

# Expression of circular RNAs in gynecological tumors

## A systematic review

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### Abstract

**Background:** The rapid development of bioinformatic technology is boosting the discovery of components hiding in the darkness. As a type of universal, conservative, tissue-specific and stable molecules, circular RNA (circRNA) is a class of endogenous non-coding RNA that has no 5' cap and 3' poly(A) tail and forms a covalently closed continuous loop. At present, 3 types of circRNAs including exonic circRNA (ecRNA), intronic circRNA (ciRNA), and axon-intronic circRNA have been reported. Nowadays informatic technology and high-throughput sequencing have verified the abundance of endogenous circRNAs in eukaryocytes, with predominantly expressed in the cell cytoplasm. Their unique sequences endow them with special functions, such as miRNA sponge, selective transcription or splicing, and attaching to RNA-binding proteins.

**Data sources:** This review was based on articles published in PubMed databases up to January, 2019, with the following keywords: "circular RNA", "database", and "reproductive tumor" (Flow chart).

**Objectives:** Original articles and reviews on the topics were selected.

**Results:** Studies have uncovered the interplay between circRNAs and the development of ovarian epithelial tumors, ovarian carcinoma, and cervical carcinoma, which suggesting the potential of circRNAs as biomarkers or therapeutic targets for human diseases.

**Conclusions:** Circular RNA has been found to play a role in gynecological tumors diseases. Meanwhile, we reviewed the studies on how CircularRNA participate in gynecological tumors, which provides a basis for the study of CircularRNA in gynecological tumors.

**Abbreviations:** CircRNA = Circular RNA, FAK = focal adhesion kinase, GFP = green fluorescent protein.

**Keywords:** circular RNA, database, embryonic development, preeclampsia, reproductive tumor

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## 1. Introduction

Circular RNA (circRNA) appears in the splicing process of transcription, and single-stranded RNA molecules form a ring via covalent bonding. Accumulating evidence revealed that circRNA can be generated from protein-coding genes, intergenic spacer between tRNA and LncRNA, or antisense transcript.<sup>[1]</sup> CircRNAs have several characteristics:<sup>[2,3]</sup>

- (I) Predominantly expressed in the cytoplasm
- (II) Regulate the expression of target gene via the response element through interaction with miRNA;
- (III) Most of the circRNAs are generated from the exons; Most of the circRNAs regulate the expression of endogenous ncRNA; Most of the circRNAs play functions before and after transcription;
- (IV) Tissue-specific and developmental-stage-specific;
- (V) Often found in extracellular body fluids with high expression levels;
- (VI) Evolutionary conservation in various species;
- (VII) Having a covalently closed loop that is highly resistant to RNA exonuclease or RNase R.

Existed evidence demonstrate that CircRNA can act as miRNA sponge or RNA-binding protein, and can be translated into protein (Fig. 1).<sup>[4]</sup> For instance, CiRS-7, which containing a total of 73 miR-7 binding sites that can sponge up miR-7, and

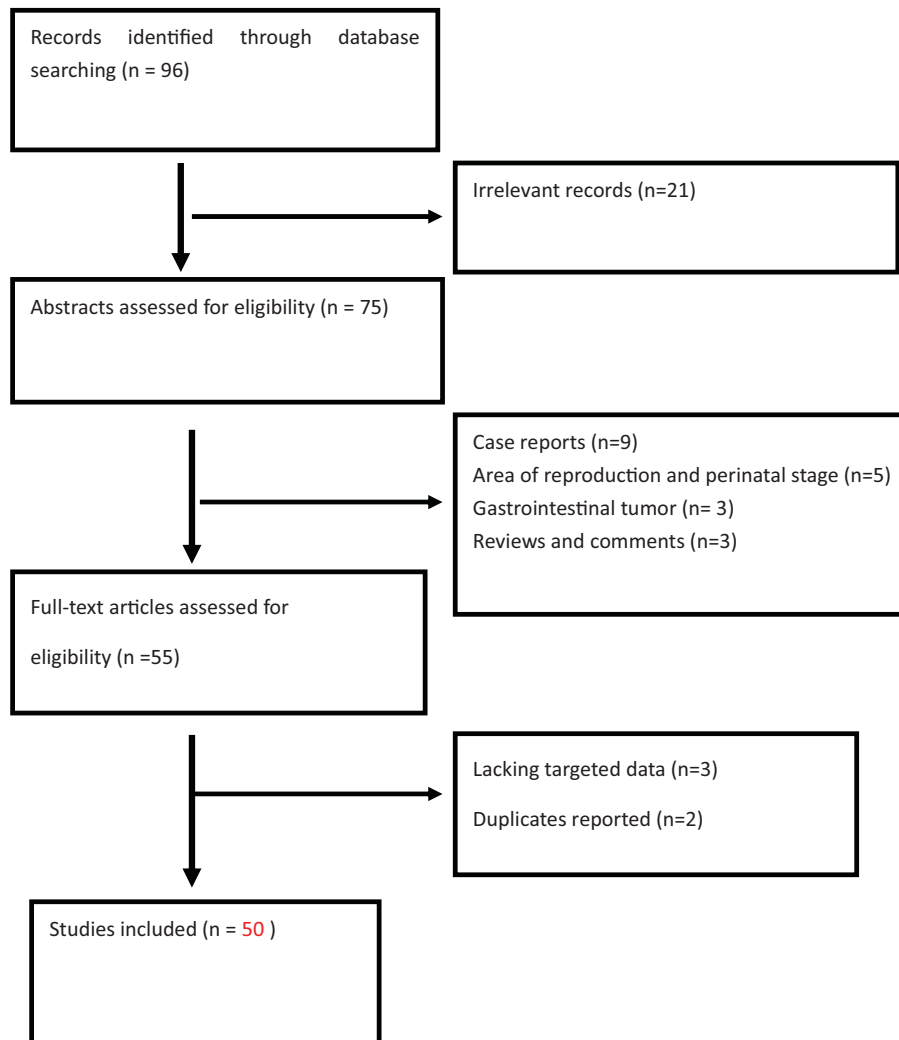


Figure 1. Flow chart of articles identified, included, and excluded.

simultaneously inhibit its biological function and increase the expression of gene that targeted by miR-7. However, to date, only a small number of these circRNAs and their sponge functions have been clarified.<sup>[5]</sup> RNA-binding proteins (RBP) were reported to be participated in cellular processes via post-transcriptional regulation on RNA.<sup>[6–8]</sup> Some circRNAs have been reported to cooperate with RNAs, such as protein-binding circ-Foxo3 that interacts with cyclin dependent protein kinase 2 (CKD2) to arrest the cell cycle at the phase of G1/S.<sup>[9]</sup> CircRNAs also can alter the stability of mRNAs. For instance, CDR1 can act as that cooperates with mRNA to build a stable duplex.<sup>[10]</sup> As a type of ncRNA, circRNAs seldom encode proteins. Nevertheless, once an internal ribosome entry site (IRES) is inserted into the upstream of a circRNA's start codon, the coding takes place, which will produce a transcript functionally that different from a linear transcript.<sup>[11]</sup> In *Bacillus Coli*, transfecting the circRNA that containing an open reading frame (ORF) for green fluorescent protein (GFP) can initiate GFP expression. Unfortunately, until now, only viral circRNAs have been reported to code proteins in eukaryotes.<sup>[12]</sup> The translation of viral circRNAs may be associated with specific viral mediators. Although their ability to translate proteins is still obscure, some eukaryotic circRNAs

have showed their protein-coding potential, as evidenced by the circRNA-synthesized transcript.<sup>[13]</sup>

## 2. Databases

The quantity and quality of research tools were increased as the research area of circRNA expands. Data of the circRNA's research can be available from free online databases, including GenBank (Table 1). But none is perfect. Each has its own advantages and disadvantages, and updates at varying time points. Users can acquire the data which they need only through a comprehensive method.

## 3. The working mechanism of CircRNAs in tumors

### 3.1. The Role of CircRNAs in tumor mechanism

**3.1.1. Effect of CircRNAs on tumor proliferation, invasion, and metastasis.** CircRNAs play important roles in the proliferation, invasion, and metastasis of tumor cells.<sup>[21]</sup> Researches show that hsa\_circ\_0001649 may have the effect of tumor suppression in several types of cancers. Xing et al<sup>[22]</sup> revealed that downregulation of it can lead to poor prognosis of retinoblastoma through AKT/mTOR pathway. Other studies

**Table 1****Free access online database of CircRNA.**

Name	New version	Introduction	URL
StarBase v2. 0 <sup>[14]</sup>	July 2013	Allows users to search for functional	<a href="http://starbase.sysu.edu.cn">http://starbase.sysu.edu.cn</a>
CircBase <sup>[15]</sup>	July 2017	Classes or procedures	<a href="http://www.circbase.org">http://www.circbase.org</a>
Circ2Traits <sup>[16]</sup>	December 2013	Provides a wealth of information about the genome position of circRNA-related diseases and several circRNAs	<a href="http://gyanxet-beta.com/circdb">http://gyanxet-beta.com/circdb</a>
Nc2Cancer <sup>[17]</sup>		–	<a href="http://www.Bioinfo.Tsinghua.edu.cn">http://www.Bioinfo.Tsinghua.edu.cn</a>
CircNet <sup>[18]</sup>	December 2015	Contains the most circulatory annotations, especially the human circRNA	<a href="http://circnet.mbc.nctu.edu.tw">http://circnet.mbc.nctu.edu.tw</a>
DeepBase v2. 0 <sup>[19]</sup>	November 2015		<a href="http://biocenter.sysu.edu.cn/deepBase">http://biocenter.sysu.edu.cn/deepBase</a>
CircInteractome <sup>[20]</sup>	January 2016	With information on the matching of the circRNA with the associated RNA binding protein	<a href="http://circinteractome.nia.nih.gov">http://circinteractome.nia.nih.gov</a>

With BLAST Web interface, comparable to the sequence of the circRNA; CircNet is the only database provided the circRNA expression with the samples.

have found that circ-cbfb and circ-itch can regulate the Wnt/beta-catenin pathway associated with the proliferation of tumor cells by binding miRNAs.<sup>[23,24]</sup> In addition, circRNAs also influence tumor cell proliferation by regulating NOTCH and JAK1/STAT3 signaling pathways.<sup>[25,26]</sup> Besides their effect on tumor proliferation, Wang et al<sup>[27]</sup> still found circHIAT1 can affect invasion and metastasis of renal clear cell carcinoma, the mechanism is that it can directly increase the stability of mir195-5p/29a-3p/29c-3p by acting as a “miRNAs reservoir”.

### 3.2. CircRNAs regulate tumor apoptosis

It has been found that circRNAs (CirUBAP2, hsa\_circ\_0001649, hsa\_circ\_0007534) may influence cell apoptosis by regulating bcl-2/caspase-3 pathway.<sup>[28,29]</sup> Liu et al<sup>[30]</sup> found that circ-ZFR could modulate PTEN and sponge mir-130a/mir-107, that promoting tumor cell apoptosis and inhibiting cell proliferation, and playing a role in tumor inhibition.

**3.2.1. Regulation of CircRNAs on tumor cell cycle.** It is reported that hsa\_circ\_0014717 may affect the tumor cell cycle by regulating the expression of p16.<sup>[31]</sup> It is reported that circ-zeb1.33 can increase the proportion of S-phase cells and promote cell proliferation through circ-zeb1.33/mir-200a3p/CDK6 axis.<sup>[32]</sup> It is reported that circFOXO3 can form circ-foxo3-p21-CDK2 complex with p21 and CDK2, which blocks the cell cycle by inhibiting the function of CDK2.<sup>[9]</sup> Furthermore, it has been confirmed that circRNAs can encode proteins, and FBXW7-185aa is a circ-FBXW7 encoded protein (about 21 kDa), which inhibits proliferation of cancer cells and blocks cell cycle progression.<sup>[33]</sup>

### 3.3. The CircRNAs involved in Gynecological tumors diseases

**3.3.1. Epithelia ovarian carcinoma.** Tumorigenesis is usually triggered by the dysregulation of signaling pathways that mediate cellular proliferation and differentiation. These pathways including NF-kB, TGF-β, ILK-regulated EMT, and PI3K-AKT-JAKSTAT-regulated cell proliferation. Using paired-end RNA sequencing, Ahmed et al found that circRNAs were highly expressed in epithelia ovarian carcinoma samples, and even more dramatically increased in variety lesions (primary sites, peritoneal, and lymph node metastases) as compared with mRNAs. In the meanwhile, high expression levels of mRNA were associated with decreased circRNA levels. For instance, miRNA let-7, which negatively regulated RAS and MYC (2 proto-oncogenes), showed obviously lower expression level in the primary lesion than peritoneal metastases. However, the gene that code circRNAs

containing multiple let-7 binding sites was highly expressed in the primary lesion, which may be explained that circRNAs can act as the sponge of miRNAs.<sup>[20]</sup>

**3.3.2. Cervical carcinoma.** Using human cervical carcinoma HeLa cells, Abdelmohsen et al verified that circPABPN1 could competitively bind to HuR, thus suppressing HuR's binding to PABPN1 mRNA and translation.<sup>[34]</sup> Bachmayr-Heyda et al found that the global circRNA abundance was negatively correlated with proliferation rate in 13 types of human tissues. CDR1as (also called CiRS-7) and SRY (a testis-specific RNA) are 2 typical circRNAs containing elements which bind to suppressor miR-7 in ovarian carcinoma<sup>[35-37]</sup> and miR-138 in cervical carcinoma,<sup>[38,39]</sup> respectively. CiRS-7 is stably expressed in HeLa cells.<sup>[40]</sup> Further studies should be conducted to clarify the negative regulatory mechanism between CiRS-7 and miR-7, or SRY and miR-138, and how this regulatory axis works in the development of ovarian carcinoma and cervical carcinoma.

CDR1as showed a higher expression levels in cervical carcinoma tissues than in para-carcinoma tissues, and which is opposite to miR-7. In HeLa and C33A cells of cervical carcinoma, overexpressed CDR1as can enhance the expression of focal adhesion kinase (FAK, target of miR-7) through suppressing the activity of miR-7. And FAK over-expression will promote the proliferation, invasion, and metastasis of cervical carcinoma cells, which indicating the intricate cooperation between CDR1as, miR-7 and FAK. Therefore, molecular targeted treatment based on CiRS-7 regulatory network has potential efficacy in the prevention, diagnosis and treatment of cervical carcinoma.<sup>[41]</sup> (Table 2).

**3.3.3. Ovarian carcinoma.** Ovary plays a dominant role in female reproductive system with 2 main functions: germinating and releasing oocytes, secreting gonadal hormones to guarantee the development of follicles, estrous cycles, and post-pregnancy hormonal level. As the major health threat of females, ovarian carcinoma has a high incidence (just lower than cervical carcinoma and endometrial carcinoma) and mortality (the highest in all gynecological carcinomas). Studies have uncovered the association between circRNAs and the invasive metastasis of ovarian carcinoma.<sup>[42]</sup> Using RNA sequencing for the primary site, peritoneal and lymph node metastases of epithelial ovarian carcinoma (stage IIIC), researchers found the upregulated mRNAs and the downregulated circRNAs that associated NFkB, PI3k/AKT and TGF (both containing multiple miR-24/let-7 binding sites) were upregulated in metastatic carcinoma, which indicated that circRNAs may use their circularization to

**Table 2**  
**CircRNAs expression in female reproduction and gynecological diseases.**

Tumor	CircRNA	Function	Role
Ovarian carcinoma <sup>[42]</sup>	Cirs-7	Mir-7 sponge	CircRNAs may use their circularization to competitively inhibit the linear splicing and sponge function of miRNAs, and modulate the expression of metastasis-evoking genes, all contributing to the metastasis of ovarian carcinoma
Cervical carcinoma <sup>[40]</sup>	CDR1as	miRNA sponge (miR-7)	Tumor suppressor was performed by inhibiting the tumorigenic effect of mir-7
	CircHIPK3	miRNA sponge	Regulation of cell growth
	Hsa_circ_0018289	miRNA sponge (miR-497)	Promote tumor cell proliferation, migration and invasion
Breast cancer <sup>[46]</sup>	CDR1as	miRNA sponge (miR-7)	Tumor suppressor was performed by inhibiting the tumorigenic effect of mir-7
	Circ-ABCB10	miRNA sponge (miR-1271)	Promote tumor cell proliferation
	hsa_circ_0001982	–	Potential tumor biomarkers
Triple-negative breast cancer <sup>[48]</sup>	hsa_circ_0058514	–	The expression of circRNA hsa_circ_0058514 is significantly upregulated in triple-negative breast cancer tissues and MDA-MB-231 and BT-549 cells. It may serve as an oncogene in the development and progression of triple-negative breast cancer

competitively inhibit the linear splicing and sponge function of miRNAs, and modulate the expression of metastasis-evoking genes, thus contributing to the metastasis of ovarian carcinoma (Table 2).

**3.3.4. Breast cancer.** As the sponge of miR-7, CDR1as can negatively regulate the activity of miR-7 and attenuate its suppressive effect on ECF, IRS-1, IRS-2, ak1, Raf1, Ack1, and PIK3CD, thus promoting the development of tumors, including breast cancer.<sup>[43,44]</sup> Besides, once miR-671 binds to CDR1as, an AGO-mediated splitting action is initiated to decrease the expression level of CDR1as, suggesting that miR-671 can indirectly regulate the activity of miR-7 *via* weakening the expression of CDR1as. Reddy found miR-7 could inhibit the expression of p21-activated kinase (PAK1), a kinase that were upregulated in multiple tumors.<sup>[45]</sup> The expression of miR-7 is positively regulated by its upstream gene HOXD10, the low expression of which can enhance cancer invasiveness. In breast cancer cell model, the invasive ability was enhanced when PAK1 levels elevate, while the miR-7 and HOXD10 levels were declined. Studies found that miR-7 was lowly expressed in malignant breast cancer tissues, and its expression level was negatively associated with the metastatic ability. Inducing of miR-7 expression in the cell lines of invasive breast cancer can inhibit the anchorage-independent proliferation of monolayer cells.<sup>[46]</sup> miR-7 can also inhibit epithelial-mesenchymal transition and metastasis *via* directly regulating the expression of focal adhesion kinase (FAK), an interbody for signals of extracellular matri- integrin and pathways of cellular movement, proliferation, and apoptosis. FAK overexpression leads to metastasis and poor prognosis in various tumors, suggesting that miR-7 expression is closely correlated with cancer's epithelial differentiation: the lower expression, the weak metastatic potency.

Studies also found that let-7 was lowly expressed in the lymphatic metastasis and proliferation of breast cancer, and it could downregulate the expression of some oncogenes (RAS, MYC) and cell-cycle-related genes.<sup>[47]</sup> Recently, circRNA hsa\_circ\_0058514 was found highly expressed in triple-negative breast cancer tissues, MDA-MB-231, and BT-549 cells. It was also found downregulation of hsa\_circ\_0058514 can decrease the abilities of proliferation, migration and invasion of triple-

negative breast cancer cells, and leading to cell apoptosis, and cell cycle arrest. It may serve as an oncogene in the development and progression of triple-negative breast cancer, and be used as a new therapeutic target.<sup>[48]</sup>

#### 4. Prospect

Circular RNAs (circRNAs) are 1 class of non-coding RNAs (ncRNAs) with function of gene expression regulating in various cells. As a “rising star” in RNA research field, increasing numbers of circRNAs that differentially expressed in human cells are being identified by applying efficient high-throughput sequencing and bioinformatic techniques. Given this huge number, their functions remain to be unveiled. Just like a tip of the hidden iceberg, the current knowledge on circRNAs should be enriched with efforts as many.

circRNAs, for their high stability, have been detected in exosomes and blood samples, suggesting their promising prospect as biomarkers in the diagnosis of ovarian cancer, cervical cancer. As described in this review, circRNAs play different roles in the development of ovarian cancer and cervical cancer.

Meanwhile, the updating databases, testing tools, and research skills turn circRNAs into possible non-invasive biomarkers for female tumors disease.

To sum up, the vibrating circRNA research has opened a doorway for us to enter the genetic regulatory network. Future studies will reveal the multiple roles of circRNA in the development of gynecological tumors diseases.

#### Author contributions

KSL, QZ collected literature and wrote the first draft of the manuscript. KSL, XDW and conceived the review and analyzed the relevant literature. XDW and HT collected literature and critically revised the manuscript. FP and KSL created the figures. All authors read and approved the final manuscript.

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