Circular RNAs in gynecological cancer: From molecular mechanisms to clinical applications (Review)

YING LIU[1,2] and HAO AI[1,2]

[1]Department of Gynecology and Obstetrics, The Third Affiliated Hospital of Jinzhou Medical University, Jinzhou, Liaoning 121000, P.R. China; [2]Liaoning Provincial Key Laboratory of Follicular Development and Reproductive Health, Jinzhou Medical University, Jinzhou, Liaoning 121000, P.R. China

Received November 17, 2024; Accepted March 14, 2025

DOI: 10.3892/ol.2025.15037

Abstract. Circular RNAs (circRNAs) have emerged as promising biomarkers and therapeutic targets in gynecological cancer. The present review explored developments in circRNA research in ovarian, endometrial and cervical cancer. circRNA biogenesis, functions and roles in cancer pathogenesis have been discussed, focusing on their potential as diagnostic and prognostic markers. Furthermore, circRNAs mechanisms of action, including miRNA sponging, protein scaffolding and peptide encoding were examined, highlighting specific circRNAs implicated in each cancer type and their clinical significance. The unique properties of circRNAs, such as stability and tissue-specific expression, make them ideal candidates for biomarker development. By synthesizing the currently available literature and identifying future research directions, the present review underscored circRNAs potential to improve gynecological cancer management through novel diagnostic tools, prognostic markers and targeted therapies.

Contents

Correspondence to: Professor Hao Ai, Liaoning Provincial Key Laboratory of Follicular Development and Reproductive Health, Jinzhou Medical University, 2 Heping Road, Jinzhou, Liaoning 121000, P.R. China
E-mail: miraclepeking2010@163.com

Key words: circular RNA, ovarian cancer, endometrial cancer, cervical cancer, vaccine

1. Introduction

Gynecological malignancies, encompassing numerous types of cancer of the female reproductive system, represent a notable global health burden. Among these malignancies, ovarian, endometrial and cervical cancer are the most prevalent. According to GLOBOCAN 2020 statistics, ovarian, endometrial and cervical cancer accounted for 313,959, 417,367 and 604,127 new global cases, respectively, and ranked 19, 17 and 9th, in terms of global cancer incidence. In addition, regarding the mortality rates, ovarian cancer, endometrial cancer and cervical cancer were responsible for 207,252, 97,370 and 341,831 deaths respectively, collectively representing 6.5% of all female cancer-related deaths (1).

Despite advances in medical science, the diagnosis and treatment of gynecological malignancies continue to pose notable challenges. Early detection methods remain elusive for a number of patients, and the current therapeutic approaches often fall short in managing advanced or recurrent disease. However, recent research into circular RNAs (circRNAs) has emerged as a promising option for both diagnostic and therapeutic innovations in gynecological oncology (2,3). circRNAs are a class of non-coding RNAs characterized by their covalently closed loop structure, which have gained considerable attention in cancer research due to their stability, tissue-specific expression and diverse regulatory functions (4). In the context of gynecological malignancies, circRNAs have been implicated in various aspects of tumor biology, including cell proliferation, metastasis and drug resistance (5). For example, in ovarian cancer, circWHSC1 has been shown to promote tumor progression by sponging microRNA (miRNA/miR)-145 and miR-1182, ultimately upregulating mucin-1 (MUC1) and human telomerase reverse transcriptase (hTERT) (6). In endometrial cancer, *homo sapiens* (hsa)_circRNA_079422 has been found to enhance tumor growth and metastasis by modulating the miR-136-5p/high-mobility group AT-hook 2 axis (7). Similarly, in cervical cancer, circRNAs serve a key regulatory role in cervical cancer progression, showing potential as therapeutic agents and novel biomarkers; however, further clinical research is needed to fully understand their therapeutic benefits (8). The unique properties of circRNAs, including their abundance, stability in bodily fluids and tissue-specific expression patterns, make them promising candidates for

biomarker development in gynecological cancer (9). Moreover, the diverse regulatory functions of circRNAs offer potential targets for novel therapeutic interventions (10).

The present review aimed to provide a comprehensive overview of recent advances in circRNA research within the context of gynecological malignancies. The biogenesis and functions of circRNAs, their roles in the pathogenesis of ovarian, endometrial and cervical cancer were explored, and as well as potential applications in diagnosis, prognosis and treatment. By summarizing current knowledge and identifying future research directions, the present review highlighted the potential of circRNAs as a novel avenue for improving the management of gynecological malignancies (Table I).

Introduction to circRNA. circRNAs represent a unique class of non-coding RNA molecules characterized by their covalently closed loop structure, which distinguishes them from linear RNAs by the absence of 5'-3' polarity and polyadenylated tails (11). This distinctive structure, first identified in viruses by Sanger *et al* (12) in 1976, confers properties of enhanced stability, cooperativity and self-complementarity. The presence of circRNAs in eukaryotic cells was subsequently demonstrated by Hsu and Coca-Prados in 1979 (13), marking the beginning of a new era in RNA biology.

Initially, the importance of circRNAs was underappreciated due to limitations in RNA sequencing technologies and bioinformatics tools. For a number of years, these molecules were dismissed as non-functional by-products of aberrant splicing events (14); however, advances in high-throughput sequencing and computational analysis have led to a paradigm shift in the understanding of circRNAs and their potential roles in cellular processes (15). A key breakthrough in circRNA research came with the discovery that these molecules often harbor numerous miRNA binding sites, enabling them to function as competitive endogenous RNAs (ceRNAs) or 'miRNA sponges' (16). This mechanism allows circRNAs to regulate gene expression by modulating the availability of miRNAs, thereby influencing various cellular processes and pathways (17). In the context of gynecological malignancies, this regulatory function has been implicated in key aspects of tumor biology, including cell proliferation, metastasis and drug resistance (3). Beyond their role as miRNA sponges, circRNAs have been shown to interact with RNA-binding proteins (RBPs), potentially modulating protein function and localization (18). In addition, some circRNAs have been reported to encode functional peptides, such as circZNF609 (19) and circFBXW7 (20), adding another layer of complexity to their regulatory potential. These diverse functions underscore the importance of circRNAs in both physiological and pathological processes, including the development and progression of gynecological cancer. As research in this field continues to evolve, circRNAs are emerging as promising biomarkers and potential therapeutic targets in gynecological oncology (21). The unique properties of circRNAs, including tissue-specific expression patterns and stability in bodily fluids, make them attractive candidates for non-invasive diagnostic and prognostic applications (22). Moreover, the ability to manipulate circRNA expression levels or function offers novel options for therapeutic interventions in gynecological malignancies (23).

Classification. The diversity of circRNAs is reflected in their classification, which is primarily based on their genomic origin and structure. Understanding these classifications is essential for elucidating their roles in gynecological malignancies. circRNAs can be categorized into three main subclasses based on their genomic origin and structure. Exonic circRNA (EcircRNA) is the most prevalent form, accounting for >80% of known circRNAs (24); these are generated through the process of 'backsplicing', where a downstream 5' splice site (donor) is joined to an upstream 3' splice site (acceptor). Circular intronic RNA (ciRNA) is derived from intron lariats that evade the typical linear splicing debranching step, retaining a 2'-5' linkage at the branch point (25). Exon-intron circRNA (EIciRNA) contains both exonic and intronic sequences and has been shown to enhance the expression of their parent genes in *cis*, suggesting a potential regulatory role (26). Other types of circRNAs include antisense circRNAs, which are derived from antisense transcripts, and intergenic circRNAs, which originate from intergenic regions or other unannotated genomic sequences (27). As research progresses, and new biotechnologies and bioinformatics strategies emerge, the understanding of circRNA classification and function could continue to evolve (28). Future studies may identify additional subtypes or refine the current classification system, providing deeper insights into the diverse roles of these unique RNA molecules in cellular processes and disease mechanisms.

The classification of circRNAs is not merely an academic exercise but has significant implications for understanding their functions in gynecological cancer. For example, EcircRNAs often act as miRNA sponges, modulating gene expression and influencing tumor progression (29). By contrast, ciRNAs and EIciRNAs tend to regulate gene expression through interactions with the transcriptional machinery (30). The ongoing exploration of circRNA classification in gynecological cancer promises to uncover novel biomarkers for early detection and prognosis, as well as potential therapeutic targets. For example, the tissue-specific expression patterns of certain circRNA classes may be exploited in the development of targeted therapies or diagnostic tools specific to ovarian, endometrial or cervical cancer (3).

Formation mechanisms of circRNA. The biogenesis of circRNAs in gynecological malignancies remains an area of active investigation, with several proposed models offering insights into their formation (4,27,31). A prominent hypothesis posits that during the splicing of mRNA precursors, a process critical in gene expression regulation, non-contiguous exons may be brought into proximity through partial folding of the transcript. This spatial rearrangement can lead to exon skipping, resulting in the formation of a lariat intermediate structure encompassing both exonic and intronic sequences. Subsequently, this lariat undergoes a reverse splicing event, culminating in the generation of a stable circRNA molecule. This mechanism may be particularly relevant in the context of gynecological tumors, where aberrant splicing events are frequently observed and could contribute to the dysregulation of circRNA formation, potentially influencing tumor progression and treatment response (32).

In the context of gynecological malignancies, an alternative model of circRNA biogenesis has gained traction,

Table I. Key circRNAs and their functions in ovarian, endometrial and cervical cancer.

Type of cancer	circRNA	Function	(Refs.)
Ovarian	circMUC16	Promotes proliferation and invasion by sponging miR-199a-5p to regulate beclin-1 and RUNX1 expression	(74)
Ovarian	circCSPP1	Promotes cancer progression by counteracting the tumor-suppressive effects of miR-1236-3p on ZEB1	(75)
Ovarian	circFBXW7	Encodes FBXW7-185aa protein, which acts as a tumor suppressor by inhibiting cancer cell proliferation and migration	(61)
Ovarian	circRNA-encoded peptide SHPRH-146aa	Inhibits tumor growth by protecting full-length SHPRH from degradation	(63)
Endometrial	circTNFRSF21	Serves a crucial role in cancer cell growth and cell cycle progression by competitively binding with miR-1227, activating the MAPK13/ATF2 signaling pathway	(104)
Endometrial	circWHSC1	Promotes cell proliferation, migration and invasion while inhibiting apoptosis	(91)
Endometrial	hsa_circ_0061140	Promotes progression and migration through a regulatory axis involving miR-149-5p and STAT3	(107)
Cervical	circE7	Encodes E7 oncoprotein, contributing to transforming properties of HPV	(62)
Cervical	hsa_circ_0023404	Promotes cancer development by sponging miR-136, leading to increased expression of TFCP2 and subsequent activation of the YAP pathway	(126)
Cervical	circ_0005576	Promotes cell proliferation and metastasis by sponging miR-153-3p and promoting kinesin family member 20A expression	(128)

circRNA, circular RNA; MUC16, mucin-16; CSPP1, centrosome and spindle pole associated protein 1; FBXW7, F-box and WD repeat domain containing 7, SHPRH, SNF2 histone linker PHD RING helicase; TNFRSF21, TNF receptor superfamily member 21; WHSC1, Wolf-Hirschhorn syndrome candidate 1; HPV, human papilloma virus.

emphasizing the role of intronic sequences in facilitating circularization. This mechanism, known as intron pair-driven circularization, involves the interaction of specific complementary sequences within flanking introns. These sequences, often found at the termini of exons, engage in reverse complementary base pairing, effectively bridging distant genomic regions. This intronic 'kissing' interaction brings downstream splice donor sites into close proximity with upstream splice acceptor sites, thereby promoting the circularization of the intervening exonic sequences. In gynecological tumors, where genomic instability and chromosomal rearrangements are common, this mechanism may be particularly relevant, potentially contributing to the aberrant expression of circRNAs observed in these malignancies. Understanding this process could provide insights into tumor-specific circRNA profiles, and their potential diagnostic or therapeutic implications in gynecological oncology (33).

Another emerging model of circRNA formation highlights the pivotal role of RBPs in the landscape of gynecological malignancies. These versatile proteins exhibit a marked capacity to influence circRNA biogenesis through specific interactions with both exonic and intronic sequences. RBPs can selectively bind to motifs located at the termini of exons and introns, subsequently forming dimeric complexes. These RBP dimers serve as molecular bridges, effectively reducing the spatial distance between distal intronic regions. This RBP-mediated proximity facilitates the circular connection of exons, promoting circRNA formation. In the context of gynecological tumors, where the aberrant expression and function of RBPs is frequently observed, this mechanism may contribute to the dysregulation of circRNA profiles. Understanding the interplay between RBPs and circRNA biogenesis in these malignancies may indicate novel diagnostic biomarkers and potential therapeutic targets, thereby advancing the understanding of tumor biology and treatment strategies in gynecological oncology (34).

Functions of circRNA. circRNAs have emerged as key regulators of gene expression and are implicated in the pathogenesis of various human diseases, including gynecological malignancies. These versatile molecules exhibit multiple functional modalities that contribute to cellular processes and disease progression. Current research has elucidated several key functions of circRNAs: i) They can modulate transcriptional activity; ii) act as ceRNAs by sequestering miRNAs; iii) serve as scaffolds for protein complexes; and iv) possess protein-coding potential under specific cellular conditions (35). These diverse functions highlight the significance of circRNAs in the complex landscape of gynecological tumor biology and present potential avenues for diagnostic and therapeutic interventions.

Transcriptional regulation by circRNA. The intricate interplay between circRNA biogenesis and transcriptional regulation has emerged as a notable area of interest in gynecological oncology (36,37). This complex relationship indicates novel

mechanisms of gene expression modulation that may be key in the development and progression of gynecological cancer. In a pioneering study, Ashwal-Fluss *et al* (38) reported a competitive relationship between circRNA splicing and pre-mRNA processing. This competition was shown to occur at the 5' and 3' splice sites, suggesting that circRNA formation may serve as a regulatory checkpoint in the gene expression cascade. In the context of gynecological tumors, where aberrant gene expression is a hallmark feature, this circRNA-mediated regulation of linear transcript levels could represent a novel layer of transcriptional control. Further elucidating this concept, research has demonstrated that optimized circRNA expression systems can markedly enhance backsplicing efficiency (39). This process effectively sequesters exons into circular structures, consequently attenuating the production of linear mRNA transcripts. For example, in ovarian cancer, the formation of circ-mucin 16 (MUC16) has been shown to reduce the expression of its linear counterpart, CA125, a well-known biomarker for ovarian cancer (40). This finding highlights the potential impact of circRNA biogenesis on the expression of clinically relevant genes in gynecological malignancies. In endometrial cancer the circRNA, circ-rho GTPase activating protein 12 (ARHGAP12), has been shown to regulate the expression of its parental gene ARHGAP12, a tumor suppressor, by competing for splicing machinery (41). This regulatory mechanism can influence cell proliferation and invasion, underscoring the functional significance of circRNA-mediated transcriptional control in gynecological cancer.

Moreover, some circRNAs have been shown to interact directly with RNA polymerase II or other components of the transcriptional machinery. For example, the ciRNA ci-ankyrin repeat domain 52 has been reported to accumulate at its sites of transcription and modulate the elongation of its parent gene by associating with RNA polymerase II (42). While this specific circRNA has not been studied in gynecological cancer, similar mechanisms could occur, potentially influencing the expression of key oncogenes or tumor suppressors. The ability of circRNAs to influence linear mRNA production through competitive splicing mechanisms may have notable implications for tumor biology, potentially affecting key oncogenic or tumor-suppressive pathways. These findings underscore the potential of circRNAs as key modulators of gene expression in gynecological malignancies. The complex interplay between circRNA biogenesis and transcriptional regulation offers new perspectives on the molecular mechanisms underlying these types of cancer. Further investigation into this regulatory axis could identify new targets for therapeutic intervention and contribute to the understanding of the complex transcriptional landscape in gynecological cancer. As research in this field progresses, it will be necessary to elucidate the tissue-specific and cancer-specific aspects of circRNA-mediated transcriptional regulation. This knowledge may lead to the development of novel diagnostic tools and therapeutic strategies tailored to specific gynecological malignancies, potentially improving patient outcomes.

miRNA sponges. circRNAs have emerged as key regulators of gene expression in gynecological malignancies, primarily through their function as miRNA sponges. This mechanism is characterized by the presence of multiple miRNA binding sites within circRNA molecules, enabling them to competitively sequester miRNAs (43). By preventing miRNAs from binding to their target mRNAs, circRNAs effectively reduce the inhibitory effect of miRNAs on translation, leading to the increased expression of target genes (44). This competitive binding phenomenon, known as the 'miRNA sponge' effect, represents an important paradigm in post-transcriptional gene regulation (45). An example of this regulatory mechanism is circ-cerebellar degeneration-related protein 1 antisense (CDR1as, also known as ciRS-7), which has been extensively studied due to its marked capacity to bind miR-7 (46). While initially identified in neurological contexts, recent research has begun to elucidate its potential roles in various types of cancer, including gynecological tumors (47). For example, in ovarian cancer, circ_CDR1 has been shown to sponge miR-1270, leading to the upregulation of suppressor of cancer cell invasion and subsequent inhibition of tumor progression (48). In the context of gynecological oncology, the miRNA sponge function of circRNAs has been implicated in various aspects of tumor biology. For example, in cervical cancer, circRNA_0000745 may act as a sponge for miR-3178, upregulating the expression levels of FOXO4 and inhibiting tumor growth (49). Similarly, in endometrial cancer, circ_0002577 has been demonstrated to sponge miR-625-5p, thereby regulating the insulin-like growth factor 1 signaling pathway and influencing tumor progression (50). Understanding these circRNA-miRNA-mRNA regulatory axes in gynecological malignancies offers new insights into the molecular mechanisms underlying tumor development and progression. Moreover, it presents potential opportunities for the development of novel diagnostic biomarkers and therapeutic targets in gynecological oncology (51).

Protein scaffolds or sponges. In addition to their role as miRNA sponges, circRNAs have emerged as important regulators of protein function in various types of cancer, including gynecological malignancies. This function is primarily achieved through their ability to act as protein scaffolds or sponges, facilitating or inhibiting protein-protein interactions and modulating protein activity (36). A well-characterized example of this mechanism is circFOXO3, which has been shown to form a ternary complex with CDK2 and the CDK inhibitor 1, p21. This interaction effectively inhibits CDK2 function, leading to cell cycle arrest (52). While initially studied in cardiac senescence, a research has begun to elucidate the potential roles of circFOXO3 in gynecological cancer (53). For example, in ovarian cancer, circFOXO3 has been shown to drive ovarian cancer progression by orchestrating exosome-mediated intercellular communication targeting the miR-422a/proteolipid protein 2 axis, potentially serving as a valuable biomarker for early detection and treatment monitoring in this aggressive malignancy (54).

Another notable example is circACC1, which forms a ternary complex with the β and γ regulatory subunits of AMP-activated protein kinase (AMPK); this interaction promotes AMPK holoenzyme activity, enabling cancer cells to adapt to metabolic stress and grow under nutrient-limited conditions (55). While the specific role of circ-acetyl-CoA carboxylase 1 (ACC1) in gynecological tumors remains to be

fully elucidated, its function in modulating cellular metabolism suggests potential implications for tumor progression and therapeutic resistance in these types of cancer (56). In addition, circPUM1 has been shown to interact with the nuclear receptor binding protein and the androgen receptor, forming a protein complex that promotes ovarian cancer cell proliferation and invasion (57). This example highlights the diverse mechanisms by which circRNAs can influence protein function and cellular processes in gynecological malignancies. The ability of circRNAs to act as protein scaffolds or sponges adds another layer of complexity to their regulatory functions in cancer biology. By modulating protein-protein interactions and enzyme activities, circRNAs can influence various cellular processes, including cell cycle progression, metabolism and signal transduction (58). Understanding these interactions in the context of gynecological tumors may provide novel insights into disease mechanisms and therapeutic targets (59).

Translation of peptides. Traditionally, circRNAs were considered to be non-coding RNAs; however, a recent study demonstrated that, under specific conditions, some circRNAs can be translated into functional peptides, adding a new dimension to their role in cellular processes and disease pathogenesis, including gynecological malignancies (39). In a seminal study from 2017, Yang *et al* (60) provided the first comprehensive evidence that circRNAs could undergo protein translation following N6-methyladenosine (m6A) modification. These findings demonstrated that m6A-driven circRNA translation is a widespread phenomenon, with hundreds of endogenous circRNAs possessing translation potential. This discovery not only expanded the understanding of the coding capacity of the human transcriptome but also opened novel avenues for exploring circRNA functions in various diseases, including gynecological cancer. In the context of gynecological oncology, the potential for circRNAs to be translated into functional peptides has significant implications. For example, in breast cancer, circ-F-box and WD repeat domain containing 7 (FBXW7) has been shown to encode a novel 21-kDa protein, FBXW7-185aa, which acts as a tumor suppressor by inhibiting the proliferation and migration of cancer cells (61). Similarly, in cervical cancer, circE7 derived from high-risk human papillomavirus (HPV) has been shown to encode the E7 oncoprotein, contributing to the transforming properties of HPV (62). The ability of circRNAs to produce functional peptides adds another layer of complexity to their regulatory roles in gynecological malignancies. These peptides may interact with other cellular components, modulate signaling pathways or directly influence tumor progression. For example, in ovarian cancer, the circRNA-encoded peptide SNF2 histone linker PHD RING helicase (SHPRH)-146aa has been reported to suppress tumor growth by protecting full-length SHPRH from degradation (63). As research in this field progresses, elucidating the specific functions of circRNA-encoded peptides in various types of gynecological cancer will be crucial. Understanding these novel mechanisms may provide insights into tumor-specific molecular signatures and identify new options to develop innovative diagnostic and therapeutic strategies in gynecological oncology (64).

2. circRNA and ovarian cancer

Ovarian cancer is currently the most lethal type of gynecological malignancy, with a markedly high mortality rate. Globally, ovarian cancer is responsible for >200,000 deaths annually (65). The standard treatment protocol typically involves surgical resection followed by platinum-based chemotherapy in combination with paclitaxel (PTX) (66). Despite these interventions, the prognosis for patients with advanced-stage ovarian cancer remains poor, with a 5-year survival rate of ~30% (67). This poor outcome is largely attributed to late-stage diagnosis and the development of chemoresistance (68). The mechanisms underlying chemoresistance in ovarian cancer are multifaceted, involving both tumor microenvironment factors and intrinsic cellular resistance pathways (69). Given these challenges, there is an urgent need to develop novel therapeutic strategies and enhance treatment efficacy to improve patient outcomes. In recent years, circRNAs have emerged as potential biomarkers and therapeutic targets in various types of cancer, including ovarian cancer (70). These unique non-coding RNAs have been implicated in diverse biological processes, and have shown promise in modulating chemoresistance and tumor progression (71). Understanding the role of circRNAs in ovarian cancer could potentially lead to innovative diagnostic tools and targeted therapies, addressing the critical need for improved management of this disease (72).

Mechanistic studies of circRNA in ovarian cancer. Previous investigations have provided information on the roles of circRNAs in ovarian cancer progression, unveiling complex regulatory networks that contribute to tumor development and metastasis. These studies have identified specific circRNAs and their associated molecular pathways, providing valuable insights into potential therapeutic targets (40,73). A notable discovery by Gan *et al* (74) demonstrated that circMUC16 can promote ovarian cancer cell proliferation and invasion through a complex regulatory axis. circMUC16 may modulate the expression of beclin1 and RUNX1 by sponging miR-199a-5p, thereby influencing key oncogenic processes. This finding not only elucidates a novel mechanism of ovarian cancer progression but also highlights the potential of circMUC16 as a therapeutic target. In a separate study, Li *et al* (75) demonstrated the oncogenic role of circ-centrosome and spindle pole associated protein 1 (CSPP1) in ovarian cancer. This previous study demonstrated that circCSPP1 can enhance cancer progression by counteracting the tumor-suppressive effects of miR-1236-3p on ZEB1, a key transcription factor involved in epithelial-mesenchymal transition (EMT). In addition, circCSPP1 depletion was shown to inhibit tumor growth, whereas its overexpression could upregulate oncogenic proteins, further emphasizing its significance in ovarian cancer pathogenesis. These mechanistic studies underscore the complex interplay between circRNAs and their downstream targets in ovarian cancer. However, the pathogenesis of ovarian cancer involves multifaceted mechanisms, and circRNA research, while promising, represents only one aspect of this intricate disease landscape. Further comprehensive investigations are required to fully elucidate the role of circRNAs in ovarian cancer and to translate these findings into clinically relevant applications (76). As research in this field progresses,

integrating circRNA studies with other aspects of cancer biology, such as genomics, proteomics and metabolomics, may provide a more holistic understanding of ovarian cancer pathogenesis, and identify novel diagnostic and therapeutic strategies (77).

Diagnostic value of circRNA in ovarian cancer. circRNAs have emerged as promising biomarkers for ovarian cancer diagnosis, offering unique advantages due to their stability and tissue-specific expression patterns. A previous study highlighted the potential of circRNAs in early detection, disease staging and prognostic prediction for patients with ovarian cancer; Ahmed *et al* (78) pioneered the comprehensive analysis of circRNA expression profiles in ovarian cancer. This study demonstrated a significantly higher number of differentially expressed circRNAs in metastatic tissues compared with that in primary lesions, in contrast to linear mRNA patterns. Notably, circRNA expression showed negative correlation with linear mRNA in key signaling pathways, such as NF-κB and PI3K/AKT. These findings underscore the consistency and stability of circRNA expression, suggesting the potential for circRNAs as robust biomarkers for ovarian cancer detection and progression monitoring. Further research by Pei *et al* (79) identified hsa_circ_0013958 as a highly expressed circRNA in ovarian cancer tissues and cell lines. hsa_circ_0013958 demonstrated a strong association with disease stage and lymph node metastasis, highlighting its potential as a diagnostic and prognostic marker. Several survival analyses have corroborated the clinical relevance of circRNA expression in ovarian cancer (76,80). Abnormal expression levels of specific circRNAs, including hsa_circ_0078607, circ-la ribonucleoprotein 4 (LARP4) and circFAM53B, have been closely linked to pathological stage and poor prognosis (81). These findings suggest that circRNA expression profiles could serve as valuable prognostic indicators for patients with ovarian cancer. The current lack of accurate screening and early diagnostic methods for ovarian cancer underscores the urgent need for novel biomarkers. In-depth research on circRNAs offers a promising avenue for developing early detection strategies for ovarian lesions. By enabling timely diagnosis and treatment initiation, circRNA-based diagnostics could potentially improve patient survival rates (82). As research in this field progresses, integrating circRNA biomarkers with existing diagnostic tools may enhance the accuracy and reliability of ovarian cancer detection. Moreover, the tissue-specific nature of circRNA expression could facilitate the development of personalized diagnostic and prognostic approaches, tailored to the molecular profiles of individual patients (83).

Therapeutic value of circRNA in ovarian cancer. Recent advances in circRNA research have revealed the promising therapeutic potential of circRNA in ovarian cancer treatment. These unique non-coding RNAs have been demonstrated to possess the ability to modulate various oncogenic pathways, offering new avenues for targeted therapies (84,85). Notably, Lu *et al* (86) investigated the tumor-suppressive role of circLARP4 in ovarian cancer and elucidated that circLARP4 can inhibit ovarian cancer progression through the miR-513b-5p/LARP4 axis. This finding not only sheds light on the complex regulatory networks in ovarian cancer but also presents circLARP4 as a potential therapeutic target. Further research has focused on circ-itchy E3 ubiquitin protein ligase (ITCH), another circRNA with notable antitumor properties in ovarian cancer. Overexpression of circITCH has been shown to significantly suppress cell proliferation and to promote apoptosis through direct interaction with miR-10a, by acting as a ceRNA and regulating the circITCH/miR-145/RASA1 axis. These mechanisms have been shown to effectively inhibit ovarian cancer cell proliferation both *in vitro* and *in vivo* (87). The dual functionality of circITCH underscores its potential as a versatile therapeutic agent. The emerging understanding of these circRNA-mediated tumor suppression mechanisms demonstrates novel possibilities for ovarian cancer treatments. By targeting specific circRNAs or their downstream pathways, it may be possible to develop more effective and less toxic therapeutic strategies (88). Moreover, the tissue-specific expression patterns of circRNAs offer the potential for highly targeted therapies with reduced off-target effects. This characteristic could be particularly beneficial in developing personalized treatment approaches for patients with ovarian cancer (2). As research in this field progresses, it is essential to further investigate the safety and efficacy of circRNA-based therapies. Future studies should focus on optimizing delivery methods, understanding potential side effects and exploring combination therapies with existing treatment modalities (89). The therapeutic value of circRNAs in ovarian cancer is increasingly evident. These molecules offer promising targets for developing novel treatment strategies that could potentially improve outcomes for patients with this type of malignancy.

Potential of circRNA as a vaccine candidate in ovarian cancer. circRNAs have emerged as promising candidates for cancer vaccines, with potential applications extending to ovarian cancer. Their unique stability and capacity for durable protein expression make them particularly suitable for vaccine development, offering potential options in the field of hard-to-treat malignancies. Li *et al* (90) demonstrated the efficacy of circRNA cancer vaccines in driving immunity against challenging types of cancer. This previous study established a novel circRNA vaccine platform by encapsulating antigen-coding circRNA in lipid nanoparticles (LNPs). This innovative approach triggered robust innate and adaptive immune activation, showing superior antitumor efficacy in multiple mouse tumor models. Furthermore, the circRNA-LNP vaccine exhibited higher stability and initiated more durable protein expression than its linear counterpart *in vitro*; *in vivo*, the circRNA-LNP vaccine elicited marked innate immune responses and potent antigen-specific T-cell responses, comparable to modified mRNA-LNP vaccines. While specific studies on circRNA vaccines for ovarian cancer are currently limited, the potential is considerable. Certain circRNAs, such as circ-Wolf-Hirschhorn syndrome candidate 1 (WHSC1), have been identified as being highly expressed in ovarian cancer tissues, and serve crucial roles in cancer cell proliferation, apoptosis, migration and invasion (91). These circRNAs could potentially serve as targets for vaccine development. The ability of circRNAs to regulate key cancer-related proteins, such as MUC1 and hTERT in the case of circWHSC1, provides a molecular basis for their potential as vaccine candidates. However, it is important to note that the

application of circRNA vaccines in ovarian cancer is still in its early stages. Further research is needed to identify ovarian cancer-specific circRNAs suitable for vaccine development and to optimize circRNA-LNP formulations for maximum efficacy in ovarian cancer models. In addition, the safety and immunogenicity of circRNA vaccines should be evaluated in preclinical ovarian cancer studies, and potential combinations with existing immunotherapies or targeted treatments should be investigated. As research progresses, the unique properties of circRNAs, such as their resistance to exonuclease degradation and ability to be translated into proteins without 5' capping or polyadenylation, may prove advantageous in developing effective and long-lasting vaccines against ovarian cancer (20). While specific applications in ovarian cancer require further investigation, the initial results of circRNA vaccines in other cancer models are promising and could potentially revolutionize immunotherapy strategies for ovarian cancer in the future (92).

3. circRNA and endometrial cancer

Endometrial cancer is a significant health concern, ranking as the second most prevalent gynecological malignancy in China and the foremost in developed nations. In 2022, China reported ~84,520 new cases of endometrial cancer (93). Various risk factors have been associated with this type of cancer, including obesity, diabetes, polycystic ovary syndrome, infertility, early menarche and late menopause (94). Current screening methods for endometrial cancer primarily rely on transvaginal ultrasound, hysteroscopy and endometrial biopsy (95). However, these techniques have the following limitations: Transvaginal ultrasound results can be subjective, whereas hysteroscopy and endometrial biopsy are invasive procedures, restricting their widespread use in clinical screening (96). The standard treatment approach for endometrial cancer typically involves surgery followed by chemotherapy, often using a combination of carboplatin and PTX (97). Despite these interventions, challenges persist, including poor prognosis and drug resistance in some cases (98). Given these challenges, there is a pressing need to explore novel diagnostic and therapeutic strategies to enhance survival rates for patients with endometrial cancer. circRNAs have emerged as promising candidates in this regard. These unique RNA molecules, characterized by their covalently closed loop structure, have shown potential in both the diagnosis and treatment of various types of cancer, including endometrial cancer (99). A previous study demonstrated that circRNAs serve key roles in endometrial cancer pathogenesis, influencing cell proliferation, invasion and metastasis (100). Moreover, certain circRNAs have been identified as potential biomarkers for early detection and prognostic prediction in endometrial cancer (101). The exploration of circRNA-based therapeutic approaches, such as circRNA-mediated gene therapy or circRNA-targeted drug delivery systems, represents a notable option in endometrial cancer research (102).

Mechanistic studies of circRNA in endometrial cancer. A previous study has provided valuable insights into the biogenesis mechanisms of circRNAs, which can be categorized into three main models: The intron pairing model, the exon skipping model and the RBP model. The intron pairing model posits that complementary sequences within introns form stable secondary structures, such as hairpins, which facilitate back-splicing and the formation of circRNAs (103). In endometrial cancer, the intron pairing model may explain the high expression levels of specific circRNAs, such as circTNFRSF21, which is significantly upregulated and competes with miR-1227 to activate the MAPK13/ATF2 signaling pathway, promoting cancer cell proliferation and cell cycle progression (104). Similarly, overexpression of circWHSC1, driven by intron pairing, enhances cell proliferation, migration and invasion while inhibiting apoptosis (105). The exon skipping model suggests that certain exons are skipped during the normal linear splicing process, leading to the formation of circRNAs (106). In endometrial cancer, hsa_circ_0061140 is formed through exon skipping and interacts with miR-149-5p to upregulate STAT3, thereby promoting cancer progression and migration (107). The RBP model involves the direct modulation of back-splicing by specific RBPs, such as Quaking and Muscleblind. In endometrial cancer, the abnormal expression of these proteins may contribute to the biogenesis of circRNAs like circWHSC1 and hsa_circ_0061140, influencing cancer development (3).

Diagnostic value of circRNA in endometrial cancer. Previous studies have highlighted the potential of circRNAs as diagnostic biomarkers in endometrial cancer. These investigations have demonstrated distinctive circRNA expression patterns in cancer tissues, offering novel potential for early detection and prognostic prediction (102,108). In 2019, Ye *et al* (104) used sequencing techniques to compare circRNA expression profiles in stage III endometrial cancer tissues with adjacent non-cancerous endometrial tissues; significant differential expression of circRNAs between these tissue types was demonstrated. Through bioinformatics analysis, it was identified that the hsa_circ_0039659/hsa-miR-542-3p/hsa-let-7c-5p pathway may be a critical predictor for stage III endometrial cancer. This discovery not only enhances the understanding of the molecular mechanisms underlying endometrial cancer progression but also presents a potential diagnostic tool for advanced-stage disease. Further supporting the diagnostic value of circRNAs, Chen *et al* (109) noted that, while no significant difference in the number of linear RNA transcripts was detected between endometrial cancer tissues and healthy tissues, a marked reduction in circRNA levels was observed within cancer tissues. The comprehensive analysis identified ~120 differentially expressed circRNAs, which may contribute to the susceptibility of endometrial tissues to carcinogenesis. This distinct circRNA signature in cancer tissues underscores the potential of these molecules as specific and sensitive biomarkers for endometrial cancer. These findings collectively suggest that circRNAs hold considerable promise as diagnostic and prognostic biomarkers for endometrial cancer. The unique expression patterns of circRNAs in cancer tissues, coupled with their stability and tissue-specific expression, make them attractive candidates for non-invasive diagnostic tests. Moreover, the identification of specific circRNA-miRNA-mRNA pathways, such as the hsa_circ_0039659/hsa-miR-542-3p/hsa-let-7c-5p axis, provides possibilities for targeted therapies and personalized medicine approaches. Future research should focus on validating these findings in larger, diverse patient cohorts and

exploring the potential of circRNA-based liquid biopsies for the early detection of endometrial cancer. Additionally, investigating the functional roles of these differentially expressed circRNAs may provide deeper insights into the pathogenesis of endometrial cancer and identify new therapeutic targets.

Therapeutic value of circRNA in endometrial cancer. Advances in circRNA research have demonstrated promising therapeutic potential in endometrial cancer. A notable discovery in this field is the identification of hsa_circ_0001860, a novel circRNA associated with medroxyprogesterone acetate (MPA) resistance in patients with endometrial cancer. This circRNA has been shown to be negatively correlated with histological grade and lymph node metastasis, suggesting its potential as a biomarker for disease progression and treatment response (110). Further investigation into the molecular mechanisms of hsa_circ_0001860 has reported a role in regulating SMAD7 expression levels and activating the SMAD7/EMT signaling pathway. Notably, hsa_circ_0001860 has been shown to enhance cancer cell sensitivity to MPA by targeting miR-520h. Experimental studies have demonstrated that overexpression of hsa_circ_0001860, coupled with miR-520h knockdown, can significantly increase cellular sensitivity to MPA treatment. These findings highlight the potential of hsa_circ_0001860 as a therapeutic target for MPA-resistant endometrial cancer (110). By modulating hsa_circ_0001860, it may be possible to overcome drug resistance and improve treatment outcomes in patients with advanced or recurrent endometrial cancer. This approach aligns with the growing interest in circRNAs as both diagnostic biomarkers and therapeutic targets in various types of cancer, including endometrial cancer (111). The discovery of hsa_circ_0001860 and its role in MPA resistance provides novel options for personalized medicine in endometrial cancer treatment. Future research should focus on developing strategies to manipulate this circRNA *in vivo* and to assess its efficacy in clinical settings. Additionally, exploring the interactions between hsa_circ_0001860 and other molecular pathways involved in endometrial cancer progression could provide a more comprehensive understanding of its therapeutic potential. As knowledge regarding circRNA biology is improved, it is likely that more circRNAs with therapeutic value in endometrial cancer will be identified. This emerging field offers possibilities for improving endometrial cancer diagnosis, prognosis and treatment, potentially leading to more effective and targeted therapies for patients with this malignancy.

Potential as a vaccine candidate in endometrial cancer. circRNAs have emerged as promising molecules in cancer research, particularly for gynecological malignancies such as endometrial cancer. Initially recognized for their potential as biomarkers and therapeutic targets, recent advances have highlighted circRNAs as novel vaccine candidates (112). The unique properties of circRNAs, including high stability and resistance to exonuclease-mediated degradation, make them attractive for vaccine development (113). The covalently closed structure circRNAs enables efficient protein expression and potentially allows for rolling circle translation. When engineered and encapsulated in LNPs, circRNA vaccines have demonstrated the ability to elicit robust innate and adaptive immune responses, showing superior antitumor efficacy in preclinical models (114). Research has indicated that circRNA-LNP complexes can induce potent antigen-specific T-cell responses, which are crucial for combating solid tumors such as endometrial cancer (115). The circRNA vaccine platform offers an innovative approach for developing cancer RNA vaccines that may be particularly applicable to endometrial cancer, which is often considered challenging to treat. The potential of circRNA vaccines extends beyond monotherapy; a previous study suggested that circRNA-based approaches may serve as both primary and adjuvant therapies, potentially synergizing with existing immunotherapies to combat obesity-related endometrial cancer (116). For example, a circRNA OVA-luc-LNP vaccine has exhibited efficacy in suppressing immune-exclusive tumor progression, inducing regression in immune-desert tumors and preventing metastasis (90). Compared with traditional mRNA vaccines, circRNA vaccines demonstrate superior stability, prolonged protein expression and the ability to initiate robust immune responses without nucleotide modifications (117). These characteristics position circRNA vaccines as a promising alternative in cancer immunotherapy and have potential to improve endometrial cancer treatment and outcomes in the future. The ability of circRNA vaccines to collaborate with adoptive cell transfer therapy and to suppress late-stage immune-exclusive tumor progression by enhancing T-cell receptor T-cell therapy (TCR-T) cell persistence demonstrates their potential as a cancer therapy (90). Further investigation into circRNA vaccines for endometrial cancer is warranted, as it could lead to novel therapies. The unique properties of circRNAs, combined with their potential for enhanced translation efficiency through engineering, position them as a promising option in effective cancer vaccine development.

4. circRNA and cervical cancer

Cervical cancer remains a notable health issue for women worldwide, ranking as the second most common malignancy after breast cancer. It is also associated with a high mortality rate, being a leading cause of global cancer-related mortality. Persistent infection with HPV is the primary driver of cervical cancer progression. In China, cervical cancer mortality is slightly higher in rural areas than in urban regions, with midwestern areas exhibiting mortality rates about twice those in eastern regions (118). Additionally, recent trends have indicated a decreasing average age of onset for cervical cancer, suggesting a rise in incidence among younger women (119,120). Current treatments for cervical cancer typically involve a combination of surgery, chemotherapy and radiotherapy. However, poor prognosis and low survival rates due to distant metastasis and lymphatic spread continue to challenge patient outcomes (121). Thus, there is an urgent need to identify new therapeutic approaches and early diagnostic biomarkers to improve survival rates. circRNAs have garnered significant attention in cancer research due to their unique properties, including high stability and resistance to exonuclease-mediated degradation (122). These characteristics make circRNAs promising candidates for developing novel therapeutic strategies and diagnostic tools for cervical cancer (123). Studies have suggested that circRNAs can serve as effective biomarkers for

early detection and may offer new opportunities for targeted therapies (5,124). For example, some circRNAs (including circ_0010235 and circCCDC66) have been shown to interact with miRNAs and proteins involved in cancer pathways, influencing tumor growth and metastasis (125). The potential application of circRNA-based therapies could lead to more effective treatment options for cervical cancer, addressing the current limitations of conventional therapies. Research into the role of circRNAs in cervical cancer is still in its early stages but holds promise. Advances in circRNA studies may identify breakthrough therapies, improving prognosis and survival rates for patients with cervical cancer (Table II).

Mechanistic studies of circRNA in cervical cancer. Previous research has unveiled significant roles of circRNAs in the pathogenesis and progression of cervical cancer, offering novel insights into potential diagnostic and therapeutic approaches (47). Notably, survival analyses on hsa_circ_0023404 demonstrated an inverse correlation between hsa_circ_0023404 expression and overall patient survival, with higher expression levels associated with poorer outcomes. Mechanistically, hsa_circ_0023404 functions as a miRNA sponge, specifically targeting miR-136. This interaction led to increased expression levels of the transcription factor CP2 and subsequent activation of the YAP pathway, ultimately driving cancer progression (126). Another notable circRNA, circ_0005576, has been shown to be markedly upregulated in cervical cancer tissues. Localized in the cytoplasm, this circRNA serves a key role in cell proliferation and metastasis (127). Functional studies have demonstrated that knockdown of circ_0005576 can inhibit these malignant behaviors, while its overexpression may enhance them. The underlying mechanism involves circ_0005576 sponging miR-153-3p, thereby promoting the expression of KIF20A, a key player in cancer cell division and movement (128). Given that HPV infection is the primary etiological factor in cervical cancer, exploring the interplay between HPV and circRNAs presents a promising avenue for future research. Understanding these relationships could potentially identify novel therapeutic targets and strategies for cervical cancer treatment (129). These mechanistic studies highlight the complex regulatory networks involving circRNAs in cervical cancer and underscore their potential as both biomarkers and therapeutic targets. Further investigation into the functional roles of circRNAs and their interactions with other molecular players in cervical cancer pathogenesis is warranted to fully harness their clinical potential.

Diagnostic value of circRNA in cervical cancer. circRNAs have emerged as promising diagnostic and prognostic biomarkers in cervical cancer due to their stability and tissue-specific expression patterns. A previous study highlighted the potential of specific circRNAs in predicting disease progression and patient outcomes; Tang *et al* (130) demonstrated that lower serum levels of circFoxO3a are associated with positive lymph node metastasis and increased depth of stromal invasion in patients with cervical cancer. Notably, patients with lower circFOXO3a serum levels exhibited higher overall survival and relapse-free survival rates, suggesting its complex role in cancer progression and its potential as a prognostic marker. Further emphasizing the diagnostic potential of circRNAs, Ding and Zhang (131) identified circ-ATPase phospholipid transporting 8A2 (ATP8A2) as being significantly upregulated in both cervical cancer tissues and cell lines. This finding indicated that elevated levels of circATP8A2 may be strongly associated with advanced International Federation of Gynecology and Obstetrics staging and the degree of myometrial invasion. This association underscores the potential of circATP8A2 as a biomarker for disease severity and progression. These studies collectively demonstrate the promising role of circRNAs as diagnostic and prognostic biomarkers in cervical cancer. The differential expression of circRNAs such as circFOXO3a and circATP8A2 in relation to clinicopathological features offers new avenues for non-invasive diagnosis and personalized treatment strategies. However, further large-scale clinical studies are required to validate these findings and to establish standardized protocols for circRNA-based diagnostics in cervical cancer management.

Therapeutic value of circRNA in cervical cancer. Previous research has unveiled the potential of circRNAs as therapeutic targets in cervical cancer, particularly in addressing drug resistance. In a novel study from 2021, Dong *et al* (132) provided information on the role of circMYBL2 in PTX resistance, a common challenge in cervical cancer treatment, demonstrating that circMYBL2 may serve a key role in modulating the sensitivity of cervical cancer cells to PTX. Overexpression of circ-MYB proto-oncogene like 2 (MYBL2) was found to significantly reduce the growth-inhibitory effects of PTX on cancer cells; by contrast, the knockdown of circMYBL2 enhanced the efficacy of PTX, demonstrating its potential as a therapeutic target. The mechanism underlying this effect was shown to involve the regulation of miR-665; the study showed that overexpression or inhibition of miR-665 could reverse the effects of circMYBL2 on PTX sensitivity. These findings suggest that circMYBL2 functions as a positive regulator of drug resistance and malignant behavior in cervical cancer cells through its interaction with miR-665. This discovery provides novel options for developing targeted therapies for patients with PTX-resistant cervical cancer. By manipulating circMYBL2 levels or disrupting its interaction with miR-665, it may be possible to re-sensitize resistant tumors to PTX treatment. The identification of circMYBL2 as a key player in drug resistance highlights the broader potential of circRNAs as therapeutic targets in cervical cancer. This research not only provides insights into the mechanisms of drug resistance but also offers a promising strategy for overcoming this notable clinical challenge. Future studies may focus on developing circRNA-based therapeutics or using circMYBL2 as a biomarker for predicting PTX response in patients with cervical cancer (133). Several other circRNAs, such as circEIF4G2 (134) and circ_0006528 (135), have also been implicated in cervical cancer progression and drug resistance, further highlighting the therapeutic potential of circRNAs in this malignancy.

Potential as a vaccine candidate in cervical cancer. Advances in circRNA research have demonstrated potential for their application as cancer vaccines, including for

Table II. Summary of potential circRNA biomarkers and therapeutic targets in cervical cancer.

circRNA	Expression change	Potential as biomarker	Potential as a therapeutic target	Related mechanism	(Refs.)
hsa_circ_0000745	Upregulated	Diagnostic marker	Inhibition of tumor progression	Regulates miR-3178/E2F3 signaling pathway	(49)
circMYBL2	Upregulated	Early diagnostic marker	Inhibition of tumor growth	Regulates FUS/EGFR signaling pathway	(132)
hsa_circ_0023404	Upregulated	High (negatively correlated with overall survival)	High	Promotes cancer development by sponging miR-136, leading to increased expression of TFCP2 and subsequent activation of the YAP pathway	(126)
circ_0005576	Upregulated	High	High	Promotes cell proliferation and metastasis by sponging miR-153-3p and promoting kinesin family member 20A expression	(128)
circFOXO3a	Downregulated in serum	High (lower levels associated with lymph node metastasis and deeper stromal invasion)	Potential (complex role)	Lower serum levels associated with higher overall survival and recurrence-free survival	(130)
circATP8A2	Upregulated	High (associated with advanced FIGO stage and myometrial invasion depth)	Potential	Upregulation closely related to disease severity and progression	(131)

MYBL2, MYB proto-oncogene like 2; E2F3, E2F transcription factor 3; TFCP2, transcription factor CP2; ATP8A2, ATPase phospholipid transporting 8A2; FIGO, International Federation of Gynecology and Obstetrics.

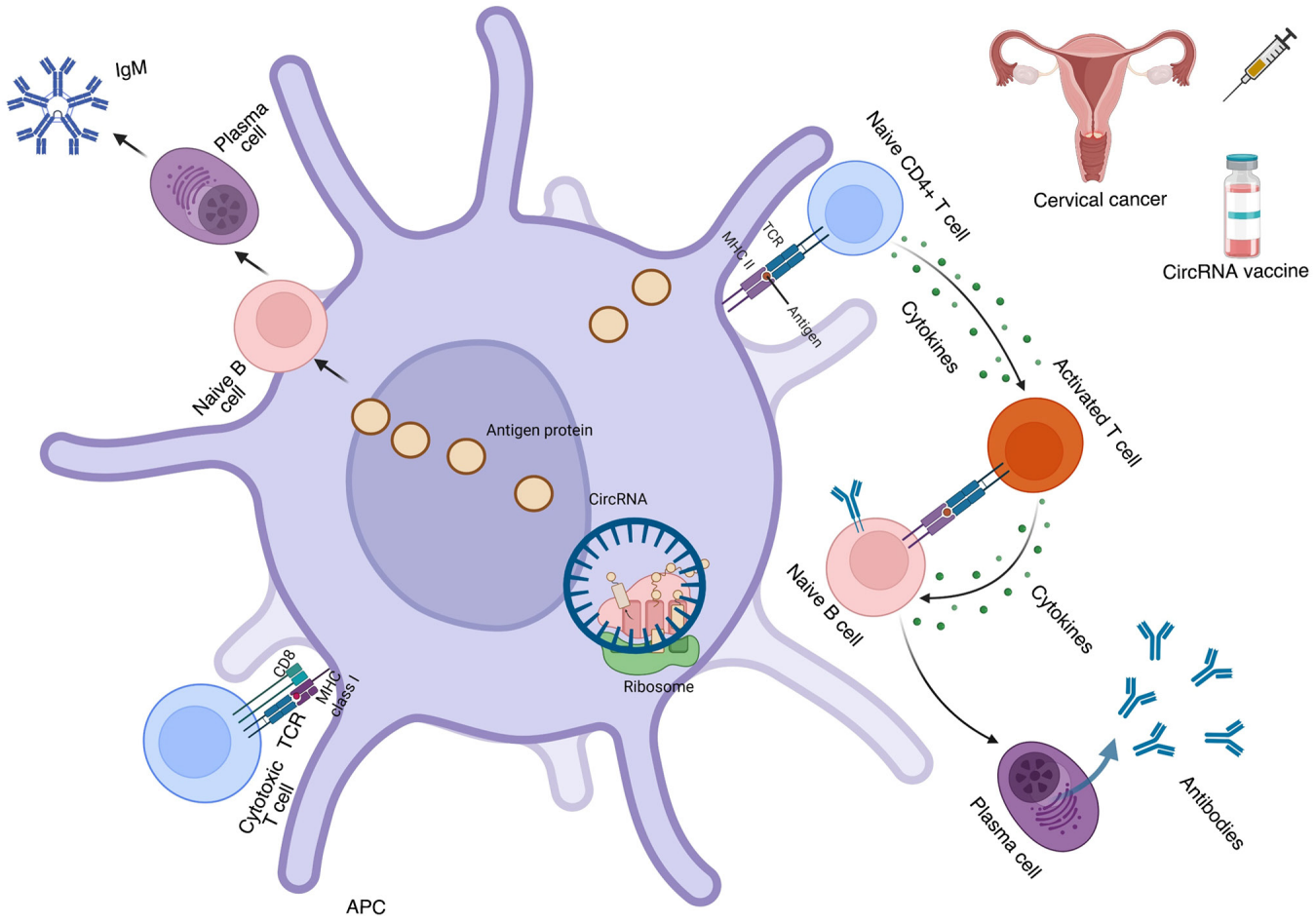

Figure 1. Mechanism of circRNA as a cervical cancer vaccine candidate. Illustration of the immune response triggered by a circRNA-based cervical cancer vaccine, which begins with intramuscular injection, internalization by APCs and translation of circRNAs into cervical cancer-specific antigens. These antigens are presented on MHC I and II molecules, activating $CD8^+$ T cells, $CD4^+$ T cells and B cells, leading to the production of IgM and IgG antibodies and enhancing both cellular and humoral immune responses against cervical cancer. circRNA, circular RNA; APC, antigen-presenting cells; MHC, major histocompatibility complex; TCR, T-cell receptor. This image was created with BioRender.com.

cervical cancer. This approach leverages the unique properties of circRNAs to stimulate robust immune responses against malignancies. For example, Niu *et al* (136) demonstrated the ability of a circRNA-based cancer vaccine to induce potent innate and adaptive immune responses in preclinical models, showcasing its therapeutic potential against types of difficult-to-treat cancer. For instance, combining circRNA-LNP vaccines with adoptive T cell transfer (OT-I cells) achieved complete tumor regression in all treated mice with advanced B16-OVA melanoma, while monotherapy (circRNA vaccine alone) resulted in 60% survival. This combination strategy extended survival beyond 60 days in 100% of mice, compared with rapid mortality in control groups. The potential mechanism is illustrated in Fig. 1.

While direct studies on circRNA-based vaccines for cervical cancer are limited, research on the role of circRNAs in cervical cancer progression provides valuable insights into their potential as vaccine candidates. For example, Ou *et al* (137) reported that circAMOTL1 can promote cervical cancer growth by acting as a sponge for miR-485-5p, leading to increased AMOTL1 levels. This finding highlights the possibility of targeting specific circRNAs involved in cancer progression for vaccine development. Furthermore, Wang *et al* (138) emphasized the significance of genome-wide perturbations in A-to-I RNA editing in dysregulating circRNAs and promoting cervical cancer development. This previous study identified three RNA editing sites as potential biomarkers or therapeutic targets, underscoring the therapeutic potential of focusing on RNA editing dysregulation in cervical cancer treatment. The unique stability and tissue-specific expression patterns of circRNAs make them attractive candidates for vaccine development. By designing circRNA vaccines that encode specific tumor antigens or target circRNAs involved in cervical cancer progression, researchers may be able to elicit more targeted and effective immune responses against this disease. While these findings are promising, it is important to note that the development of circRNA-based vaccines for cervical cancer is still in its early stages. Further research is needed to fully elucidate the mechanisms by which circRNA vaccines stimulate antitumor immunity, and to optimize their delivery and efficacy in clinical settings. Nonetheless, the potential of circRNAs as vaccine candidates offers a potential new option for cervical cancer immunotherapy, which may lead to more effective and personalized treatment strategies in the future.

Challenges and limitations of circRNA-based therapies for gynecological cancer. CircRNAs hold potential as therapeutic tools; however, efficiently and safely translating them into effective treatments requires addressing several critical challenges. Despite the significant potential of circRNAs, efficient and safe delivery remains a major challenge. Current strategies for delivering circRNAs include lipid nanoparticles, viral vectors and exosomes. Each of these delivery systems has its limitations. For instance, viral vectors, while highly efficient, can trigger immune responses or insertional mutagenesis (139). Lipid nanoparticles, on the other hand, require further optimization for stability and tissue specificity (140). Additionally, ensuring that circRNAs are delivered to tumor sites while minimizing their accumulation in non-targeted tissues is a pressing issue (141).

The ability of circRNAs to regulate gene expression by interacting with miRNAs and RBPs can also lead to non-specific targeting effects, causing off-target effects. circRNAs may simultaneously regulate multiple miRNAs, thereby affecting multiple signaling pathways and leading to unintended biological consequences (124). Therefore, in developing circRNA therapies, extensive *in vivo* studies and high-throughput screening are necessary to ensure the specificity of their targeting effects while avoiding interference with normal cellular functions (142).

The clinical translation of circRNA therapies also depends on strict regulatory requirements. As an emerging biotherapeutic tool, circRNAs must meet the standards of international drug regulatory agencies such as the U.S. Food and Drug Administration. Research on the long-term safety, immunogenicity and metabolic pathways of circRNA drugs is still in its early stages. Before circRNA therapies can be used clinically, uniform quality control standards must be established, and rigorous preclinical and clinical trials must be conducted to ensure their safety and efficacy (143).

5. Conclusion

The emerging field of circRNA research offers promising options for advancing the understanding and management of gynecological malignancies. The present review has highlighted the diverse roles of circRNAs in ovarian, endometrial and cervical cancer, from their involvement in tumor progression to their potential as diagnostic and prognostic biomarkers. The unique properties of circRNAs, including their stability, tissue-specific expression and diverse regulatory functions, position them as valuable tools in gynecological oncology. The roles of circRNAs as miRNA sponges, protein scaffolds and even potential peptide encoders underscore their complex involvement in cancer pathogenesis. While notable progress has been made in elucidating the functions of circRNAs in gynecological cancer, much remains to be explored. Future research should focus on validating circRNA-based biomarkers, investigating tissue-specific and cancer-specific circRNA-mediated transcriptional regulation, exploring the therapeutic potential of targeting circRNAs and elucidating the functional significance of circRNA-encoded peptides in gynecological cancer. As the understanding of circRNAs in gynecological malignancies improves, the development of novel diagnostic tools, prognostic markers and targeted therapies is anticipated. These advances hold the potential to markedly improve patient outcomes and to reshape the landscape of gynecological cancer management.

Acknowledgements

Not applicable.

Funding

The present study was provided financial support from the following projects: the scholarship under the China Scholarship Council (grant no. 202308210316), Liaoning Province Science and Technology Program Joint Program Fund Project (grant no. 2023-MSLH-059), Postgraduate Education Teaching Research and Reform Project of Jinzhou Medical University (grant no. YJ2023-018), Jie Bang Gua Shuai Project of Science & Technology Department of Liaoning Province (grant no. 2022JH1/10800070) and Basic Scientific Research Project of Colleges and Universities of Education Department of Liaoning Province (key project) (grant no. 1821240403).

Availability of data and materials

Not applicable.

Author's contributions

YL was responsible for writing the manuscript and investigation of the subject, such as conducting literature reviews to understand the current state of research. HA edited, conceptualized and supervised the present study. Data authentication is not applicable. All authors have read and approved the manuscript.

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. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A and Bray F: Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 71: 209-249, 2021.
2. Conn VM, Chinnaiyan AM and Conn SJ: Circular RNA in cancer. Nat Rev Cancer 24: 597-613, 2024.
3. Qin M, Zhang C and Li Y: Circular RNAs in gynecologic cancers: Mechanisms and implications for chemotherapy resistance. Front Pharmacol 14: 1194719, 2023.
4. 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.
5. Zhang J, Luo Z, Zheng Y, Duan M, Qiu Z and Huang C: CircRNA as an Achilles heel of cancer: Characterization, biomarker and therapeutic modalities. J Transl Med 22: 752, 2024.

6. Zong ZH, Du YP, Guan X, Chen S and Zhao Y: CircWHSC1 promotes ovarian cancer progression by regulating MUC1 and hTERT through sponging miR-145 and miR-1182. J Exp Clin Cancer Res 38: 437, 2019.
7. Li Y, Yang Z, Zeng M, Wang Y, Chen X, Li S, Zhao X and Sun Y: Circular RNA differential expression profiles and bioinformatics analysis of hsa_circRNA_079422 in human endometrial carcinoma. J Obstet Gynaecol 43: 2228894, 2023.
8. Heidari-Ezzati S, Moeinian P, Ahmadian-Nejad B, Maghbbouli F, Abbasi S, Zahedi M, Afkhami H, Shadab A and Sajedi N: The role of long non-coding RNAs and circular RNAs in cervical cancer: Modulating miRNA function. Front Cell Dev Biol 12: 1308730, 2024.
9. Lei B, Tian Z, Fan W and Ni B: Circular RNA: A novel biomarker and therapeutic target for human cancers. Int J Med Sci 16: 292-301, 2019.
10. He AT, Liu J, Li F and Yang BB: Targeting circular RNAs as a therapeutic approach: Current strategies and challenges. Signal Transduct Target Ther 6: 185, 2021.
11. Misir S, Wu N and Yang BB: Specific expression and functions of circular RNAs. Cell Death Differ 29: 481-491, 2022.
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. Hsu MT and Coca-Prados M: Electron microscopic evidence for the circular form of RNA in the cytoplasm of eukaryotic cells. Nature 280: 339-340, 1979.
14. Salzman J, Gawad C, Wang PL, Lacayo N and Brown PO: Circular RNAs are the predominant transcript isoform from hundreds of human genes in diverse cell types. PLoS One 7: e30733, 2012.
15. Nisar S, Bhat AA, Singh M, Karedath T, Rizwan A, Hashem S, Bagga P, Reddy R, Jamal F, Uddin S, *et al*: Insights into the role of CircRNAs: Biogenesis, characterization, functional, and clinical impact in human malignancies. Front Cell Dev Biol 9: 617281, 2021.
16. Papadopoulos N and Trifylli EM: Role of exosomal circular RNAs as microRNA sponges and potential targeting for suppressing hepatocellular carcinoma growth and progression. World J Gastroenterol 30: 994-998, 2024.
17. Panda AC: Circular RNAs Act as miRNA sponges. Adv Exp Med Biol 1087: 67-79, 2018.
18. Hentze MW and Preiss T: Circular RNAs: Splicing's enigma variations. EMBO J 32: 923-925, 2013.
19. Legnini I, Di Timoteo G, Rossi F, Morlando M, Briganti F, Sthandier O, Fatica A, Santini T, Andronache A, Wade M, *et al*: Circ-ZNF609 Is a circular RNA that can be translated and functions in myogenesis. Mol Cell 66: 22-37.e9, 2017.
20. Chen YG, Chen R, Ahmad S, Verma R, Kasturi SP, Amaya L, Broughton JP, Kim J, Cadena C, Pulendran B, *et al*: N6-methyladenosine modification controls circular RNA immunity. Mol Cell 76: 96-109.e9, 2019.
21. Wang Y, Mo Y, Gong Z, Yang X, Yang M, Zhang S, Xiong F, Xiang B, Zhou M, Liao Q, *et al*: Circular RNAs in human cancer. Mol Cancer 16: 25, 2017.
22. Tashakori N, Mikhailova MV, Mohammedali ZA, Mahdi MS, Ali Al-Nuaimi AM, Radi UK, Alfaraj AM and Kiasari BA: Circular RNAs as a novel molecular mechanism in diagnosis, prognosis, therapeutic target, and inhibiting chemoresistance in breast cancer. Pathol Res Pract 263: 155569, 2024.
23. Holdt LM, Kohlmaier A and Teupser D: Circular RNAs as therapeutic agents and targets. Front Physiol 9: 1262, 2018.
24. Ragan C, Goodall GJ, Shirokikh NE and Preiss T: Insights into the biogenesis and potential functions of exonic circular RNA. Sci Rep 9: 2048, 2019.
25. Wang T, Zhang X and Zheng B: Identification of intronic lariat-derived circular RNAs in arabidopsis by RNA deep sequencing. Methods Mol Biol 2362: 93-100, 2021.
26. Zhong Y, Yang Y, Wang X, Ren B, Wang X, Shan G and Chen L: Systematic identification and characterization of exon-intron circRNAs. Genome Res 34: 376-393, 2024.
27. Zhang XO, Dong R, Zhang Y, Zhang JL, Luo Z, Zhang J, Chen LL and Yang L: Diverse alternative back-splicing and alternative splicing landscape of circular RNAs. Genome Res 26: 1277-1287, 2016.
28. Guo Z, Cao Q, Zhao Z and Song C: Biogenesis, features, functions, and disease relationships of a specific circular RNA: CDR1as. Aging Dis 11: 1009-1020, 2020.
29. Zhu J, Li Q, Wu Z, Xu W and Jiang R: Circular RNA-mediated miRNA sponge & RNA binding protein in biological modulation of breast cancer. Noncoding RNA Res 9: 262-276, 2024.
30. Conn SJ, Pillman KA, Toubia J, Conn VM, Salmanidis M, Phillips CA, Roslan S, Schreiber AW, Gregory PA and Goodall GJ: The RNA binding protein quaking regulates formation of circRNAs. Cell 160: 1125-1134, 2015.
31. Jeck WR, Sorrentino JA, Wang K, Slevin MK, Burd CE, Liu J, Marzluff WF and Sharpless NE: Circular RNAs are abundant, conserved, and associated with ALU repeats. RNA 19: 141-157, 2013.
32. Pisignano G, Michael DC, Visal TH, Pirlog R, Ladomery M and Calin GA: Going circular: History, present, and future of circRNAs in cancer. Oncogene 42: 2783-2800, 2023.
33. Zhao X, Zhong Y, Wang X, Shen J and An W: Advances in circular RNA and its applications. Int J Med Sci 19: 975-985, 2022.
34. Li L, Wei C, Xie Y, Su Y, Liu C, Qiu G, Liu W, Liang Y, Zhao X, Huang D and Wu D: Expanded insights into the mechanisms of RNA-binding protein regulation of circRNA generation and function in cancer biology and therapy. Gen Dis: 101383, 2024.
35. Chen LL: The expanding regulatory mechanisms and cellular functions of circular RNAs. Nature reviews. Nat Rev Mol Cell Biol 21: 475-490, 2020.
36. Huang A, Zheng H, Wu Z, Chen M and Huang Y: Circular RNA-protein interactions: functions, mechanisms, and identification. Theranostics 10: 3503-3517, 2020.
37. Chen L and Shan G: CircRNA in cancer: Fundamental mechanism and clinical potential. Cancer Lett 505: 49-57, 2021.
38. Ashwal-Fluss R, Meyer M, Pamudurti NR, Ivanov A, Bartok O, Hanan M, Evantal N, Memczak S, Rajewsky N and Kadener S: circRNA biogenesis competes with pre-mRNA splicing. Mol Cell 56: 55-66, 2014.
39. Hwang HJ and Kim YK: Molecular mechanisms of circular RNA translation. Exp Mol Med 56: 1272-1280, 2024.
40. 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.
41. Gao S, Zhao T, Meng F, Luo Y, Li Y and Wang Y: Circular RNAs in endometrial carcinoma (Review). Oncol Rep 48: 212, 2022.
42. Zhang Y, Zhang XO, Chen T, Xiang JF, Yin QF, Xing YH, Zhu S, Yang L and Chen LL: Circular intronic long noncoding RNAs. Mol Cell 51: 792-806, 2013.
43. Ye C, Liu Z, Xie Q, Tang Y, Zeng J, Feng Z, Liu J and Xie H: Adeno-associated virus mediated artificial circular RNA for triggering cancer immunotherapy to treat prostate cancer. Front Oncol 15: 1443571, 2025.
44. Lv H, Wei X and Lin Y: Immunoregulatory role of exosomal CircRNAs in the tumor microenvironment. Front Oncol 15: 1453786, 2025.
45. Jarlstad Olesen MT and S Kristensen L: Circular RNAs as microRNA sponges: Evidence and controversies. Essays Biochem 65: 685-696, 2021.
46. Piwecka M, Glažar P, Hernandez-Miranda LR, Memczak S, Wolf SA, Rybak-Wolf A, Filipchyk A, Klironomos F, Cerda Jara CA, Fenske P, *et al*: Loss of a mammalian circular RNA locus causes miRNA deregulation and affects brain function. Science 357: eaam8526, 2017.
47. Heydarnia E, Dorostgou Z, Hedayati N, Mousavi V, Yahyazadeh S, Alimohammadi M, Gheibi M, Heidari P, Igder S, Mafi A and Vakili O: Circular RNAs and cervical cancer: Friends or foes? A landscape on circRNA-mediated regulation of key signaling pathways involved in the onset and progression of HPV-related cervical neoplasms. Cell Commun Signal 22: 107, 2024.
48. Ghafouri-Fard S, Khoshbakht T, Hussen BM, Sarfaraz S, Taheri M and Ayatollahi SA: Circ_CDR1as: A circular RNA with roles in the carcinogenesis. Pathol Res Pract 236: 153968, 2022.
49. Jiao J, Zhang T, Jiao X, Huang T, Zhao L, Ma D and Cui B: hsa_circ_0000745 promotes cervical cancer by increasing cell proliferation, migration, and invasion. J Cell Physiol 235: 1287-1295, 2020.
50. Wang Y, Yin L and Sun X: CircRNA hsa_circ_0002577 accelerates endometrial cancer progression through activating IGF1R/PI3K/Akt pathway. J Exp Clin Cancer Res 39: 169, 2020.
51. Ma Y, Zheng L, Gao Y, Zhang W, Zhang Q and Xu Y: A comprehensive overview of circRNAs: Emerging biomarkers and potential therapeutics in gynecological cancers. Front Cell Dev Biol 9: 709512, 2021.

52. Du WW, Yang W, Liu E, Yang Z, Dhaliwal P and Yang BB: Foxo3 circular RNA retards cell cycle progression via forming ternary complexes with p21 and CDK2. Nucleic Acids Res 44: 2846-2858, 2016.
53. Rao D, Yu C, Sheng J, Lv E and Huang W: The emerging roles of circFOXO3 in cancer. Front Cell Dev Biol 9: 659417, 2021.
54. Wang L, Chen J and Lu C: Circular RNA Foxo3 enhances progression of ovarian carcinoma cells. Aging 13: 22432-22443, 2021.
55. Li Q, Wang Y, Wu S, Zhou Z, Ding X, Shi R, Thorne RF, Zhang XD, Hu W and Wu M: CircACC1 regulates assembly and activation of AMPK complex under metabolic stress. Cell Metab 30: 157-173.e7, 2019.
56. Zhou M, Yang Z, Wang D, Chen P and Zhang Y: The circular RNA circZFR phosphorylates Rb promoting cervical cancer progression by regulating the SSBP1/CDK2/cyclin E1 complex. J Exp Clin Cancer Res 40: 48, 2021.
57. 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.
58. Zhou WY, Cai ZR, Liu J, Wang DS, Ju HQ and Xu RH: Circular RNA: Metabolism, functions and interactions with proteins. Mol Cancer 19: 172, 2020.
59. Xue C, Li G, Lu J and Li L: Crosstalk between circRNAs and the PI3K/AKT signaling pathway in cancer progression. Signal Transduct Target Ther 6: 400, 2021.
60. Yang Y, Fan X, Mao M, Song X, Wu P, Zhang Y, Jin Y, Yang Y, Chen LL, Wang Y, *et al*: Extensive translation of circular RNAs driven by N^6-methyladenosine. Cell Res 27: 626-641, 2017.
61. Ye F, Gao G, Zou Y, Zheng S, Zhang L, Ou X, Xie X and Tang H: circFBXW7 inhibits malignant progression by sponging miR-197-3p and encoding a 185-aa protein in triple-negative breast cancer. Mol Ther Nucleic Acids 18: 88-98, 2019.
62. Zhao J, Lee EE, Kim J, Yang R, Chamseddin B, Ni C, Gusho E, Xie Y, Chiang CM, Buszczak M, *et al*: Transforming activity of an oncoprotein-encoding circular RNA from human papillomavirus. Nat Commun 10: 2300, 2019.
63. Ju X, Tang Y, Qu R and Hao S: The emerging role of circ-SHPRH in cancer. Onco Targets Ther 14: 4177-4188, 2021.
64. Lei M, Zheng G, Ning Q, Zheng J and Dong D: Translation and functional roles of circular RNAs in human cancer. Mol Cancer 19: 30, 2020.
65. Zhang S, Cheng C, Lin Z, Xiao L, Su X, Zheng L, Mu Y, Liao M, Ouyang R, Li W, *et al*: The global burden and associated factors of ovarian cancer in 1990-2019: Findings from the global burden of disease study 2019. BMC Public Health 22: 1455, 2022.
66. Bowtell DD, Böhm S, Ahmed AA, Aspuria PJ, Bast RC Jr, Beral V, Berek JS, Birrer MJ, Blagden S, Bookman MA, *et al*: Rethinking ovarian cancer II: Reducing mortality from high-grade serous ovarian cancer. Nat Rev Cancer 15: 668-679, 2015.
67. Torre LA, Trabert B, DeSantis CE, Miller KD, Samimi G, Runowicz CD, Gaudet MM, Jemal A and Siegel RL: Ovarian cancer statistics, 2018. CA Cancer J Clin 68: 284-296, 2018.
68. Colombo N, Ledermann JA and Lorusso D: Newly diagnosed and relapsed epithelial ovarian cancer: ESMO clinical practice guideline for diagnosis, treatment and follow-up. Ann Oncol 34: 127-144, 2023.
69. Tendulkar S and Dodamani S: Chemoresistance in ovarian cancer: Prospects for new drugs. Anticancer Agents Med Chem 21: 668-678, 2021.
70. Xing Y, Liang X, Lv X, Cheng Y, Du J, Liu C and Yang Y: New insights into the role of circular RNAs in ovarian cancer. Pathol Res Pract 238: 154073, 2022.
71. Xu J, Ji L, Liang Y, Wan Z, Zheng W, Song X, Gorshkov K, Sun Q, Lin H, Zheng X, *et al*: CircRNA-SORE mediates sorafenib resistance in hepatocellular carcinoma by stabilizing YBX1. Signal Transduct Target Ther 5: 298, 2020.
72. Luo Y, Fu Y, Huang R, Gao M, Liu F, Gui R and Nie X: CircRNA_101505 sensitizes hepatocellular carcinoma cells to cisplatin by sponging miR-103 and promotes oxidored-nitro domain-containing protein 1 expression. Cell Death Discov 5: 121, 2019.
73. Wang H, Zhang Y, Miao H, Xu T, Nie X and Cheng W: CircRAD23B promotes proliferation and carboplatin resistance in ovarian cancer cell lines and organoids. Cancer Cell Int 24: 42, 2024.
74. 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.
75. Li QH, Liu Y, Chen S, Zong ZH, Du YP, Sheng XJ and Zhao Y: circ-CSPP1 promotes proliferation, invasion and migration of ovarian cancer cells by acting as a miR-1236-3p sponge. Biomed Pharmacother 114: 108832, 2019.
76. Foruzandeh Z, Zeinali-Sehrig F, Nejati K, Rahmanpour D, Pashazadeh F, Seif F and Alivand MR: CircRNAs as potent biomarkers in ovarian cancer: A systematic scoping review. Cell Mol Biol Lett 26: 41, 2021.
77. Vo JN, Cieslik M, Zhang Y, Shukla S, Xiao L, Zhang Y, Wu YM, Dhanasekaran SM, Engelke CG, Cao X, *et al*: The landscape of circular RNA in cancer. Cell 176: 869-881.e13, 2019.
78. Ahmed I, Karedath T, Andrews SS, Al-Azwani IK, Mohamoud YA, Querleu D, Rafii A and Malek JA: Altered expression pattern of circular RNAs in primary and metastatic sites of epithelial ovarian carcinoma. Oncotarget 7: 36366-36381, 2016.
79. Pei C, Wang H, Shi C, Zhang C and Wang M: CircRNA hsa_circ_0013958 may contribute to the development of ovarian cancer by affecting epithelial-mesenchymal transition and apoptotic signaling pathways. J Clin Lab Anal 34: e23292, 2020.
80. Sun Y, Chen X, Shi Y, Teng F, Dai C, Ge L, Xu J and Jia X: hsa_circ_0020093 suppresses ovarian cancer progression by modulating LRPPRC activity and miR-107/LATS2 signaling. Biol Direct 19: 69, 2024.
81. Zhang N, Jin Y, Hu Q, Cheng S, Wang C, Yang Z and Wang Y: Circular RNA hsa_circ_0078607 suppresses ovarian cancer progression by regulating miR-518a-5p/Fas signaling pathway. J Ovarian Res 13: 64, 2020.
82. Shabaninejad Z, Vafadar A, Movahedpour A, Ghasemi Y, Namdar A, Fathizadeh H, Pourhanifeh MH, Savardashtaki A and Mirzaei H: Circular RNAs in cancer: New insights into functions and implications in ovarian cancer. J Ovarian Res 12: 84, 2019.
83. Malviya A and Bhuyan R: Circular RNAs in cancer: Roles, mechanisms, and therapeutic potential across colorectal, gastric, liver, and lung carcinomas. Discov Oncol 16: 5, 2025.
84. Zhu Y, Liang L, Zhao Y, Li J, Zeng J, Yuan Y, Li N and Wu L: CircNUP50 is a novel therapeutic target that promotes cisplatin resistance in ovarian cancer by modulating p53 ubiquitination. J Nanobiotechnology 22: 35, 2024.
85. Wang Y, Chen X and Yang Y: CircRNA-regulated glucose metabolism in ovarian cancer: An emerging landscape for therapeutic intervention. Clin Transl Oncol 26: 584-596, 2024.
86. Lu H, Guo Q, Mao G, Zhu J and Li F: CircLARP4 suppresses cell proliferation, invasion and glycolysis and promotes apoptosis in non-small cell lung cancer by targeting miR-135b. Onco Targets Ther 13: 3717-3728, 2020.
87. Luo L, Gao YQ and Sun XF: Circular RNA ITCH suppresses proliferation and promotes apoptosis in human epithelial ovarian cancer cells by sponging miR-10a-α. Eur Rev Med Pharmacol Sci 22: 8119-8126, 2018.
88. Verduci L, Tarcitano E, Strano S, Yarden Y and Blandino G: CircRNAs: Role in human diseases and potential use as biomarkers. Cell Death Dis 12: 468, 2021.
89. Arnaiz E, Sole C, Manterola L, Iparraguirre L, Otaegui D and Lawrie CH: CircRNAs and cancer: Biomarkers and master regulators. Semin Cancer Biol 58: 90-99, 2019.
90. Li H, Peng K, Yang K, Ma W, Qi S, Yu X, He J, Lin X and Yu G: Circular RNA cancer vaccines drive immunity in hard-to-treat malignancies. Theranostics 12: 6422-6436, 2022.
91. Zhang X, Yuan Y, Wang X, Wang H, Zhang L and He J: CircWHSC1 (CircNSD2): A novel circular RNA in multiple cancers. Clin Med Insights Oncol 18: 11795549241254781, 2024.
92. Du Y, Zuber PK, Xiao H, Li X, Gordiyenko Y and Ramakrishnan V: Efficient circular RNA synthesis for potent rolling circle translation. Nat Biomed Eng: Dec 13, 2024 (Epub ahead of print).
93. Li J, Li X, Quan C, Li X, Wan C and Wu X: Genomic profile of Chinese patients with endometrial carcinoma. BMC Cancer 23: 888, 2023.
94. Morice P, Leary A, Creutzberg C, Abu-Rustum N and Darai E: Endometrial cancer. Lancet 387: 1094-1108, 2016.
95. Du Y, Xu Y, Qin Z, Sun L, Chen Y, Han L and Zheng A: The oncology safety of diagnostic hysteroscopy in early-stage endometrial cancer: A systematic review and meta-analysis. Front Oncol 11: 742761, 2021.
96. Clarke MA, Long BJ, Del Mar Morillo A, Arbyn M, Bakkum-Gamez JN and Wentzensen N: Association of endometrial cancer risk with postmenopausal bleeding in women: A systematic review and meta-analysis. JAMA Intern Med 178: 1210-1222, 2018.

97. Colombo N, Creutzberg C, Amant F, Bosse T, González-Martín A, Ledermann J, Marth C, Nout R, Querleu D, Mirza MR, *et al*: ESMO-ESGO-ESTRO consensus conference on endometrial cancer: Diagnosis, treatment and follow-up. Ann Oncol 27: 16-41, 2016.
98. Kok PS, Antill YC, Scott CL and Lee CK: The impact of single agent PD-1 or PD-L1 inhibition on advanced endometrial cancers: Meta-analysis. ESMO Open 7: 100635, 2022.
99. Tao M, Zheng M, Xu Y, Ma S, Zhang W and Ju S: CircRNAs and their regulatory roles in cancers. Mol Med 27: 94, 2021.
100. Xu H, Gong Z, Shen Y, Fang Y and Zhong S: Circular RNA expression in extracellular vesicles isolated from serum of patients with endometrial cancer. Epigenomics 10: 187-197, 2018.
101. Zhang W, Xu C, Yang Z, Zhou J, Peng W, Zhang X, Li H, Qu S and Tao K: Circular RNAs in tumor immunity and immunotherapy. Mol Cancer 23: 171, 2024.
102. Włodarczyk K, Kuryło W, Pawłowska-Łachut A, Skiba W, Suszczyk D, Pieniądz P, Majewska M, Boniewska-Bernacka E and Wertel I: circRNAs in endometrial cancer-a promising biomarker: State of the art. Int J Mol Sci 25: 6387, 2024.
103. Das A, Sinha T, Shyamal S and Panda AC: Emerging role of circular RNA-protein interactions. Noncoding RNA 7: 48, 2021.
104. Ye F, Tang QL, Ma F, Cai L, Chen M, Ran XX, Wang XY and Jiang XF: Analysis of the circular RNA transcriptome in the grade 3 endometrial cancer. Cancer Manag Res 11: 6215-6227, 2019.
105. Liu Y, Chen S, Zong ZH, Guan X and Zhao Y: CircRNA WHSC1 targets the miR-646/NPM1 pathway to promote the development of endometrial cancer. J Cell Mol Med 24: 6898-6907, 2020.
106. Mumtaz PT, Taban Q, Dar MA, Mir S, Haq ZU, Zargar SM, Shah RA and Ahmad SM: Deep insights in circular RNAs: From biogenesis to therapeutics. Biol Proced Online 22: 10, 2020.
107. Liu Y, Chang Y and Cai Y: Hsa_circ_0061140 promotes endometrial carcinoma progression via regulating miR-149-5p/STAT3. Gene 745: 144625, 2020.
108. Shi R, Zhao R, Shen Y, Wei S, Zhang T, Zhang J, Shu W, Cheng S, Teng H and Wang H: IGF2BP2-modified circular RNA circCHD7 promotes endometrial cancer progression via stabilizing PDGFRB and activating JAK/STAT signaling pathway. Cancer Gene Ther 31: 1221-1236, 2024.
109. Chen BJ, Byrne FL, Takenaka K, Modesitt SC, Olzomer EM, Mills JD, Farrell R, Hoehn KL and Janitz M: Analysis of the circular RNA transcriptome in endometrial cancer. Oncotarget 9: 5786-5796, 2017.
110. Yuan S, Zheng P, Sun X, Zeng J, Cao W, Gao W, Wang Y and Wang L: Hsa_Circ_0001860 promotes Smad7 to enhance MPA resistance in endometrial cancer via miR-520h. Front Cell Dev Biol 9: 738189, 2021.
111. Su M, Xiao Y, Ma J, Tang Y, Tian B, Zhang Y, Li X, Wu Z, Yang D, Zhou Y, *et al*: Circular RNAs in cancer: Emerging functions in hallmarks, stemness, resistance and roles as potential biomarkers. Mol Cancer 18: 90, 2019.
112. Ren Y, Manoharan T, Liu B, Cheng CZM, En Siew B, Cheong WK, Lee KY, Tan IJ, Lieske B, Tan KK and Chia G: Circular RNA as a source of neoantigens for cancer vaccines. J Immunother Cancer 12: e008402, 2024.
113. Xie J, Ye F, Deng X, Tang Y, Liang JY, Huang X, Sun Y, Tang H, Lei J, Zheng S and Zou Y: Circular RNA: A promising new star of vaccine. J Transl Int Med 11: 372-381, 2023.
114. Liu X, Zhang Y, Zhou S, Dain L, Mei L and Zhu G: Circular RNA: An emerging frontier in RNA therapeutic targets, RNA therapeutics, and mRNA vaccines. J Control Release 348: 84-94, 2022.
115. Li W, Liu JQ, Chen M, Xu J and Zhu D: Circular RNA in cancer development and immune regulation. J Cell Mol Med 26: 1785-1798, 2022.
116. Takenaka K, Olzomer EM, Hoehn KL, Curry-Hyde A, Jun Chen B, Farrell R, Byrne FL and Janitz M: Investigation of circular RNA transcriptome in obesity-related endometrial cancer. Gene 855: 147125, 2023.
117. Su P, Zhang L, Zhou F and Zhang L: Circular RNA vaccine, a novel mRNA vaccine design strategy for SARS-CoV-2 and variants. MedComm (2020) 3: e153, 2022.
118. Xiaohui C: Analysis cervical cancer among urban and rural residents in Xiangyang, Hubei, 2017-2019. Prog Med Sci 9: 1-5, 2025.
119. Agarwal R, King JB, Gopalani SV and Senkomago V: Cervical cancer incidence and trends among women aged 15-29 years by county-level economic status and rurality-United States, 2007-2020. Cancer Epidemiol 94: 102730, 2025.
120. Tanaka S, Palmer M and Katanoda K: Trends in cervical cancer incidence and mortality of young and middle adults in Japan. Cancer Sci 113: 1801-1807, 2022.
121. Liu X, Meng Q, Wang W, Zhou Z, Zhang F and Hu K: Predictors of distant metastasis in patients with cervical cancer treated with definitive radiotherapy. J Cancer 10: 3967-3974, 2019.
122. Ogasawara A and Hasegawa K: Recent advances in immunotherapy for cervical cancer. Int J Clin Oncol 30: 434-448, 2025.
123. Wan J, Wang Z, Wang L, Wu L, Zhang C, Zhou M, Fu ZF and Zhao L: Circular RNA vaccines with long-term lymph node-targeting delivery stability after lyophilization induce potent and persistent immune responses. mBio 15: e0177523, 2024.
124. Saleem A, Khan MU, Zahid T, Khurram I, Ghani MU, Ullah I, Munir R, Calina D and Sharifi-Rad J: Biological role and regulation of circular RNA as an emerging biomarker and potential therapeutic target for cancer. Mol Biol Rep 51: 296, 2024.
125. Ma Y, Wang T, Zhang X, Wang P and Long F: The role of circular RNAs in regulating resistance to cancer immunotherapy: Mechanisms and implications. Cell Death Dis 15: 312, 2024.
126. Zhang J, Zhao X, Zhang J, Zheng X and Li F: Circular RNA hsa_circ_0023404 exerts an oncogenic role in cervical cancer through regulating miR-136/TFCP2/YAP pathway. Biochem Biophys Res Commun 501: 428-433, 2018.
127. Shi Y, He R, Yang Y, He Y, Shao K, Zhan L and Wei B: Circular RNAs: Novel biomarkers for cervical, ovarian and endometrial cancer (Review). Oncol Rep 44: 1787-1798, 2020.
128. Ma H, Tian T, Liu X, Xia M, Chen C, Mai L, Xie S and Yu L: Upregulated circ_0005576 facilitates cervical cancer progression via the miR-153/KIF20A axis. Biomed Pharmacother 118: 109311, 2019.
129. Hsu CY, Faisal A, Jumaa SS, Gilmanova NS, Ubaid M, Athab AH, Mirzaei R and Karampoor S: Exploring the impact of circRNAs on cancer glycolysis: Insights into tumor progression and therapeutic strategies. Noncoding RNA Res 9: 970-994, 2024.
130. Tang C, Xie Y, Yu T, Liu N, Wang Z, Woolsey RJ, Tang Y, Zhang X, Qin W, Zhang Y, *et al*: m^{6}A-dependent biogenesis of circular RNAs in male germ cells. Cell Res 30: 211-228, 2020.
131. Ding L and Zhang H: Circ-ATP8A2 promotes cell proliferation and invasion as a ceRNA to target EGFR by sponging miR-433 in cervical cancer. Gene 705: 103-108, 2019.
132. Dong M, Li P, Xie Y, Wang Z and Wang R: CircMYBL2 regulates the resistance of cervical cancer cells to paclitaxel via miR-665-dependent regulation of EGFR. Drug Dev Res 82: 1193-1205, 2021.
133. Zhou M, Liu L, Wang J and Liu W: The role of long noncoding RNAs in therapeutic resistance in cervical cancer. Front Cell Dev Biol 10: 1060909, 2022.
134. Mao Y, Zhang L and Li Y: circEIF4G2 modulates the malignant features of cervical cancer via the miR-218/HOXA1 pathway. Mol Med Rep 19: 3714-3722, 2019.
135. Liu G, Zhang Z, Song Q, Guo Y, Bao P and Shui H: Circ_0006528 contributes to paclitaxel resistance of breast cancer cells by regulating miR-1299/CDK8 axis. Onco Targets Ther 13: 9497-9511, 2020.
136. Niu D, Wu Y and Lian J: Circular RNA vaccine in disease prevention and treatment. Signal Transduct Target Ther 8: 341, 2023.
137. Ou R, Lv J, Zhang Q, Lin F, Zhu L, Huang F, Li X, Li T, Zhao L, Ren Y and Xu Y: circAMOTL1 motivates AMOTL1 expression to facilitate cervical cancer growth. Mol Ther Nucleic Acids 19: 50-60, 2020.
138. Wang Y, Xu X, Yu S, Jeong KJ, Zhou Z, Han L, Tsang YH, Li J, Chen H, Mangala LS, *et al*: Systematic characterization of A-to-I RNA editing hotspots in microRNAs across human cancers. Genome Res 27: 1112-1125, 2017.
139. Liu Y, Ou Y and Hou L: Advances in RNA-based therapeutics: Challenges and innovations in RNA delivery systems. Curr Issues Mol Biol 47: 22, 2024.
140. Xu F, Xiao Q, Du WW, Wang S and Yang BB: CircRNA: Functions, applications and prospects. Biomolecules 14: 1503, 2024.
141. Zhang F, Jiang J, Qian H, Yan Y and Xu W: Exosomal circRNA: Emerging insights into cancer progression and clinical application potential. J Hematol Oncol 16: 67, 2023.
142. Feng XY, Zhu SX, Pu KJ, Huang HJ, Chen YQ and Wang WT: New insight into circRNAs: Characterization, strategies, and biomedical applications. Exp Hematol Oncol 12: 91, 2023.
143. O'Leary E, Jiang Y, Kristensen LS, Hansen TB and Kjems J: The therapeutic potential of circular RNAs. Nat Rev Genet 26: 230-244, 2025.