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REVIEW

Circular RNAs: A Promising Biomarker for Endometrial Cancer

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Abstract: Endometrial cancer (EC) is one of the most common malignant tumors of the female reproductive tract. EC patients have high morbidity and mortality rates and remain an important cause of cancer-related morbidity and mortality worldwide. More and more studies have shown that a large number of non-coding RNAs (such as microRNAs and long non-coding RNAs) are associated with the occurrence of diseases. Circular RNAs (circRNAs) is an endogenous non-coding RNA. It has a unique covalent structure. Many studies in recent years have found circRNAs differential expression in a variety of tumor tissues compared to matched normal tissues. In endometrial carcinoma, there also are multiple circRNAs differentially expressed and therefore circRNAs perhaps can be used as a diagnostic and prognosis biomarkers of EC. In this review, we described the biogenesis, function and characteristics of circRNAs, and the circRNAs with potential influence and clinical significance on the development of EC were summarized. Adenocarcinoma is the most common form of EC, so this review focuses on endometrioid adenocarcinoma.

Keywords: circRNA, biogenesis, back-splicing, function, endometrial cancer, biomarker

Background

Endometrial cancer (EC) is one of the most common malignant tumors of the female reproductive tract. Each year, approximately 142,000 women worldwide develop endometrial cancer and an estimated 42,000 women die of this cancer.[1] It is the fourth most common cancer among women in the United States, after breast, lung, and colorectal cancers.[2] Most cases of EC are diagnosed after menopause and the highest incidence rate is around 70 years old. Estrogen therapy, early menstruating, late menopause, tamoxifen therapy, infertility, polycystic ovary syndrome, increased age, obesity, hypertension, diabetes, and hereditary nonpolyposis colorectal cancer can all be risk factors.[3] Survival is usually determined by the stage and histology of the disease, and the prognosis of endometrial cancer varies greatly in different stages and histological types. The most common lesions (type I) are typically hormone-sensitive and low-stage and have a good prognosis, while type II tumors have a high grade and are prone to relapse even in the early stages.[4] The majority of type I EC are endometrioid carcinoma. The main treatments for EC are total hysterectomy and bilateral salpingo-oophorectomy. Radiation and chemotherapy can also play a role in treatment.[3] However, morbidity and mortality rates among patients with EC remain high and EC remains an important cause of cancer-related morbidity and mortality globally. Studies have shown that a large number of

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non-coding RNAs (such as microRNAs and long non-coding RNAs) are associated with the occurrence of gynecological diseases.[5–9] Recently, some studies aimed to investigate the expression and function of circRNAs in EC.[10,11]

CircRNAs are the latest members of a growing world of RNA molecules. Different from classical RNA formation, circRNAs are formed by back-splicing, a special splicing method, in which the 5 '-end of more than one exon or intron is covalently connected to the 3′ -end to form circular RNA molecules.[12,13] With the wide application of gene sequencing technology and bioinformatics methods, many studies have shown that circRNAs are abnormally expressed in many malignant tumors.[14–16] Due to the covalent ring structure of circRNAs, they are not easy to be degraded by exonuclease, and because of their tissue stability and specificity, more and more circRNAs have been confirmed as diagnostic and prognostic biomarkers for various diseases.

Therefore, circRNAs may be used as diagnostic and therapeutic biomarkers for EC. In this review, we describe recent research progress of circRNAs in the biogenesis and function of endometrioid adenocarcinoma, so as to prepare for further research on the application of circRNAs in EC diagnosis, prognosis and treatment.

Biogenesis of circRNAs

In all eukaryotes, the removal of introns and linking exons is a major part of the RNA splicing process, transforming the precursor mRNAs (pre-mRNAs) containing introns into intron-less mRNAs. Most eukaryotic circRNAs are produced by pre-mRNAs. In recent years, another common splicing method has been found in eukaryotes. It can covalently connect the 5 '-end of more than one exon or intron to the 3′ -end to form a circular RNA molecule. This splicing method is called back-splicing.[12,17]

The splicing regulatory mechanisms of circRNAs biogenesis are different from the linear isoforms. CircRNAs demonstrate significant and diverse back-splicing events catalyzed by typical spliceosome mechanisms in different cell lines.[13,18–20] CircRNAs are pervasive in molecular biology. According to splicing mode, circRNAs can be divided into four types: exonic circRNAs (ecRNAs), exon-intron circRNAs (EIciRNAs), intronic circRNAs (ciRNAs) and intergenic circRNAs (IciRNAs).[21–23] So far, six biogenesis mechanism of circRNAs have been proposed, including lariat-driven circularization, intron pairing-driven circularization, RNA-binding proteins (RBPs)-mediated circularization, direct circularization of lariat introns, tRNA splicing-driven circularization, and ribosomal RNA (rRNA) splicing-driven circularization.[24–27]This review focuses on the first three mechanisms.

The first biogenesis mechanism of circRNAs is lariat-driven circularization. This model that leads to back-splicing is exon skipping, in which one or more exons are missing from the mature mRNAs. The 3′ -end splicing ligands of exons covalently bind to the 5′ -end splicing receptors of exons, and then the introns are excised to form circRNAs. In this model, the lariat-driven circularization is formed by the connection of two non-adjacent exons, and finally producing a lariat structure, a mRNA with skipped exons and a circular RNA transcript. The exon-skipping events produce an exon-containing lariat, which could then itself be internally spliced to an exon circle (Figure 1). In other words, exon-skipping leads to a lariat, whose restricted structure promotes circularization.[28–30] Moreover, intronic lariats can form intronic circRNAs (ciRNAs) (Figure 2). Intron cyclization mainly exists in the nucleus, and their formation depends on 7 nucleotide GU enrichment elements containing adjacent 5′ splicing sites and 11 nucleotide C enrichment elements containing adjacent branch sites, with a small number of miRNA targets.[27,31]

The second biogenesis mechanism of circRNAs is intron pairing-driven circularization. Exons of the former mRNA or two introns on either side of the exon that can be connected to each other. The flanking introns are close

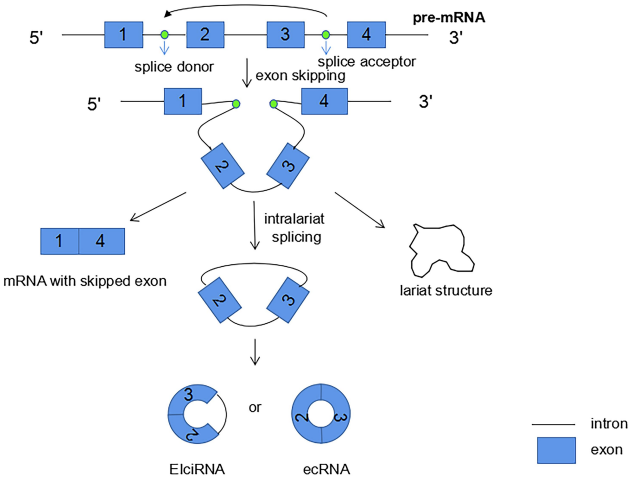

Figure 1 Lariat-driven circularization: due to the exon skipping mechanism, back-splicing can occur, which leads to the formation of a lariat. The 3 'end splice donor of exon 1 is covalently bound to the 5′ splice acceptor of exon 4, and then the introns are excised to form circRNA. And finally three different products are synthesized: a circRNA, a mRNA with skipped exon, and a lariat structure.

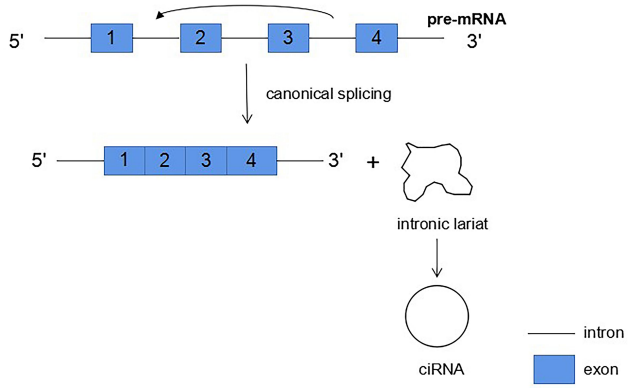

Figure 2 Intronic lariats can form intronic circRNAs (ciRNAs).

to each other, forming a secondary conformation, which enables the splicing site to undergo back-splicing (Figure 3). Most of the intron-pairing patterns are facilitated by ALU repetition.[32] In other words, the two non-adjacent introns were first paired with each other to form a ring structure, then the introns were excised, and finally circRNA was formed. From the first model we can see that, ecRNA can be formed by lariat-driven circularization. Alternatively, ecRNA could also be formed by alternative 5′ to 3′ splicing of nascent transcripts.[28]

The third circRNAs formation mechanism is by RNA-binding proteins (RBPs). This mechanism involves the ability of protein factors that bind to the former mRNA to link flanking introns, a process induced by protein dimerization that produces RNA rings (Figure 4). And muscleblind like splicing regulator 1 (MBNL1) protein is one of the most popular RBPs responsible for circRNA biogenesis.

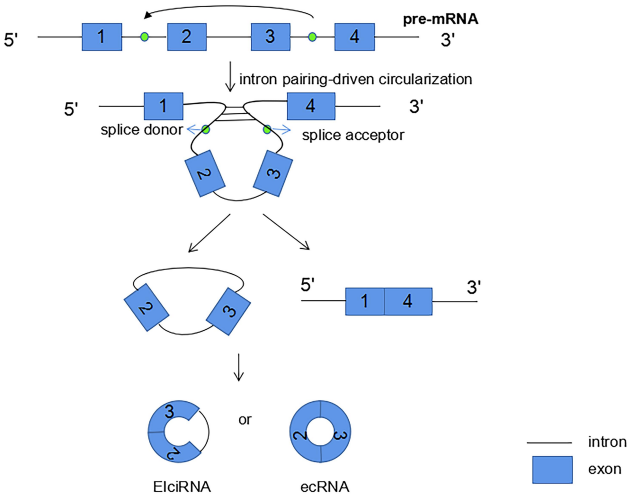

Figure 3 Intron pairing-driven circularization: introns are paired by base pairing to form a circular structure, which promotes 3′ downstream splice donor connecting to the 5′ upstream splice acceptor, then the introns are excised to form circRNA.

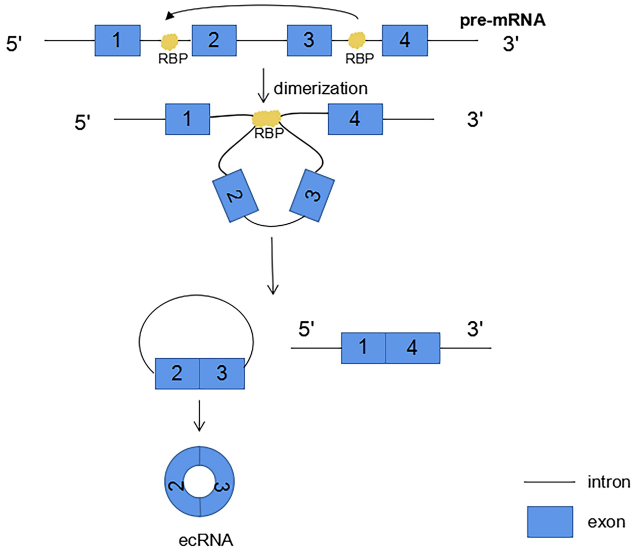

Figure 4 RNA binding proteins (RBP) bind to introns on both sides of the exon that forms circRNA. RBP dimerization promotes the back splicing process.

MBNL1 was shown to bind to its own pre-mRNA and binds the two flanking introns together.[13] CircRNA MBL/MBNL1 itself contains conservative muscleblind (MBL) binding sites, so it is easy to bind to the MBL protein. This binding effect promotes the biosynthesis of circMBL, and the MBL level is important to determine the cyclization rate of bracketed exons. MBL expression may reduce the production of parental mRNA by promoting circMBL production.[13,33–35] Another RNA-binding proteins (RBPs), adenosine deaminase 1 acting on RNA (ADAR1), have been reported to play a role in circRNAs biogenesis. The down-regulation of ADAR1 specifically up-regulated the expression of some circRNA, suggesting that ADAR1 plays a role in inhibiting the biogenesis of circRNA.[32,34] This regulation is associated with Adenosine-to-Inosine (A-to-I) editing.[32] Double stranded RNA (dsRNA) paired structures are called A-to-I RNA editing targets by ADARs.[36,37] Under normal conditions, high-enrichment A-to-I editing of dsRNA regions can reduce RNA pairing structure, resulting in a reduction in RNA pairing and thus a reduction in the efficient back-splicing of circRNAs formation. However, with the decrease of A-to-I editing level after ADAR1 gene knockout, the pairings of RNA to cross-introns became more stable, which was conducive to back-splicing to produce circRNAs.[32]

Function of CircRNAs

CircRNAs are rich and evolutionarily conserved RNAs of largely unknown function. CircRNAs have a wide range of biological functions. Here, we introduce some

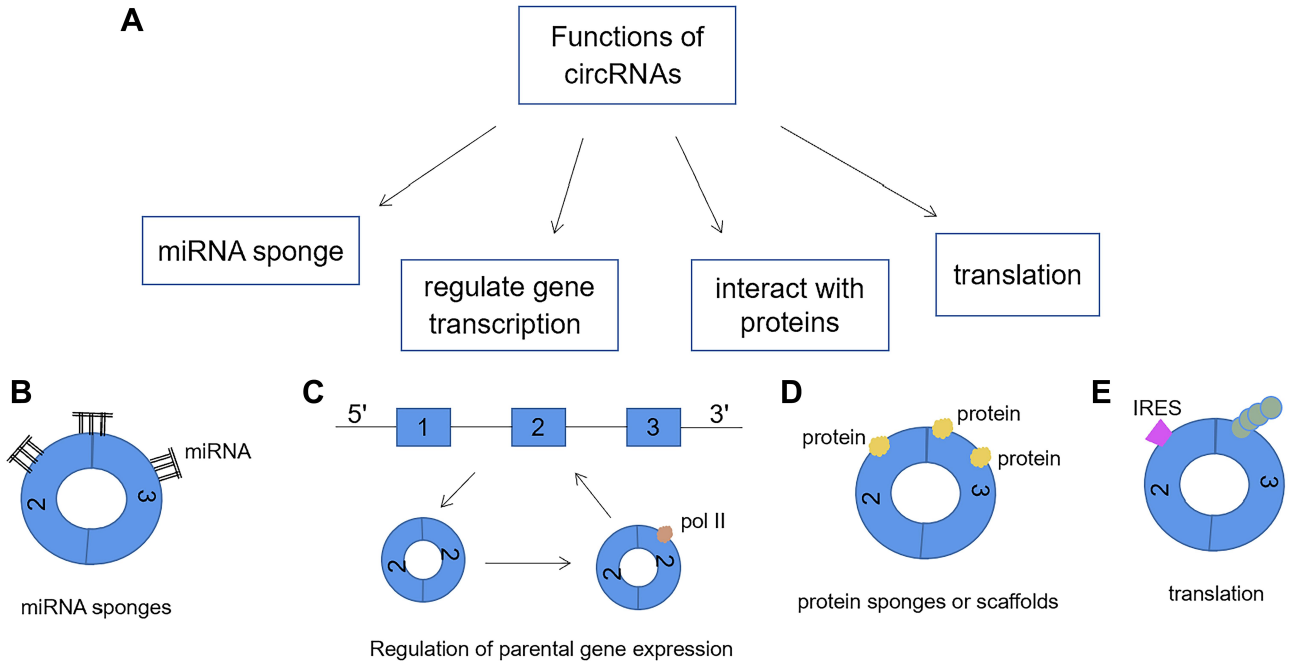

Figure 5 (**A**) The functions of circRNAs: (**B**) CircRNA can act as a microRNA sponge by combining with miRNA and inhibiting its function. (**C**) CircRNA may bind to Pol II to enhance transcription of their parental genes. (**D**) By binding proteins, circRNA can act as a protein sponge to regulate gene expression. In addition, circRNAs can also be scaffolds for protein interactions. (**E**) As a template for protein synthesis. CircRNA containing internal ribosomal entry site (IRES) elements and an open reading frame can be translated into proteins or polypeptide.

of its functions (Figure 5A). This is described further below.

CircRNA Act as miRNA Sponge (Figure 5B)

The most common function of circRNAs is the miRNA sponge. MicroRNAs (miRNAs) are another type of non-coding RNA that is transcribed from the precursors of short hairpins.[38] CircRNAs can act as microRNA (miRNA) sponge by binding to miRNA and inhibiting its function, thereby releasing downstream target genes from miRNA-mediated repression and inhibiting the ability of miRNA to perform its post-transcriptional repression. MiRNAs are important post-transcriptional regulators of gene expression and play their roles through direct base pairing with the target sites in the non-translational region of messenger RNAs. And the activity of miRNAs has been shown to be influenced by the presence of miRNA sponge transcripts, so-called competitive endogenous RNAs in humans and target imitations in plants.[39–41] miRNA sponges are widespread regulators of miRNA activity in many eukaryotes. CircRNA is a highly prevalent RNA species in human transcripts.[42] Many abundant endogenous circRNAs molecules are naturally resistant to the decline of extracellular dissolved RNA and can be used as effective miRNA sponges to increase the growing lineage of gene expression regulation.

Antisense to the cerebellar degeneration-related protein 1 transcript (CDR1as) and the testis-specific circRNA, Sex-determining region Y(Sry) are the most representative miRNA sponges.[40,43,44] The exonic circRNAs of CDR1as and Sry have been shown to bind miRNAs without being degraded, making them excellent candidates for competing endogenous RNA activity.[12] CDR1as acts as a microRNA-7 (miR-7) sponge, therefore, we also term this circular transcript ciRS-7 (circular RNA sponge for miR-7). And Sry serves as a miR-138 sponge. Nowadays, many studies have found extensive involvement of miR-7 as a key regulator of many cancer pathways, so CIRS-7 may be an important factor associated with cancer.[45,46]

CircRNA Regulates Gene Transcription (Figure 5C)

CircRNAs constitute a transcription family with unique structures and still largely unknown functions. Because the source of introns circRNA (ciRNA) contains very little of microRNAs binding sites, and the small amount of binding sites is more dispersed, so they are not ordinary type circRNA have the role of miRNA sponges, but

ciRNA has positive regulation of RNA polymerase II transcriptional activity function.[27,47]

Li et al revealed a new role for circRNAs in regulating gene expression in the nucleus. Some EIciRNA regulate the transcription of parental genes by interacting with U1 small nuclear RNA (snRNP). First, EIciRNA and U1 small nuclear ribonucleoprotein (snRNP) form the EIciRNA-U1 snRNP complex, then the compound with RNA polymerase II transcription complex interaction to promote gene expression.[48] This mode of RNA-RNA interaction to regulate transcription not only enriches the functions of circRNAs, but also provides a new direction for the research of circRNAs.

CircRNA Interacts with Proteins (Figure 5D)

CircRNAs can interact with proteins and thus affect the function of proteins. CircRNAs can stably bland to AGO proteins and RNA polymerase II.[28,49] CDR1as and Sry in exonic circRNA bind to the miRNA effector Argonaute (AGO).[27,49] In addition, they can be combined with a variety of RBPs to act as RBP scaffolds.[12] CircRNA may also be used as a target sequence element to simultaneously bind RBP, RNA or DNA using its complementary sequences.[49] CDR1as contains 74 miR-7 seed sequence matches and is tightly bound by Argonaute proteins (the proteins that bind to miRNAs).[12,49] Similarly, when miR-138 is overexpressed, the circular Sry transcript has 16 binding sites for miR-138 and co-precipitates with Argonaute 2 (AGO2).[40]

Ankyrin repeat domain 52 circular intronic RNA (ciankrd52), eukaryotic translation initiation factor 3 subunit J circular RNA (circEIF3J) and poly-adenylate-binding protein-interacting protein 2 circular RNA (circPAIP2) can interact with the RNA polymerase II complex and ultimately regulate transcription.[27]

Ashwal-Fluss et al found that the circMBL can bind to RBPs. When the cells contain excessive MBL protein, circMBL will be promoted to reduce the mRNA production of the protein, while circMBL will bind to the excessive MBL protein, making the MBL protein content tend to be normal.[13]

Du et al found that circ-Foxo3 can stay in the cytoplasm through interactions with anti-aging and stress protein-related factors inhibitor of DNA-binding 1 protein (ID-1), focal adhesion kinase (FAK), and hypoxia inducible factor 1α (HIF1α) in humans, thereby inhibiting the corresponding resistance process.[50] The circRNAs can also form the circ-Foxo3-P21-CDK2 ternary complex, inhibit the function of cyclin- dependent kinase 2(CDK2) and block the cell cycle process.[51]

CircRNA is Involved in Protein Translation (Figure 5E)

If circRNA contains internal ribosomal entry sites (IRES), it may guide protein synthesis. Eukaryotic ribosome 40s small subunits can enter the IRES of these circRNA to guide protein synthesis.[52] It turns out that if circRNA contains bases that are multiples of 3, the circRNA encoding the protein circulates around the reading frame, translating a repeated polypeptide sequence. Some studies have showed that some circRNAs carry open reading frames, and can be translated into peptides or proteins.[53,54] The presence of IRES has been demonstrated that circRNA translation is driven by a cap-independent mechanism.[55]

So far it's been found that circRNA of hepatitis delta virus (HDV) and circRNA in rice yellow mottle virus can code proteins.[56,57] HDV contains a single stranded circular RNA molecule. This is the first animal virus to be identified as a circRNAs genome. CircRNAs have only been found in plant viruses.[58] Peptides or proteins encoded by circRNAs play a key role in mediating cancer development. Therefore, it seems necessary to investigate whether proteins translated from circRNA have function in gynecological cancers.[59,60]

General Characteristics of CircRNAs

1. Unlike linear RNA, circRNA forms a covalent circular structure, with no 5′ end caps or 3′poly(A) tails, which is not easy to be degraded by exonuclease and is more stable than linear RNA.[61]

2. CircRNAs are a wide variety, and some are more abundant than their linear mRNA analogues.[26,62] CircRNA was formed from introns, exons, and intergene regions, and even 50 and 30 untranslated fragments.[27,49,63]

3. CircRNAs are mainly composed of exons and a small part of circRNA is formed by intron cyclization.

4. Some circRNAs, rich in microRNA response elements (MRE), can play the role of competitive endogenous RNAs, bind with miRNAs, play the role of miRNA sponge in cells, and inhibit the function of miRNAs so as to regulate gene expression levels.[40]

5. CircRNAs are expressed in tissue-specific, cell-specific, and developmental stage-specific patterns.[64,65] It

is dynamically expressed during development and expressed in a tissue-specific manner.[48,49,66,67]

6. Most circRNAs are endogenous ncRNA, but only some exogenous circRNAs can be translated and expressed, such as hepatitis delta virus (HDV) and engineered circRNA with internal ribosome entry site (IRES).[52,68]

7. CirRNAs are evolutionarily conservative between different species.[28,49,66,69]

8. With the exception of intron-containing circRNA mainly present in the nucleus, most circRNAs are exported to the cytoplasm in a size-dependent manner after biogenesis.[70]

These characteristics of circRNA suggest that it may play an important role at both transcriptional and post-transcriptional levels and may be an ideal marker for disease diagnosis.

Circular RNAs and Endometrial Cancer (EC)

More and more studies have confirmed abnormal circRNAs expression in multiple tumor tissues compared with matched normal tissues. For example, many researches have studied the relationship between circRNAs and cervical cancer, and the results show that circRNAs are involved in the development of cervical cancer through various mechanisms, among which the spongification of miRNA is the most important one. Studies have shown that has_circ_0018289, has_circ_0001445, has_circ_0023404, has_circ_0000263, circRNA-000284, circRNA8924, has_circRNA_101996, circ-ATP8A2, circ_0067934 and circEIF4G2 are abnormally expressed in cervical cancer cells.[71–76] In addition, in ovarian cancer, circHIPK3 was found to be highly expressed in epithelial ovarian cancer (EOC) and ovarian cancer cells A2780, HO-8910, SKOV3 and CAOV3.[77]

Endometrial Cancer (EC)

Endometrial cancer is a group of malignant epithelial neoplasms occurring in the endometrium. It usually occurs in perimenopausal and postmenopausal women. Endometrial cancer is one of the most common tumors of the female reproductive system and the third most common gynecologic malignancy leading to death (second only to ovarian cancer and cervical cancer). The disease is closely related to lifestyle. And the incidence varies from region to region. EC is rare in less developed countries because of fewer risk factors, but specific mortality rates are higher.[78,79] The incidence rate in North America and Europe is 10 times higher than that in less developed countries. In North America and Europe, the incidence rate is second only to breast cancer, lung cancer and colorectal cancer, and it ranks the first among female reproductive system cancers.[2,80]

EC is generally classified into type I and type II according to histological type.[4] Type I EC are usually low stage and low grade, positive for estrogen and progesterone receptors, and has a good prognosis. In contrast, type II EC is usually estrogen-independent and has a poor prognosis.[10,81] The majority of type I EC are endometrioid carcinoma and a few were mucinous adenocarcinoma. Estrogen-independent endometrial carcinoma includes serous carcinoma, clear cell carcinoma and so on.[1] The most common histological subtype of EC is endometrioid adenocarcinoma,[81] which is also main described in this review. Endometrioid carcinoma is classified into three levels according to the degree of cell differentiation or the proportion of solid components. It is highly differentiated (G1), moderately differentiated (G2) and poorly differentiated (G3), and the malignant degree of poorly differentiated tumor is high.[1,82]

The incidence of EC increases with the increase in life expectancy. Age-adjusted morbidity increased even with hysterectomy.[83] The rise is linked to an epidemic of obesity and physical inactivity.[84] EC is one of the few human malignancies with rising mortality rates,[85] highlighting the urgent need to develop more effective strategies to diagnose and treat the disease. To explore the relationship between circRNAs and EC is helpful for further understanding and treatment of EC.

Expression of CircRNAs in Endometrial Cancer

CircRNAs have covalently closed structure and are more stable than other RNAs. This stability may prove to be an ideal property for circRNA in their future development as biomarkers.[14,86–88] CircRNAs have also been shown to be useful molecules in the treatment of a variety of diseases, including neurological disorders, cardiovascular disease, cancer and so on.[65,89–91] The role of circRNAs in cancer pathology has recently been the subject of numerous studies.[92–94] CircRNAs have been linked to many cancers. CircRNAs from tumor suppressor gene FBXW7 could be translated into protein products that reduced the half-life of

c-Myc.[95] There are also two types of circRNAs, circHIPK3 and circDOCK1, regulate cell growth and act as cancer biomarkers.[96,97] For example, in colorectal cancer and ovarian cancer, the abundance of circRNAs, as measured by the ratio of circRNAs to linear isoforms, is lower in tumor samples.[98] And the ratio was negatively correlated with the proliferation rate of tumor cells. In addition, compared with healthy controls, peripheral blood exosome circRNAs showed unique expression patterns in colon cancer patients.[99] The functional significance of these circRNAs in cancer is not fully established, but they may serve as potential biomarkers for EC diagnosis or developmental monitoring. Although there is increasing evidence that circRNAs play a role in tumorigenesis and cancer progression, their role in EC is completely unknown.

So far, few studies have been published on circRNAs in EC. The expression profile of circRNAs in EC tissues was changed compared with that in adjacent normal tissues.[10] Similarly, studies have confirmed that circRNAs expression in grade 3 EC tissues is significantly different from that in adjacent non-cancerous endometrium, which may provide new molecular candidates for the diagnosis and clinical treatment of grade 3 EC.[11] The overall abundance of circRNAs in EC was lower than normal endometrium. There was no difference in the number of transcripts between EC and normal endometrium for linear RNA. In addition, there are many hotspot genes for circRNAs transcription that may account for changes in circRNAs expression between normal and malignant endometrium.[10]

One study listed the top 10 unique hotspot genes expressed in normal tissue and 8 unique hotspot genes expressed in EC tissue:DNAH14, MT-RNR2, RABGAP1, ESR1, FIP1L1, GFPT1, INADL, PCNX.[10] Hotspot genes are defined as the production of more than a dozen different circRNA isoforms in a given tissue or cell.[100] Some studies have found that the expression changes of circRNAs in EC are the result of the expression changes of specific back-spliced isoforms and some circular isoforms, in which the specific exons are expressed by a single gene site.[10]

DMD and DMBT1

There were 29 specific circRNA isoforms expressed in normal endometrial tissues and 14 expressed in EC tissues, among which the number of Dystrophin gene (DMD) isoforms decreased the most in EC tissues, from 29 in the normal endometrium to 14 in EC. However, the number of circRNA isoforms expressed by the Deleted In Malignant Brain Tumors 1 gene (DMBT1) was increased, from 32 in the normal endometrium to 50 in EC.[10] Among the common hotspot genes expressed in normal and EC tissues, the circular transcriptional composition of these two genes changed significantly. DMD forms a specific circRNA in normal skeletal muscles. The specific circRNA formation may be the result of multi-exon skipping during DMD specific splicing.[101] However, DMBT1 was elevated in biliary intraepithelial neoplasia, and its absence in the biliary tract was associated with poor survival in patients, suggesting that the expression of DMBT1 had an inhibitory effect on tumor growth.[102] The special expression of DMD and DMBT1 in EC suggests that circRNA may be related to the development of EC.

DNAH14

DNAH14, which encodes the dynein heavy chain, is a unique hotspot gene in EC. DNAH14 produced 3 circular isoforms in normal endometrial tissue and 18 circular isoforms in EC tissue. With the increase of the number of DNAH14 isoforms, the expression of circular and linear transcripts in EC tissues were up-regulated. Chang et al found that DNAH14 is one of 21 passenger genes in EC, suggesting that DNAH14 abnormalities may interfere with cancer-related pathways.[10,103]

HSPG2 and RP11-255H23.4

Introns circRNA (HSPG2 and RP11255H23.4) were only expressed in normal endometrial tissue, but not in EC tissues. However, in endometrial tissues, the expression of miRNAs transcribed from their parent genes increased, indicating that these circRNAs can competitively bind to related miRNAs and play an important role in the occurrence and development of endometrial cancer. In the basement membrane, HSPG2 binds to growth factors to regulate the growth and regeneration of endothelial cells.[10,16] This process is formed by its heparin sulfate glycosaminoglycan (HS-GAG) chain. And the decreased expression of HS-GAG was associated with EC progression.[104]

Although we do not know how each individual circRNAs expression contributes to the occurrence and development of tumors, it will be helpful and provide a basis for future studies on the functions and mechanisms of EC-related circRNAs.

Some CircRNAs That May Play a Role in EC as miRNA Sponges are Listed Below

Circ-ITCH

As microRNA (miRNA) sponges, circRNA protects target genes from miRNA-mediated mRNA cleavage, and is involved in the occurrence of various cancers such as liver cancer, gastric cancer and colorectal cancer. These circRNA-miRNA regulatory networks act on target genes involved in cell cycle regulation, signal transduction, epigenetic regulation or transcriptional regulation, and ultimately regulate the proliferation, differentiation, invasion and metastasis of cancer cells.[15]

Circ-ITCH is a circRNA produced by several exons of the itchy E3 ubiquitin protein ligase (ITCH) and tumor suppressor genes that act as sponges for specific miRNAs that target the ITCH parental transcript.[49,105,106] Circ-ITCH can competitively bind to miRNA-17 and miRNA-224, a process that leads to differential expression of P21 and phosphatase and tensin homology (PTEN).[107] P21 and PTEN are a cyclin-dependent kinase inhibitor or a well-known tumor suppressor. PTEN prevents angiogenesis in cancer tissue, inhibits cell division, proliferation, invasion and migration, and accelerates apoptosis.[9] The mutation or deletion of PTEN inactivates its enzyme activity, thus losing its ability to inhibit cell proliferation. In addition, early studies have shown that various carcinogenic miRNAs promote the malignancy of tumors by neutralizing the expression of P21 or PTEN.[108,109] Circ-ITCH is down-regulated in esophageal squamous cell carcinoma, colorectal cancer, hepatocellular carcinoma, and lung cancer by classical pathways. Circ-ITCH acts as a sponge for specific miRNAs, protecting the parent transcript ITCH and blocking downstream Wnt/β-catenin signaling, thereby preventing tumor progression.[106,110–112] Studies have shown that circ-ITCH inhibits the aggressive biological behavior of BCa by stimulating the expression of target genes P21 and PTEN of miR-17 and miR-224 up-regulated by miR-17 and miR-224.[104,107,113,114] Therefore, circ-ITCH inhibited BCa progression by eliminating the carcinogenic effects of miR-17 or miR-224 and forming the circ-ITCH/miR-17, miR-224/P21, PTEN axis. Therefore, we speculated that the differential expression of P21 and PTEN made the cells highly malignant and might develop into EC. In other words, P21 and PTEN may also perform similar regulation in EC through the sponge function of circRNAs.

Circ-ITCH targets tumor inhibition via novel circ-ITCH/miR-17, miR-224/P21, PTEN axis, which may provide a potential biomarker and target for EC treatment.

Hsa_Circ_0039569

Ye et al found that the expression of circRNAs in grade 3 EC tissues was different from that in matched non-tumor tissues. In women with grade 3 EC and adjacent non-cancerous endometrium tissue, a total of 62,167 unique circRNAs were significantly altered. Among them, 25,735 genes were significantly up-regulated and 36,432 genes were down-regulated. Among them, circRNAs such as hsa_circ_0039569, hsa_circ_0001523, hsa_circ_0001610, hsa_circ_0001400, hsa _circ_0007905 were up-regulated, while the circRNAs such as hsa_circ_0000437, hsa_circ_0009043, hsa_circ_0000471, and hsa_circ_0014606 were down-regulated.[11] At the same time, these circRNAs were significantly differentially expressed in grade 3 EC and grade 1–2 EC.

The expression of hsa_circ_0039569 and hsa_circ_0001610 in grade 3 EC was more significant than that in grade1-2 EC. They have a higher level of expression in the grade 3 EC. Hsa_circ_0009043, hsa_circ_0000437 and hsa_circ_0001776 were significantly down-regulated in grade 3 EC and grade 1–2 EC tissues compared with adjacent non-malignant endometrium tissues. The expression levels of hsa_circ_0009043 and hsa_circ_0001776 in grade 3 non-cancer endometrium tissue were higher than that in grade 1 non-cancer endometrium tissue, while the expression levels of hsa_circ_0000437 were lower.[11]

The results of Ye et al also showed that the expression level of hsa_circ_0039569 was significantly correlated with tumor differentiation, but not with age, lymph node metastasis, tumor size, FIGO stage, or muscular invasion.

Most circRNAs that have a clear role in cancer act as miRNA sponges through the circRNA-miRNA axis.[40,115–118] Studies have shown that interaction between hsa_circ_0039569 and hsa-miR-542-3p/hsa-let-7c-5p. And hsa-miR-542-3p and hsa-let-7c-5p were downregulated in the grade 3 EC. Therefore, hsa_circ_003956 was negatively correlated with hsa-miR-542-3p and hsa-let-7c-5p.[11] Hsa_circ_0039569 can be used as an important predictor of level 3 EC.

Circ-ZNF91

ZNF91 belongs to a C_2H_2 zinc finger (ZNF) gene family, which has been greatly expanded in the primate lineage and is known to contain unusually rich targets of multiple

miRNA families, including miR-23, miR-181 and miR-199.[119] Circular ZNF91 had 24 binding sites with miR-23 and 7 binding sites with miR-199.[120] Studies have shown that the expression of circular ZNF91 in EC is negatively correlated with the expression of miR-23B, miR-122A2 and miR-199.[104] This suggests that circRNAs may act as miRNA sponges to inhibit the expression of miR-23B, miR-122A2 and miR-199.[10] These miRNAs have been shown to be associated with a variety of human cancers, and their target genes and effects (promotion or inhibition) are different in different types of cancer. In prostate cancer, for example, miR-23B leads to decreased Sre expression, which slows tumor growth in nude mice. MiR-23B has also been shown to inhibit metastasis in colon cancer, and its targets include FZD7 or MAP3K1.[121]

Circ-8073

Cell cycle progression usually affects cell proliferation, and cell cycle disruption is considered to be a common cause of cell proliferation inhibition.[122] Circ-8073 has been proved to be an important regulator of endometrial epithelial cell proliferation. As a miR-449a sponge, circ-8073 regulates endometrial epithelial cells (EECs) proliferation and cell cycle by regulating centrosomal protein of 55 (CEP55) expression. Circ-8073 gene knockout can induce EECs cell cycle arrest in G1/S phase. In addition, CEP55 promotes proliferation of glioma cells and reduces apoptosis through AKT/mTOR signaling pathway.[123] Circ-8073 promotes EECs proliferation through the PI3K/AKT/mTOR pathway.[124]

CircPUM1

The expression level of circPUM1 in endometrial carcinoma tissues was significantly higher than that in normal tissues. Its upregulation can promote the proliferation, migration and invasion of endometrial cancer cells. CircPUM1 can bind to miR-136 and lead to the upregulation of NOTCH3, thus promoting the development of endometrial cancer.[125] MiR-136 has been studied in a variety of cancers and has been identified as a tumor suppressor gene in a variety of adenocarcinomas such as colon, breast and lung cancers.[126–128] Notch signaling affects many cellular processes, including being involved in cell fate decisions, maintaining undifferentiated states, inducing terminal differentiation, and other functions associated with cancer development.[129] Therefore, circPUM1 promotes the development of EC by regulating miR-136/NOTCH3 axis.

Hsa_CircRNA_0001776

In EC tissues and cells, circ_0001776 and leucine-rich repeats and immunoglobulin-like domains 2 (LRIG2) expressions were down-regulated and miR-182 expressions were up-regulated.[130] Low expression of circ_0001776 was associated with 5-year survival rate of EC patients. Up-regulation of circ_0001776 could inhibit cell proliferation and glycolysis, and promote cell apoptosis. In addition, circ_0001776 also regulated the expression of LRIG2 by acting as a sponge for miR-182, and CIRC_0001776 inhibited EC progression through miR-182/LRIG2 axis.[11,131]

Circ_0001776 has obvious inhibition on tumor growth in vivo. In other words, circ_0001776 inhibits the occurrence and development of EC through miR-182/LRIG2 axis, providing a potential target for the treatment of EC.[131]

Regulatory Pathways Involving QKI, CircRNA and ESRP2

The interactions between circRNAs and RNA-binding proteins have been proven to affect the progression of cancer.[64] It has been reported that circRNA regulatory factor QKI protein level is positively correlated with 35 circRNAs,[132] while epithelial splicing regulatory proteins 2 (ESRP2) level is negatively correlated with 20 circRNAs. These RBPs may act as major regulators of circRNAs. QKI is up-regulated in the epithelial to mesenchymal transition (EMT) process and promotes EMT by adjusting hundreds of variable splicing targets.[132–134] It was found that relative QKI protein levels were positively correlated with EMT activators ZEB1 and ZEB2.[85,135,136] ESRP2 levels, which play an important role in maintaining epithelial characteristics, were negatively correlated with QKI levels.[137–139] ESRP2 regulates alternative splicing events associated with cellular epithelial phenotypes and plays a key role in EMT by regulating the isoforms of FGFR2, CD44, CTNND1, and ENAH.[140,141]

CircRNAs can act as miRNA sponges to regulate miRNA activity, while miRNAs play an important role in EMT.[142] EMT is characterized by the transformation from polarized immobile epithelial cells to motional mesenchymal cells and is a powerful process of tumor metastasis, invasion and tumorigenesis.[143,144] EMT is an important component of EC development and has prognostic significance.[145]

MiRNAs are important regulators of malignant transformation and metastasis. And many miRNAs are known to inhibit a variety of important cancer-related genes.[146] It was found that the miR-200 family has abnormal expression in cancer and is involved in the initiation and progression of malignant transformation. The inhibitory effect of miR-200 members on metastasis is closely related to pathological EMT.[147–150] Dou et al predicted miRNA binding sites in 35 circRNAs related to QKI level and found 36 potential binding sites of miRNA.[85] It was also found that the activity of miRNA was negatively correlated with QKI expression.[85]

RNA-binding protein QKI was positively correlated with circRNAs, while QKI was negatively correlated with the activity of specific miRNAs, indicating a potential pattern that QKI, circRNAs and miRNAs form a regulatory feedback loop in EC.

The above is the summary of circRNAs that has an influence on the development of EC. At the same time, we also put these circRNAs and their functions in the table (Table 1). We found that most circRNAs function through the pathway of miRNA sponge, and altered miRNA expression plays a crucial role in the occurrence and development of endometrial cancer. Various miRNAs act as oncogenes or tumor suppressors and can regulate the occurrence and progression of tumors. Studies have found that after bortezomib treatment, the expression of miR-17-5p in endometrial cancer cells was decreased. It acts as an oncogene and acts in coordination with c-Myc, a oncogenic transcription factor that is often mutated or amplified in human cancers. A single microRNA may regulate a wide range of target genes, thus having a global impact on gene expression.[151] Other studies have found that overexpression of miR-423 enhances the proliferation of endometrial cancer cells and increases their migration and invasion. MiR-423 has also been shown to play an important role in the tumorigenesis and development of endometrial cancer cells.[152] MicroRNAs (miRNAs) involve in fine-tuning gene expression and releasing miRNAs that may lead to cascade cellular events that ultimately promote tumorigenesis.[153–156] In addition, circRNAs can be released into the extracellular space and subsequently detected in the blood, plasma, serum and exosomes of gynecological cancer patients.[157–160] Exosomes are small membranous vesicles of endocytic origin secreted by most cell types. They contain specific proteins, mRNAs and microRNAs that regulate the behavior of recipient cells and can be used as biomarkers for diagnosing human diseases.[161] Studies have shown that circRNAs are enriched in exosomes compared to producing cells by RNA-seq analysis, and more than 1000 circRNAs have been identified in human serum exosomes. CircRNAs can bind to miRNAs, which are also abundant in exosomes.[99] Serum exo-circRNA may distinguish cancer patients from healthy

Table 1 The Role of circRNAs in Endometrial Carcinoma

CircRNAs	Function	Upregulated/ Downregulated in Cancer	References
DMD	/	Downregulated	[10,101]
DMBT1	/	Upregulated	[10,102]
DNAH14	hotspot gene	Upregulated	[10,103]
HSPG2 and RP11255H23.4	/	Not express	[10,16]
circ-ITCH	miR-17, miR-224 sponge (circ-ITCH/miR-17, miR-224/P21, PTEN axis)	Downregulated	[106–114]
hsa_circ_0039569	hsa_circ_0039569-hsa-miR-542-3p/hsa-let-7c-5p axis	Upregulated	[11]
circ-ZNF91	miR-23B, miR-122A2 and miR-199 sponge	Upregulated	[10,104,119,120]
circ-8073	miR-449a sponge (Circ-8073, miR-449a and CEP55 regulated the PI3K/AKT/mTOR signal pathway in EECs)	Upregulated	[123,124]
circPUM1	miR-136 sponge (CircPUM1/miR-136/NOTCH3 axis)	Upregulated	[125]
hsa_circRNA_0001776	miR-182 sponge (hsa_circRNA_0001776/miR-182/LRIG2 axis)	Downregulated	[11,130,131]
regulatory feedback loop:regulatory pathways involving QKI, circRNA and ESRP2			[85,132–141]

controls, suggesting its great translational potential as a biomarker in cancer diagnosis.

Discussion and Prospects

In this review, we described the biogenesis, function and characteristics of circRNAs as well as their application in EC diagnosis and treatment. As we summarized in this review, circRNAs have an important role in the development of EC, and we summarizes the current circRNAs may have an impact on EC development. It is important to note that many studies have found that circRNAs abnormal expression in many tumor diseases, therefore they have great potential applications in the tumor treatment. Exogenous circRNAs may be ideal for diagnosis or therapeutic intervention in diseases due to its unique structure, high stability, and organ and tissue-specific expression patterns. Although more and more studies on circRNAs have provided us with a general understanding of the newest member of the RNA molecular world, the specific biogenesis and function of circRNAs are still unclear. At present, there are still many circRNAs to be studied.

CircRNAs abnormal expression of tumour disease has become the current hot research topic, but the circRNAs of abnormal expression of different diseases are different. With regard to the expression of circRNA in EC, few specific studies have carried out, and the sample size of the studies in this area is very small. At the same time, because of the complexity of the tumor pathogenesis, exact function of circRNAs is not clear in the EC. Therefore, the use of circRNAs as a biomarker for the diagnosis and prognosis of EC disease needs further study and is far from clinical application. The research of circRNAs in the field of disease is still in the preliminary stage, and there is still a lot of research to be done before it can be further developed.

Disclosure

The authors report no conflicts of interest in this work.

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