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Circular RNAs: Novel biomarkers for cervical, ovarian and endometrial cancer (Review)

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Abstract. Cervical, ovarian and endometrial cancer are the three most common types of malignant tumor and the leading causes of cancer-associated death in women. Tumor debulking surgery followed by platinum and paclitaxel chemotherapy is the current treatment regime of choice. However, as a result of late diagnosis and chemoresistance, the survival rates of patients with advanced gynecological cancers remains unsatisfactory. Circular RNAs (circRNAs) are stable noncoding RNAs that are present in a wide variety of tissue and cell types. With the enhancement of RNA sequencing methods, increasing numbers of circRNAs have been identified, and their functions are gradually being revealed. In recent years, circRNAs have received increasing attention for their regulatory roles in cervical, ovarian and endometrial cancer. The aim of the present review was to summarize the possible mechanisms of recently identified circRNAs; we hypothesize that a novel diagnostic and therapeutic biomarker may be identified to prolong the survival time of patients with gynecological malignancies.

Contents

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1. Introduction

Circular RNAs (circRNAs) differ from other types of RNA due to their covalently closed-loop structures, and as such, have received increasing research interest since their discovery in 1976 (1). As members of the non-coding RNA family, circRNAs have been considered as secondary byproducts of linear mRNA splicing events (2). However, recent advancements in experimental and next-generation RNA sequencing methods have helped to identity and elucidate the functions of various novel circRNAs (3). CircRNAs have been revealed to influence a number of disease processes, including those involved in cardiovascular diseases, cancer and neurological disorders. Increasing research has confirmed the aberrant expression of numerous circRNAs in gynecological tumors, which influence the occurrence and development of these malignancies through multiple channels. This provides further evidence for the potential of circRNAs as biomarkers for the diagnosis, treatment and prognosis of gynecological cancers. The aim of the present review was to summarize our knowledge of the biogenesis and function of circRNAs, and to discuss the advantages and limitations of circRNA as biomarkers for cervical, ovarian and endometrial cancer, with the aim to identify novel biomarkers.

2. CircRNA biogenesis

As the name implies, circRNAs are closed circular structures with covalently linked 3' and 5' ends, which distinguish them from other types of RNA (1). Most circRNAs are generated by pre-mRNA splicing, and their circular structures make them relatively stable and resistant to RNase digestion (4,5). Due to their various different sources, circRNAs can be categorized into three types: i) Exonic circRNAs (ecircRNAs), which are the product of back-spliced exons; ii) intronic circRNAs (ciRNAs), the product of intronic sequences; and iii) exon-intron circRNAs (EliciRNAs), the products of circularized exons with introns

retained between them (3). These circRNAs are distributed differently within cells; ciRNAs and EliciRNAs are primarily present in the nucleus, while ecircRNAs are largely located in the cytoplasm (6). There are also three primary models for the formation of circRNA loops, namely lariat-driven, intron-pairing-driven and RNA-binding protein (RBP)-driven circularization (Fig. 1). These models can be further divided into two mechanisms; direct back-splicing and exon skipping (1). In the lariat-driven circularization model (exon skipping), a splice site 30 nucleotides upstream of an exon is ligated into a site 50 nucleotides downstream, leading to exon-skipping and the formation of an RNA lariat consisting of several exons and introns. The introns are then removed to generate ecircRNAs (4). Additionally, exons are circularized with introns that are retained between the exons, resulting in the generation of EliciRNAs (2). For the intron-pairing- and RBP-driven circularization models (direct back-splicing), reverse complementary sequences such as Alu repeats (located in the upstream and downstream introns), and certain trans-acting activator RNA-binding proteins binding to each of the flanking introns, bring the splice donor and acceptor sites close enough to form a loop (7-9). As for circular intron RNA biogenesis, the conserved motifs at both ends, including a 7-nt GU-rich element near the 5' splice site and an 11-nt C-rich element near the branch-point site, are joined together (10) to prevent introns from forming looped branches, and instead promote the formation of a loop structure. The 3'end of the intron is then relocated to the branch point to produce a stable circular structure.

CircRNAs are widely present in various human cell types. Their expression is cell type-specific; cells with low proliferative capacity, such as cardiomyocytes, have higher expression levels compared with cells that proliferate more readily, such as those in the liver (7). In addition, the high level of circRNAs in some tissues is primarily the result of accumulation, which is likely due to the high stability of these molecules. Due to a lack of free ends, circRNAs are more stable and resistant to RNase R compared with linear RNAs (11). Owing to these aforementioned features, we hypothesized that circRNAs may serve as novel biomarkers for the diagnosis and treatment of essential hypertension (12), inflammatory bowel disease (13) and a variety of different cancer types (14). For example, in hepatocellular carcinoma, hsa_circ_0001649 is more sensitive and specific than the known biomarker alpha fetoprotein (15). Another circRNA, hsa_circ_025016, has proven to be a potential plasma biomarker for the prediction of postoperative atrial fibrillation (16).

3. CircRNA functions

MicroRNA (miRNA/miR) sponging. An increasing number of scholars are focusing on the roles of circRNAs in cancer, of which miRNA sponging is a major mechanism (Fig. 2A). CDR1as/ciRS-7 is a well-known circRNA that acts as an miRNA sponge to inhibit tumor growth in breast, colorectal, gastric and cervical cancer (17-20). Another highly investigated, typical competing endogenous RNA is circHIPK3, which is also involved in antioncogenic processes. By sponging miR-558, circHIPK3 suppresses the malignant properties of bladder cancer cells, including migration, invasiveness and angiogenesis (21). Similarly, another study indicated that circHIPK3 overexpression significantly suppressed the proliferation, migration and invasiveness of osteosarcoma cells *in vitro* (22). Furthermore, circHIPK3 was found to promote the proliferation and progression of gallbladder and lung cancer cells, potentially by sponging miR-124 (23,24). These findings suggest that the properties of circRNAs are a double-edged sword.

Protein interactions. Another regulatory function of circRNAs is achieved through their ability to interact with RNA-binding proteins (Fig. 2B), the results of which depend on the protein (and circRNA) in question. For example, p21 and cyclin-dependent kinase 2 strongly and specifically bind with circFoxo3 to form a circFoxo3-Cdk2-p21 complex, which inhibits transition from the G_1 to the S phase of the cell cycle (25). Additionally, Du *et al* (26) revealed that circFoxo3 could bind p53 and mouse double minute 2 homolog to promote the ubiquitination and further degradation induced by p53. circMbl is able to bind the mannose-binding lectin (MBL); Ashwal-Fluss *et al* (27) revealed that the biosynthesis of circMbl was affected by the levels MBL via a feedback loop mechanism, and the process of MBL pre-mRNA translation into circMbl was also affected by high levels of MBL protein. Moreover, circMbl was found to bind MBL and attenuate its bioavailability. Another study identified a number of other circRNAs that bind multiple different proteins, serving regulatory roles in cell functioning (28).

Gene expression regulation. The majority of the circRNAs that regulate gene expression through sponge activity are localized in the cytoplasm (Fig. 2C). However, recent research has reported a small number of circRNAs that are localized in the nucleus, which can regulate gene expression at the transcriptional level. Li *et al* (29) found that circEIF3J and circPAIP2 are localized to the nucleus and promote the expression of parental genes, which involves the RNA polymerase II, U1 small nuclear RNA and several promoter regions. ciRNAs identified by Zhang *et al* (10) were also revealed to act as positive regulators of RNA polymerase-II transcription, and to promote parental gene expression. Similarly, ci-ankrd52 and ci-sirt7 were revealed to interact with RNA polymerase II to modulate the transcriptional rate of parental genes by accumulating at the active transcription site (10). Moreover, FECR1 circRNA, which binds to the promoter region and recruits TET1 DNA demethylase, was revealed to regulate the expression of the FLI1 gene, inducing DNA demethylation (30). These aforementioned circRNAs include those of intronic, exonic and exon-intron origin.

Protein translation. Although circRNAs are members of the non-coding RNA family, increasing data has revealed that circRNAs are also involved in protein translation (Fig. 2D). Unlike linear RNAs, circRNAs lack 7-methylguanosine cap structures and poly(A) tails, which prevents ribosomal recognition and translation into protein. Since the discovery of the internal ribosome entry site, the translation of circRNAs has become evident (31). A recent study indicated that circ-ZNF609, which regulates myoblast proliferation, contains an open reading frame that can be translated into protein with in cap-independent manner (32). Circ-FBXW7 is abundantly expressed in the normal human brain, and encodes a novel protein that regulates the proliferation and cycling of cancer

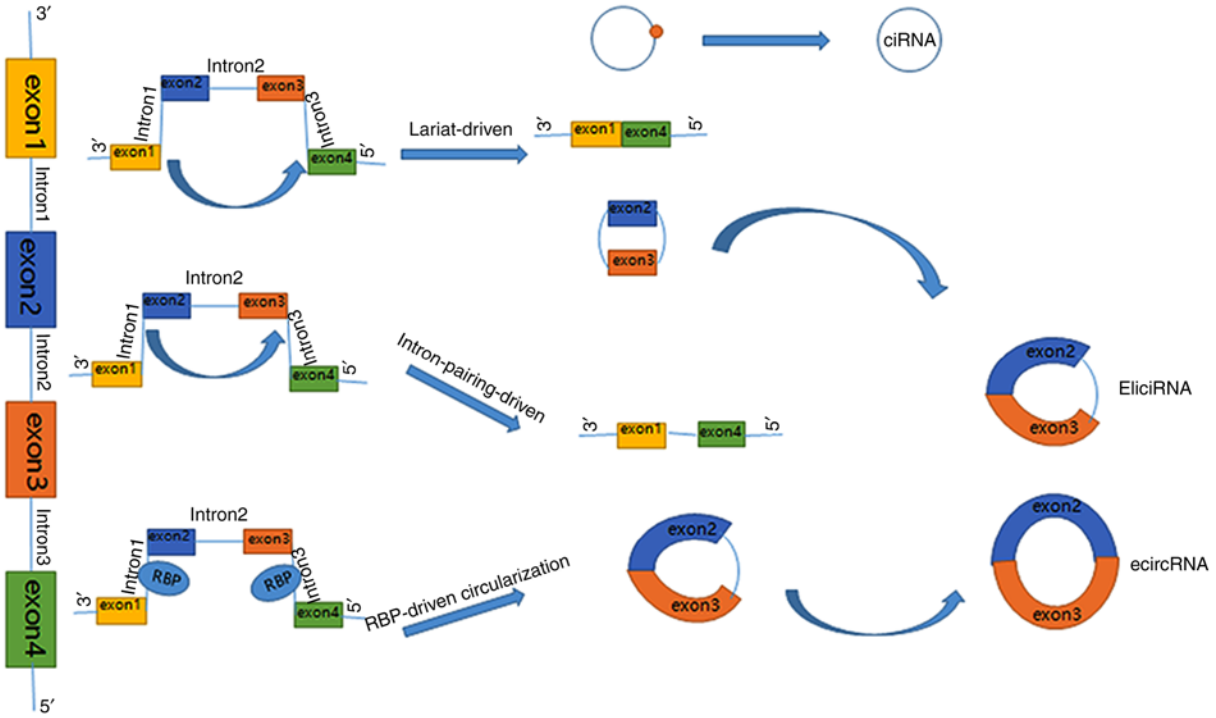

Figure 1. Biogenesis of circRNAs. CircRNA biogenesis is primarily regulated via three different mechanisms: Lariat-driven, intron-pairing-driven and RBP-driven circularization. circRNA, circular RNA; RBP, RNA-binding protein.

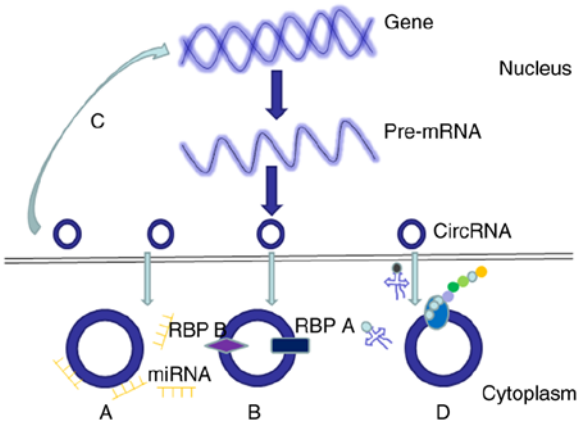

Figure 2. Functions of circRNAs. (A) CircRNAs act as miRNA sponges, regulating cellular proliferation. (B) CircRNAs bind to RBPs to regulate cell functions. (C) CircRNAs regulate the transcription of parental genes. (D) CircRNAs with IRESs can be translated into peptides or proteins. CircRNA, circular RNA; RBP, RNA-binding protein; IRES, internal ribosome entry site.

cells (33). Furthermore, circ-SHPRH encodes SHPRH-146aa, which regulates the proliferation and tumorigenicity of cancer cells *in vitro* (34). However, to date, few circRNAs have been found to be translated into protein, thus further studies in this area are warranted.

4. CircRNAs as potential biomarkers of gynecological tumors

A growing number of studies have focused on the relationship between gynecological tumors and circRNAs. The present review summarizes the most recent findings surrounding circRNA regulation in cervical, ovarian and endometrial cancer, with the aim to identify novel biomarkers and therapeutic approaches.

CircRNAs and cervical cancer (Table I). Cervical cancer is one of the most common malignant tumors in women, with an incidence rate second only to that of breast cancer (35). It has a high mortality rate and is the second major cause of tumor-related death worldwide (36). Continuous infection with high-risk human papillomavirus (HPV) is a major pathogenic factor for cervical cancer progression (37). Although the administration of HPV vaccines among patients with cervical cancer is increasing globally, mortality and morbidity rates remain high in numerous developed countries (38). In 2018, ~570,000 newly-diagnosed cases of cervical cancer, and ~311,000 deaths, were recorded worldwide (39). Surgery followed by radiotherapy and chemotherapy is currently the primary method of cervical cancer treatment. However, the poor prognosis and low survival rate caused by distant metastasis and high lymphatic metastasis are still problematic (40). Therefore, the identification of novel treatments and biomarkers for earlier diagnosis is necessary for increasing survival rates.

A previous study revealed that circRNAs are stable and expressed to a high degree in various cancer cell lines (41). Additionally, circRNA detection methods are more sensitive and specific than those for the detection of proteins, and circRNAs are more easily detectable than miRNAs (42). For these reasons, there is a high probability that circRNAs will make suitable novel biomarkers for cancers. Currently, several studies have investigated the roles of circRNAs in cervical cancer, of which miRNA sponging may be the most significant

Table I. Expression and functional characterization of circRNAs in cervical cancers.

circRNAs	Expression	Binding miRNA	Function	Biomarker	(Refs.)
Circ_0067934	Up	miR-545	Promotes cervical cancer progression	Metastasis(+)	(48)
circ-ATP8A2	Up	miR-433	Promotes cell progression and suppressing the expression of epidermal growth factor receptor	Lymph node invasion and FIGO stage(+)	(49)
circ-0000745	Up	NA	Acts as a tumor promoter	Vascular/lymphatic invasion(+)	(45)
circ_0005576	Up	miR-153-3p	Promotes cervical cancer progression	Pathological stage and lymph node metastasis(+)	(50)
circRNA_101308	Down	miR-26a-5p, miR-196a-5p, miR-196b-5p, miR-335-3p, and miR-1307-3p	Tumor suppressor	Deep myometrial invasion and lymph node metastasis(-)	(51)
circSLC26A4	Up	miR-1287-5p	Facilitates cancer progression	Poor prognosis	(52)
Circ_0018289	Up	miR-497	Promotes tumorigenesis	Poor prognosis	(53)
hsa_circ_0023404	Up	miR-136	Promotes tumorigenesis	Poor prognosis	(54)
circ-ITCH	Down	miR-93-5p	Suppresses proliferation and metastasis	NA	(61)
hsa_circ_0000263	Up	miR-150-5p	NA	NA	(62)

circRNAs, circular RNAs; Ref., reference; NA, not available.

mechanism. The existing mechanisms (to the best of our knowledge) are discussed in detail below.

Expression of circRNAs in cervical cancer. Various studies have highlighted the presence of multiple circRNAs in cervical cancer. Among 526 dysregulated circRNAs, Zheng *et al* (43) found that 352 were upregulated and 174 were downregulated, indicating that circRNAs may be potential biomarkers for the diagnosis and treatment of cervical cancer. Gao *et al* (44) conducted a high-throughput microarray study using four pairs of cervical cancer and adjacent noncancerous tissues, revealing 19 downregulated and 26 upregulated circRNAs in cervical cancer. Jiao *et al* (45) studied circRNA expression profiles using microarray analysis, and found that 178 circRNAs were differentially expressed between cervical cancer and matched normal cervical tissues, of which 101 were downregulated and 77 were upregulated. By classifying the 77 upregulated circRNAs, they also identified 68 exonic, 3 intronic, 1 antisense and 5 intragenic circRNAs in cervical cancer tissues, as well as 101 downregulated circRNAs (including 81 exonic, 13 intronic, 3 antisense and 4 intragenic variants).

Although numerous studies aim to investigate the expression of ring-shaped RNAs in cervical cancer, there are often certain limitations. For example, the sample size of these studies is small, making it especially difficult to understand the expression profiles of different histological grades and pathological stages. It is therefore necessary to perform larger-scale sequencing studies to obtain more detailed data on the expression of circRNAs in cervical cancer.

i) CircRNAs as biomarkers of cervical cancer. The early diagnosis and treatment of cervical cancer can effectively improve the survival rates of patients. With the development of high-throughput sequencing and biochip technologies, a growing number of circRNAs have exhibited potential as diagnostic biomarkers.

ii) CircRNA expression in cervical cancer tissues samples. Research by Wang *et al* (46) highlighted that the expression level of hsa_circ_0001038 was higher in cervical cancer tissues than in adjacent non-cancerous tissues. Moreover, Chen *et al* (47) discovered that circRNA_0000285 was frequently upregulated in cervical cancer tissues compared with adjacent normal tissues.

iii) CircRNAs as biomarkers of cervical cancer metastasis. The expression of circ_0067934 was found to be increased in cervical cancer tissues and cell lines, compared with that in adjacent normal tissues (48). High circ_0067934 expression was also associated with positive lymphatic metastasis in patients with cervical cancer, indicating its use as a potential biomarker of cervical cancer metastasis. Ding *et al* (49) demonstrated that circ-ATP8A2 was upregulated in cervical cancer tissues and cell lines, and further confirmed that high levels of circ-ATP8A2 were associated with a higher FIGO

stage, positive lymph node invasion and myometrial invasion. In addition, has-circ-u0000745 was upregulated in cervical cancer tissues and cell lines, which was found to be correlated with various clinicopathological features, such as poorly differentiated tumors and positive vascular/lymphatic invasion (45). Another circRNA, circ_0005576, has been associated with a higher pathological stage and lymph node metastasis (50). However, alternative studies have indicated that reduced circRNA expression also promotes metastasis; Jiao *et al* (51) revealed that low expression levels of circRNA_101308 were associated with deep myometrial invasion and lymph node metastasis. Therefore, selecting the appropriate circRNA biomarker for a specific pathology requires more thorough consideration.

CircRNAs as biomarkers of cervical cancer prognosis. It is important to identify patients with a poor prognosis in order to implement effective treatment. Therefore, there is an urgent requirement for the discovery of novel prognostic biomarkers for cervical cancer. CircRNAs are differentially expressed in tumors of different histological grades and pathological stages, and those with lymph node or distant metastases, suggesting that circRNAs have potential prognostic value as biomarkers of cervical cancer. For instance, Ji *et al* (52) revealed that the expression level of circSLC26A4 was upregulated in cervical cancer tissues compared with adjacent normal tissues, and that high circSLC26A4 expression was associated with a poor patient prognosis. Circ_0018289 has also been revealed to be markedly upregulated in cervical cancer tissues compared with adjacent normal tissues (53), which was significantly correlated with decreased overall survival, suggesting that circ_0018289 may be a potential biomarker for evaluating prognosis. Additionally, hsa_circ_0023404 was found to be upregulated in cervical cancer tissues and cell lines (54). As a result of Kaplan-Meier analysis, patients with high hsa_circ_0023404 expression levels exhibited poorer overall survival rates than those with low hsa_circ_0023404 expression levels. The primary associated mechanism was that hsa_circ_0023404 sponged miR-136, inducing yes-associated protein (YAP) pathway activation by promoting α globin transcription factor CP2 (TFCP2) expression, resulting in the development and progression of cervical cancer. This study revealed that hsa_circ_0023404 plays a pivotal role in the regulation of cervical cancer progression through the hsa_circ_0023404-miR-136-TFCP2-YAP axis. A number of other circRNAs, such as hsa_circ_0000515 (55), circ_0005576 (50) and circ-0000745 (45) have also been revealed to be highly expressed in cervical cancer, and associated with poor patient prognosis. The discovery of these circRNAs provides predictive possibility for the prognosis of cervical cancer.

CircRNAs suppress tumor progression. Cervical cancer results from the complex interaction between various factors and signaling pathways. Currently, the primary consensus is that this involves persistent infection with high-risk HPV. Multiple circRNAs have been revealed to play important roles in the progression of cervical cancer, and may therefore help to improve our understanding of the mechanisms underlying cancer progression.

CircSMARCA5 (hsa_circ_0001445), which is located on chr4:144464661-144465125 and forms the circular exon 15 and 16 of SMARCA5, is widely expressed in human cells. Previous studies have found that circSMARCA5 can regulate cellular proliferation by sponging miRNAs. For example, in prostate cancer, circSMARCA5 promoted tumor progression by sponging miR-432, but suppressed the progression of multiple myeloma by targeting miR-767-5p (56,57). In cervical cancer, circSMARCA5 acted as a tumor suppressor with reduced expression in cancerous tissues, binding and inhibiting the expression of miR-620. High expression levels of circSMARCA5 suppressed the proliferation, migration and invasiveness of cancer cells by sponging miR-620 (58). CircRNA_101308 expression was also revealed to be decreased in cervical cancer tissues and cell lines, compared with that in normal tissues. CircRNA_101308 can bind various different miRNAs and regulate their downstream genes to suppress the proliferation, invasiveness and metastasis of cervical cancer cells, both *in vitro* and *in vivo* (51). Furthermore, circ-ITCH has been revealed to be associated with the regulation of tumor growth, and the proliferation and apoptosis of cancer cells in bladder (59) and breast cancer (60). In cervical cancer, circ-ITCH expression was low and functioned as an miRNA sponge for miR-93-5p. As the target of miR-93-5p, forkhead box protein K2 (FOXK2) regulated multiple cancer cell features. In cervical cancer, the overexpression of circ-ITCH suppressed the proliferation and metastasis of cervical cancer cells by interacting with the circ-ITCH/miR-93-5p/FOXK2 axis, and thus upregulating the expression of FOXK2 (61).

CircRNAs promote tumor progression. Previous research on circRNAs has improved our understanding of cervical cancer pathogenesis. Ma *et al* (50) recently discovered a novel circ_0005576-miR-153-3p-kinesin family member 20A (KIF20A) axis that regulates cervical cancer growth and invasion. They identified a potentially new form of circ_0005576 that is primarily located in the cytoplasm, and is significantly upregulated in cervical cancer. Circ_0005576-knockdown was found to suppress cellular proliferation, colony formation and metastasis, and circ_0005576 overexpression increased the expression of KIF20A by sponging miR-153-3p, which may provide a new perspective into the pathogenesis of cervical cancer. Moreover, hsa_circ_0000263 was revealed to be upregulated in cervical cancer cells, and cellular proliferation, migration and the cell cycle were inhibited by knocking down hsa_circ_0000263. In a murine model, the expression of murine double minute 4 (MDM4) was regulated by hsa_circ_0000263, which ultimately affected the expression of the p53 gene. Therefore, the hsa_circ_0000263/miR-150-5p/MDM4/p53 network has been suggested to serve a vital role in the regulation of cervical cancer (62). Furthermore, Hu *et al* (48) revealed that circ_0067934 was upregulated and associated with advanced stage, lymph node metastasis, and poor prognosis, providing new insights into the pathogenesis of cervical cancer. Tumor growth and cellular proliferation were inhibited by knocking down circ_0067934 *in vitro* and *in vivo*, and loss-of-function analysis revealed that increased miR-545 expression suppressed eukaryotic translation initiation factor 3 subunit C (EIF3C) expression by silencing circ_0067934. This study revealed that circ_0067934 influences cellular

proliferation, migration and invasiveness in cervical cancer via the circ_0067934/miR-545/EIF3C axis.

CircRNAs as potential therapeutic targets. CircRNAs may represent potential targets for the treatment of cervical cancer. A previous study revealed that hsa_circ_0000515 was upregulated in cervical cancer, and acted as a ceRNA of miR-326 to increase the expression of ETS transcription factor (ELK1). The *in vitro* results indicated that proliferation and invasiveness, as well as induced apoptosis and autophagy, were suppressed by silencing hsa_circ_0000515 or overexpressing miR-326. ELK1 overexpression also suppressed apoptosis and autophagy, but enhanced the proliferation and invasiveness of cervical cancer cells. These findings indicate that hsa_circ_0000515 may be a tumor promoter and provide evidence for its therapeutic use in cervical cancer (55). Another circRNA, has-circ-0000745, was revealed to be upregulated in patients with cervical cancer, and high expression levels were associated with poorly differentiated tumors or vascular/lymphatic invasion. Knocking down hsa_circ_0000745 was found to upregulate E-cadherin expression, inhibiting the proliferation, migration and invasiveness of cervical cancer cells, indicating a potential target for cervical cancer treatment (45). Ding *et al* (49) revealed that circ-ATP8A2, which is highly expressed in cervical cancer specimens and cell lines, enhanced cellular proliferation, migration, invasiveness and apoptosis in cervical cancer. The same effects were observed for ectopically expressed circ-ATP8A2. The experimental results indicated that circ-ATP8A2 exerted its inhibitory effects on epidermal growth factor receptor (EGFR) expression at the post-transcriptional level, by sponging miR-433. These findings suggest a therapeutic effect of regulating the circ-ATP8A2/miR-433/EGFR axis to mediate tumor progression. Furthermore, the expression levels of circRNA_0000285 were higher in cervical cancer samples than in adjacent, non-cancerous tissues, and circRNA_0000285-knockdown *in vitro* significantly inhibited the proliferation and migration abilities of cervical cancer cells. circRNA_0000285 expression may also be correlated with that of the RNA-binding protein FUS, which was found to be regulated by circRNA_0000285. In a nude mouse model, the formation and metastasis of cervical cancer were significantly inhibited by circRNA_0000285-knockdown (47). Collectively, these data provide insights into the pathogenic mechanisms and potential treatment targets for cervical cancer.

Perspectives. At present, the association between cervical cancer and circRNAs is receiving extensive research attention. Researchers have identified numerous circRNAs that are aberrantly expressed in cervical cancer, as well as the molecular mechanisms underlying these phenomena. However, the mechanisms of a large number of circRNAs are yet to be elucidated. Currently, cervical cancer and normal adjacent tissues are the preferred specimen types for the study of circRNAs, and there is a lack of more readily available clinical specimen types, such as serum and urine, which would be more convenient for cervical cancer diagnosis. Therefore, additional research is required to improve our understanding of the relationship between circRNAs and cervical cancer.

CircRNAs and ovarian cancer (Table II). Ovarian cancer is a common, but life-threatening gynecological malignancy that represents 3.6% of neoplasms in women worldwide (63). Although it ranks 20th among the most common global cancer types, ovarian cancer has the highest mortality rate of all gynecological malignancies, and is the eighth leading cause of death among women worldwide (63,64). In 2018, ovarian cancer resulted in an estimated 295,414 new cases and 184,799 deaths worldwide (39). Tumor debulking surgery followed by platinum and paclitaxel chemotherapy is currently the preferred clinical treatment (65). However, the survival rate of patients with advanced ovarian cancer is ~30%, which is primarily due to late diagnosis and chemoresistance, the latter of which is influenced by the tumor microenvironment and the inherent resistance of ovarian cancer cells to chemotherapy (66). Thus, improving the response to treatment and developing novel therapies is crucial for improving survival rates.

Expression of circRNA in ovarian cancer. Among 4,505 newly identified circRNAs, Teng *et al* (67) highlighted 2,431 that were significantly upregulated and 3,120 that were downregulated. Furthermore, circHIPK3 was indicated to regulate the proliferation and apoptosis of ovarian cancer and normal ovarian epithelial cells via the circHIPK3-miRNA-mRNA axis. Another study revealed that among 4,388 circRNAs with an expression fold change of ≥2, 2,556 were upregulated and 1,832 were downregulated. Further analysis indicated that differentially expressed circRNAs may serve a pathogenetic role in epithelial ovarian cancer, as well as acting as potential diagnostic and prognostic biomarkers (68). Moreover, of 710 differentially expressed circRNAs screened via high-throughput sequencing, circRNA1656 exhibited the highest fold change, with low expression in ovarian cancer tissues and cell lines, which was correlated with FIGO stage in high-grade serous ovarian cancer (69).

CircRNAs as biomarkers for the diagnosis, metastasis and prognosis of ovarian cancer. Early diagnosis prior to cancer metastasis significantly improves prognosis, and the prognostic evaluation of ovarian cancer also extends patient survival time (70). The pathogenesis of ovarian cancer is complex, and current diagnostic methods, including the detection of tumor markers, ultrasound, CT, MRI and histopathology, are not sufficient. Therefore, novel indicators for diagnosis, metastasis and prognosis are urgently required.

Researchers are now paying close attention to the regulation of circRNAs in ovarian cancer, with the aim to identify novel diagnosis biomarkers. Pei *et al* (71) discovered that hsa_circ_0013958 was highly expressed in ovarian cancer tissues and cell lines, and that hsa_circ_0013958 upregulation was closely associated with patient FIGO stage and lymph node metastasis. Further analysis revealed that hsa_circ_0013958 was a highly sensitive and specific indicator for the diagnosis of ovarian cancer. Previous studies have revealed that circLARP4 sponges miR-424 to regulate gastric cancer progression. In ovarian cancer, the expression of circLARP4 was found to be significantly downregulated, which was associated with FIGO stage and lymph node metastasis. Survival analysis revealed that a low level of circLARP4 was an independent risk factor for ovarian cancer prognosis, suggesting its potential use as a prognostic biomarker (72). Furthermore, circRNA_MYLK was revealed to be highly expressed in ovarian cancer compared

Table II. Expression and functional characterization of circRNAs in ovarian cancers.

circRNAs	Expression	Binding miRNA	Function	Biomarker	(Refs.)
circMAN1A2	Up	NA	NA	Serum biomarker	(70)
hsa_circ_0013958	Up	NA	Plays a role as an oncogene in ovarian cancer	FIGO stage and lymph node metastasis	(71)
circLARP4	Down	miR-424	NA	Prognostic biomarker	(72)
CircRNA_MYLK	Up	microRNA-652	Promotes the malignant progression	Prognostic biomarker	(73)
hsa_circ_0051240	Up	miR-637	Promotes ovarian cancer cell proliferation, migration and invasion	NA	(74)
circ-ABCB10	NA	miR-1271 miR-1252 miR-203	Promotes cell proliferation but reduces cell apoptosis	Poor prognosis and advanced FIGO stage	(75)
Circ-SMAD7	Up	NA	Promotes the progression	NA	(76)
VPS13C-has-circ-001567	Up	NA	Inhibits apoptosis and promotes proliferation	NA	(77)
hsa_circ_0078607	Down	miR-518a-5p	Leads to cell apoptosis	NA	(79)
circ_100395	Down	miR-1228	Inhibits cell growth and metastasis	NA	(80)
circSETDB1	Up	NA	Predicts chemotherapy response	Chemoresistant	(81)
CDR1as	Down	miR-1270	Suppression of cisplatin resistance, cell proliferation, and apoptosis. Enhances the sensitivity of ovarian cancer to platinum	NA	(82)

circRNAs, circular RNAs; Ref., reference; NA, not available.

with adjacent normal tissues, and high circRNA_MYLK expression was positively associated with pathological stage. Kaplan-Meier survival analysis indicated that high expression levels of circRNA_MYLK were closely related to a poor prognosis in patients with ovarian cancer (73). CiRS-7 has also been revealed to be upregulated in ovarian cancer, which is positively associated with TNM stage, lymph node metastasis status and poor prognosis. Moreover, Fan *et al* (70) discovered that circ-MAN1A2 was highly expressed in the serum of patients with various malignant tumors, including ovarian cancer, indicating its potential use as a serum biomarker. However, further clinical investigation is required to support these findings.

CircRNAs in tumor progression. Currently, the most common clinical treatment for ovarian cancer is tumor debulking surgery followed by platinum and paclitaxel chemotherapy. However, the poor prognosis of patients with advanced ovarian cancer remains a problem worldwide, and exploratory studies of pathogenesis and potential therapeutic methods are necessary. Zhang *et al* (74) revealed that hsa_circ_0051240 was upregulated in ovarian cancer compared with normal tissues, and that silencing hsa_circ_0051240 inhibited the proliferation, migration, invasion and tumor formation of ovarian cancer *in vivo*. The data also indicated that hsa_circ_0051240 was able to sponge miR-637, which directly targets KLK4 mRNA in ovarian cancer cells. It was therefore speculated that the hsa_circ_0051240-miR-637-KLK4 axis may be a potential treatment target for regulating the proliferation, migration and invasion of ovarian cancer.

circ-ABCB10 was also revealed to be upregulated in ovarian cancer, and was closely associated with large tumor size, poor differentiation, poor prognosis and an advanced FIGO stage. Chen *et al* (75) found that upregulated circ-ABCB10 expression reduced apoptosis but promoted cellular proliferation *in vitro*, and was also associated with the negative regulation of miR-1271, miR-1252 and miR-203. In addition, the upregulation of circ-SMAD7 negatively regulated Krüppel-like factor 6, mediating ovarian cancer progression, metastasis and cellular proliferation (76). Moreover, the capacity of VPS13C-has-circ-001567 to regulate the apoptosis and proliferation of ovarian cancer cells indicates that it may hold potential as a therapeutic target. VPS13C-has-circ-001567-knockdown inhibited the proliferation and tumorigenicity, but promoted the apoptosis of ovarian cancer *in vitro*; the cell cycle was arrested at the G_1 phase, and the percentage of S_1 phase cells was decreased (77). Collectively, these findings suggest that circRNAs play indispensable roles in the regulation of ovarian cancer cell proliferation, migration and invasiveness, highlighting their potential use as therapeutic agents.

CircRNAs suppress ovarian cancer progression. Chen *et al* (78) observed that circRNA CDR1as acted as a vital factor in the growth and metastasis of ovarian cancer. Hypoxia-inducible factor 1α inhibitor (HIF1AN) is an asparagine hydroxylase that is closely associated with cancer progression. As an miRNA sponge, CDR1 as inhibited miR-135b-5p to increase the expression of downstream HIF1AN, thus ultimately contributing to the suppression of ovarian cancer. hsa_circ_0078607 has also been found to be significantly downregulated in ovarian cancer (79). Additionally, hsa_circ_0078607 sponging of miR-518a-5p enhanced the expression of tumor necrosis factor receptor superfamily member 6 (Fas), which interacts with its receptor Fas ligand to induce the death signal cascade, resulting in apoptosis. This indicated that hsa_circ_0078607 suppressed ovarian cancer progression via the miR-518a-5p/Fas signaling pathway. Furthermore, Li *et al* (80) observed that circ_100395 facilitated the expression of p53 by modulating miR-1228, further inhibiting the growth and metastasis of ovarian tumors.

CircRNAs as biomarkers of ovarian cancer chemoresistance. Chemoresistance is a common phenomenon during cancer therapy that is caused by drug resistance, and results in treatment failure and poor patient prognosis. Chemoresistance frequently occurs in those with ovarian cancer, making it difficult to meet the chemotherapeutic standards of efficacy. It is therefore necessary to improve our understanding of the molecular mechanisms involved in ovarian cancer chemoresistance.

Wang *et al* (81) determined the levels of serum circSETDB1 in 60 patients with serous ovarian cancer, in order to evaluate its association with progression-free survival. They observed that higher levels of serum circSETDB1 were significantly associated with lymph node metastasis and advanced clinical stage, and could act as distinguishing indicators of patients and healthy volunteers. Notably, the levels of serum circSETDB1 were significantly increased in patients with primary chemoresistance, suggesting that serum circSETDB1 may be a predictor of progression, response to chemotherapy and relapse in ovarian cancer. To investigate the potential mechanisms involved, Zhao *et al* (82) evaluated the expression of circRNAs in cisplatin-resistant and -sensitive ovarian cancer tissues. Cisplatin-resistant patient tissues and cells exhibited lower expression levels of Cdr1as. Also, Cdr1as was determined to sponge miR-1270 and regulate the suppression of cancer cell invasiveness. These data indicate that ovarian cancer sensitivity to platinum may be enhanced by Cdr1as via the miR-1270/SCAI signaling pathway.

Perspectives. To date, the abnormal expression of numerous circRNAs has been detected in ovarian cancer, as well as the underlying mechanisms of some of these circRNAs. However, the resulting data are still limited by insufficient sample size and the lack of an expression profile for pathological classification. Therefore, further studies are required to fully address this clinical issue.

CircRNAs and endometrial cancer (Table III). Endometrial cancer is the fourth most common female malignant tumor worldwide, with ~300,000 newly diagnosed cases annually (39). The incidence of endometrial cancer is region-dependent, but is increasing with the aging of the population (83). Obesity, diabetes, polycystic ovary syndrome, infertility, early menarche and late menopause have all been reported as potential risk factors (84,85). Although obesity and hyperinsulinemia in young women have increased significantly, the primary age of onset for endometrial cancer is in postmenopausal women, and the average age of cancer diagnosis is 63 years (86,87). According to histological subtype, endometrial cancer can be classified into four types, including endometrioid, serous, clear cell and mixed endometrial cancer. It can also be divided into two types depending on the tumor response to estrogen. Type I tumors are estrogen-responsive, account for ~80-90% of endometrial cancer cases, and are associated with a more favorable prognosis. By contrast, type II tumors are usually estrogen-independent, and are associated with a high grade and poor prognosis; despite accounting for only 10-20% of all cases, type II tumors are responsible for 40% of the total deaths from endometrial cancer (87-89). A recent study of overall mutational burden introduced novel classification criteria with different clinical outcomes. The Cancer Genome Atlas includes four types of endometrial cancer, including those with p53, polymerase epsilon and phosphatase and TENsin homolog mutations, microsatellite instability and histology (90). Early detection tends to result in improved prognosis; although postmenopausal bleeding is the most common symptom of endometrial cancer, it is a diagnostic indicator in only 5-10% of cases. At present, the primary screening methods for endometrial cancer are transvaginal ultrasound scanning, outpatient hysteroscopy and endometrial biopsy. These procedures are expensive, and due to interference, can be difficult to perform effectively. Surgery combined with chemotherapy is currently the most commonly used therapeutic method for endometrial cancer, and a combination of carboplatin and paclitaxel is the first-line treatment of choice (91). However, poor prognosis with a rapid onset of resistance is still a significant issue. In summary, it is necessary to identity novel diagnostic and therapeutic methods to increase the survival rate of patients with endometrial cancer.

Expression and biomarker potential of circRNAs in endometrial cancer. A number of potential cancer biomarkers have been identified using high-throughput technologies. These include circRNAs, which serve regulatory roles in various physiological and pathological processes. In endometrial cancer, the roles of circRNAs in cells and tissues are gradually being revealed. Recent studies have shown that 75,928 unique circRNAs are abnormally expressed in endometrial cancer, and that 62,167 of these are significantly up- or downregulated in endometrial cancer tissues compared with adjacent normal tissues (92)C. The top 10 up- and downregulated circRNAs were selected for further investigation. Among them, the expression levels of hsa_circ_0001610 and hsa_circ_0039569 were lower in grade 1-2, compared with grade 3 endometrial cancer tissues, and age, tumor size, lymph node metastasis, myometrial invasion and FIGO stage were not associated with hsa_circ_0039569 expression level. However, hsa_circ_0001610 and hsa_circ_0039569 were significantly associated with tumor differentiation. The correlation between these circRNAs

Table III. Expression and functional characterization of circRNAs in endometrial cancers.

circRNAs	Expression	Binding miRNA	Function	Biomarker	(Refs.)
hsa_circ_0039569	Up	miR-542	NA	Diagnosis	(92)
Circ-ITCH	NA	miRNA-17 miRNA-224	NA	Diagnosis	(95)
circWHSC1	Up	miR-646	Promotes endometrial cancer development	Prognostic biomarker	(97)

circRNAs, circular RNAs; Ref., reference; NA, not available.

and miRNAs was also analyzed, indicating that that the hsa_circ_0039569-has-miR-542-3p/has-let-7c-5p axis serves a regulatory role in grade 3 endometrial cancer. In summary, this study indicated that circRNAs may play a vital role in the diagnosis and treatment of grade 3 endometrial cancer, for which hsa_circ_0039569 may be a predictive indicator. Another study identified 209 upregulated and 66 downregulated circRNAs in extracellular vesicles, that were separated from the serum of patients with endometrial cancer. Of these 275 differentially expressed circRNAs, only hsa_circ_0109046 and hsa_circ_0002577 reached a fold-change >2, thus the potential interactions between these two circRNAs and miRNAs were predicted.

circRNAs have also been revealed to be potential biomarkers for the diagnosis of endometrial cancer (93). Chen *et al* (94) highlighted that the overall abundance of circRNAs is higher in the normal endometrium than in endometrial cancer tissues. Further research revealed 120 circRNAs that are differentially expressed between normal endometrial and endometrial cancer tissues, the majority of which are derived from exons. The transcriptional products of these circRNAs predispose endometrial tissues to malignancy. In summary, the results of the aforementioned studies indicate that circRNAs may serve as potential biomarkers for the diagnosis and progression of endometrial cancer.

The tumor suppressor gene PTEN plays an indispensable role in a number of biological processes, including cellular survival and apoptosis, proliferation and the maintenance of genomic stability. Circ-ITCH can combine with miRNA-17 and miRNA-224 to induce the differential expression of p21 and PTEN. In animal models, PTEN-knockdown promoted the development of endometrial cancer and its precursors (95). Also, women carrying germline PTEN mutations are at a higher risk of developing endometrial cancer (96), suggesting that different molecular mechanisms are involved in the regulation of circRNAs in this malignancy. Another study revealed that two circRNAs, HSPG2 and RP11255H23.4, are expressed in normal endometrial tissues, but not in endometrial cancer tissues. In normal tissues, the expression levels of the corresponding miRNAs were also increased, indicating that circRNAs can competitively bind to related miRNAs, promoting the development of endometrial cancer. The interaction between HSPG2 and various growth factors was also found to regulate endothelial growth and regeneration. Collectively, these findings suggest that circRNAs may act as diagnostic biomarkers and therapeutic targets for endometrial cancer.

CircRNAs in endometrial cancer progression. At present, few studies have investigated the roles of circRNAs in endometrial cancer progression. Liu *et al* (97) discovered that circWHSC1, which is highly expressed in cancer tissues compared with normal tissues, could regulate nucleophosmin 1 (NPM1), a downstream target of miR-646. This was subsequently found to be associated with the clinical stage and histological grade of endometrial cancer. CircWHSC1 may therefore promote the development of endometrial cancer by sponging miR-646 and targeting NPM1.

5. Conclusions

Bioinformatics and sequencing techniques have been used to identity numerous novel circRNAs involved in the development of cancer. Current studies indicate that circRNAs play an important role in the regulation of cellular proliferation, migration and invasiveness in cervical, ovarian and endometrial cancer, primarily via the miRNA sponging mechanism. Due to the stability of circRNAs, they possess great potential in tumor diagnosis and treatment. Furthermore, circRNAs can regulate gynecological tumors through a variety of molecular mechanisms, and blocking these pathways may represent novel therapeutic methodologies.

Although sequencing techniques have identified a growing number of circRNAs, their functions in gynecological cancer are still largely unclear. Moreover, the sample populations of recent studies have been relatively small and from a single study center, thus the reliability of the results cannot be fully guaranteed. Therefore, the introduction of more clinically available sample types, such as serum and urine, would improve study convenience. In addition, current research is primarily focused on the sponging function of circRNAs, with limited research into other functions. Moreover, due to the complexity of tumor pathogenesis, the mechanisms of circRNAs in tumors are not particularly clear, and further research is required to investigate these mechanisms in more depth.

Based on current research, the present review summarizes the potential of circRNAs as novel biomarkers for the diagnosis and treatment of cervical, ovarian cancer and endometrial cancer. However, further research is required to support these findings.

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Authors' contributions

YS and RH contributed to the conception of the manuscript and wrote the draft. YY collected and prepared the literature. YH and KS revised the manuscript. LZ and BW provided funding and proofread the manuscript. All authors read and reviewed the final manuscript version.

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Competing interests

The authors declare that they have no competing interests.

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