

# MicroRNAs in Ovarian Cancer Metastasis

Subjects: **Oncology**

Contributor: Vu Hong Loan Nguyen , Chenyang Yue , Kevin Y. Du , Mohamed Salem , Jacob O'Brien , Chun Peng

Epithelial ovarian cancer (EOC) is the deadliest gynecological cancer, and the major cause of death is attributed to metastasis. EOC metastasizes mainly through the transcoelomic pathway, in which cells disseminate from the primary EOC tumor by undergoing epithelial-to-mesenchymal transition (EMT), float freely as spheroids in the ascitic fluid, and then attach onto the mesothelium lining or invade deeper into the peritoneal organs. In addition, metastatic EOC cells can transit in the blood or lymph vessels and undergo extravasation to establish new tumors in hematogenous and lymphatic metastasis. MicroRNAs (miRNAs) are a group of small non-coding RNAs that exert important regulatory functions in many biological processes through their effects on regulating gene expression. Numerous studies have reported that miRNAs can suppress or promote EOC metastasis by regulating the expression of genes involved in various events related to metastasis, such as EMT, cell migration and invasion, as well as tumor angiogenesis and immune suppression.

epithelial ovarian cancer

metastasis

microRNAs (miRNAs)

## 1. Introduction

Ovarian cancer is the fifth leading cause of cancer-related deaths in females <sup>[1]</sup>. Based on the cell origin where ovarian tumors arise, ovarian cancer is classified into three categories: epithelial, germ cell, and stromal ovarian cancer. Several types of extremely rare ovarian cancer, such as small cell carcinoma and sarcomas, have also been reported <sup>[2]</sup>. Among them, epithelial ovarian cancer (EOC) accounts for more than 85% of ovarian cancer cases and is responsible for most ovarian cancer-related deaths <sup>[3]</sup>. EOC is further grouped into five different histological subtypes, including high-grade serous carcinomas (HGSC), low-grade serous carcinomas (LGSC), endometrioid carcinomas (EC), clear cell carcinomas (CCC), and mucinous carcinomas (MC) <sup>[3]</sup>. Though the morbidity of ovarian cancer is lower than that in endometrial and cervical cancers, it has the highest mortality rate among gynecological cancers <sup>[1]</sup>. The five-year survival rate of EOC is less than 45% <sup>[4]</sup>, and relapse and poor prognosis occur in 80% of patients with advanced stages <sup>[5][6]</sup>. EOC is difficult to detect at the early stages as there are no effective screening methods and the presenting symptoms are vague. Therefore, patients are often diagnosed at the advanced stages when the tumor metastasis is already taking place <sup>[5]</sup>.

MicroRNAs (miRNAs) are small non-coding RNAs that regulate gene expression within cells <sup>[7][8]</sup>. Studies have shown that 30–60% of human protein-coding genes are regulated by miRNAs <sup>[9]</sup>. Through regulation of the target gene expression, miRNAs are reported to control many biological processes, including proliferation, differentiation, cell cycle progression, apoptosis, and immune response <sup>[10]</sup>. Aberrant expression of miRNAs is implicated in many diseases, including cancer. Studies have demonstrated that miRNAs are involved in the progression of EOC <sup>[11][12]</sup>.

Their levels are up- or down-regulated in EOC tumors and/or patient plasma samples, and their abnormal expression is highly associated with EOC metastasis [11][13]. In this review, we provide a brief overview of the biogenesis and mechanisms of actions of miRNAs and metastasis in EOC. We then discuss the dysregulation of miRNAs in EOC and the roles of miRNAs in promoting or suppressing cellular processes related to metastasis. Finally, we point out some limitations of current studies and suggest future research directions.

## 2. Ovarian Cancer Metastasis

Metastasis is a complex multistep process in which cancer cells **disseminate** from primary tumors and start new tumors at different sites in the body. This process is regulated by a specific set of genes and signaling pathways. EOC cells mainly metastasize through the transcoelomic pathway [14], in which cells disseminate from the primary EOC tumor by undergoing epithelial-to-mesenchymal transition (EMT) [14] and float freely as spheroids in the ascitic fluid within the peritoneal cavity. The metastatic cells then attach onto the mesothelium lining or invade deeper into the peritoneal organs [15]. In addition, metastatic ovarian cancer cells can transit in the blood or lymph vessels and undergo extravasation to establish new tumors in hematogenous and lymphatic metastasis [15][16]. EOC metastasis to secondary sites accounts for approximately 90% of all ovarian cancer deaths [15]. Therefore, understanding the underlying mechanisms of EOC metastasis could lead to the development of more effective therapeutic tools.

EMT is a biological process which is activated during normal embryonic and organ development, as well as tissue repair [17]. The role of EMT in tumor metastasis has been established in many types of cancers, including EOC [18][19][20]. In EMT, epithelial cells undergo phenotypic alterations through the loss of cell polarity, cell–cell attachment, and gain mesenchymal phenotypes, such as fibroblastoid morphology with increased migratory and invasive properties. EMT is a critical step in ovarian cancer metastasis [21]. Downregulation of epithelial cadherin (E-cadherin, CDH1) and upregulation of mesenchymal neural cadherin (N-cadherin, CDH2) are key elements of EMT. E-cadherin is a transmembrane glycoprotein that associates with  $\beta$ -catenin at the adherens junctions [21]. Loss of E-cadherin results in the destabilization of adherens junctions, promoting cell migration, invasion, and metastasis. E-cadherin expression is repressed directly by many transcription factors, including Snail (SNAI1), Slug (SNAI2), and zinc finger E-box binding homeobox (ZEB)1 and ZEB2, and indirectly by TWIST and TCF4 [22][23]. In addition, Vimentin (VIM), a component of intermediate filaments, is abundantly expressed in mesenchymal cells [24] and exerts inhibitory effects on E-cadherin expression, and cell–cell adhesion, while promoting cell migration and invasion [25]. Therefore, Vimentin is not only an EMT marker but also directly promotes EMT in EOC.

In EOC, EMT is induced by several signaling pathways, including transforming growth factor-  $\beta$  (TGF- $\beta$ )/Smads, Wnt/ $\beta$ -catenin, PI3K/AKT, Hedgehog, Sonic, and Notch [26]. Wnt signaling promotes the localization of  $\beta$ -catenin into the nucleus, which, in turn, interacts with T-cell factors (TCF/LEF) to regulate transcription [27]. The pathway inhibits E-cadherin by promoting the expression of E-cadherin repressors, such as Snail, Slug, and TWIST [27][28]. TGF- $\beta$  also enhances EMT through its downstream mediators, SMAD2, SMAD3, and SMAD4 [29]. In addition, the MAPK and PI3K/AKT pathways, activated by many growth factors, or through cross-talks with other signaling molecules, also play critical roles in promoting EMT. For example, epidermal growth factor (EGF) signals through

the ERK1/2 and PI3K/AKT pathways to induce EMT [30]. Hepatocyte growth factor (HGF) acts through its receptor, c-Met, and enhances EMT by activating multiple signaling pathways, including MAPK, Wnt/ $\beta$ -catenin, and PI3K/AKT [31][32][33]. Hedgehog glioma-associated oncogene1 (Shh-Gli1) positively regulates EMT via crosstalk with PI3K-AKT [34]. In addition to functions in mitotic progression, Aurora kinase A (AURKA) has been reported to regulate EOC cell migration and invasion in vitro and in vivo [35]. Treatments with AUKA inhibitors, such as alisertib, inhibited migration, adhesion, and EMT via the PI3K/AKT/mTOR- and Sirtuin-1-mediated pathways [35][36], suggesting a potential therapeutic advancement in controlling EOC dissemination. Finally, focal adhesion kinase (FAK) is an important component of various pro-metastatic signaling pathways which promote cancer metastasis, including cell motility [37], cell survival [38][39], invasion [40][41], and EMT [42]. Increased FAK levels are found in several cancers, including EOC [41][42]. In addition, FAK activation, which is determined by p-FAK, increases with tumor progression [42].

Actin filament dynamics are regulated strictly to maintain cell shape and control cell motility [15]. The increase in EOC cell mobility is mediated by actin filament remodeling via the activation of GTPase signaling pathways. For example, GTPase RAP1B has been reported to activate Src and JNK to facilitate integrin-mediated actin remodeling and thereby promote metastasis [43]. DAAM1, which is upregulated in EOC tumors, activates RHOA, induces the formation of microfilaments, and promotes cell migration and invasion [44]. In addition, Lim kinase 1 (LIMK1), a member of serine-threonine protein kinases that acts downstream of RHO GTPase signaling, also participates in actin remodeling in EOC [45]. LIMK1 is a key player in the reorganization of the actin cytoskeleton by inactivating actin-binding factor cofilin through phosphorylation [46]. LIMK1 protein levels are upregulated in EOC and correlated with poor differentiation [45]. In addition, knockout of LIMK1 inhibited migration and invasion of EOC cells [45], supporting its role in promoting EOC cell mobility.

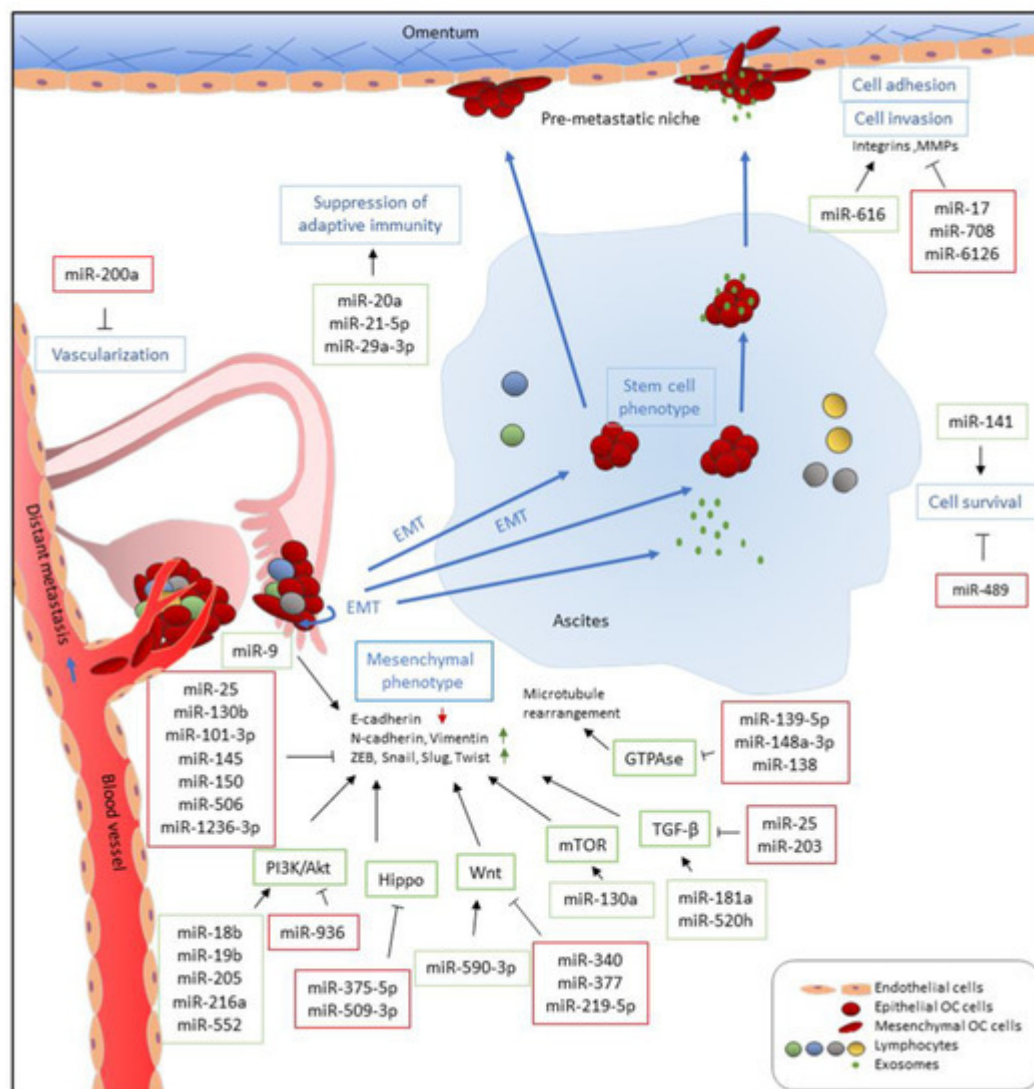
Most EOC metastasis occurs in the peritoneal cavity. Once escaping the primary site, ovarian tumor cells transit in the ascitic fluid as single cells or aggregated cells, referred to as spheroids, and exhibit cancer stem-like properties [47][48]. Cancer cells then adhere to the mesothelium lining of the peritoneum through the binding of integrin receptors to the extracellular matrix (ECM) elements of the mesothelial cells [15]. The integrin-ECM interaction was suggested to activate integrin-linked kinase (ILK) through phosphorylation, promoting a phosphorylation cascade of a variety of ILK-intracellular substrates, including protein kinase B (PKB/AKT), glycogen synthase kinase-3 (GSK-3), and myosin light chain at focal adhesions, and promoting cell adhesion and invasion to the mesothelium [49]. In addition, ovarian tumor cells increase the production of proteolytic enzymes, such as matrix metalloproteases (MMPs), which recognize and degrade ECM elements, enhancing invasive behavior. MMPs play a role in EMT and they are also activated by genes and signaling pathways that induce EMT [50]. In EOC, it has been reported that knockdown of SNAI1 reduced MMP2 but upregulated its inhibitor, TIMP2, suggesting that Snail induces MMP activity [51]. Moreover, EOC cells avoid apoptosis while detaching from primary sites and circulating in ascites or transiting to a distant location by resisting anoikis, a programmed cell death which is activated to inhibit anchorage-independent growth or cell adhesion to an inappropriate matrix [52]. Among steps that occur in cancer metastasis, escaping apoptosis is critical in tumor development and metastasis [53].

Interaction between cancer cells and the tumor environment also plays a role in metastasis. Hypoxia is commonly observed in fast-growing tumors with an insufficient supply of oxygen. Under hypoxic conditions, the association of stabilized hypoxia-inducible factor (HIF)-1 $\alpha$  and HIF-2 $\alpha$  [54] with HIF-1 $\beta$  induces the expression of downstream target genes that are involved in cell invasion, and metastasis [55]. LOX, one of the target genes induced by HIF-1 complex, has been shown to cross-link collagen and provide a linear track for cell migration [56][57]. In addition, HIF-1 complex modulates the downregulation of DMN2, resulting in decreased endocytosis, an energy-consuming cellular process [56]. Hypoxia has also been reported to down-regulate BRCA1 expression via Retinoblastoma-associated protein E2F transcription factor and suppresses homologous recombination in hypoxic cancer cells, potentially increasing genomic instability [58][59]. Furthermore, the behaviors of metastatic EOC cells are influenced by secreted factors residing in ascites. Cytokine CXCL12 and hyaluronic acid in ascitic fluid have been demonstrated to interact with CXCR4 and CD44 receptors on EOC cell surface respectively, stimulating cell migration, angiogenesis, and localization to the peritoneal surface [15][60][61][62].

Lastly, the metastasis of EOC cells is enhanced by an immunosuppressive microenvironment. Tumor-infiltrating lymphocytes (TILs), such as T cells, B cells, macrophages, and natural killer cells, were also found to be present in ascites and pelvic peritoneal biopsies of advanced ovarian cancer patients [63]. Among them, tumor-associated macrophages (TAMs) play a role in the suppression of adaptive immunity. TAMs induced the imbalance of Treg/Th17 and promoted angiogenesis and metastasis via cross-talk with endothelial cells in EOC [64][65]. In addition, TIL-produced cytokines, such as IL-6, IL-10, ARG-1, and CCL-2, have been reported to promote tumor progression and metastasis, and are involved in immune subversion [66][67]. In addition, EOC cells promote immune evasion via downregulating tumor-associated surface ligands. MHC class I chain-related molecules A and B (MICA and MICB) are widely expressed on epithelial tumor cells and targeted by cytotoxic lymphocytes such as CD8<sup>+</sup> T cells and natural killer (NK) cells [68]. Downregulation and internalization of MICA/B have been reported in EOC [69], allowing EOC malignant cells to escape immune surveillance.

### 3. Roles of miRNAs in Ovarian Cancer Metastasis

Numerous studies have reported the functions of miRNAs in EMT, cell migration, invasion, and metastasis in EOC. In addition, miRNAs also participate in inducing angiogenesis and modulating tumor microenvironments [64][67][68], which contribute to tumor metastasis (Figure 1). The majority of studied miRNAs exert negative regulatory effects on metastasis, while some miRNAs serve as positive regulators of metastasis. In addition, some miRNAs have been reported to exhibit both pro-metastatic and anti-metastatic effects, probably depending on the genes they targeted under different cancer contexts.



**Figure 1.** Functions of miRNAs in EOC metastasis. miRNAs which are upregulated and promote metastasis-related processes are depicted in green boxes while downregulated miRNAs which inhibit metastatic-related processes are listed in red boxes. miRNAs directly and indirectly regulate epithelial-to-mesenchymal transition (EMT) by targeting E-cadherin and E-cadherin repressors, such as ZEB, Snail, Slug, and Twist, and associated signaling pathways. miR-9 directly targets E-cadherin to activate EMT while miR-25, miR-101-3p, miR-130b, miR-145, miR-150, and miR-1236-3b directly inhibit expression of E-cadherin repressors, including *ZEB1*, *SNAI2*, and  *Twist1*. Multiple miRNAs, such as miR-18b, miR-19b, miR-205, miR-216b, and miR-552, promote EMT by targeting *PTEN*, leading to the activation of the PI3K/AKT pathway. In addition, upregulation of miR-590-3p, miR-130a, miR-181a, and miR-520h induces Wnt, mTOR, and TGF- $\beta$  signaling, respectively, which are known pathways that promote EMT. In contrast, miR-936, miR-375-5p, miR-509-3p, miR-340, miR-377, miR-219-5p, miR-25, and miR-203 attenuate PI3K/AKT, Hippo, Wnt, and TGF- $\beta$  signaling pathways and inhibit cell migration, invasion, and EMT. Furthermore, downregulation of miR-139-5p, miR-148a-3p, and miR-138, which has been reported to inhibit *ROCKs* and *LIMK1* expression, increases cell motility via GTPase signaling. Metastatic EOC cells float in ascites as single cells or spheroids which exhibit stem cell-like properties. To survive after detaching from primary site and inside ascites, metastatic EOC cells upregulate miR-141 and downregulate miR-489 to modulate anoikis resistance. In the transcoelomic pathway, EOC metastatic cells then adhere to the mesothelium



lining and invade peritoneal organs. Upregulation of miR-616 and downregulation of miR-17 and miR-6126 increase cell adhesion via increased expression and activities of integrins and MMPs which recognize and degrade the extracellular matrix (ECM) of the mesothelial cells, respectively. In addition, downregulation of miR-708 increases focal adhesion formation through promoting focal adhesion kinase (FAK) activities. EOC metastasis occurs in an immune-suppressive environment which are modulated by miRNAs. miR-21-5p and miR-29a-3p promote adaptive immune suppression via upregulation of tumor-associated macrophages (TAMs) and induction Treg/Th17 imbalance while miR-20a downregulates *MICA/B* to avoid recognition by cytotoxic T-cells. Furthermore, EOC tumors increase vascularization and angiogenesis via downregulation of miR-200a, implicating them in distant metastasis through a perfusion pathway.

## 4. Conclusions and Future Direction

Cancer metastasis is one of the main factors that leads to poor clinical outcomes for EOC patients. Accumulating evidence demonstrates that miRNAs play important roles in EOC metastasis. Aberrant expression of miRNAs has been reported in EOC. Such dysregulation can be attributed to alterations at the DNA level, such as amplification and hypermethylation at the promoter regions of miRNA genes. In addition, altered transcriptional controls and defects in miRNA biogenesis machinery also contribute to the abnormality of miRNA levels. Many studies have reported that miRNA expression profiles correlate with clinical features, such as tumor stage, grade, and overall survival of patients, raising the possibility of using miRNAs as diagnostic and/or prognostic markers.

Due to the heterogeneity of EOC, it is a challenge to find effective biomarkers for detecting EOC in different tumors [70]. miRNA profiling studies have sometimes reported inconsistent findings. One of the underlying issues could be the controls used. Some researchers used normal ovarian tissues as the control while others used benign tumors. Methylation patterns of some miRNA genes have been shown to be correlated with metastasis [71][72]. In addition, miRNAs are detected in biological fluids, which can serve as a non-invasive tool for EOC diagnosis. Further efforts in validating the specificity and sensitivity of miRNA signatures in a large cohort of EOC patients are needed for the development of miRNAs as diagnostic and prognostic biomarkers.

Metastasis of ovarian cancer is orchestrated by several interconnected biological processes, including EMT, increase in cell migration and invasion, destruction of the ECM, formation of spheroids, avoidance of apoptosis, angiogenesis, and immune suppression [53]. Some miRNAs have been reported to promote metastasis, mainly by targeting negative regulators of these processes. On the other hand, most miRNAs that have been studied exert suppressive effects on metastasis, mainly by inhibiting transcription factors that induce the expression of mesenchymal markers, or key signaling pathways that promote EMT, motility, and tumor angiogenesis. Therefore, the upregulation of metastasis-promoting miRNAs and downregulation of metastasis-suppressing miRNAs would lead to a dysregulated signaling network and promote metastasis. However, more work is required to better understand the role of miRNAs and the underlying mechanisms by which they regulate metastasis. Among the studies reported so far, some are comprehensive, but most only examined the effects of miRNAs using established EOC cell lines in vitro. Therefore, further in vivo experiments would verify the roles of those miRNAs in metastasis of EOC. Moreover, miRNAs can target many genes and it is possible that they could exert tumor-promoting or

tumor-suppressive effects, depending on the relative abundance and/or functions of target genes in different tumor contexts. Most studies have been focused on one or a few target genes. Additional studies in identifying critical targets that are directly involved in the induction of EOC metastasis would enhance our understanding of the roles of miRNAs in these processes. Finally, EOC consists of multiple histological subtypes, each one with unique origins and distinct molecular features [3]. More work on examining the dysregulation and functions of miRNAs in different subtypes of EOC is warranted as it may help to develop precise therapeutics. miRNAs have been suggested as promising therapeutic targets for cancer treatment [73]. miRNA-based therapies have been established for lung cancer treatment and further trials are anticipated to address clinical treatment efficacy [73]. It is possible that the restoration of down-regulated miRNAs that inhibit metastasis or inhibition of up-regulated miRNAs that promote metastasis could be used in the future as a therapeutic approach for EOC.

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