# Research Progress of microRNA in Regulating Gynecological Tumours

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**Abstract:** The incidence of gynaecological tumours, the main factor threatening women 's health and safety, is increasing with the daily heavier pressure of women's life and work; Due to its serious threat to women, the disease has grasped increasingly more vigilance and attention. The discovery and research of micro ribonucleic acid (microRNA), a general term for a class of small-molecule RNA, showed that there was a close relationship between microRNA and the occurrence and development of gynaecological tumours. In this paper, based on the recent researches on the relationship between microRNA and gynaecological tumours, a comprehensive analysis was made to do a favour for scientific research and clinical treatment of gynaecological tumours.

**Keywords:** Gynaecological tumour; Micro ribonucleic acid (microRNA); Ovarian cancer (OC); Cervical cancer (CC); Endometrial cancer (EC)

MiRNA is a type of small molecule RNA with a length of 21-25 nucleotides discovered in recent years. More than 1,900 kinds[1] have been found in modern research, accounting for about 1% to 2% of the total amount of human genes[2]. Its main function is to participate in the regulation of protein expression in the human body, that is, to participate in the regulation of cell growth and differentiation, metabolism, apoptosis and other important and basic cellular physiological processes by combining the target gene to inhibit the expression of target genes. Since the relationship between miRNA and tumour was first reported in chronic lymphocytic leukaemia in 2002, miRNA has been gradually confirmed to have a close relationship with tumour's occurrence, development, metastasis, recurrence and prognosis[3]. Due to its difficulty in finding, curing, and poor prognosis, gynaecological tumours are increasingly becoming the major cause of death of female diseases. Besides, with an increasing tendency, it has seriously threatened women's lives and health[4]. The most prominent and deadly gynecologic malignant tumours in the clinic include ovarian cancer, CC and EC. While the discovery and research of miRNA provide new ideas and methods for the intervention and treatment of gynaecological tumours.

## 1 MicroRNA regulation and ovarian cancer (OC)

As one of the gynaecological malignant tumours, OC is generally divided into epithelial tumours and non-epithelial tumours clinically. The main feature of its morbidity is that 70% of patients were found to be late and would die within five years after finding, and the

recurrence rate was 70%. Most patients were treated with surgery, supplemented by radiotherapy and chemotherapy[5].

## 1.1 MicroRNA & The occurrence and development of OC

During the occurrence of OC, dysregulation of miRNA expression is a significant feature. Medeiros *et al*[6]. co-cultured SKOV-3 cancer cells with primary cultured human normal fibroblasts (FP-96) and found that the co-culture increased the migration of SKOV-3 cells and down-regulated the expression of the tumour suppressor miR-29b. However, the co-culture increased the activity of MMP-2, which is one of the targets of miR-29 and involved in extracellular matrix remodelling and strengthened the cell's movement. At the same time, the co-culture system induced the expression of α-SMA in FP-96 fibroblasts, which is also a common marker in cancer-associated fibroblasts (CAFS). This indicates that the potential connection between cancer cells and fibroblasts in the tumour microenvironment may play a key role in the progression of OC. Modern medical research has found that miR-1 is associated with various cancers, but its relationship with OC is still unclear. The Stope experiment[7] examined the effect of miR-1 on the growth of OC cells; and found that the recombinant miR-1 was over-expressed in human OC cell lines OVCAR-3, SKOV-3, TOV-112D and TOV-21G, as well as the overexpression of miR-1 in the OC cells after transfection by analysing cell growth. However, compared with the control cells, no significant difference in proliferation was observed between the transient and stable transfected cells. Lee[8] detected the expressions of 9 small RNAs (miR-181d, miR-30a-3p, miR-30e-3p, miR-368, miR-370, miR-493-5p, miR-532-5p, miR -30c, and miR-30d) with the Taqman technology. It was found that, compared with poorly differentiated tumours, the expression of miR-30A-3p was higher in those highly differentiated tumours (*P*<0.05), and the expression of miR-370 in Phase I/II was higher than that in Phase III/IV (*P*<0.05), and all were accompanied with over-expression of HER-2/neu. At the same time, it was also found that the high expression of miR-181d, miR-30c, miR-30D and miR-30e-3p were associated with the overall survival rate of OC, while the low expression of miR-30c,miR-30d,miR-30e-3p and miR-532-5p was related to the over-expression of HER-2/neu. It was suggested that these 9 miRNAs were correlated with the histology, clinical stages, survival rate and oncogene expression of OC. Through experiments, Liu Lishuang[9] found that miR-3613-3P, miR-7515, miR-8084 and miR-3198 miRNA were all lowly expressed in the treatment of primary ovarian epithelial carcinoma of OC, indicating that these four microRNAs were involved in the development of OC. Kinose *et al*[10] conducted micro-polymerase chain reaction display analysis on the cells of two OC cell lines (CAOV3 and RMUG-S) and found that miR-199a-3p was down-regulated under hypoxic conditions and its expression was negatively correlated with c-Met expression in OC. This finding indicates that miR-199a-3p can inhibit the progression of OC by down-regulating c-Met expression under hypoxic conditions. An experiment[11] tested the effects of miR-449 and miR-34 on the growth, cell cycle and target gene expression of OC cell lines SKOV3 and SKOV3-ipl. They were successfully expressed in SKOV3-ipl cells after the transfection between two microRNAs. According to the experiment, miR-449b caused a decrease in the expression of CDK6 and CDC25a. After co-transfection with miR-449b and miR-34c, the expression of CDK6, CDC25a and CyclinA decreased significantly, indicating that miR-449b and miR-34c could induce the cell cycle arrest of SKOV3-ipl cells and down-regulate CDK6, CDC25a and CyclinA expression, thereby inhibiting the progression of OC.

## 1.2 MicroRNA and OC prognosis

As the only feasible treatment for OC nowadays, chemotherapy still has the key problem, its tolerance. The study found that miR was also associated with chemotherapy and the prognosis of OC. In clinical evaluation of miRNA expression in OC, Ram[12] found that the difference existed in 18 microRNAs in patients received platinum-based chemotherapy as first-line treatment from the Phase I to Phase III of the disease (*P*<0.05). There were significant differences in the expression of seven miRNAs in the tumours of platinum-sensitive patients and platinum-resistant patients (*P*<0.05). The five miRNAs were associated with significant differences in survival rates or relapse-free survival rates (*P*<0.05). Moreover, high expression of HSA-miR-27a is a signal of poor prognosis of OC. Qin Qiaohong *et al*[13] found that, besides lower than that in normal ovarian tissues and benign OC tissues, the expression of miR-126 in epithelial OC tissues was related to FIGO phasing of epithelial OC and lymph node metastasis, indicating that miR-126 may be related to the prognosis of epithelial OC. Studies[14] that inserted miR-200a response elements into OC cell lines

through lentivirus-mediated transgene in vitro found that miR-200a significantly improved the chemical sensitivity of paclitaxel (PTX). It was proved that up-regulation of miR-200a can promote the proliferation of OC cell lines and inhibit the CSCS phenotype and the "side-effects" of proliferation can be effectively eliminated through combining cell cycle targeting drug PTX, indicating that this gene can inhibit the expression of OC cell lines. TEGY may be a prospect for the treatment of OC.

## 2 MicroRNA and CC

As the most common malignant tumour in gynaecology, CC has a high incidence in China[15]. Mostly caused by human papillomavirus (HPV), CC is an invasive squamous cell carcinoma, and clinically divided into four phases with the boundary of the uterus, pelvic wall and true pelvis, and various complications may occur[16]. Surgery, radiotherapy and chemotherapy serve as the main treatments[17].

### 2.1 Diagnosis of CC and microRNA

A study[18] detected the expression of CCAT1 in CC cells with the QRT-PCR technology and found that the expression of CCAT1 in CC cells was higher than that in adjacent normal tissues. Over-expression of CCAT1 can promote cell proliferation, colony formation and in-vitro invasion of CC. The increase of CCAT1 inhibited the expression of miR-181A, while promoted the expression of MMP-14 and HB-EGF, indicating that CCAT1 may be a key oncogene related to CC, and can promote the proliferation and invasion of CC cells by regulating the miR-181a-5p/mmp14 axis. When evaluating the relationship between the single nucleotide polymorphisms (SNPs) of miR-146a (rs2910164), miR-196a (rs11614913) and miR-499 (rs3746444) and the susceptibility of CC in the Indian population. Thakur[19] found that polymorphisms of miR-146a, miR-196a and miR-499 can become biomarkers of CC through genotyping the 300 samples using polymerase chain reaction (PCR) restriction fragment length polymorphism (RFLP). Kong et al[20] studied and found that the diagnostic threshold, sensitivity and specificity of miR-92a for CC were 1.52, 69.6% and 80.4% respectively, indicating miR-92a can be used as an independent marker for CC diagnosis. Next, they found that over-expression of HPV E7 protein promoted the expression of miR-21 and enhanced the proliferation and invasion of

HeLa cells; While inhibiting the over-expression of E7 can inhibit the expression of miR-21 to reduce the proliferation and invasion of HeLa cells, but does not significantly affect the activity of Caspase-3. This indicates that E7 protein is one of the key factors for the occurrence and development of CC[21]. Through the OC curve analysis, Zhang et al[22] found that GICHG can accurately distinguish CC patients from the healthy control group, indicating that GIHCG may be a non-invasive diagnostic biomarker and a potential target for CC treatment. Also, it was found that the expression of miR-200b was negatively correlated with that of GIHCG in CC tissues. And, the over-expression of miR-200b can inhibit the role of GIHCG in promoting CC growth in vivo.

### 2.2 MicroRNA and its treatment prospect for CC

Some studies claimed that the effect of competitive long non-coding RNA2 (lncRNA 2) was an important regulator of tumorigenesis and progression of Let-7b (ceRNA2). Min Wang et al[23] studied and found that the expression of ceRNA2 in CC tissue was significantly higher than that in adjacent normal cervical tissue. They observed that, compared with primary CC tissues, metastatic lymph nodes had higher levels of ceRNA2 expression, which was associated with advanced clinical phase, lymph node metastasis, distant metastasis, poor histological grade and low overall survival rate of patients with CC. It was believed that ceRNA2 was a carcinogenic lncRNA, and may also be a potential therapeutic target for CC. Han[24] found that MALAT1 can positively regulate the expression of periosteal protein by negatively regulating miR-202-3p. Periosteum protein can be regulated by the MALAT1/miR-202-3p axis, and play an important role in regulating cell viability, migration and invasion, and EMT of CC cells by activating the AKT/mTOR signaling pathway. It is also reported that miRNA-802 (miR-802) is a tumour suppressor, and can be observed in various human malignant tumours. Zhang[25] found that miR-802 was down-regulated in CC tissues and cell lines. Introduction of miR-802 mimics into CC cells can inhibit their proliferation and colony formation, and promote cell cycle arrest and apoptosis in the G0/G1 phase. It was found that miR-802 could directly target the 3' untranslated region and inhibit the expression of SRSF9. Another group of the experiment confirmed that over-expression of SRSF9 could reverse the inhibitory effect of MIR-802

on CC cells. This indicates that miR-802 can inhibit tumours in CC. The miRNA-130a has been reported to promote the growth of CC. Yin's research[26] showed that HPV18-E6 promoted the expression of miR-130a, then inhibited the expression of TIMP2, and promoted the invasion of CC cells. Therefore, HPV/miR-130a/ TIMP2 signal may be a potential target for preventing CC metastasis. Zhu[27] evaluated the effects of EGCG of seven different concentrations (100, 80, 60, 40, 20, 10, and 0 μg/ml) on HeLa cell proliferation. The results showed that EGCG can inhibit the growth of CC cells by regulating the expression of miRNA, indicating its potential as a therapeutic target for control and prevention of CC. Also, EGCG can be considered as a new anti-CC drug. Li et al[28] studied and explored 132 patients with CC and 120 healthy subjects. The expression of miR-224 and PYX3 was detected in peripheral blood. It was found that the over-expression of miR-224 and the silence of PTX3 both promoted the proliferation, migration and invasion of cancer cells, but when the miR-224 expression was inhibited, the above characteristics were also inhibited. It showed that the progression of CC could be prevented by inhibiting miR-224 via the targeting PTX3 gene. Sara[29] studied and found that during the progression of CC, the expression level of miR-21 in cancerous samples increased significantly, while the expression level of miR-29 decreased significantly (p<0.0001). It showed that miR-21 and miR-29a could be used as oncogenes and tumour inhibitors. Jiang[30] studied and found that miR-302-3p played an inhibitory role in CC metastasis by directly targeting DCUN1D1 and MiR-302-3p/ DCUN1D1 might be a potential target for CC treatment. According to the microarray data of GSE63514 and GSE27678, Wei[31] found that the expression of NCK1-AS1 and MSH2 increased in CC tissue, while the expression of miR-134-5p decreased. NCK1-AS1 and miR-134-5p regulate MSH2 through competitive binding, which simulated the decrease of MSH2 activity and the increase of cisplatin-induced apoptosis in CC cells. It proved that NCK1-AS1 may become a new target to improve the chemotherapy response and survival rate of CC patients. Phuah[32] found that miR-210 could bind to the 3' UTR sequence of SMAD4. When miR-210 was over-expressed, SMAD4 protein expression decreased; However, when the expression of miR-210 was inhibited, SMAD4 protein expression increased. Also, Phuah found that the over-expression of SMAD4 enhanced the anti-proliferation and apoptosis

induction of ACA, indicating that to down-regulate the expression of miR-210 can make CC cells sensitive to ACA via targeting SMAD4. Yong[33] studied and found that miR-99b inhibited the migration and invasion of CC cells by down-regulating the PI3K/AKT/mTOR signalling pathway, which provided a new therapeutic approach for the treatment of CC. Wang Ping[34] studied and found that miR-124-3P could inhibit the growth and metastasis of CC by directly regulating IGF2BP to achieve the effect of treating CC. Jianglin Cong [35] found that miR-634 could inhibit the proliferation, migration and invasion of CC cells through targeted regulation of the mTOR signalling pathway. The block of miR-634 enhanced the expression of mTOR at the mRNA and protein levels, and negatively regulated mTOR expression, indicating that miR-634 was an effective target for CC. Also, Tang[36] studied and found that the over-expression of miR-152 could reduce the proliferation of HeLa cells by inhibiting the expression of WNT1 and ERBBBB3 to inhibit the occurrence and development of CC.

# 3 EC and microRNA

As a common gynaecological malignant tumour, EC is clinically divided into estrogen-dependent and non-estrogen-dependent types based on estrogen dependence[37.] Meanwhile, numerous experimental studies have found that the EC PI3K-AKT-mTOR signalling pathway activation and Notch signalling pathway expression decrease was associated with mutation of p53 gene, PTEN gene, LKB1 and so on. At the same time, it was found that obesity, smoking, infertility, diabetes and hypertension also served as the high-risk factors for EC[38].

## 3.1 Pathogenesis of EC and microRNA

As a common mechanism of all subtypes of EC, the activation of PI3K/AKT/MTOR signalling pathway always plays an important role in the occurrence and development of many cancers. Inhibitors for the components in this pathway may provide a new and effective way for future EC targeted therapy. The experiment found that AKT1 and mTOR, the two main members of this pathway, have been reported as miR-99A putative target genes. Li[39] studied and found that in EC tissues, miR-99a expression was significantly inhibited, which was negatively correlated with tumour differentiation. Over-expression of miR-99a can induce inhibition of cell proliferation, block G1/S phase

transition, induce apoptosis, inhibit cell invasion and tumour growth in vivo. Besides inducing the apoptosis of cancer cells, this mediation inhibits the proliferation of cancer cells by inhibiting cell proliferation, apoptosis, tumour growth, and through the double inhibition of PI3K/AKT/MTOR pathway. This indicated that miR-99a may be a potential biomarker and therapeutic target for EC. The over-expression of miR-326 can effectively inhibit the invasion and angiogenesis of HUECSCS in the extracellular matrix. The research team of Gao[40] found that the G protein-coupled receptor 91 (GPR91) gene was one of the potential targets of miR-326. According to the experiment, the over-expression of miR-326 could significantly inhibit the tumorigenicity and angiogenesis of cancer cells. Both quantitative real-time PCR and WB confirmed that over-expression of miR-326 significantly reduced the expression of GPR91/STAT3/VEGF pathway members in nude mouse tissues, as well as the phosphorylation level of key molecules in this pathway. It was confirmed that miR-326 could inhibit the activation of the GPR91/STAT3/VEGF signalling pathway, and significantly reduce the activity of EC stem cells, thereby inhibiting the differentiation and proliferation of cancer cells. Oliver[41] identified 47 microRNAs that downregulated E2 and 25 microRNAs that upregulated E2 through microarray analysis. The miR-203 that upregulated E2 was chosen for further analysis. It was found that 43 genes up-regulated by miR-203 in vitro were down-regulated by E2 in the uterus. Among them, with one or more seed sequence matched in their 3′ UTR, ACER2, ZBTB20, PTEN, RCBTB2, MUM111, HMGN3, and NFAT5 might be the target of miR-203. E2 can be regulated by targeting miR-203 to regulate estrogen-dependent EC. Sun[42] studied and found that the expression of miR-490-3p in EC was significantly lower than that in normal endometrial tissue. The expression of miR-490-3p was negatively correlated with the depth of invasion and lymph node metastasis. The over-expression of miR-490-3p reduced cell proliferation, promoted G1 phase arrest and apoptosis and inhibited migration and invasion by directly targeting TGFα through its 3' untranslated region, indicating that miR-490-3p can play an inhibitory role in EC tumorigenesis and progression via the target TGFα. Young[43] studied and found that, compared with normal endometrial tissues, the expression of miR-200c increased in endometrial cancer. Pre-miR-200c can regulate the survival, proliferation and apoptosis

of endometrial cancer cells and affect cytotoxicity. Through microarray analysis of mRNA, it was found that miR-200c can inhibit the translocation of β-catenin from the cytoplasm to the nucleus by inhibiting BRD7, and increase the expression of its transcription target genes Cyclin D1 and c-MYC, and further regulate and inhibit the proliferation and differentiation of cancer cells.

## 3.2 EC treatment prognosis and microRNA

As a common phenomenon in tumours, the abnormal expression of miRNA is mainly manifested in the imbalance of the four major mechanisms of epigenetic modification, genetic variation, biological origin changes and transcriptional repression. MiRNAs with an abnormal expression not only affect the development of tumours, but are also associated with the development of tumour resistance to anticancer drugs[44]. Wang[45] comprehensively analyzed the genome-wide microRNA expression profiles and related clinical features of 348 UCEC patients downloaded from the Cancer Genome Atlas (TCGA) data portal. A total of 144 microRNAs have different expressions in tumour tissues. In the middle, 5 microRNAs (hsa-miR-15A, hsa-miR-3170, hsa-miR-1976, hsa-miR-142, and hsa-miR-146A) were significantly associated with OS in UCEC patients. The risk index established by 6-miRNA marker is an independent prognostic factor (risk ratio = 0.391; 95% CI: 0.195-0.783; P = 0.008). Tan Feifei et al[46] found that MIR-373 was highly expressed in endometrial cancer tissues, and its expression level was related to the malignant degree of EC and had reference significance to the prognosis of EC. Meanwhile, miR-373 was believed to be a potential therapeutic target for EC. Jeong[47] conducted an in vitro experiment using EC cells with anti-microRNA (ANTI-miR) to evaluate the effect of microRNA highly expressed in EC on cell proliferation and chemical regulation. It was found that, compared with normal endometrial tissue, the miR-200 family was highly expressed in EC and may play an important role in tumour growth; while the anti-miR-429 can enhance the cytotoxic effect of cisplatin on EC. Therefore, the miR-200 family may provide new candidate targets for the treatment of these cancer patients and improve the prognosis of cisplatin treatment.

## 4 Prospects

A large number of studies in recent years have shown

that microRNA played an important role in the occurrence, development, hyperplasia, metastasis and inhibition as well as the prognosis of gynaecological tumours. How to find and use more related microRNA to gynaecological tumours in clinical treatment is still the research directions in the future.

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