Advance in vasculogenic mimicry in ovarian cancer (Review)

XINYUAN TIAN[1*], QIN SI[2*], MENGHE LIU[1*], JIANPING SHI[3], RONGWEI ZHAO[4], YANG XIONG[5], LEI YU[6], HONGWEI CUI[7] and HAIBIN GUAN[1]

[1]School of Pharmacy, Inner Mongolia Medical University, Hohhot, Inner Mongolia Autonomous Region 010107; [2]Scientific Research Department, Inner Mongolia Cancer Hospital and Affiliated People's Hospital of Inner Mongolia Medical University, Hohhot, Inner Mongolia Autonomous Region 010020; [3]School of Traditional Chinese Medicine, Inner Mongolia Medical University, Hohhot, Inner Mongolia Autonomous Region 010107; [4]Department of Obstetrics and Gynecology, Inner Mongolia Medical University, Affiliated Hospital of Inner Mongolia Medical University, Hohhot, Inner Mongolia Autonomous Region 010050; [5]Department of Hepatobiliary Surgery, General Surgery Department of Ordos Central Hospital, Ordos, Inner Mongolia Autonomous Region 017000; [6]Department of Pharmacy, Traditional Chinese Medicine Hospital of Inner Mongolia Autonomous Region, Hohhot, Inner Mongolia Autonomous Region 010020; [7]Scientific Research Department, Peking University Cancer Hospital (Inner Mongolia Campus)/Affiliated Cancer Hospital of Inner Mongolia Medical University, Hohhot, Inner Mongolia Autonomous Region 010050, P.R. China

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Abstract. Ovarian cancer (OC) is a common and highly prevalent malignant tumor in women, associated with a high mortality rate, easy recurrence and easy metastasis, which is predominantly at an advanced stage when detected in patients. This renders the cancer more difficult to treat, and consequently it is also associated with a low survival rate, being the malignancy with the highest mortality rate among the various gynecological tumors. As an important factor affecting the development and metastasis of OC, understanding the underlying mechanism(s) through which it is formed and developed is crucial in terms of its treatment. At present, the therapeutic methods of angiogenic mimicry for OC remain in the preliminary stages of exploration and have not been applied in actual clinical practice. In the present review, various signaling pathways and factors affecting angiogenic mimicry in OC were described, and the chemical synthetic drugs, natural compound extracts, small-molecule protein antibodies and their associated targets, and so on, that target angiogenic mimicry in the treatment of OC, were discussed. The purpose of this review was to provide new research ideas and potential theoretical support for the discovery of novel therapeutic targets for OC that may be applied in the clinic, with the aim of effectively reducing its metastasis and recurrence rates.

Correspondence to: Dr Hongwei Cui, Scientific Research Department, Peking University Cancer Hospital (Inner Mongolia Campus)/Affiliated Cancer Hospital of Inner Mongolia Medical University, 42 Zhaowuda Road, Saihan, Hohhot, Inner Mongolia Autonomous Region 010050, P.R. China
E-mail: cuihw2001423@163.com

Mr. Haibin Guan, School of Pharmacy, Inner Mongolia Medical University, 5 Jinshan Avenue (Niuniuying Village), Jinshan Development Zone, Hohhot, Inner Mongolia Autonomous Region 010107, P.R. China
E-mail: 20070095@immu.edu.cn

*Contributed equally

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1. Introduction

Tumor vascularization, as an important influencing factor in the development of tumorigenesis, metastasis and treatment resistance, is a process that includes neovascularization, vascular selection and angiogenic mimicry. Among them, the formation of angiogenic mimicry increases blood perfusion; through pathological specimen analysis and *in vitro* experiments, angiogenic mimicry role in clinical tumor occurrence, metastasis, and prognosis was determined. Moreover, angiogenic mimicry has been confirmed in various diseases, including glioma, melanoma and lung cancer (1). However,

to date, angiogenic mimicry in ovarian cancer (OC) has been less well, and more superficially, studied. Xu *et al* (2) administered the anti-angiogenic drug bevacizumab in the treatment of OC in mice and demonstrated through a series of *in vitro* experiments that it could promote tumor metastasis, aggravate tumor hypoxia and lead to the formation of angiogenic mimetic structures during the process of anti-tumorigenesis. Therefore, angiogenic mimicry may be an important target for the treatment of OC. In the present review, the signaling pathways associated with angiogenic mimicry in OC were investigated, including the vascular endothelial (VE)-cadherin/cadherin/ephrin-A2 (EphA2)/matrix metalloproteinase (MMP)-2/laminin 5γ2 (Ln5γ2) signaling pathway and the AKT/mammalian target of rapamycin (mTOR)/MMP-2/Ln5γ2 signaling pathway. Moreover, associated influencing factors are described, including the tumor microenvironment, epithelial-mesenchymal transition (EMT), tumor stem cells and so on, with an emphasis placed on relevant inhibitors targeting the angiogenic mimetic state of OC, and the current clinical application status of these factors.

2. OC

Concept and prevalence status. OC ranks eighth among malignant tumors worldwide, and as a highly prevalent malignant tumor in women, its mortality rate is second only to cervical and uterine cancer (3); however, due to lack of specific identification targets during the early stage of disease progression and inconspicuous pathological manifestations (4), the majority of patients are not identified until at an advanced stage, resulting in poor treatment outcomes and low patient survival (5). ~90% of its staging is epithelial OC (EOC) with high recurrence and metastasis, and the remaining 10% is ovarian clear carcinoma and ovarian plasma carcinoma (6). Moreover, the heterogeneity of different staging tumors is very high, which also makes the treatment of OC more difficult to accomplish (Fig. 1). In addition, previous studies have shown that the development of OC can be influenced by various factors, including geographical location, race (7), lifestyle and dietary habits (8).

Difficulties in treatment. The current treatment modality of OC mainly comprises surgical resection plus post-operative cisplatin (DDP) and paclitaxel combination chemotherapy, which is highly sensitive to DDP in the initial stages of chemotherapy for the majority of patients, although long-term use leads to drug resistance, which greatly reduces the therapeutic efficacy (3). With the rise of targeted therapies and immunotherapy, poly (ADP-ribose) polymerase inhibitors, epidermal growth factor receptor and anti-angiogenesis inhibitors have been widely used in terms of maintenance therapy (9). Furthermore, an increasing number of researchers have shifted their attention to herbal medicines and natural compound extracts; for example, a recently published study by Wang *et al* (10) explored the anti-OC mechanism of the classic Chinese herbal formula 'Guizhi Fuling Wan', which was found to achieve antitumor effects through inducing apoptosis, inhibiting cancer cell proliferation and enhancing immunotherapy sensitivity.

3. Vasculogenic mimicry (VM)

Original concept and research progress. Malignant tumor proliferation is dependent upon neovascularization to provide the necessary oxygen and nutrients. When the diameter of a solid tumor grows to 2 mm, the induction of neovascularization is necessary to meet the supply of oxygen and nutrients. Tumor cells undergo deformation to induce tumor cells and extracellular matrix (ECM) remodeling to form structures similar to blood vessels (Fig. 2). This angiogenetic process does not rely on endothelial cells [it is endothelial cell (for example, CD31, CD34) -negative], and cancer cells are able to be shed and metastasize within the blood at any time. Furthermore, neither necrosis nor inflammatory cell infiltration is associated with this process. The special neovascular structure was first discovered under an optical microscope in 1941 and was observed through techniques such as Periodic acid-Schiff staining in 1999, when the concept of VM was first proposed (11). VM predominantly exists in malignant tumors that have the characteristics of high recurrence, high metastasis, poor prognosis for the patient and low survival rate (12). Over a continuous period of development, the status of research has gradually advanced towards the identification of pathological structures, the establishment of *in vivo* animal models, identification of the associated signaling pathways and prospective treatments with targeted drugs (Fig. 3). However, significant obstacles remain that need to be overcome, including the lack of reliable VM formation markers and mature methods for VM identification *in vivo* (13-15).

An outline of the research progress that has been made in terms of angiogenesis mimicry, from the first discovery of angiogenic mimicry in 1941 to the three-dimensional (3D) observation of angiogenic mimicry structure in angiogenic OC in 2022, moving on towards discovering more about the processes associated with angiogenic mimicry and their development, is provided in Fig. 3.

Angiogenic mimicry and tumors. Currently, the presence of angiogenic-mimetic structures has been identified in the majority of highly aggressive tumors, including triple-negative breast cancer, glioblastoma, melanoma and renal cell carcinoma. However, the presence of angiogenic mimicry in all highly aggressive tumors has yet to be confirmed, and the means to target angiogenic mimicry to treat tumors have yet to reach a mature stage of development (16,17). Angiogenic mimicry and tumor types are listed in Table I (12,18-25).

4. Signaling pathways associated with angiogenic mimicry in OC

The VM of OC, as a key influencing factor affecting occurrence, development, invasion and metastasis of OC, has a complex mechanism of action, which is closely associated with cancer stem cells (CSCs), the tumor microenvironment, associated factors. Moreover, various regulatory components and signal pathways are also interrelated, and can affect each other. For example, VM, which provides a special means to obtain nutrients and oxygen during the malignant proliferation of tumors, is closely associated with the tumor microenvironment. An anoxic microenvironment can directly regulate vascular endothelial

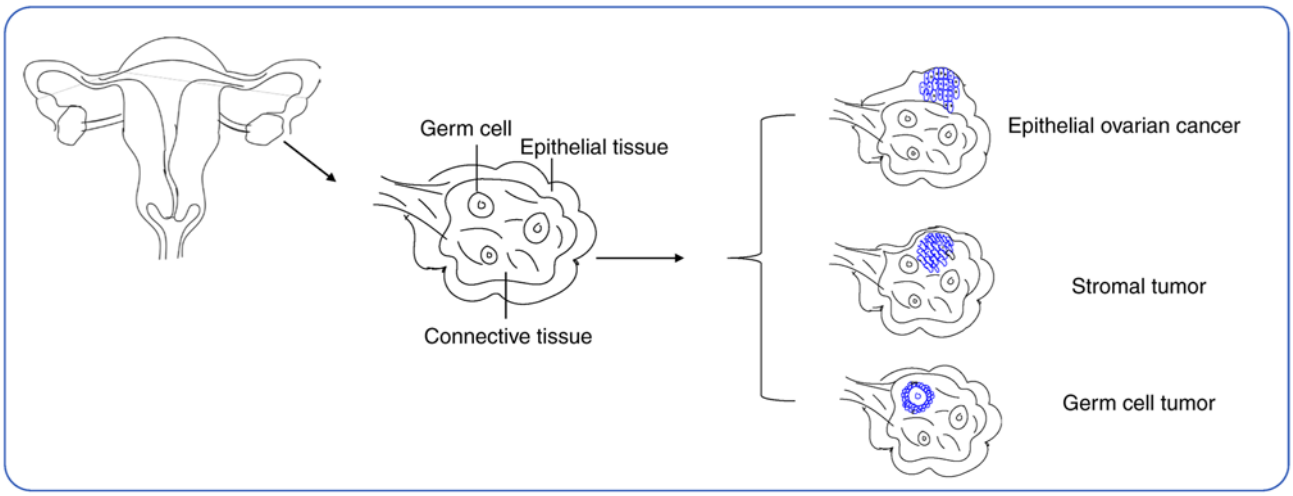


Figure 1. Classification of ovarian cancer. The ovary is composed of germ cells, epithelial tissue and connective tissue. The malignant proliferation of epithelial cells develops into epithelial cell carcinoma, and the malignant proliferation of germ cells and connective tissues develops into germ cell tumor and stromal tumors, respectively.

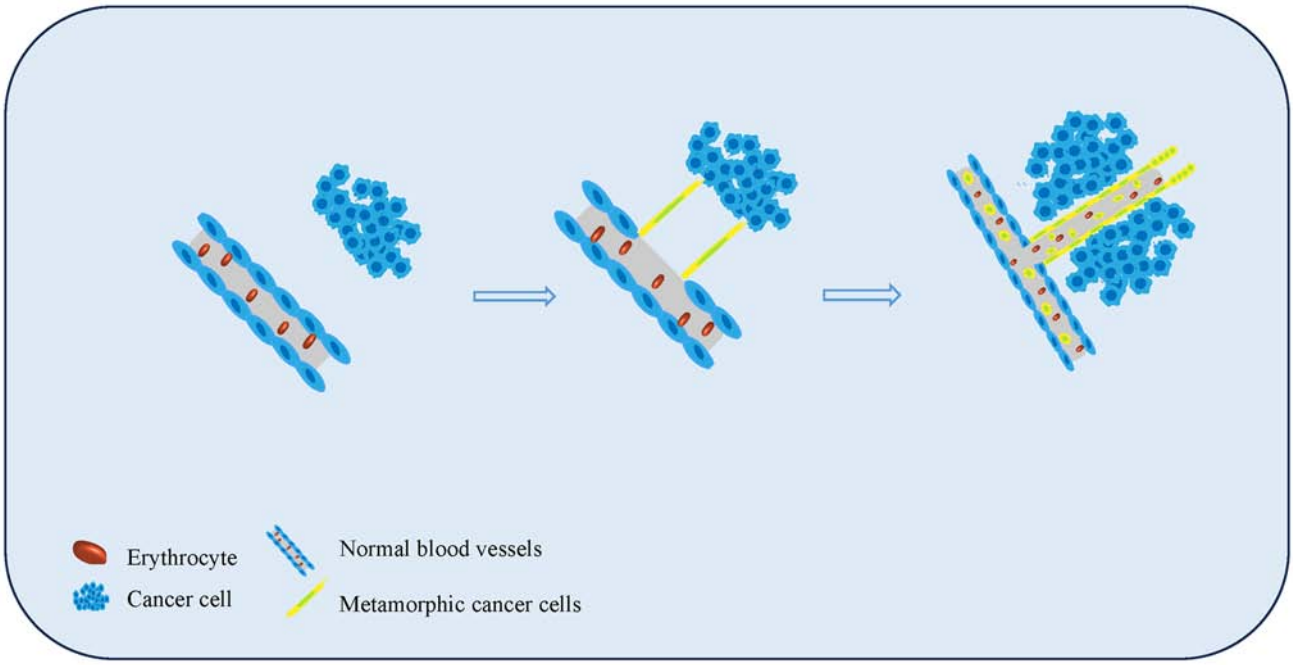


Figure 2. Vasculogenic mimicry process. Cancer cells become deformed, and form structures similar to blood vessels for the transportation of oxygen and nutrients, while the cancer cells can themselves be shed and flow into the blood.

growth factor (VEGF)-A, VEGF receptor 1 (VEGF-R1), EphA2, Twist and cyclooxygenase-2 (COX-2) signals, which indirectly regulate VE-cadherin, tissue factor (TF) and Notch signals (26) and can also induce autophagy and affect the expression of the CSC markers, CD133 and aldehyde dehydrogenase 1 (ALDH1). The acidic microenvironment is an influential factor for cancer cell metastasis and drug resistance. Recent studies have shown that hypoxia and an acidic microenvironment can also affect the growth of CSCs (27); inflammatory cytokines, interleukins and chemokines secreted by the tumor immune microenvironment also mediate angiogenesis mimicry through activating different signaling pathways (28). For example, the inflammatory factor interleukin (IL)-6 activates the JAK/STAT3 signaling pathway to mediate generation of VM, which is associated with a variety of different mechanisms of tumor chemotherapy resistance (29). In 2019, Ayala-Dominguez *et al* (1) reported how the VE-cadherin/cadherin /EphA2/MMP-2/Ln5γ2 signaling axis acted as a key signaling pathway for the formation of angiogenic mimicry in OC, wherein cancer cell metastasis was promoted through ECM remodeling. In addition, another study (30) demonstrated that there are several other signaling pathways involved in the generation of angiogenic mimicry in OC, including the AKT/mTOR/MMP-2/laminin5γ2 and the phosphoinositide 3-kinase (PI3K)/AKT/mTOR signaling pathways, and so on. Furthermore, a recent study identified that platelets, as coagulants, can function as agents of anti-VM generation in

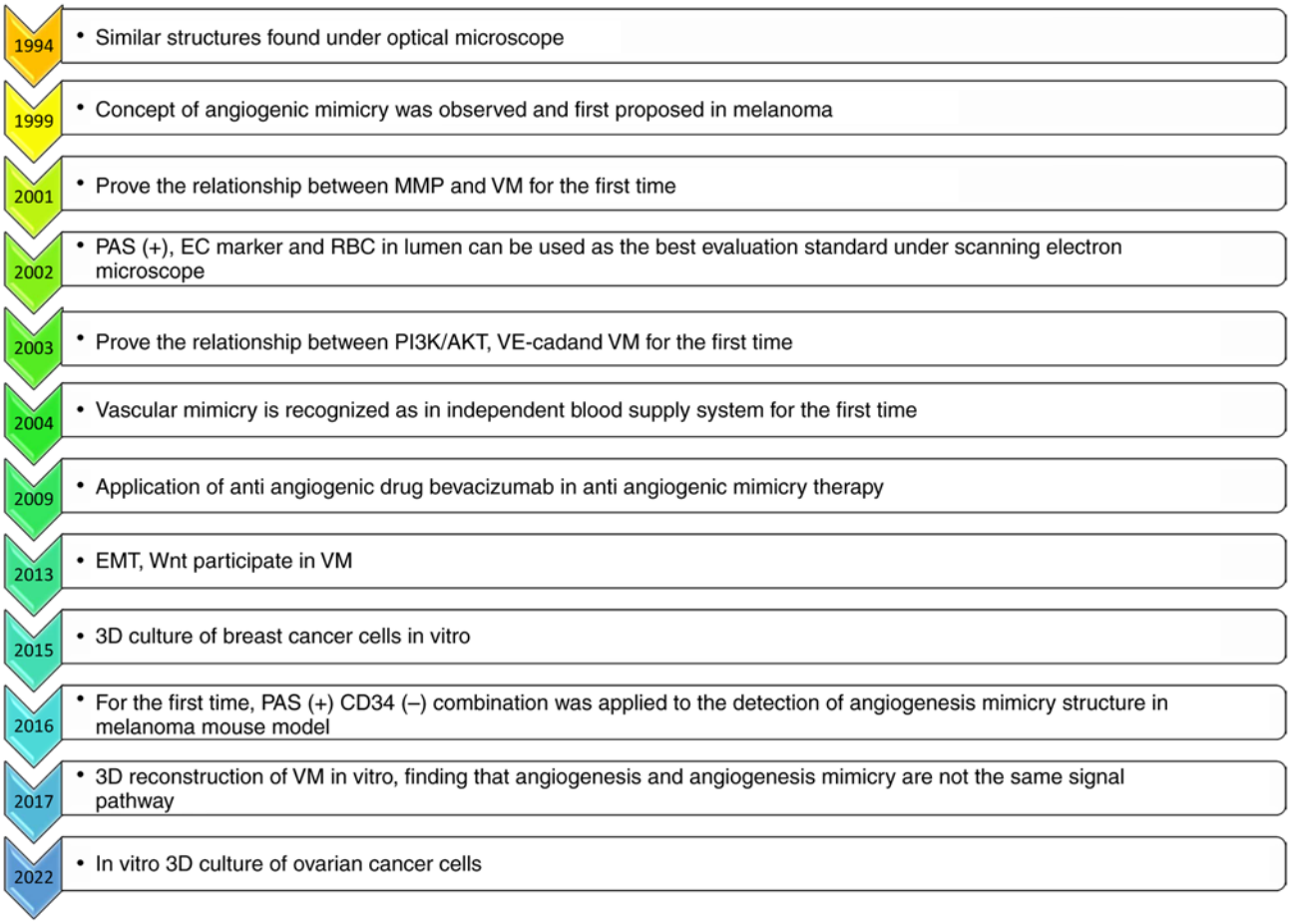


Figure 3. Research progress on angiogenesis mimicry. From the initial discovery of angiogenic mimicry in 1994 to the three-dimensional observation of angiogenic mimicry structures in angiogenic ovarian cancer in 2022, the timeline of the process of discovery and development of angiogenic mimicry is presented. VM, vasculogenic mimicry; PAS, periodic acid-Schiff.

breast cancer (31), although whether similar blood cells also have an identical role in OC requires further research, and may provide a new direction and further ideas for subsequent research strategies. A detailed introduction to the important signaling pathways and major regulatory components that affect the formation of VM in OC is provided in Fig. 4.

Signaling pathways

VE-cadherin/cadherin/EphA2/MMP-2/Ln5γ2 signaling pathway. VE-cadherin is an important protein that adheres to endothelial cells (32). The protein is closely associated with the formation of VM in OC. VE-cadherin promotes activation of the extracellular signal-regulated kinases 1 and 2 (ERK1/2) and MMP-14 through recruiting EphA2 receptors. MMP-degradable cell matrix components promote OC transfer and the generation of VM. In addition, MMP-2 and MMP-14 have been shown to induce Ln5γ2, and remodeling of the ECM further promotes the production of VM (33,34).

AKT/mTOR/MMP-2/Ln5γ2 signaling pathway. Urokinase-type plasminogen activator (uPA) is a serine protein that is able to activate the AKT/mTOR/MMP-2/Ln5γ2 signaling pathway to promote VM generation in OC. The specific mechanism involves AKT phosphorylation mediated by uPA, which thereby promotes mTOR phosphorylation. Phosphorylated mTOR promote the conversion of pro-MMP2 into MMP2, thereby enhancing the degradation of Ln5γ2 and promoting ECM reconstruction, leading to the further generation of VM (35).

PI3K/AKT/mTOR signaling pathway. Ediriweera *et al* (36) revealed that the PI3K/AKT/mTOR pathway is activated in OC, accompanied by changes in the pathway structure and gene expression of its various components (including PTEN and PI3K). At present, numerous inhibitors associated with this pathway have been applied during preclinical trials of OC, although further research is needed to improve their targeting efficiency, since this pathway not only regulates cancer cell growth and the generation of VM, but it also participates in normal cell growth.

Wnt signaling pathway. The abnormal activation of the Wnt signaling pathway in OC is closely related to the malignant proliferation and metastasis of OC. The family member Wnt5a regulates the expression of protein kinase Cα (PKCa) to promote generation of VM in OC. In addition, an increase in Wnt5a has also been shown to lead to an upregulation of the expression of PI3K, although the specific regulatory mechanism underlying this process still requires further research (35,37).

Regulatory factors.

CSCs. CSCs have unlimited proliferative potential compared with mature stem cells. In 2005, Bapat *et al* (38) discovered CSCs in the ascites of patients with OC, suggesting

Table I. Angiogenic mimicry and tumor types.

Tumor type	Mechanism	Impact	Clinical stage	(Refs.)
Breast cancer	lncRNA, CSC, multiple signaling pathways	Poor prognosis	Not in the clinic	(12)
Melanoma	ECM matrix remodeling	Tumor metastasis	Clinical trial of immunotherapy in connection with anti-VM therapy	(18)
Glioblastoma	Histone deacetylase inhibitors inhibit VM production	Tumor migration, Invasion	Not in the clinic	(19)
Hepatocellular carcinoma	CSC, EMT, hypoxia signaling factors	Tumor metastasis invasion, poor prognosis	More clinical studies are needed	(20)
Non-small cell lung cancer	AGGF1, UBE2C	Tumor metastasis, invasion and poor prognosis	Clinical sample staining and correlation study of pathological features	(21)
Colon cancer	Wnt/β-catenin signaling pathway antagonists inhibit VM	Tumor development	Clinical studies are being conducted	(22)
Prostate cancer	via hypoxia signaling factors and hyaluronic acid	New targets for tumor therapy	*In vivo* and *in vitro* experiments, not yet in clinical trials	(23)
Head and neck squamous cell carcinoma	EMT	Survival and poor prognosis	Not yet in the clinical trial stage	(24)
Renal cell carcinoma	Associated with androgen receptors	Tumor metastasis	*In vivo* and *in vitro* experiments; not yet in the clinic	(25)

EMT, epithelial-mesenchymal transition; CSC, cancer stem cells; VM, vascular mimicry; AGGF1, angiogenic factor with G-patch and FHA domains 1; UBE2C, ubiquitin-conjugating enzyme E2C.

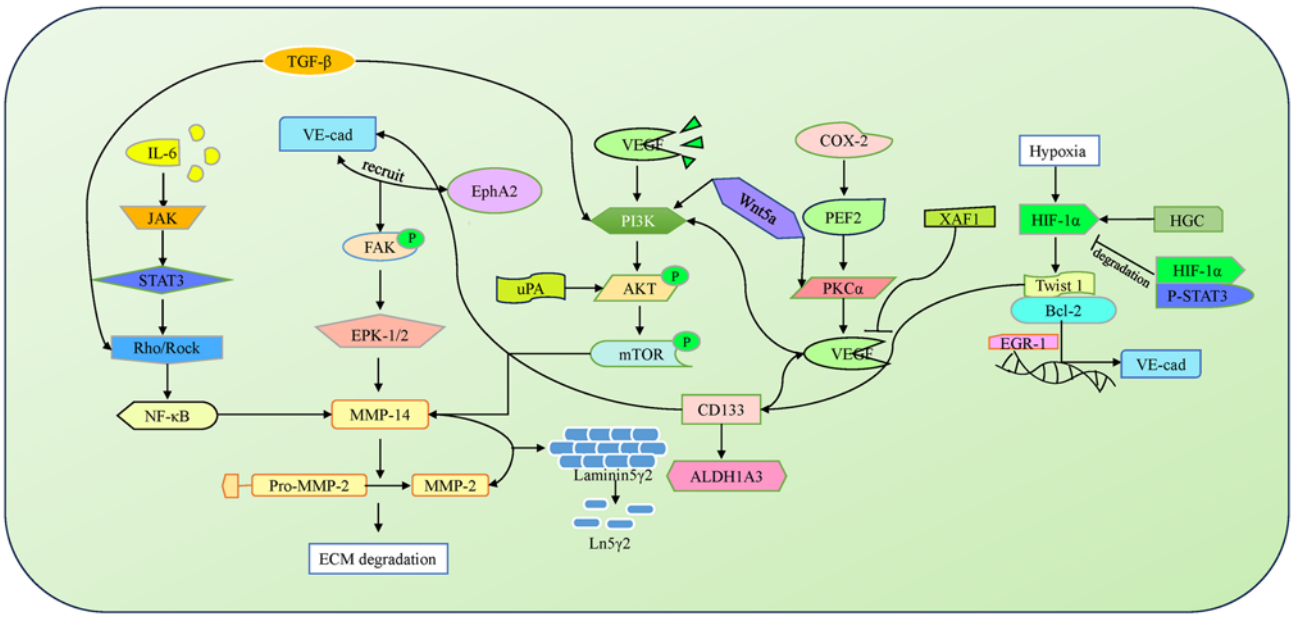


Figure 4. Angiogenesis mimicry-associated signaling pathways in ovarian cancer are shown, including the VE-cadherin/cadherin/EphA2/MMP-2/Ln5γ2, AKT/mTOR/MMP-2/Ln5γ2, PI3K/AKT/mTOR and IL-6/JAK/STAT3 signaling access.

that the high invasiveness of OC is associated with CSCs. CD133, as a marker of CSCs, is positive in patients with OC, inducing both an increase in VM and an upregulation of biomarkers associated with VM formation, including VE-cadherin and VEGF. In addition, CD133 was also found to be associated with a high expression of ALDH1, and previous studies have shown that high expression of ALDH1 is also positively correlated with the generation of VM (39,40).

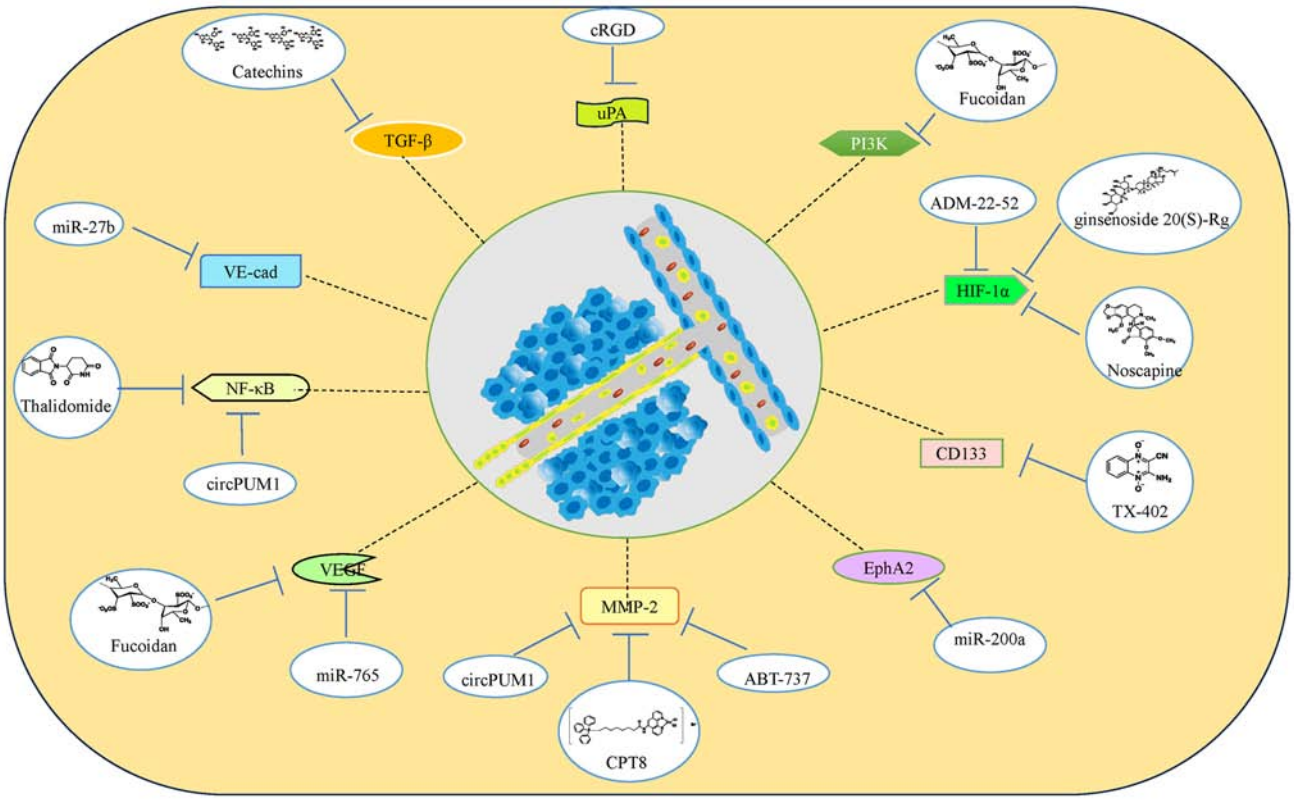


Figure 5. Angiogenesis mimicry-associated inhibitors in ovarian cancer. miR, microRNA.

Hypoxic microenvironment. Hypoxia is able to regulate various pathways of cancer generation, including angiogenic mimicry. A study *in vitro* showed that hypoxia is positively correlated with the generation of VM in melanoma, hepatocellular carcinoma, breast cancer, and other types of cancer (38). Hypoxia has been shown to upregulate the expression of VE-cadherin and p-STAT3, thereby promoting VM generation. Gest *et al* (41) found that inhibiting p-STAT3 could effectively reduce the number of VM structures in OC. Therefore, developing targeted inhibitors for p-STAT3 should provide a new source of potential inhibitors for the generation of VM.

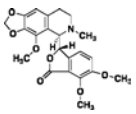
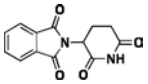
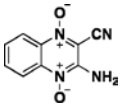
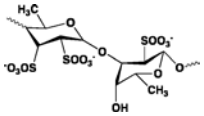
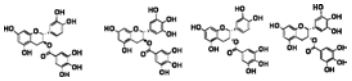
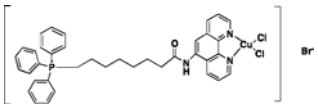
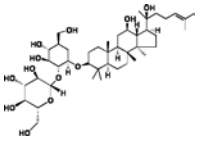
EMT and ECM reconstruction. EMT is a necessary process contributing towards cancer cell metastasis, and numerous EMT-associated molecules have been shown to fulfill important roles in the formation of VM, including transforming growth factor-β (TGF-β). Previous studies also identified that the inhibition of TGF-β induced cell migration and EMT could further inhibit the formation of VM structures in OC (42,43). The role of ECM in tumor metastasis is essentially twofold: ECM initially serves as a regional barrier against cancer cell metastasis, although when it is reshaped, it becomes an important mediator of metastasis (44,45).

Other components. Human chorionic gonadotropin (HGC) has been demonstrated to promote the production of VM through its fifth subunit *in vitro*. When the HGC is introduced externally, the overexpression of hypoxia-inducible factor-1α (HIF-1α) and significant upregulation of vascular markers, including CD31 and VEGF, induce the production of VM through the HGC/VEGF axis (46,47). In addition, *in vivo* inhibition experiments revealed that the overexpression of apoptosis-associated factors [for example, XIAP-associated factor 1 (XAF1)] and decreased expression of VEGF led to a decrease in the number of VM structures and inhibition of cell proliferation and migration. These findings suggested that XAF1 may serve as a useful inhibitor of VM generation (48).

5. OC angiogenesis mimetic-associated inhibitors

At present, the reported inhibitors associated with angiogenesis mimicry in OC can be essentially divided into the following categories: Synthetic drugs and drug analogues, natural extracts, non-coding RNAs, small-molecule inhibitors, protein peptides and associated targets (Fig. 5). Among these inhibitors, synthetic drugs and drug analogues refer to drugs that have been widely used in clinical practice for the treatment of other diseases. Therefore, their safety, efficacy, side effects and medication methods have been clearly demonstrated, although as a downside, the multiplicity of their effects does present a number of obstacles to the rational use of these drugs (49). As commonly used agents for cancer treatment, natural extracts have the advantages of low toxicity and high efficiency. However, due to their complex components and diverse impact targets, it is necessary to perform a prerequisite number of preclinical trials (50). Non-coding RNAs, small-molecule inhibitors and protein peptides all exert targeted inhibitory effects. Non-coding RNAs affect the process of angiogenic mimicry through regulating the expression of target genes, which in turn affects the occurrence, development, treatment and prognosis of OC. However, their mechanism of action, and

Table II. Chemically synthesized drugs and naturally extracted compound inhibitors associated with angiogenesis mimicry of OC.

Name	Structure	Mode of action	Limitations	(Refs.)
Noscapine		Promotes HIF-1α degradation	No clinical trials have yet been conducted	(58)
Thalidomide		Inhibits NF-κB activity	Specific mechanism unknown	(59)
TX-402		Inhibits VEGF, HIF-1α activity	Lack of further validation	(61)
Fucoidan		Inhibits PI3K and the P38-related signaling pathway	Some toxicity has been demonstrated	(64)
Catechins		Inhibits TGF-β signaling and promotes the EMT process	Only validated in a single cell line	(66)
CPT8		Decreases MMP-2 production	Mechanism needs further study	(67)
Ginsenoside 20(S)-Rg3		Activates the ubiquitin-proteasome pathway, thereby inhibiting HIF-1α	Lack of exact molecular target	(68)

HIF-1α, hypoxia-inducible factor-1α; VEGF, vascular endothelial growth factor; PI3k, phosphoinositide 3-kinase; MMP-2, matrix metalloproteinase 2; TGF-β, transforming growth factor-β; EMT, epithelial-mesenchymal transition.

overall function, remain largely unknown (51). Small-molecule inhibitors can target specific proteins or factors to affect the inhibition of angiogenic mimicry in OC and have strong specificity. However, concerning VEGF angiogenic inhibitors that are associated with angiogenic mimicry, although they can significantly inhibit angiogenesis, they are prone to drug resistance and have the ability to compensate for the increased effects of angiogenesis mimicry, thereby promoting cancer cell recurrence and metastasis (52). The mechanisms underlying the action of protein peptide drugs are relatively clear, although they are easily cleared by the organism, and therefore their efficient utilization rate continues to remain an important focus of research (53). Previous studies have also identified a new modality for angiogenesis mimicry, in that it is jointly affected by multiple signal pathways and signaling molecules. The single inhibition of a certain pathway or molecule tends to activate other signaling pathways in a compensatory manner, which suggests that multiple types of inhibitors will be required in order to improve the therapeutic effects during treatment (54-56) (Table II).

Synthetic drugs and drug analogs. Noscapine is mainly used in the clinic for cough suppression, and exerts similar effects to codeine, although it is non-addictive. Previous studies have shown that it acts as a HIF-1α inhibitor through promoting degradation of HIF-1α by associated proteases in combination with DDP to treat the proliferation of OC resistant to paclitaxel (57). Currently, clinical trials have been conducted for both lymphoma and chronic lymphatic leukemia, and *in vivo* and *in vitro* experiments have been performed to validate the use of DDP in OC (58).

Thalidomide, as an immunomodulatory inhibitor, has been used in the clinical treatment of OC, myeloma, glioblastoma and other tumors. Previous studies have found that it can be employed as an anti-angiogenesis inhibitor through exploiting its ability to effectively inhibit VEGF production, and it has also been shown to downregulate the NF-κB signaling pathway (59), which has been revealed to be closely associated with angiogenesis and cancer cell metastasis. Therefore, it has been hypothesized that the mechanism of action of thalidomide may involve decreasing the level of NF-κB, which further inhibits ECM degradation and reduces both the generation of VM and cancer cell metastasis (60).

TX-402, as a selective prodrug (61), possesses both angiogenic and HIF-1α-inhibitory effects, and exerts its function through eliminating tumor stem cell (CSC)-associated growth factors (for example, CD33 and CD44) in the hypoxic zone at the core of rapid tumor proliferation. It is anticipated that it may be used as a treatment for hypoxia-induced tumor cell proliferation and angiogenesis-resistant tumors.

In addition, lupeol is a triterpene that has a wide range of applications both *in vivo* and *in vitro*, and previous

studies have shown that it possesses favorable antitumor activity (62). In melanoma, it can inhibit the production of VM through downregulating the CSC marker, CD133. However, its anti-angiogenic mimicry effects in OC have yet to be reported on (63).

Natural extracts. Fucoidans are a class of sulfated polysaccharide analogs extracted from brown algae that exert a killing effect on a variety of cancer cells, including ovarian, breast, hepatocellular and bladder cancer. Bae *et al* (64) used fucoidan as a means of therapeutic intervention both in zebrafish *in vivo* and on ES-2 and OV-90 cells *in vitro*, and it was found that this treatment led to an increased production of reactive oxygen species (ROS) in cell lines, mitochondrial oxidative damage, the production of cytochrome *c*, to promote apoptotic vesicle cleavage. In addition, fucoidan was found to inhibit OC angiogenic mimicry through inhibiting angiogenic genes (e.g., VEGFs) and FMS-related tyrosine kinases (Fits) and kinase insertion domain receptors (KDRs), exerting synergistic effects in combination with natural antitumor agents such as DDP and paclitaxel. However, it was found to exert toxic effects on the zebrafish breeding females in the *in vivo* animal model, and therefore its application in the clinic requires further refinement of the dose used, timing of drug administration and molecular targets.

Catechins is extracted from green tea. Studies have shown that it can be used with TGF-β receptor binding, suppress TGF-β activation of pathway related downstream Smad3/P38 signal inhibits the degradation of MMPS on ECM to reduce VM production and prevent OC metastasis and chemoresistance (65,66).

Low-copper complexes [for example, the phenanthroline copper (ii) complex CPT8] are able to destroy intracellular DNA by producing ROS, thereby exerting antitumor effects. A previous study has revealed that the copper ligand compound CPT8 exhibits anti-angiogenic mimicry activity via inhibiting the production of MMP-2, thereby blocking the nutritional supply system of tumor cells and reducing the likelihood of cancer cell metastasis and recurrence (67).

EOC, a phenotype of OC that currently has a high mortality rate, is closely associated with low patient survival due to its aggressive and metastatic nature. Liu *et al* (68) showed for the first time that ginsenoside 20(S)-Rg3 inhibited EMT, which consequently affected cell invasion and metastasis both *in vitro* and *in vivo* by reducing HIF-1α expression, which in turn inhibited downregulation of the epithelial marker, E-cadherin, and upregulation of the mesenchymal marker, vimentin. Ginsenoside 20(S)-Rg3 has the advantage of being a natural inhibitor of HIF-1α with low toxicity and high efficiency, although the lack of relevant molecular targets at the present time hinders its clinical application.

The weak alkaline indole alkaloid brucine, extracted from the seeds of *Strychnos nux-vomica* L. (*Loganiacaee*), has been identified to possess antitumor activity. Xu *et al* (69) demonstrated that it can inhibit the generation of VM through inhibiting expression of EphA2 and MMP in the triple-negative breast cancer cell line MDA-MB-231 in a dose-dependent manner. Polyphyllin I (PPI), as the main component of the commonly used traditional Chinese medicine Rhizoma Paridis, has been demonstrated to inhibit both the progression of hepatocellular carcinoma and the generation of VM. It was also found to regulate the expression of Twist1 and to inhibit the generation of VM through inhibiting the PI3K/AKT/Twist1/VE-cadherin signaling pathway (70). However, whether Brucine and PPI have the same efficacy in OC angiogenesis mimicry has yet to be explored, and further studies are required to address this question.

The small-molecule drug D-39, extracted from the evergreen perennial plant *Liriope muscari*, is an inhibitor of the cysteine-rich protein, Mig-7. Its encoding gene, *Mig-7*, is a migration-inducing gene that is rich in cysteine, which was first identified in metastatic hepatocellular carcinoma, and later shown to be expressed in a variety of cancer cells, but almost not at all in normal tissues (71,72). Huang *et al* (73) showed through phenotypic studies in EOC tissues that included investigation of Mig-7 protein expression levels and histopathological status analysis, the introduction of Mig-7 cell metastasis and invasion *in vitro*, tumor volume size analysis in nude mice *in vivo*, the addition of the Mig-7 inhibitor D-39 for reverse validation experiments, and statistical analysis in combination with clinical samples, that D-39 specifically inhibited expression of VEGFA without affecting other angiogenic factors. The aforementioned study provided further clues for the development of specific Mig-7 inhibitors or monoclonal antibodies to influence VM production, and thereby increase the options available for the therapeutic treatment of OC.

Non-coding RNAs

MicroRNAs (miRNAs). Sun *et al* (74) observed the phenotype of clinical samples of OC, performed *in vitro* cellular experiments and combined with previous findings, concluded that VM is associated with disease clinicopathological typing, metastasis and survival, fulfilling an important role in OC development and prognosis. Previous studies have shown that several miRNAs are associated with development and prognosis of OC and can be used as biological targets for the diagnosis and prognosis of OC. Among them, miR-200a inhibits the production of VM by reducing the expression level of the EphA2 gene, and it has been hypothesized that a reduced level of miR-200a expression would inhibit E-cadherin expression in tumor stem cells, thereby affecting the migration and invasion of OC cells. By contrast, high expression of miR-200a may also be a predictor of a higher survival rate of patients with OC, and therefore this can be used as a predictive target for OC diagnosis and prognosis. However, the number of clinical samples included in the study by Sun *et al* (74) was small, and further studies are required to refine the conclusions. In an extensive study on the miR-27b regulation of tumor angiogenesis and cancer metastasis, Liu *et al* (75) were the first research group to have explored its inhibition of VM formation in OC through the expression of VE-cadherin. This miRNA accomplishes its function through binding to the 3'-untranslated region of VE-cadherin mRNA, resulting in reduced expression of its associated proteins, decreased expression of tight junction proteins and a decrease in invasion signals, which leads to the inhibition of tumor migration, invasion, endothelial vascularity and tumor neovascularization, and therefore, of the generation of VM. Hypoxia-regulated miRNAs serve an important role in the early regulation of VM formation, and it was shown that miR-765 regulates

the VEGFA/AKT1/SRC-α signaling axis to coordinate the formation of 3D channel-like structures (76). That study, in its investigation of miR-765's critical role in early VM formation, employed a combination of mechanistic and *in vitro* cellular experiments to demonstrate the effects exerted by miR-765 on the number of 3D channel-like structural branches and patterned tubular structures; however, a limitation to the study was that only a single cellular model was employed to study early VM formation at 48 h, and no *in vivo* experiments were performed to validate the findings. Therefore, that study lacked theoretical support for the mechanism of late VM formation, and the application of miR-765 in the clinical setting needs to be further investigated, in depth and over a longer time period.

Circular RNAs (circRNAs). CircRNAs act as non-coding RNAs, which can serve important roles via linking to the tumor microenvironment through neovascularization and tumor cell metastasis (76). A previous study revealed that circPUM1 is more highly expressed in cancerous OC tissues, and it has been surmised that it regulates the expression of NF-κB and MMP2 through targeting the miRNAs miR-615-5p and miR-6753-5p; moreover, its exosomes are able to reach the peritoneum, thereby promoting tumor cell metastasis (77). Furthermore, Shao and Lu (78) demonstrated that circPUM1 could be an important target for the generation of VM in OC in the future. Collectively, the aforementioned studies have shown that VM production is an important target for OC.

Small-molecule inhibitors. VEGR and MMP-2/-9 are positive regulators of tumor angiogenesis, and through the use of an *in vitro* pipeline by *in vitro* co-culture, angiogenesis mimetic assay and the western blotting detection of MMP-2/-9 protein expression branch formation, a research group (79) identified that treatment with ABT-737, a small-molecule inhibitor of the anti-apoptotic protein B-cell lymphoma-2 (Bcl-2), led to downregulation of VEGR and MMP-2/-9 protein expression, therefore implying that ABT-737 could inhibit VM production by affecting MMP-2/-9.

Other small-molecule target inhibitors serve roles in generation of VM. For example, histone deacetylase (HDAC) has been found to inhibit the generation of VM structure in triple-negative breast cancer and glioma, and the protein was found to exert its role through downregulating the expression of VEGF-A and EMT-associated genes, although all the studies that have been performed to date have been *in vitro* cellular experiments, and no clinical studies have yet been conducted (80); therefore, further experiments are needed to verify whether HDAC can be used as an effective inhibitor of VM and applied in the treatment of OC (81).

VEGF serves as a common influential target for angiogenesis and angiogenic mimicry, and a range of anti-angiogenic VEGF inhibitors (for example, cediranib, nintedanib, bevacizumab and humv833) have been used to reduce the production of VM (82). However, numerous studies have reported that pro-angiogenic mimicry may occur during inhibition of angiogenesis, and therefore an in-depth study of the underlying mechanisms accounting for how they are able to reduce VM production will not only lead to an improved understanding of the difference between angiogenic mimicry and angiogenesis, but it should also contribute towards future studies of specific anti-angiogenic mimicry therapy (83,84). Similarly, it remains to be identified whether further studies are necessary to investigate more deeply markers of angiogenesis, such as TEM8 (85), which, to date, has not been applied in the VM generation in OC.

A previous study (86) reported on the use of galunisertib as a TGF-β inhibitor that can inhibit autophagy and improve the survival rates of patients with breast cancer. Moreover, a close association exists between cell autophagy and VM, and thus galunisertib may inhibit angiogenesis mimicry in breast cancer via inhibiting TGF-β and autophagy. However, whether it can be applied to angiogenesis mimicry in OC needs to be validated by further research.

Protein peptides. Adrenomedullin (ADM), as a peptide substance, is expressed in various types of tumor tissue and fulfills an important role in tumor cell growth, inducing apoptosis and tumor angiogenesis. A previous study (87) observed the mimicry effect resulting from the overexpression of ADM, and by observing the effects of adding an ADM-22-52 inhibitor on OC angiogenesis through a series of *in vitro* cell experiments, it was found that ADM could upregulate HIF-1α and promote the role of VEGF in angiogenesis *in vitro*. This suggested that the inhibition of ADM may be used as a target for treating VM in the future.

As a component of a proteoglycan complex, syndecan-1 (SDC1) is mainly expressed in the epithelium, and its expression is associated with the poor prognosis of OC. As a marginal substance of benign and malignant stroma, SDC1 may be used as a predictive target. Through combining anti-SDC1 peptide with L19-IL2 factor (B-Fn-specific factor) to intervene in an EOC mouse model, it was found that it regulate EMT, alleviate hypoxia in the tumor center and promote the loss of the stemness characteristics of CSCs, thereby inhibiting the progression of OC tumors. However, further research is needed to determine whether the inhibition of angiogenesis mimicry is included as a part of the process of inhibiting the progression of OC. In addition, SDC1 has been shown to serve as a reverse target gene for miR-302a, suggesting that miR-302a may serve as a targeted inhibitor for the treatment of OC progression (88).

Cyclic Arg-Gly-Asp (cRGD) is an endogenous peptide, and in 2016 Tang *et al* (35), in their study involving tissue immunohistochemical analysis and *in vitro* culture of various OC cell lines, including SKOV-3, OVCAR and A2780 cells, found that uPA exerted a positive regulatory role in VM generation via activating the AKT/mTOR/MMP-2/laminin5γ2 signaling pathway. cRGD, a uPA inhibitor, is able to reduce VM production through downregulating its expression, and it can also inhibit the angiogenic mimetic state of OC by reversing EMT. In 2019, Wang *et al* (89) made it into a functional nanoparticle and demonstrated through performing a series of *in vivo* and *in vitro* experimental studies that it could achieve both anti-EDV and anti-VM effects by affecting MMPs and through reducing EMT production. This study provided a new direction for the use of functional nanomaterials as a novel drug delivery method at a later stage (Fig. 6).

Other associated targets. Combined with incidence and therapeutic difficulties of OC, the discovery of more specific predictive targets is indispensable for early disease screening,

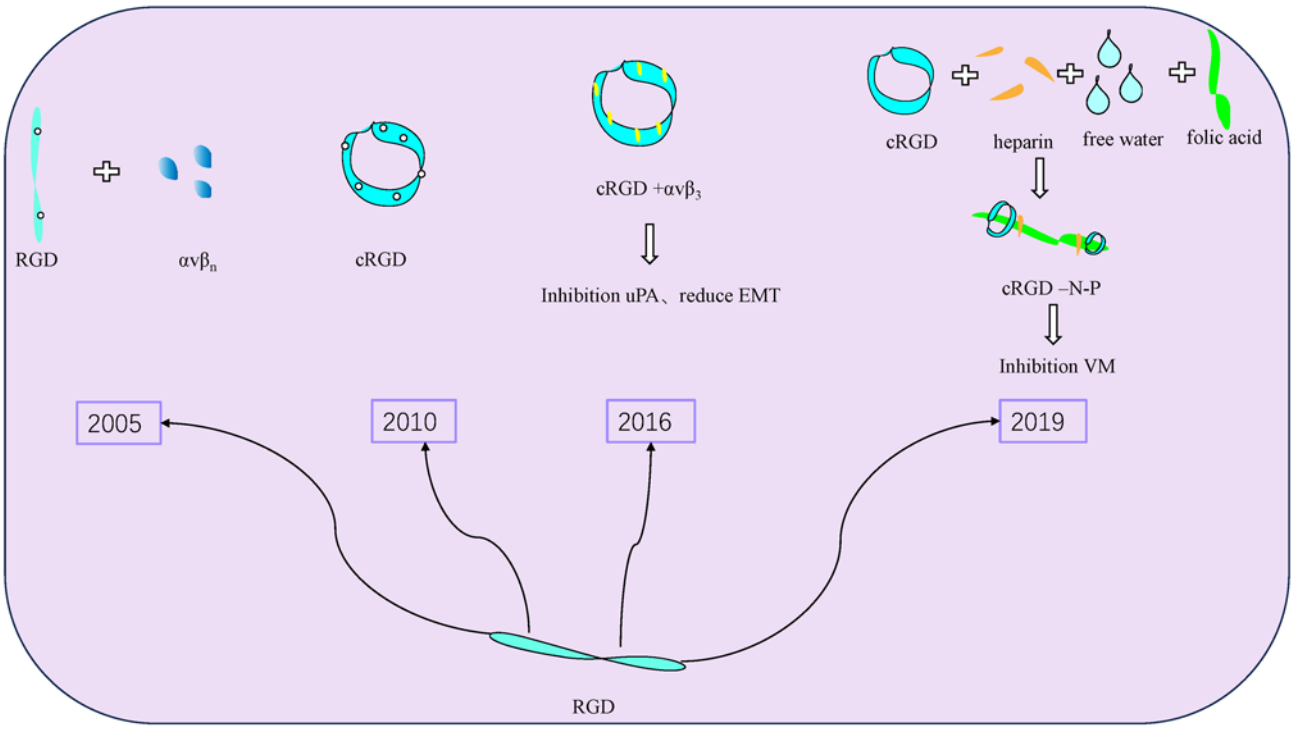


Figure 6. Research progress on cRGD. A schematic diagram of development of the application of straight-chain RGD to circular cRGD, combined with heparin, free water and folic acid in angiogenic mimicry therapy, is presented. cRGD, Cyclic Arg-Gly-Asp.

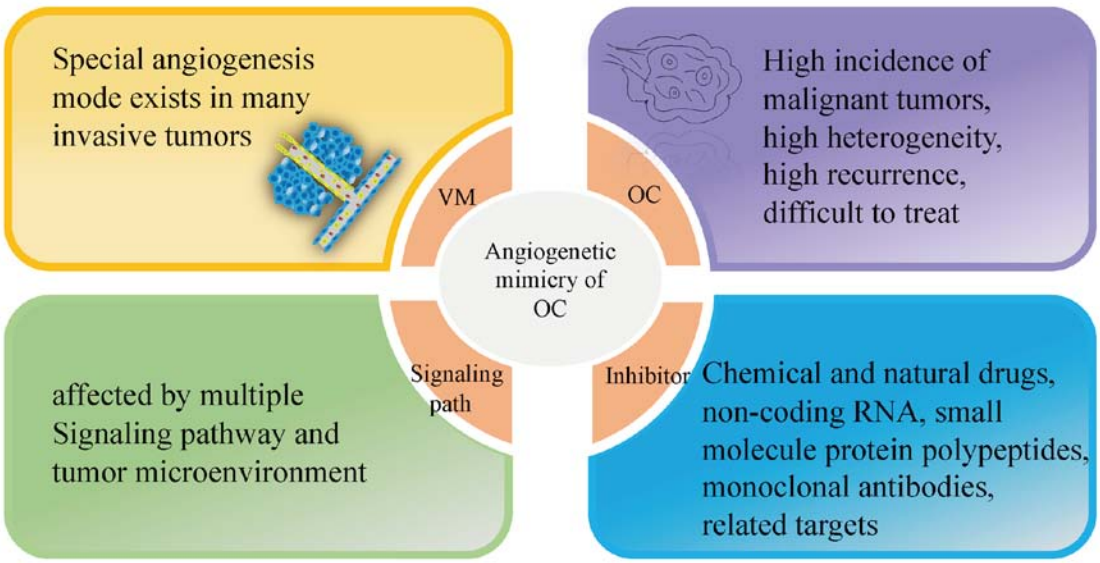


Figure 7. OC and angiogenesis mimicry. A summary of OC and angiogenesis mimicry, including associated signaling pathways and inhibitors. VM, vasculogenic mimicry; OC, ovarian cancer.

disease diagnosis and prognosis prediction. Currently, a number of specific targets have been identified through the analysis of clinical samples or by validation through the employment of *in vivo* and *in vitro* experiments, as revealed in Table III (90-95).

6. Clinical applications

As aforementioned, old and new chemical drugs, natural extracts, non-coding RNAs and small-molecule inhibitors can inhibit angiogenesis mimicry in OC, although the majority of the studies published to date are at stages prior to these compounds entering clinical trials. Monoclonal antibodies that work against the establishment of VM have been developed which target the VE-cadherin protease receptor, which inhibit its binding to achieve anti-angiogenic mimicry, and this has been shown to have a clear role in the treatment of lung cancer (96), although this has yet to be applied in treatment of OC. Due to monoclonal antibodies strong specificity, the rational and efficient application of these antibodies will be

Table III. Angiogenesis mimicry-related targets in OC.

Target	Definition	Study methodology	VM	Limitations	Role	(Refs.)
CGB5	Chorionic gonadotropin subunit V	*In vitro* plasmid transfection, *in vivo* tissue staining	As an important subunit of HCG secretion by trophoblast cells, it promotes vascular endothelial cell proliferation and VEGF expression	Lack of clinical sample analysis and in-depth study of specific mechanisms	Future use as therapeutic target	(90)
CD177	Tumor stem cell surface markers	Immunohistochemistry of clinical samples	Predicting patient survival	Small sample size and lack of long-term prognostic studies	Assessment of EOC malignancy and chemotherapy sensitivity	(91)
CD133	Tumor stem cell surface markers	Clinical sample analysis	Determine patient survival	Small clinical samples and lack of quantification of CD133 expression	Diagnosis, prognosis	(92)
ALDH1	Stem cell markers	Immunohistochemistry of clinical tissue samples	Associated with EOC development, invasion, metastasis and poor prognosis	Lack of *in vivo* and *in vitro* experimental validation	EOC prognosis	(93)
FOXC2	Embryonic transcription factors	*In vivo* and *in vitro* experimental validation	Mainly involved in EMT process, decreased VE-cadherin protein expression, and decreased tube-forming ability of cells	Few clinical samples	Metastasis, survival	(94)
PRRX1	Homologous frame transcription factors	Immunohistochemical analysis of clinical tissue samples	Acts as an EMT inducer, presumably activating the Wnt pathway for VM by promoting -catenin entry into the nucleus	Lack of *in vivo* and *in vitro* experimental validation	Prognosis	(95)

HCG, human chorionic gonadotropin; VM, vasculogenic mimicry; EMT, epithelial-mesenchymal transition; EOC, epithelial ovarian carcinoma.

expected to achieve a multiplier effect (1). In addition, the study of biomimetic mechanisms and associated inhibitors in OC remains a difficult research area. Certain anti-angiogenic mimetic drugs that have been applied to other tumors, including flavonoids (97), curcumin (98), doxycycline (20), thalidomide (60), and so on, need to be tested for their pharmaco-toxicological and pharmacokinetic properties before they can be formally applied in a clinical setting; therefore, there remains a long way to go before they can be applied for the treatment of OC angiogenic mimicry (99). Thus, there remains a long way to go before these agents can be used in therapeutic strategies for the treatment of OC angiogenic mimicry. Currently, studies have shown that the development of anti-angiogenic mimetic drugs and inhibitors is beneficial for the treatment of anti-angiogenic resistant tumors, although whether angiogenic mimetics and angiogenesis are interlinked or processes that are independent of each other, or whether there is a common signaling pathway, will impact on the therapeutic efficacy of the associated inhibitors (100).

7. Summary and outlook

As a unique way of supplying oxygen and nutrients to malignant tumors, the special mode of generation, complex signaling pathways and variety of influencing factors all increase the challenge of targeting the specificity of angiogenic mimicry, and moreover, these factors all serve to increase the complexity of the desired targeted therapies. The compounds and drugs under consideration have been applied in the treatment of numerous types of commonly occurring tumors; however, research on the treatment of OC remains in its infancy stages. In the present review, the underlying mechanisms of OC angiogenesis mimicry and its associated inhibitors have been examined and how certain specific targets can elicit effects on the occurrence were discussed, development, treatment, metastasis and prognosis of OC, although the majority of the targets require further clarification in terms of their identification criteria and the research mainly remains at an early stage (Fig. 7). However, whether a single inhibitory target or an entire signaling pathway can exert a role, or whether other targets or signaling pathways, in turn, will be activated, requires further study. Therefore, a complete understanding of the overall signaling network of OC angiogenesis mimicry and the integration of multiple pathways and targets, or even of other therapeutic modalities such as chemotherapy, should provide novel directions for future research. In conclusion, the rational use of targeted inhibition of OC angiogenesis mimicry is expected to resolve problems, namely, late detection, difficult treatment, high recurrence rates and low survival rates of patients with OC, and provide new research directions working towards improving the survival rate of patients with OC.

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Authors' contributions

HC and HG conceived and designed the present review. XT, QS and ML wrote the first draft of the manuscript. JS, RZ, YX and LY participated in writing of the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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