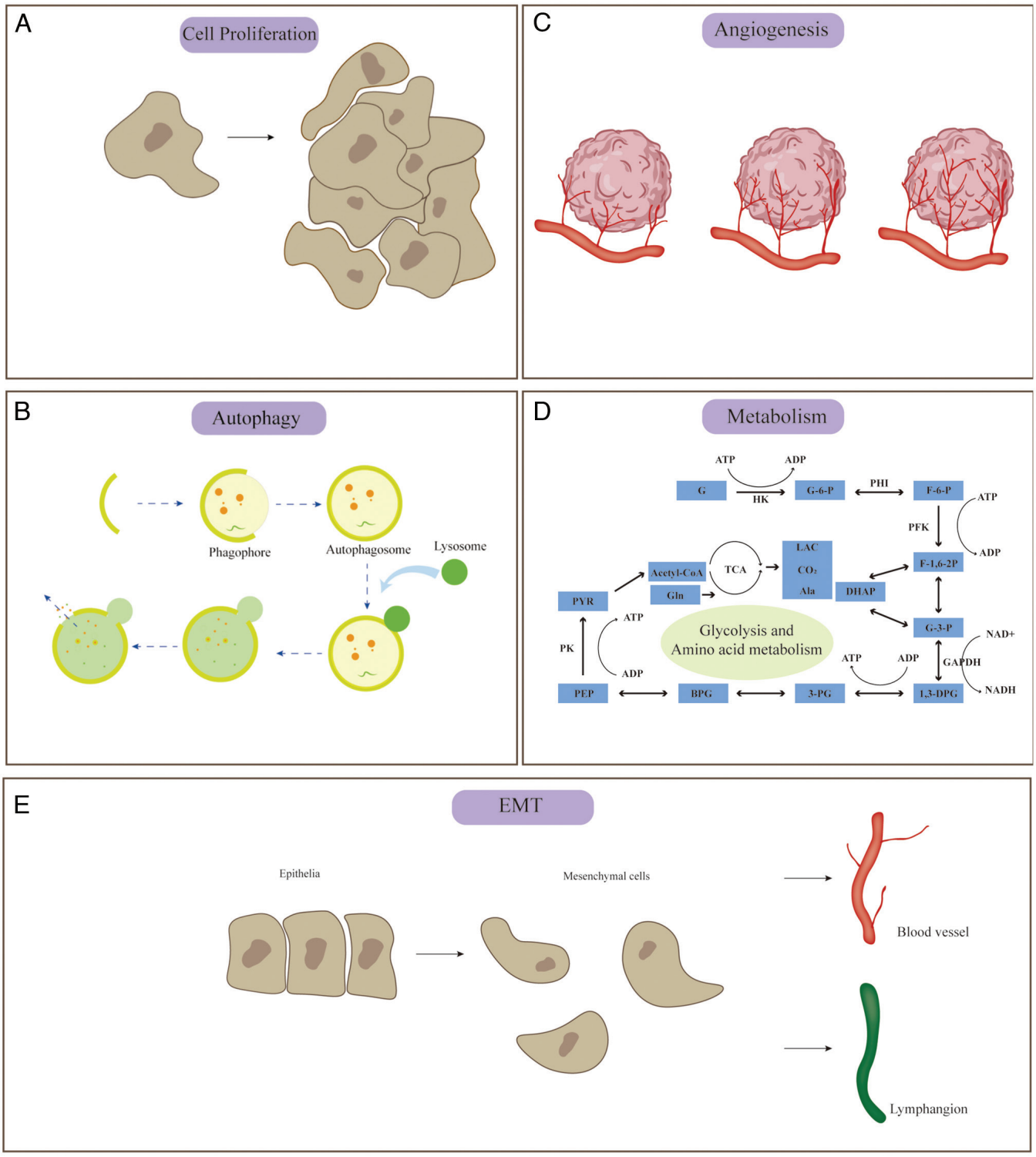

Figure 2. Mechanisms of circRNA as a competing endogenous RNA to affect cellular functions in ovarian cancer. circRNA in (A) cell proliferation, (B) angiogenesis, (C) autophagy, (D) metabolism and (E) EMT. circRNA, circular RNA; EMT, epithelial-mesenchymal transition; G, glucose; G-6-P, glucose-6-phosphate; HK, hexokinase; ATP, adenosine triphosphate; ADP, adenosine diphosphate; PHI, phosphohexose isomerase; F-6-P, fructose-6-phosphate; PFK, phospho fructo kinase; F-1,6-2P, fructose-1,6-biophosphate; DHAP, dihydroxyacetone phosphate; G-3-P, glyceraldehyde-3-phosphate; GAPDH, glyceraldehyde-3-phosohate dehydrogenase; NAD^+, nicotinamide adenine dinucleotide; 1,3-DPG, 1,3-biphodpho-glycerate; 3-PG, 3-phosoho-glycerate; BPG, 2-phosphoglycerate; PEP, phosphoenolpyruvate; PK, pyruvate kinase; PYR, pyruvic acid; Acetyl-CoA, acetyl coenzyme A; Gln, glutamine; TCA, triose carbonate cycle; LAC, lactic acid; Ala, alanine.

detecting proteins such as autophagy-related gene (ATG), LC3, p62 and Beclin1 (54). circRNAs regulate autophagy-related proteins to mediate autophagy (55). The studies demonstrating that circRNAs can act as ceRNAs, sponging miRNAs as well as targeting mRNAs, to affect cellular autophagy are described below (Fig. 2B).

CircRAB11FIP1, which is upregulated in OC, has been implicated in targeting ATG7 and ATG14 by sponging

miR-129, and therefore engaging in the autophagic process (56). Meanwhile, circRAB11FIP1 also directly binds to desmocollin 1 to mediate autophagy. It has been demonstrated that circMUC16 is upregulated in OC tissues compared with normal ovary tissues, which inhibits the autophagy flux of OC (57). The assessment of autophagic flux in the aforementioned study was based on the expression of Beclin1, a key autophagy-related factor active in the initial stages of autophagy. circRNF144B has been shown to sponge miR-342-3p, thereby regulating F-box and leucine-rich repeat protein 11 (FBXL11) and influencing the ubiquitination and subsequent degradation of Beclin1 (58). The autophagy of OC can be inhibited through the circRNF144B/miR-342-3p/FBXL11 axis. In summary, although all three aforementioned circRNAs are upregulated in OC, they exhibit divergent effects on autophagy; while circMUC16 and circRNF144B suppress autophagy, circRAB11FIP1 enhances ATG expression and promotes the autophagic pathway.

Angiogenesis. Angiogenesis is a physiological process wherein capillary or post-capillary veins form following neovascularization. circRNAs are notably abundant in angiogenesis-related diseases, which indicates an association between circRNA and angiogenesis. The studies described below demonstrate that circRNAs can act as ceRNAs, sponging miRNAs as well as targeting mRNAs, to affect angiogenesis (Fig. 2C).

Tumor angiogenesis is largely dependent on vascular endothelial growth factor A (VEGFA)-driven responses, which largely contribute to dysregulation of vascular function (59). circATRNL1 targets Smad4 by sponging miR-378, which mediates the AKT signaling pathway and inhibits cell proliferation, migration and invasion, and is involved in anti-angiogenesis in OC (60). Angiogenesis is affected by the restoration of Smad, which downregulates the expression of VEGF and upregulates the expression of thrombospondin-1 to inhibit angiogenesis (61). In addition, circASH2L silencing was found to inhibit the invasion and growth of OC cells and to inhibit the angiogenesis and lymphangiogenesis of transplanted tumors via the miR-665/VEGFA axis (62). Furthermore, circ_0061140 is elevated in OC tissues and cells, and promotes proliferation, migration, invasion and angiogenesis through the miR-761/leucine zipper-EF-hand containing transmembrane protein 1 axis (63).

EMT. EMT is a highly complex phenotypic transition during embryonic development that drives tissue formation and is important for tumor metastasis (64). EMT is also a cause of tumor progression and poor prognosis in patients with cancer. A study has suggested that circRNAs are associated with EMT transcription factors (such as snail, vimentin and twist) and EMT-related signaling pathways (such as the TGF-β/Smad and Wnt signaling pathways) (65). The studies described below demonstrate that circRNAs can act as ceRNAs, sponging miRNAs as well as targeting mRNAs, to affect EMT (Fig. 2E).

EMT can be assessed via the detection of EMT-related proteins such as E-cadherin, N-cadherin and Vimentin (65). circPLEKHM3 mediates OC cell migration and EMT by sponging miR-9 and targeting BRCA1/DNAJ homolog subfamily B member 6 (DNAJB6)/Krüppel-like factor 4 (KLF4) (66). BRCA1, DNAJB6 and KLF4 contribute to the metastasis of tumors. GATA binding protein 3 mediates BRCA1 to suppress EMT, inhibiting the metastasis of breast cancer (67). DNAJB6, a member of HSP40 family, inhibits the EMT of tumors (68). KLF4 activates the expression of epithelial genes, playing a notable role in EMT (69). circCELSR1 targets bromodomain-containing protein 4 (BRD4) by sponging miR-598 to promote the EMT of OC cells (70). BRD4 also inhibits EMT in renal cell carcinoma (71). In summary, circRNAs mediate the EMT of OC cells by targeting EMT-related mRNA. circFGFR3 (72), circPTK2 (73), ciRS-7 (74) and hsa_circ_0061140 (75) all regulate downstream genes to promote EMT in OC (76-79).

Metabolism. Tumor metabolism mainly includes glucose, lipid and amino acid metabolism. Tumor cells mainly produce nutrients through aerobic glycolysis to maintain the basal cellular requirements for upregulated proliferation. The 'Warburg effect' is a process in which tumor cells convert glucose to lactate in the presence of oxygen (80). It is considered that circRNAs are associated with lipid metabolism in hepatocytes, adipocytes and macrophages (81). Glutamine is an essential source of energy for cell survival, and tumor cells will overtake glutamine to maintain abnormal cell growth. A previous study has indicated that ncRNAs can regulate tumor metabolism and thus participate in the biological functions of tumors (82). The studies described below demonstrate that circRNAs can act as ceRNAs, sponging miRNAs as well as targeting mRNAs, to affect tumor metabolism (Fig. 2D).

circRNAs have a significant impact on glycolysis in OC. For example, circITCH has been shown to attenuate cell proliferation, invasion and glycolysis in OC through the miR-106a/E-cadherin axis (83). Additionally, has_circ_0002711 facilitates aerobic glycolysis via the miR-1244/Rho-associated protein kinase 1 pathway in OC (84). circ_0025033 targets LSM4 through the sponging of miR-184 to promote glycolytic metabolism in OC (85). Furthermore, LSM4 is closely associated with cell cycle, cell replication, focal adhesion and multiple metabolism-related pathways, including fatty acid metabolism, in hepatocellular carcinoma (86). Moreover, silencing circ_0023033 enhances glutamine metabolism in OC (87). However, the role of circRNA in the regulation of lipid metabolism within tumors remains to be thoroughly investigated. The role of circRNAs as ceRNAs in OC is shown in Fig. 2.

5. Clinical applications of circRNAs as ceRNAs in OC

Prognostic biomarkers. Due to the highly stable and specific expression of circRNAs in OC, certain circRNAs may serve as useful diagnostic and prognostic biomarkers. A study demonstrated that circ-ABCB10 may help distinguish OC tissue from adjacent tissue, affirming its value as a diagnostic biomarker [area under the curve (AUC)=0.766; 95% confidence interval (CI), 0.690-0.842] (88). circBNC2 has also demonstrated value in distinguishing OC tissue from benign ovarian cysts [receiver operating characteristic (ROC) AUC=0.879; 95% CI, 0.822-0.937; sensitivity, 96.4%; specificity, 80.7%] (89). Plasma circN4BP2L2 expression significantly differentiated OC tissue from benign ovarian tumor tissue (ROC AUC=0.82; sensitivity, 72%; specificity, 87%) and from normal ovarian tissue (ROC

Table I. circRNA-related signaling pathways in ovarian cancer progression.

First author, year	circRNA	Regulation	Axis	Signaling pathway	Biological process	(Refs.)
Gong *et al*, 2020	circ9119	↓	miR-21-5p/PTEN	AKT signaling pathway	Proliferation, apoptosis	(103)
Wang *et al*, 2021	circATRNL1	↓	miR-378/Smad	AKT signaling pathway	Proliferation, invasion, migration, angiogenesis	(60)
Zhang *et al*, 2019	circPLEKHM3	↓	miR-9/BRCA1/ DNAJB6/KLF4	AKT1 signaling pathway Wnt/β-catenin signaling pathway	Proliferation, migration	(66)
Guo *et al*, 2020	Has_circ_0000714	↑	miR-370-3p/RAB17	CDK6/RB signaling pathway	Proliferation, PTX resistance	(104)
Ji *et al*, 2022	Has_circ_0001756	↑	IGF2BP2-RAB5A	EGFR/MAPK signaling pathway	Proliferation, invasion, EMT	(105)
Zhang *et al*, 2020	circPGAM1	↑	miR-542-3p/CDC5L/ PEAK1	ERK1/2 signaling pathway, JAK signaling pathway	Proliferation, invasion, migration, apoptosis	(106)
He *et al*, 2022	circAHNAK	↓	miR-28/EIF2B5	JAK2/STAT3 signaling pathway	Proliferation, invasion, migration, apoptosis, EMT	(107)
Lu *et al*, 2021	circVPS13C	↑	miR-145	MEK/ERK signaling pathway	Proliferation, cell cycle, invasion, migration, apoptosis	(108)
Fu *et al*, 2023	circFAM169A	↓	miR-160a-5p, miR-519d-3p/RPS6KA2	p38/MAPK signaling pathway	Proliferation	(109)
Wang *et al*, 2021	Has_circ_0000745	↑	miR-3187-3p/ERBB4	PI3K/AKT signaling pathway	Proliferation, invasion, migration, stemness	(110)
Wu *et al*, 2022	circFBXO7	↓	miR-96-5p/MTSS1	Wnt/β-catenin signaling pathway	Proliferation, migration	(111)
Lin *et al*, 2021	circABCB10	↑	miR-1271/Capn4	Wnt/β-catenin signaling pathway	Proliferation, invasion, apoptosis	(112)
Wu *et al*, 2023	Hsa_circ_0001445	↓	miR-576-5p/SFRP1	Wnt/β-catenin signaling pathway	Proliferation, invasion, migration	(113)

PTEN, phosphatase and tensin homolog; Smad, small mothers against decapentaplegic; BRCA1, breast cancer gene 1; DNAJB6, DnaJ heat shock protein family (Hsp40) member B6; KLF4, Kruppel-like factor 4; RAB17, member RAS oncogene family; IGF2BP2, insulin like growth factor 2 mRNA binding protein 2; JAK, Janus kinase; RAB5A, member RAS oncogene family; CDC5L, cell division cycle 5-like protein; PEAK1, pseudopodium enriched atypical kinase 1; RPS6KA2, S6 kinase ribosomal protein S6 kinase 2; ERBB4, erb-b2 receptor tyrosine kinase 4; MTSS1, metastasis suppressor 1; Capn4, calpain small subunit 1; circRNA, circular RNA; EMT, epithelial-mesenchymal transition; miR, microRNA.

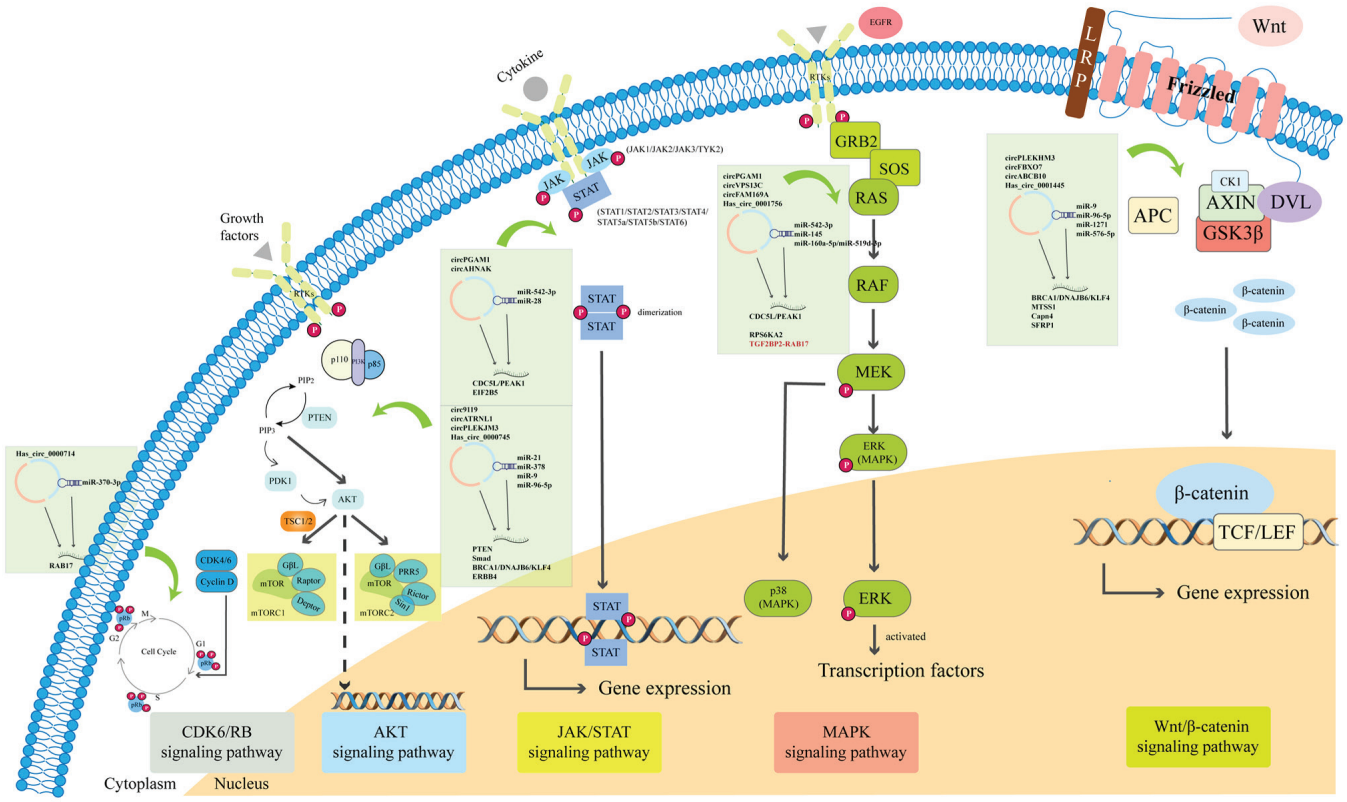

Figure 3. circRNA-related signaling pathways in ovarian cancer. circRNA, circular RNA. LRP, lipoprotein Receptor-Related Protein; APC, adenomatous polyposis coli; CK1, Casein kinase 1; DVL, dishevelled; GSK3β, Glycogen synthase kinase 3; AXIN, axis inhibition; TCF, T-cell factor; LEF, lymphoid enhancer factor; EGFR, epidermal growth factor receptor; RTKS, receptor tyrosine kinase; GRB2, growth factor receptor-bound protein 2; SOS, son of sevenless; JAK, Janus kinase; PIP2, phosphatidylinositol 4,5-bisphosphate; PIP3, phosphatidylinositol 3,4,5-triphosphate; PTEN, phosphatase and tensin homolog; PDK1, 3-phosphoinositide-dependent protein kinase-1; TSC1/2, tuberous sclerosis complex; mTOR, mammalian target of rapamycin; PRR5, proline rich 5; RB, retinoblastoma protein.

AUC=0.90; sensitivity, 77%; specificity, 88%) (90). In addition, high expression of circ-ABCB10 was associated with significantly decreased overall survival (OS) time in patients with OC [hazard ratio (HR)=2.994; P<0.05] (88), and high expression of circ-ITCH was associated with a significantly longer OS in patients with OC (HR=0.207; 95% CI, 0.066-0.065; P<0.05) (83). A recent study has also demonstrated specific expression of circRNAs in the blood (91). Therefore, this non-invasive test (just withdrawing blood) may provide portability in detecting circRNAs as tumor markers in the future, meaning that it would not be necessary to obtain pathological tissue through invasive methods to detect circRNA.

Therapeutic targets. The aforementioned studies indicate that circRNAs play an important role in the progression of OC. Therefore, circRNAs may also act as molecular targets for targeted therapy, in which the target circRNA is overexpressed or knocked down to affect tumor progression or drug resistance, thus impacting patient treatment outcomes. Upregulation of circEXOC6B tends to imply an earlier TNM stage, less lymph node metastasis and a higher survival rate, and is associated with decreased paclitaxel resistance in OC (92). Conversely, circ_0061140 is known to enhance paclitaxel resistance by sponging miR-136 and targeting chromobox 2, showing significant upregulation of circ_0061140 in paclitaxel-resistant OC tissues and cells (93). circ_0025033 targets FOXM1 by sponging miR-532-3p, and circ_0025033 is significantly upregulated in paclitaxel-resistant cells of OC (94). Furthermore, downregulation of circ_0025033 in the exosomes of paclitaxel-resistant cells inhibits the malignant effects of OC cells. circTNPO3 and circCELSR1 have also been implicated in paclitaxel resistance, sponging miR-1299 and miR-1252, respectively, to target NIMA related kinase 2 and FOXR2 in OC, respectively (16,95). Resistance to cisplatin (DDP), another cornerstone in OC chemotherapy, has also been associated with circRNAs. Downregulation of circ_0067934 was shown to decrease DDP resistance in OC (96), while overexpression of circFoxp1 was associated with increased DDP drug resistance (97). In addition, circ-LPAR3 promotes DDP resistance by sponging miR-634 and targeting pyruvate dehydrogenase kinase 1 in OC (98). The aforementioned studies have therefore demonstrated that circRNAs may be used as therapeutic targets in OC, to affect drug resistance such as for the two classic chemotherapy drugs, paclitaxel and DDP. Beyond OC, circRNAs synthesized *in vitro* have shown promise in gastric cancer treatment strategies by sponging miRNAs to target genes (99). This insight verifies the possibility of circRNAs, functioning as ceRNAs, as targeted therapeutic markers in the management of OC.

6. Signaling pathways involving circRNAs in OC

As aforementioned, circRNAs mediate biological processes, including proliferation, migration and invasion,

in various diseases through regulating signaling pathways. The signaling pathways mainly include Notch, janus kinase (JAK)/STAT, Wnt/β-catenin, TGF-β/Smad and AMP-activated protein kinase signaling pathways (100). Wang *et al* (101) demonstrated that differential circRNAs in the serum of 20 patients with OC were enriched in Fcγ R-mediated phagocytosis, VEGF signaling, transcriptional misregulation in cancer, chemokine signaling, ErbB signaling and TNF signaling pathways, according to a Kyoto Encyclopedia of Genes and Genomes analysis. Recent studies have demonstrated that circRNAs mainly participate in the Wnt/β-catenin, AKT, MAPK, JAK/STAT and CDK/retinoblastoma protein signaling pathways in OC (Table I). The specific signaling pathways involving circRNAs are presented in Fig. 3.

7. Conclusions and outlook

In recent years, the role of circRNAs in tumors has become a research hotspot. In OC, circRNAs are mainly studied extensively as ceRNAs. circRNAs affect the proliferation, invasion, migration and apoptosis of OC cells through sponging miRNA and subsequently modulating the target genes, thus changing the clinical course of solid tumors. circRNAs can also regulate OC progression through mediating autophagy, angiogenesis, the cell cycle, EMT and metabolism. Autophagy, a process with dichotomous roles in tumor promotion and suppression, requires further investigation to elucidate its dual regulatory mechanisms within the OC context. Currently, research regarding circRNA-mediated metabolism mainly focuses on glycometabolism and amino acid metabolism, and lipid/nuclear acid metabolism is rarely involved. circRNAs mainly participate in the Wnt/β-catenin, AKT and MAPK signaling pathways. Moreover, circRNAs may serve as valuable predictive markers and therapeutic targets for OC. In addition, recent studies have not only focused on the downstream mechanisms of circRNAs, but also on the upstream mechanisms. One study found that circRNAs also play a role in the tumor microenvironment, which is involved in the immunotherapy of tumors (102). circUHRF1, secreted by hepatocellular hepatoma cells in exosomes, is involved in immunosuppression by inducing natural killer cell dysfunction. Moreover, overexpression of circUHRF1 was found to decrease the effect of anti-programmed cell death 1 (PD-1) drug therapy, while the targeting of circUHRF1 restored the sensitivity of anti-PD1 therapy (102). However, this research is still in the nascent phase and requires further exploration. In view of the research described in the present review, circRNAs have a certain prospect as biomarkers and therapeutic targets not only in OC but also in other tumors and diseases.

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Availability of data and materials

Not applicable.

Authors' contributions

NX, QW and WLY contributed to the study conception and design, material preparation, literature collection and conclusion. The first draft of the manuscript was written by YML and WLY, and all authors commented on subsequent versions of the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Siegel RL, Miller KD, Wagle NS and Jemal A: Cancer statistics, 2023. CA Cancer J Clin 73: 17-48, 2023.
2. La Vecchia C: Ovarian cancer: Epidemiology and risk factors. Eur J Cancer Prev 26: 55-62, 2017.
3. Kuroki L and Guntupalli SR: Treatment of epithelial ovarian cancer. BMJ 371: m3773, 2020.
4. Armstrong DK, Alvarez RD, Backes FJ, Bakkum-Gamez JN, Barroilhet L, Behbakht K, Berchuck A, Chen LM, Chitiyo VC, Cristea M, *et al*: NCCN guidelines® insights: Ovarian cancer, version 3.2022. J Natl Compr Canc Netw 20: 972-980, 2022.
5. Meng S, Zhou H, Feng Z, Xu Z, Tang Y, Li P and Wu M: Circrna: Functions and properties of a novel potential biomarker for cancer. Mol Cancer 16: 94, 2017.
6. Franco-Zorrilla JM, Valli A, Todesco M, Mateos I, Puga MI, Rubio-Somoza I, Leyva A, Weigel D, García JA and Paz-Ares J: Target mimicry provides a new mechanism for regulation of microRNA activity. Nat Genet 39: 1033-1037, 2007.
7. Ebert MS, Neilson JR and Sharp PA: MicroRNA sponges: Competitive inhibitors of small RNAs in mammalian cells. Nat Methods 4: 721-726, 2007.
8. Tang X, Ren H, Guo M, Qian J, Yang Y and Gu C: Review on circular RNAs and new insights into their roles in cancer. Comput Struct Biotechnol J 19: 910-928, 2021.
9. Ding J, Wang Q, Guo N, Wang H, Chen H, Ni G and Li P: CircRNA circ_0072995 promotes the progression of epithelial ovarian cancer by modulating miR-147a/CDK6 axis. Aging (Albany NY) 12: 17209-17223, 2020.
10. Guan X, Zong ZH, Liu Y, Chen S, Wang LL and Zhao Y: circPUM1 promotes tumorigenesis and progression of ovarian cancer by sponging miR-615-5p and miR-6753-5p. Mol Ther Nucleic Acids 18: 882-892, 2019.
11. Mattick JS and Makunin IV: Non-coding RNA. Hum Mol Genet 15: R17-R29, 2006.
12. Sanger HL, Klotz G, Riesner D, Gross HJ and Kleinschmidt AK: Viroids are single-stranded covalently closed circular RNA molecules existing as highly base-paired rod-like structures. Proc Natl Acad Sci USA 73: 3852-3856, 1976.
13. Cocquerelle C, Mascrez B, Hétuin D and Bailleul B: Mis-splicing yields circular RNA molecules. FASEB J 7: 155-160, 1993.
14. Jeck WR and Sharpless NE: Detecting and characterizing circular RNAs. Nat Biotechnol 32: 453-461, 2014.
15. Suzuki H and Tsukahara T: A view of pre-mRNA splicing from RNase R resistant RNAs. Int J Mol Sci 15: 9331-9342, 2014.

16. Zhang S, Cheng J, Quan C, Wen H, Feng Z, Hu Q, Zhu J, Huang Y and Wu X: circCELSR1 (hsa_circ_0063809) contributes to paclitaxel resistance of ovarian cancer cells by regulating FOXR2 expression via miR-1252. Mol Ther Nucleic Acids 19: 718-730, 2020.
17. Wang F, Nazarali AJ and Ji S: Circular RNAs as potential biomarkers for cancer diagnosis and therapy. Am J Cancer Res 6: 1167-1176, 2016.
18. Yang X, Mei J, Wang H, Gu D, Ding J and Liu C: The emerging roles of circular RNAs in ovarian cancer. Cancer Cell Int 20: 265, 2020.
19. Hansen TB, Wiklund ED, Bramsen JB, Villadsen SB, Statham AL, Clark SJ and Kjems J: miRNA-dependent gene silencing involving Ago2-mediated cleavage of a circular antisense RNA. EMBO J 30: 4414-4422, 2011.
20. Huang A, Zheng H, Wu Z, Chen M and Huang Y: Circular RNA-protein interactions: Functions, mechanisms, and identification. Theranostics 10: 3503-3517, 2020.
21. Qu S, Yang X, Li X, Wang J, Gao Y, Shang R, Sun W, Dou K and Li H: Circular RNA: A new star of noncoding RNAs. Cancer Lett 365: 141-148, 2015.
22. Panda AC, Grammatikakis I, Munk R, Gorospe M and Abdelmohsen K: Emerging roles and context of circular RNAs. Wiley Interdiscip Rev RNA 8: 10.1002/wrna.1386, 2017.
23. Su Q and Lv X: Revealing new landscape of cardiovascular disease through circular RNA-miRNA-mRNA axis. Genomics 112: 1680-1685, 2020.
24. Su L, Li R, Zhang Z, Liu J, Du J and Wei H: Identification of altered exosomal microRNAs and mRNAs in Alzheimer's disease. Ageing Res Rev 73: 101497, 2022.
25. Zhang J, Luo Q, Li X, Guo J, Zhu Q, Lu X, Wei L, Xiang Z, Peng M, Ou C and Zou Y: Novel role of immune-related non-coding RNAs as potential biomarkers regulating tumour immunoresponse via MICA/NKG2D pathway. Biomark Res 11: 86, 2023.
26. Lu S, Zhu N, Guo W, Wang X, Li K, Yan J, Jiang C, Han S, Xiang H, Wu X, *et al*: RNA-Seq revealed a circular RNA-microRNA-mRNA regulatory network in hantaan virus infection. Front Cell Infect Microbiol 10: 97, 2020.
27. Yang X, Ye T, Liu H, Lv P, Duan C, Wu X, Jiang K, Lu H, Xia D, Peng E, *et al*: Expression profiles, biological functions and clinical significance of circRNAs in bladder cancer. Mol Cancer 20: 4, 2021.
28. Najafi S: Circular RNAs as emerging players in cervical cancer tumorigenesis; A review to roles and biomarker potentials. Int J Biol Macromol 206: 939-953, 2022.
29. Najafi S: The emerging roles and potential applications of circular RNAs in ovarian cancer: A comprehensive review. J Cancer Res Clin Oncol 149: 2211-2234, 2023.
30. Fattahi M, Shahrabi S, Saadatpour F, Rezaee D, Beyglu Z, Delavari S, Amrolahi A, Ahmadi S, Bagheri-Mohammadi S, Noori E, *et al*: microRNA-382 as a tumor suppressor? Roles in tumorigenesis and clinical significance. Int J Biol Macromol 250: 125863, 2023.
31. Pordel S, Khorrami M, Saadatpour F, Rezaee D, Cho WC, Jahani S, Aghaei-Zarch SM, Hashemi E and Najafi S: The role of microRNA-185 in the pathogenesis of human diseases: A focus on cancer. Pathol Res Pract 249: 154729, 2023.
32. Najafi S, Aghaei Zarch SM, Majidpoor J, Pordel S, Aghamiri S, Fatih Rasul M, Asemani Y, Vakili O, Mohammadi V, Movahedpour A and Arghiani N: Recent Insights into the roles of circular rnas in human brain development and neurologic diseases. Int J Biol Macromol 225: 1038-1048, 2023.
33. Xu YX, Pu SD, Li X, Yu ZW, Zhang YT, Tong XW, Shan YY and Gao XY: Exosomal ncRNAs: Novel therapeutic target and biomarker for diabetic complications. Pharmacol Res 178: 106135, 2022.
34. Wang Y, Liu J, Ma J, Sun T, Zhou Q, Wang W, Wang G, Wu P, Wang H, Jiang L, *et al*: Exosomal circRNAs: Biogenesis, effect and application in human diseases. Mol Cancer 18: 116, 2019.
35. Karreth FA and Pandolfi PP: ceRNA cross-talk in cancer: When ce-bling rivalries go awry. Cancer Discov 3: 1113-1121, 2013.
36. Salmena L, Poliseno L, Tay Y, Kats L and Pandolfi PP: A ceRNA hypothesis: the Rosetta Stone of a hidden RNA language? Cell 146: 353-358, 2011.
37. Hansen TB, Jensen TI, Clausen BH, Bramsen JB, Finsen B, Damgaard CK and Kjems J: Natural RNA circles function as efficient microRNA sponges. Nature 495: 384-388, 2013.
38. Lan C, Peng H, Hutvagner G and Li J: Construction of competing endogenous RNA networks from paired RNA-seq data sets by pointwise mutual information. BMC Genomics 20 (Suppl 9): S943, 2019.
39. Kristensen LS, Andersen MS, Stagsted LVW, Ebbesen KK, Hansen TB and Kjems J: The biogenesis, biology and characterization of circular RNAs. Nat Rev Genet 20: 675-691, 2019.
40. Peng Z, Fang S, Jiang M, Zhao X, Zhou C and Gong Z: Circular RNAs: Regulatory functions in respiratory tract cancers. Clin Chim Acta 510: 264-271, 2020.
41. Li R, Jiang J, Shi H, Qian H, Zhang X and Xu W: CircRNA: A rising star in gastric cancer. Cell Mol Life Sci 77: 1661-1680, 2020.
42. Rong Z, Xu J, Shi S, Tan Z, Meng Q, Hua J, Liu J, Zhang B, Wang W, Yu X and Liang C: Circular RNA in pancreatic cancer: A novel avenue for the roles of diagnosis and treatment. Theranostics 11: 2755-2769, 2021.
43. Chaichian S, Shafabakhsh R, Mirhashemi SM, Moazzami B and Asemi Z: Circular RNAs: A novel biomarker for cervical cancer. J Cell Physiol 235: 718-274, 2020.
44. Razavi ZS, Tajiknia V, Majidi S, Ghandali M, Mirzaei HR, Rahimian N, Hamblin MR and Mirzaei H: Gynecologic cancers and non-coding RNAs: Epigenetic regulators with emerging roles. Crit Rev Oncol Hematol 157: 103192, 2021.
45. Sang Y, Chen B, Song X, Li Y, Liang Y, Han D, Zhang N, Zhang H, Liu Y, Chen T, *et al*: circRNA_0025202 regulates tamoxifen sensitivity and tumor progression via regulating the miR-182-5p/FOXO3a axis in breast cancer. Mol Ther 27: 1638-1652, 2019.
46. Wang J, Zhao X, Wang Y, Ren F, Sun D, Yan Y, Kong X, Bu J, Liu M and Xu S: circRNA-002178 act as a ceRNA to promote PDL1/PD1 expression in lung adenocarcinoma. Cell Death Dis 11: 32, 2020.
47. Huang G, Liang M, Liu H, Huang J, Li P, Wang C, Zhang Y, Lin Y and Jiang X: CircRNA hsa_circRNA_104348 promotes hepatocellular carcinoma progression through modulating miR-187-3p/RTKN2 axis and activating Wnt/β-catenin pathway. Cell Death Dis 11: 1065, 2020.
48. Hanahan D and Weinberg RA: Hallmarks of cancer: The next generation. Cell 144: 646-674, 2011.
49. Liu T, Yuan L and Zou X: Circular RNA circ-BNC2 (hsa_circ_0008732) inhibits the progression of ovarian cancer through microRNA-223-3p/FBXW7 axis. J Ovarian Res 15: 95, 2022.
50. Xu Q, Deng B, Li M, Chen Y and Zhuan L: circRNA-UBAP2 promotes the proliferation and inhibits apoptosis of ovarian cancer though miR-382-5p/PRPF8 axis. J Ovarian Res 13: 81, 2020.
51. Li M, Chi C, Zhou L, Chen Y and Tang X: Circular PVT1 regulates cell proliferation and invasion via miR-149-5p/FOXM1 axis in ovarian cancer. J Cancer 12: 611-621, 2021.
52. Liang Y, Meng K and Qiu R: Circular RNA Circ_0013958 functions as a tumor promoter in ovarian cancer by regulating miR-637/PLXNB2 axis. Front Genet 12: 644451, 2021.
53. Yu W, Goncalves KA, Li S, Kishikawa H, Sun G, Yang H, Vanli N, Wu Y, Jiang Y, Hu MG, *et al*: Plexin-B2 mediates physiologic and pathologic functions of angiogenin. Cell 171: 849-864. e25, 2017.
54. Li X, He S and Ma B: Autophagy and autophagy-related proteins in cancer. Mol Cancer 19: 12, 2020.
55. Wang Y, Mo Y, Peng M, Zhang S, Gong Z, Yan Q, Tang Y, He Y, Liao Q, Li X, *et al*: The influence of circular RNAs on autophagy and disease progression. Autophagy 18: 240-253, 2022.
56. Zhang Z, Zhu H and Hu J: CircRAB11FIP1 promoted autophagy flux of ovarian cancer through DSC1 and miR-129. Cell Death Dis 12: 219, 2021.
57. Gan X, Zhu H, Jiang X, Obiegbusi SC, Yong M, Long X and Hu J: CircMUC16 promotes autophagy of epithelial ovarian cancer via interaction with ATG13 and miR-199a. Mol Cancer 19: 45, 2020.
58. Song W, Zeng Z, Zhang Y, Li H, Cheng H, Wang J and Wu F: CircRNF144B/miR-342-3p/FBXL11 axis reduced autophagy and promoted the progression of ovarian cancer by increasing the ubiquitination of Beclin-1. Cell Death Dis 13: 857, 2022.
59. Claesson-Welsh L and Welsh M: Vegfa and tumour angiogenesis. J Intern Med 273: 114-127, 2013.
60. Wang J, Li Y, Zhou JH, Shen FR, Shi X and Chen YG: CircATRNL1 activates Smad4 signaling to inhibit angiogenesis and ovarian cancer metastasis via miR-378. Mol Oncol 15: 1217-1233, 2021.
61. Schwarte-Waldhoff I and Schmiegel W: Smad4 transcriptional pathways and angiogenesis. Int J Gastrointest Cancer 31: 47-59, 2002.

62. Chen J, Li X, Yang L, Li M, Zhang Y and Zhang J: CircASH2L promotes ovarian cancer tumorigenesis, angiogenesis, and lymphangiogenesis by regulating the miR-665/VEGFA axis as a competing endogenous RNA. Front Cell Dev Biol 8: 595585, 2020.
63. Ma L, Liu W and Li M: Circ_0061140 contributes to ovarian cancer progression by targeting miR-761/LETM1 signaling. Biochem Genet 61: 628-650, 2023.
64. Pastushenko I and Blanpain C: EMT transition states during tumor progression and metastasis. Trends Cell Biol 29: 212-226, 2019.
65. Shang BQ, Li ML, Quan HY, Hou PF, Li ZW, Chu SF, Zheng JN and Bai J: Functional roles of circular RNAs during epithelial-to-mesenchymal transition. Mol Cancer 18: 138, 2019.
66. Zhang L, Zhou Q, Qiu Q, Hou L, Wu M, Li J, Li X, Lu B, Cheng X, Liu P, *et al*: CircPLEKHM3 acts as a tumor suppressor through regulation of the miR-9/BRCA1/DNAJB6/KLF4/AKT1 axis in ovarian cancer. Mol Cancer 18: 144, 2019.
67. Bai F, Zhang LH, Liu X, Wang C, Zheng C, Sun J, Li M, Zhu WG and Pei XH: GATA3 functions downstream of BRCA1 to suppress EMT in breast cancer. Theranostics 11: 8218-8233, 2021.
68. Menezes ME, Mitra A, Shevde LA and Samant RS: DNAJB6 governs a novel regulatory loop determining Wnt/β-catenin signalling activity. Biochem J 444: 573-580, 2012.
69. Tiwari N, Meyer-Schaller N, Arnold P, Antoniadis H, Pachkov M, van Nimwegen E and Christofori G: Klf4 is a transcriptional regulator of genes critical for EMT, including Jnk1 (Mapk8). PLoS One 8: e57329, 2013.
70. Zeng XY, Yuan J, Wang C, Zeng D, Yong JH, Jiang XY, Lan H and Xiao SS: circCELSR1 facilitates ovarian cancer proliferation and metastasis by sponging miR-598 to activate BRD4 signals. Mol Med 26: 70, 2020.
71. Li X, Lin S, Mo Z, Jiang J, Tang H, Wu C and Song J: CircRNA_100395 inhibits cell proliferation and metastasis in ovarian cancer via regulating miR-1228/p53/epithelial-mesenchymal transition (EMT) axis. J Cancer 11: 599-609, 2020.
72. Zhou J, Dong ZN, Qiu BQ, Hu M, Liang XQ, Dai X, Hong D and Sun YF: CircRNA FGFR3 induces epithelial-mesenchymal transition of ovarian cancer by regulating miR-29a-3p/E2F1 axis. Aging (Albany NY) 12: 14080-14091, 2020.
73. Wu SG, Zhou P, Chen JX, Lei J, Hua L, Dong Y, Hu M, Lian CL, Yang LC and Zhou J: circ-PTK2 (hsa_circ_0008305) regulates the pathogenic processes of ovarian cancer via miR-639 and FOXC1 regulatory cascade. Cancer Cell Int 21: 277, 2021.
74. Zhang F, Xu Y, Ye W, Jiang J and Wu C: Circular RNA S-7 promotes ovarian cancer EMT via sponging miR-641 to up-regulate ZEB1 and MDM2. Biosci Rep 40: BSR20200825, 2020.
75. Chen Q, Zhang J, He Y and Wang Y: hsa_circ_0061140 knockdown reverses FOXM1-mediated cell growth and metastasis in ovarian cancer through miR-370 sponge activity. Mol Ther Nucleic Acids 13: 55-63, 2018.
76. Wang T, Chen X, Qiao W, Kong L, Sun D and Li Z: Transcription factor E2F1 promotes EMT by regulating ZEB2 in small cell lung cancer. BMC Cancer 17: 719, 2017.
77. Li Y and Chen X: miR-4792 inhibits epithelial-mesenchymal transition and invasion in nasopharyngeal carcinoma by targeting FOXC1. Biochem Biophys Res Commun 468: 863-869, 2015.
78. Caramel J, Ligier M and Puisieux A: Pleiotropic roles for ZEB1 in cancer. Cancer Res 78: 30-35, 2018.
79. Katoh M, Igarashi M, Fukuda H, Nakagama H and Katoh M: Cancer genetics and genomics of human FOX family genes. Cancer Lett 328: 198-206, 2013.
80. Wang Y and Patti GJ: The Warburg effect: A signature of mitochondrial overload. Trends Cell Boil 33: 1014-1020, 2023.
81. Yu G, Yang Z, Peng T and Lv Y: Circular RNAs: Rising stars in lipid metabolism and lipid disorders. J Cell Physiol 236: 4797-4806, 2021.
82. Yu T, Wang Y, Fan Y, Fang N, Wang T, Xu T and Shu Y: CircRNAs in cancer metabolism: A review. J Hematol Oncol 12: 90, 2019.
83. Lin C, Xu X, Yang Q, Liang L and Qiao S: Circular RNA ITCH suppresses proliferation, invasion, and glycolysis of ovarian cancer cells by up-regulating CDH1 via sponging miR-106a. Cancer Cell Int 20: 336, 2020.
84. Xie W, Liu LU, He C, Zhao M, Ni R, Zhang Z and Shui C: Circ_0002711 knockdown suppresses cell growth and aerobic glycolysis by modulating miR-1244/ROCK1 axis in ovarian cancer. J Biosci 46: 21, 2021.
85. Hou W and Zhang Y: Circ_0025033 promotes the progression of ovarian cancer by activating the expression of LSM4 via targeting miR-184. Pathol Res Pract 217: 153275, 2021.
86. Chen L, Lin YH, Liu GQ, Huang JE, Wei W, Yang ZH, Hu YM, Xie JH and Yu HZ: Clinical significance and potential role of LSM4 overexpression in hepatocellular carcinoma: An integrated analysis based on multiple databases. Front Genet 12: 804916, 2022.
87. Ma H, Qu S, Zhai Y and Yang X: circ_0025033 promotes ovarian cancer development via regulating the hsa_miR-370-3p/SLC1A5 axis. Cell Mol Biol Lett 27: 94, 2022.
88. Chen Y, Ye X, Xia X and Lin X: Circular RNA ABCB10 correlates with advanced clinicopathological features and unfavorable survival, and promotes cell proliferation while reduces cell apoptosis in epithelial ovarian cancer. Cancer Biomark 26: 151-161, 2019.
89. Hu Y, Zhu Y, Zhang W, Lang J and Ning L: Utility of plasma circBNC2 as a diagnostic biomarker in epithelial ovarian cancer. Onco Targets Ther 12: 9715-9723, 2019.
90. Ning L, Lang J and Wu L: Plasma circN4BP2L2 is a promising novel diagnostic biomarker for epithelial ovarian cancer. BMC Cancer 22: 6, 2022.
91. Wang S, Zhang K, Tan S, Xin J, Yuan Q, Xu H, Xu X, Liang Q, Christiani DC, Wang M, *et al*: Circular RNAs in body fluids as cancer biomarkers: the new frontier of liquid biopsies. Mol Cancer 20: 13, 2021.
92. Zheng Y, Li Z, Yang S, Wang Y and Luan Z: CircEXOC6B suppresses the proliferation and motility and sensitizes ovarian cancer cells to paclitaxel through miR-376c-3p/FOXO3 axis. Cancer Biother Radiopharm 37: 802-814, 2022.
93. Zhu J, Luo JE, Chen Y and Wu Q: Circ_0061140 knockdown inhibits tumorigenesis and improves PTX sensitivity by regulating miR-136/CBX2 axis in ovarian cancer. J Ovarian Res 14: 136, 2021.
94. Huang H, Yan L, Zhong J, Hong L, Zhang N and Luo X: Circ_0025033 deficiency suppresses paclitaxel resistance and malignant development of paclitaxel-resistant ovarian cancer cells by modulating the miR-532-3p/FOXM1 network. Immunopharmacol Immunotoxicol 44: 275-286, 2022.
95. Xia B, Zhao Z, Wu Y, Wang Y, Zhao Y and Wang J: Circular RNA circTNPO3 regulates paclitaxel resistance of ovarian cancer cells by miR-1299/NEK2 signaling pathway. Mol Ther Nucleic Acids 21: 780-791, 2020.
96. Yuan D, Guo T, Qian H, Ge H, Zhao Y, Huang A, Wang X, Cao X, Zhu D, He C and Yu H: Icariside II suppresses the tumorigenesis and development of ovarian cancer by regulating miR-144-3p/IGF2R axis. Drug Dev Res 83: 1383-1393, 2022.
97. Luo Y and Gui R: Circulating exosomal circFoxp1 confers cisplatin resistance in epithelial ovarian cancer cells. J Gynecol Oncol 31: e75, 2020.
98. Liu X, Yin Z, Wu Y, Zhan Q, Huang H and Fan J: Circular RNA lysophosphatidic acid receptor 3 (circ-LPAR3) enhances the cisplatin resistance of ovarian cancer. Bioengineered 13: 3739-3750, 2022.
99. Cheng Y, Ban R, Liu W, Wang H, Li S, Yue Z, Zhu G, Zhuan Y and Wang C: MiRNA-409-3p enhances cisplatin-sensitivity of ovarian cancer cells by blocking the autophagy mediated by Fip200. Oncol Res: Jan 2, 2018 (Epub ahead of print).
100. Ghafouri-Fard S, Khoshbakht T, Bahranian A, Taheri M and Hallajnejad M: CircMTO1: A circular RNA with roles in the carcinogenesis. Biomed Pharmacother 142: 112025, 2021.
101. Wang J, Wu A, Yang B, Zhu X, Teng Y and Ai Z: Profiling and bioinformatics analyses reveal differential circular RNA expression in ovarian cancer. Gene 724: 144150, 2020.
102. Zhang PF, Gao C, Huang XY, Lu JC, Guo XJ, Shi GM, Cai JB and Ke AW: Cancer cell-derived exosomal circUHRF1 induces natural killer cell exhaustion and may cause resistance to anti-PD1 therapy in hepatocellular carcinoma. Mol Cancer 19: 110, 2020.
103. Gong J, Xu X, Zhang X and Zhou Y: Circular RNA-9119 suppresses in ovarian cancer cell viability via targeting the microRNA-21-5p-PTEN-Akt pathway. Aging (Albany NY) 12: 14314-14328, 2020.
104. Guo M, Li S, Zhao X, Yuan Y, Zhang B and Guan Y: Knockdown of circular RNA Hsa_circ_0000714 can regulate RAB17 by sponging miR-370-3p to reduce paclitaxel resistance of ovarian cancer through CDK6/RB pathway. Onco Targets Ther 13: 13211-13224, 2020.

105. Ji J, Li C, Wang J, Wang L, Huang H, Li Y and Fang J: Hsa_circ_0001756 promotes ovarian cancer progression through regulating IGF2BP2-mediated RAB5A expression and the EGFR/MAPK signaling pathway. Cell Cycle 21: 685-696, 2022.
106. Zhang C, Li Y, Zhao W, Liu G and Yang Q: Circ-PGAM1 promotes malignant progression of epithelial ovarian cancer through regulation of the miR-542-3p/CDC5L/PEAK1 pathway. Cancer Med 9: 3500-3521, 2020.
107. He SL, Zhao X and Yi SJ: CircAHNAK upregulates EIF2B5 expression to inhibit the progression of ovarian cancer by modulating the JAK2/STAT3 signaling pathway. Carcinogenesis 43: 941-955, 2022.
108. Lu H, Zheng G, Gao X, Chen C, Zhou M and Zhang L: Propofol suppresses cell viability, cell cycle progression and motility and induces cell apoptosis of ovarian cancer cells through suppressing MEK/ERK signaling via targeting circVPS13C/miR-145 axis. J Ovarian Res 14: 30, 2021.
109. Fu Z, Ding C, Gong W and Lu C: ncRNAs mediated RPS6KA2 inhibits ovarian cancer proliferation via p38/MAPK signaling pathway. Front Oncol 13: 1028301, 2023.
110. Wang S, Li Z, Zhu G, Hong L, Hu C, Wang K, Cui K and Hao C: RNA-binding protein IGF2BP2 enhances circ_0000745 abundancy and promotes aggressiveness and stemness of ovarian cancer cells via the microRNA-3187-3p/ERBB4/PI3K/AKT axis. J Ovarian Res 14: 154, 2021.
111. Wu M, Qiu Q, Zhou Q, Li J, Yang J, Zheng C, Luo A, Li X, Zhang H, Cheng X, *et al*: circFBXO7/miR-96-5p/MTSS1 axis is an important regulator in the Wnt signaling pathway in ovarian cancer. Mol Cancer 21: 137, 2022.
112. Lin X, Chen Y, Ye X and Xia X: Circular RNA ABCB10 promotes cell proliferation and invasion, but inhibits apoptosis via regulating the microRNA-1271-mediated Capn4/Wnt/β-catenin signaling pathway in epithelial ovarian cancer. Mol Med Rep 23: 387, 2021.
113. Wu Y, Zhou J, Li Y, Shi X, Shen F, Chen M, Chen Y and Wang J: Hsa_circ_0001445 works as a cancer suppressor via miR-576-5p/SFRP1 axis regulation in ovarian cancer. Cancer Med 12: 5736-5750, 2023.