Review and Research on Cancer Treatment
Volume 8, Issue 1 (2022)

The main mechanisms of blood vessels formation in ovarian cancer

Anna Figat[1], Dorota M. Radomska-Leśniewska[2]

[1] Histology and Embryology Students' Science Association HESA, Medical University of Warsaw

[2] Department of Histology and Embryology, Medical University of Warsaw

ABSTRACT

Introduction: Ovarian cancer (OC) is often detected (70%) in an advanced stage of development, which results in poor treatment outcomes and poor prognosis. The characteristic of this disease is the low survival rate: 20-25% for stage III tumours (according to FIGO) and 5% for stage IV tumours. Despite numerous studies, the pathogenesis of OC is not fully understood. The study aimed to review and analyse the literature on the mechanisms of blood vessel formation in OC.

Material and methods: In order to search for scientific articles, the PubMed database was used with the following keywords: ovarian cancer, tumour angiogenesis, vasculogenic mimicry, antiangiogenic therapy, VEGF, and VEGFR.

Results: In the pathogenesis of OC, the formation of blood vessels determines rapid tumour growth, tumour spread, and metastasis. The most common mechanism of the formation of new blood vessels in a tumour is sprouting angiogenesis. It is a complex and multi-step process involving: the production of pro-angiogenic growth factor by neoplastic cells as a result of hypoxia, activation, proliferation, and migration of host vascular endothelial cells, formation of new vessel sprouts and their elongation, formation of lumen and maturation of new vessels. Another angiogenesis-independent mechanism of tumour vascularization is the vascular mimicry in which neoplastic cells participate. In OC therapy, drugs from the group of angiogenesis inhibitors are used. In cases of developing resistance to anti-angiogenic drugs, treatment aimed at inhibiting the formation of vessels in the mechanism of vasculogenic mimicry opens up the possibility of an effective OC therapy.

Summary: Angiogenesis and vasculogenic mimicry play a key role in the development and progression of OC. The knowledge of the factors influencing these processes may contribute to increasing the effectiveness of OC therapy.

INTRODUCTION

Ovarian cancer (OC) is often (around 70%) detected in advanced stages (III and IV AJCC stages), which are characterized by a low 5-year survival rate (41% for stage III and 20% for stage IV), with an overall survival – 47% (Torre, 2018). Despite many studies pathogenesis of the OC is not fully understood. It is known that the formation of new blood vessels is involved in the pathogenesis of OC and it determines the rapid growth of the tumour, tumour spread, and metastasis. There are several mechanisms for the new blood vessels formation in OC, such as vasculogenesis, sprouting angiogenesis, intussusceptive angiogenesis, vascular cooption, and vasculogenic mimicry (Cao, 2013; Viallard, 2017). Vasculogenesis is the formation de novo of new blood vessels from endothelial progenitor cells. It occurs mainly in embryonic and foetal life, and after birth this process is at a low level. In sprouting angiogenesis blood vessels are created from the existing vasculature. Intussusceptive angiogenesis relies on the intravascular splitting of the vessels. Vessel cooption is formed by the migration of tumour cells along existing blood vessels and incorporation into the tumor. Vasculogenic mimicry (VM) is an angiogenesis-independent mechanism, in which cancer cells differentiate into endothelium-like phenotypes to create structures acting as blood vessels (Cao, 2013; Viallard, 2017 , Luo, 2020). Among the above-described mechanisms, angiogenesis and VM play a key role in the pathomechanism and development of OC (Cortez, 2018).

In this review, we discuss the key mechanisms of new blood vessels formation in OC, namely sprouting angiogenesis and vasculogenic mimicry, along with potential targets for antineoplastic therapy in OC.

SEARCH STRATEGY ANF SELECTION CRITERIA

The aim of the work was to collect data about angiogenesis mechanisms in OC, determine the importance of vasculogenic mimicry in OC, and show new possible treatment options. The authors review information's from original articles published since 2002. The articles were searched in the PubMed database, using the following keyword: ovarian cancer, tumour angiogenesis, vasculogenic mimicry, antiangiogenic therapy, VEGF, and VEGFR. Manually selected materials related to the topic were added.

ANGIOGENESIS

The most common mechanism of new blood vessels formation in a neoplastic tissue is sprouting angiogenesis, which is the formation of new blood vessels from pre-existing vasculature (Liu, 2021). Sprouting angiogenesis is a complex and multi-stage process usually caused by hypoxia (Viallard, 2017). Hypoxia in neoplastic cells produces and stabilizes the hypoxia-inducible factor-1 (HIF), which is composed of α and β subunits. The HIF-1α subunit is known to be sensitive to hypoxia which contributes to its stabilization. The active HIF is a transcription factor that induces the expression of pro-angiogenic genes, e.g., vascular endothelial growth factor (VEGF) and its receptor (VEGFR2) as well as other proangiogenic factors (Gupta, 2016; Zimna, 2015).

VEGF is the master stimulator of both physiological and pathological angiogenesis and lymphangiogenesis and occurs in four isoforms: VEGF-A, -B, -C, -D. Isoforms VEGF-A, -B, stimulate endothelial cell proliferation, regulate the formation of blood vessels from pre-existing vessels at a later stage, and increase vascular permeability and chemotaxis of vascular endothelial cells (Ferrara, 2005; Benedito, 2012). Isoforms VEGF-C, -D, regulate lymphangiogenesis. VEGF interacts with three subtypes of VEGF receptors occurring on the cellular membrane known as VEGFR-1, VEGFR-2, and VEGFR-3. All these receptor types possess their own intracellular tyrosine kinase activity. The VEGFR-1 and VEGFR-2 regulate angiogenesis and vascular permeability, and the VEGFR-3 mainly regulates lymphangiogenesis (Alitalo, 2002). Interaction of VEGF with particular subtypes of receptors activates signalling pathways, e.g. PI3K/Akt, Ras/Raf- MEK/Erk, eNOS/NO, and IP3/Ca^{2+} (Shibuya, 2011). These participate in the generation of specific biological responses including proliferation, migration, increasing vascular permeability, or promoting endothelial cell survival.

The solid tumour, including OC, grows up to 2-3 mm without blood vessels. At this stage, the tumour tissue contains a huge number of cancer cells. The cells placed in the centre are hypoxic and malnourished because nutrients and gases enter them only by diffusion leading to hypoxia condition and consequently to the production and secretion of many pro-angiogenic molecules, including VEGF. These molecules migrate in the tumour environment reaching the host's blood vessel and binds to its receptors localized on the endothelial cells (EC) (Garrido, 2019). Activated endothelial cells secrete metalloproteinases (MMPs) that break down the basal membranes and the matrix around the host vessel. Fibroblasts, smooth muscle cells, and leukocytes can also participate in this process (Bellon, 2004). Increased concentration of VEGF under hypoxic conditions leads to the activation of plasminogen and, as a consequence of its activity, plasmin is formed. Like MMPs plasmin belongs to proteolytic enzymes that is also involved in the breakdown of basement membranes and components of the extracellular matrix. This process is very important as it determines the proper course of angiogenesis. Too low a degree of matrix digestion causes insufficient angiogenesis while too high degree of digestion also disturbs angiogenesis (Quintero-Fabián, 2019). The next step of angioge-nesis is the proliferation and migration of endothelial cells. The activated ECs begin to migrate in response to proangiogenic cytokines and consequently form a bud (sprout) of a new vessel (Saman, 2020). Characteristic of this process is the structural and functional heterogeneity of endothelial cells. There are tip and stalk cells in the forming vessel. The tip cells are located at the top of the budding vessel. They have a receptor for VEGFR-2 on their surface and characteristic filopodia, enabling them to migrate in the VEGF gradient. The stalk cells stand out of high proliferative potential and have VEGFR-1 receptor. They participate in the formation of the new vessel lumen and are also involved in the formation of intercellular connections as well as the synthesis of the components of the basement membrane in the new vessel. The differentiation of both these cell types is mainly controlled by the VEGFA and Notch signalling pathways (Liu, 2021). Integrins, transmembrane proteins, participate in the migration process and influence EC differentiation, proliferation, and survival. Two integrins are particularly important for angiogenesis: αvβ3 and αvβ5 (Zhu, 2010). Afterwards, endothelial cells still proliferate and migrate, which elongates the tubes of new vessels. Subsequently, the vessel lumen is formed and finally, new blood vessel matures thanks to the recruitment of pericytes and smooth myocytes (Zhu, 2010; Saman, 2020).

ANTI-ANGIOGENIC THERAPY

Standard treatment of patients with ovarian cancer, regardless of the clinical stage, relies on surgical resection of neoplastic lesions and implementation of chemotherapy based on platinum derivatives (carboplatin) and toxoids (paclitaxel). Such treatment allows obtaining of complete responses in approximately 75% of patients. However, in 3/4 of them, the disease recurrence is observed. Ultimately, as was mentioned above, the 5-year survival rate is low (41% for stage III and 20% for stage IV) (Cortez, 2018). In addition to chemotherapy, therapy that inhibits neovascularization is increasingly used in OC patients. Antiangiogenic treatment includes drugs that block angiogenic growth factors, especially VEGF, as well as inhibitors of angiogenic growth factors receptors (Chelariu-Raicu, 2019).

Nowadays, the standard first-line treatment for advanced OC patients remains a combination of paclitaxel and carboplatin with or without bevacizumab (Liu, 2021). Bevacizumab (Avastin), a recombinant, humanized monoclonal anti-VEGF A antibody is the most common anti-angiogenic treatment in OC patients and it used to treat advanced and recurrent ovarian cancer. It inhibits the formation of new blood vessels in the tumour and destroys existing blood vessels (Lim, 2020; Reinthaller, 2016; Markowska, 2017) leading to delays in tumour progression. Unfortunately, therapy by bevacizumab prolongs progression-free life only by 2-4 months (Cortez, 2018). Its synergic action with immune checkpoint inhibitors is currently being explored (Garcia Garcia, 2020).

Tyrosine kinase inhibitors, which act as inhibitors of angiogenic growth factors receptors, constitute a large group of antiangiogenic drugs (table 1). Cediranib is a VEGF 1-3 tyrosine kinase inhibitor that has been shown to improve progression-free survival (Ledermann, 2016). Pazopanib, a multi-kinase inhibitor, inhibits VEGFR, PDGFR, c-KIT, c-Fms, and FGFR. Good treatment results of this drug were observed in platinum-resistant and platinum-sensitive ovarian cancer treatment regimens (du Bois, 2014; Floquet, 2015). Nintedanib, a multi-kinase inhibitor inhibits both receptor tyrosine kinases, such as VEGFR, PDGFR, FLT3 FGFR, and non-receptor tyrosine kinases, such as Lyn tyrosine kinase, lymphocyte-specific tyrosine kinase (Lck) and proto-oncogenic Src kinase. Phase III studies have shown that nintedanib used in combination with carboplatin and paclitaxel gives very good therapeutic effects (du Bois, 2016; Chelariu-Raicu,2019). Unfortunately, other investigators reported little benefit of these drugs in OC clinical trials (Yang, 2020 Kurnit, 2021) (Table 1, Figure 1).

Other signaling pathways that are targeted in OC therapy include the action of PDGF, FGF, and angiopoietins activating the Tie 2 receptor (Saharinen, 2017). Trebananib is an example of a VEGF-independent inhibitor, that binds to angiopoietin 1 and 2 and inhibits angiogenesis. Angiopoietins are involved in the final stage of angiogenesis. Good effects of these therapeutic agents have been noted in patients treated with paclitaxel in recurrent ovarian cancer (Monk, 2014) (Table 1, Figure 1).

Table 1. Drugs targeting angiogenesis in OC therapy

Drug name	Regulated pathway/molecule	Type of drug
bevacizumab	VEGF A	Humanized monoclonal antibody
cediranib	VEGF 1-3	Tyrosine kinase inhibitor
pazopanib	VEGFR, PDGFR, c-KIT, c-Fms, and FGFR	Tyrosine kinase inhibitor
ninentanib	VEGFR, PDGFR, FLT3, FGFR, Lyn tyrosine kinase, lymphocyte-specific tyrosine kinase (Lck), proto-oncogenic Src kinase	Tyrosine kinase inhibitor
trebananib	angiopoietin 1 and 2	Peptibody

Anti-angiogenic drugs are currently an important element in the treatment of ovarian cancer (Cortez, 2018). However, these types of drugs are not completely effective because they cannot effectively stop tumour neovascularization. The reason is, among others, antiangiogenic treatment-induced hypoxia, which can induce VM formation and reduce the effect of cancer treatment. Xu et.al. reported in animal model studies that short-term treatment with bevacizumab in OC increases metastases and VM structures formation (Xu, 2012). This fact points

to a likely mechanism of resistance development to anti-VEGF therapy. It can therefore be suspected that substances targeting VM could be a chance for effective treatment of OC. So it is essential to know the pathways and molecules that regulate the VM.

VASCULOGENIC MIMICRY

VM is a tumour microcirculation that does not depend on endothelial cells and can provide sufficient blood supply for tumour growth. VM is responsible for creating over 40% of new vessels in ovarian cancer (Cao, 2013). The mechanism of VM formation include the epithelial-mesenchymal transition, particularly its subtype called epithelial-endothelial transition (Wei, 2021). Mimetic vessels of VM are tubes lined with cancer cells resting on a discontinuous basement membrane-like structure (Valdivia, 2019), they do not have the pericytes characteristic of blood vessels. Among the glycoproteins of this membrane are type I and IV collagens, as well as Laminin5γ2 and its split products 5γ2x and 5γ2 ' (Wechman, 2020). Clinically, VM is identified by positive and negative staining methods; using periodic Schiff acid (PAS) to stain glycoproteins and using antibody-based labelling to identify vessels containing endothelial cells using CD31. Histologically, vessel-like structures PAS-positive a CD31/34-negative are consi-dered signs of VM (Wechman, 2020).VM has two distinct types: tubular and patterned matrix type (Luo, 2020). VM of tubular type are lined by EC-like tumour cells and covered by secretory glycoprotein, and the patterned matrix type is covered by the PAS-positive matrix (Cao, 2013; Viallard, 2017; Luo, 2020).

VM SIGNALLING PATHWAYS

Multiple extracellular factors as well as tumour hypoxia and autophagy are involved in VM. The intracellular regulators of VM follow three major signalling pathways: VE-Cadherin, Notch, and the HIF family of transcription factors (Wechman, 2020). VE-cadherin (CD144) / EphA2 / FAK / ERK1 / 2 / MMP2 / laminin5γ2 is one of the main signalling pathways. VE-Cadherin modulates the phosphorylation of EphA2 kinase associated with its ligand, ephrin-A1. PI3K mediates the phosphorylation of EphA2 and VE-cadherin, which increases the activity of MMP-14 and MMP-2. MMPs are known to cleave laminin5γ2 into γ2 ′ and γ2 fragments, leading to VM. VEGF-A was reported to increase the expression of EphA2, MMP-2, MMP-9, and VE-cadherin (Zhang, 2019). Another important signalling pathway is Nodal / Notch / Smad2 / 3 and Twist 1 which enhances the expression of VE-Cadherin. Wei described the p-STAT3 / HIF-1α and HIF-2α signalling pathway inducing tumour shoots and the expression of numerous cytokines and transcription factors, such as VEGF, Twist, Snail, Zinc Finger E-Box Binding Homeobox 1 (ZEB2), transforming growth factor beta-3 (TGF-β3), Lysyl Oxidase (LOX), and MMP-14, MMP-9, MMP2 (Wei, 2021). Colorectal cancer 1 (MACC1) metastases are also known to trigger HGF / c-Met signalling and induce epithelial mesenchymal transition (EMT) in VM. Qi reported the contribution of the Wnt / PKCα / PI3K / Snail, a non-canonical (β-catenin independent) pathway, in the VM. Wnt activates phospholipase C via frizzled receptor. Frizzled is a family of atypical G protein-coupled receptors that serve as receptors in the Wnt signaling pathway and other signaling pathways. This activation leads to increased plasma calcium levels, which activates PKC. Wnt can also upregulate PI3K and Snail expression. This increases the motility and invasiveness of OC cells and enhances EMT which leads to VM (Qi, 2014). Ayala-Domínguez presented that VM can be stimulated by a migration-inducing protein (Mig-7) that is induced by EGFR activated by Ln5γ2 (Ayala-Domínguez, 2019). The effect of TGF-β on VM has been also elucidated. TGF-β binds to type I and type II receptors, leading to phosphorylation of the transcription factor Smad-3 and contributing to EMT and then to VM (Sicard, 2021).

Cancer stem cells (markered with CD44 and ALDH1 expression) are also considered to play a role in VM. Their presence provides a poorer prognosis (Wechman, 2020). The marker of cancer stem cells is CD133 which is associated with VM, resistance to chemotherapy, and shorter survival (Liang, 2016). VM correlates also with the expression of the CD177 gene encoding NB1 protein (Jiang, 2020). *In vitro* study shows that SEMA4D and VEGF have a synergic effect on promoting VM (Chen, 2018). VEGF-A/EphA2/ MMP9/2 pathway play also an important role in VM development (Lim, 2020) (Figure 1).

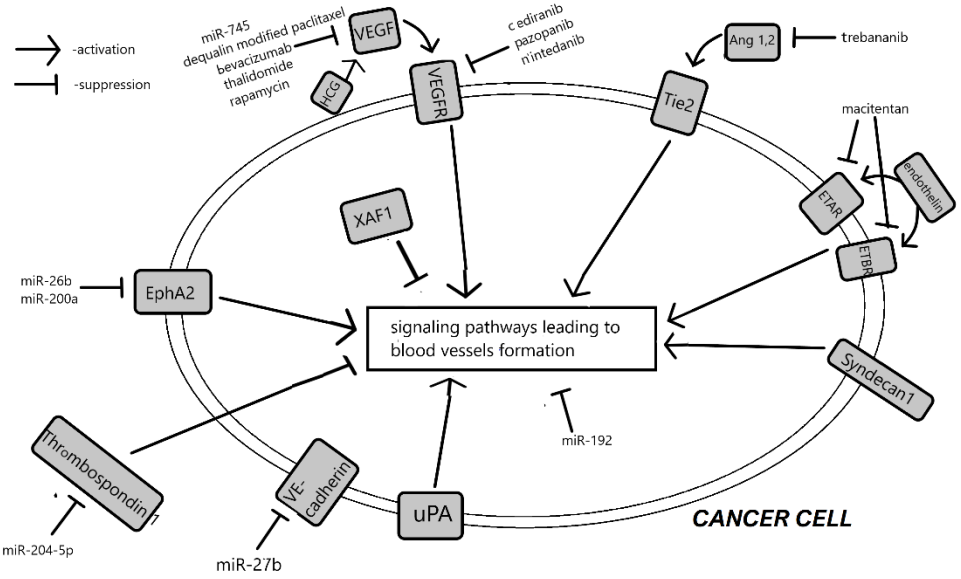

Figure 1. Molecules modulating signaling pathways involved in the formation of new blood vessels formation by angiogenesis and vascular mimicry in ovarian cancer

Ang 1, 2 – angiopoietin-1 and -2; EphA2 – ephrin type-A receptor 2; ETAB, ETBR – endothelin-1 and endothelin B type receptor; HCG – human chorionic gonadotropin; miR – microRNA; Tie2 – angiopoietin-1 receptor; uPA – urokinase-type plasminogen activator; VE-cadherin – vascular endothelial cadherin; VEGF – vascular endothelial growth factor; VEGFR – vascular endothelial growth factor receptor; XAF1 – X-linked inhibitor of apoptosis (XIAP)-associated factor 1

THERAPEUTIC TARGETING OF VM

Many anti-angiogenic drugs, such as those mentioned above, are currently used to treat a variety of cancers, including OC. However, they are not fully effective, as their use leads to hypoxia that can induce the formation of VM channels. Therefore, a therapeutic approach that targets both angiogenesis and VM is currently being promoted. It is believed that this approach will ensure a more effective treatment of aggressive cancers, such as OC (Chen, 2014).

There are several anti-VM therapies with agents (Xie, 2019; Li, 2018) (Table 2, Figure 1). One of which is dequalin (DQA) modified paclitaxel plus several other drugs such as ligustrazine micelles, thalidomide, trastuzumab, tapamycin, and resveratrol which inhibit VM by targeting VEGF (Chen, 2014). Both thalidomide and rapamycin are known to target VEGF to inhibit tumour VM formation (Su, 2008; Zhang, 2008). The in vitro studies showed that macitentan, an antagonist of both ETAR / ETBR endothelin receptors, was able to inhibit VM by blocking endothelin-1-induced activation of Akt and MAPK signalling pathways (Sestito, 2016). Urokinase plasminogen activator (uPA) has the ability to degrade the extracellular matrix (ECM), which is an important step in VM. Tang reported that uPA downregulating molecules such as arginine-glycine-aspar-tate cyclic motif (cRGD) can inhibit VM (Tang, 2016). It was also shown that over-expression of the X-linked inhibitor of apoptosis-related factor 1 (XAF1) is associated with lower VEGF expression and fewer VM structures (Wang, 2017). In vivo studies showed that human chorionic gonadotropin (HCG) upregulates endothelial markers CD31, VEGF, and factor VIII and induces VM. Therefore, it is possible to speculate that the use of anti-HCG therapeutic targeting may provide a novel opportunity to circumvent tumours that express HCG, such as ovarian cancer (Gao S, 2016).

Moreover, an important role in VM plays also syndecan-1 (SDC1). In ovarian cancer models, the anti-SDC1 46F2SIP antibody, in combination with L19-IL2, a B-fibronectin specific immunocytokine modulates EMT markers, stemness and alleviates hypoxia, and may be effective in suppressing VM (Orecchia, 2019).

Various miR molecules are among the VM negatively regulating molecules (table 2). Of such molecules is miR-765 suppressing VEGFA/AKT1/SRC-α axis. MiR-745 was described by Salinas-Vera YM to target VEGFR/ AKT1/SRC-α pathway. It suppresses VM formation by decreasing the levels of VEGFA, AKT1, and SRC-α transducers and exerts

a negative regulation of VEGFA by specific binding to its 3′-untranslated region (3'UTR) (Salinas-Vera, 2019). miR-27b targeting VE-cadherin was shown to inhibit ovarian cancer cell migration and VM via binding to the 3′UTR of VE-cadherin mRNA (Liu, 2017). The target of miR-200a, which was studied on ovarian cancer, and miR-26b is ephrin A2 (EphA2). As authors have shown it inhibits EphA2 expression thus suppressing VM formation (Sun, 2014). Wu et al. have shown that miR-192 inhibits many genes associated with angiogenesis in many orthotopic mouse models of ovarian and kidney cancer (Wu, 2016). Lower levels of miR-192 in tumours are associated with high angiogenesis and low overall survival in patients with OC or clear cell carcinoma kidneys. Chen et al. proved that miR-204-5p can promote angiogenesis in ovarian tumours via Thrombospondin 1 (THBS1) (Chen, 2019) (Table 2, Figure1).

To effectively inhibit angiogenesis, multiple angiogenic/VM pathways need to be blocked simultaneously. Therefore, miRNAs may be an ideal therapeutic approach in this context.

Table 2. Molecules targeting VM in ovarian cancer

Molecule	Regulated pathway/molecule	Type of impact
dequalin (DQA) modified paclitaxel	VEGF	suppression
thalidomide	VEGF	suppression
rapamycin	VEGF	suppression
macitentan	ETAR / ETBR endothelin receptors	suppression
arginine-glycine-aspartate cyclic motif (cRGD)	Urokinase plasminogen activator (uPA)	suppression
X-linked inhibitor of apoptosis-related factor 1 (XAF1)	VEGF	suppression
human chorionic gonadotropin (HCG)	CD31, VEGF, factor VIII	induction
L19-IL2 Immunocytokine with the Anti-Syndecan-1 46F2SIP Antibody	syndecan-1 (SDC1)	suppression
miR-745	VEGFA/AKT1/SRC-α	suppression
miR-27b	VE-cadherin	suppression
miR-26b	EphA2	suppression
miR-200a	EphA2	suppression
miR-192	many genes associated with angiogenesis	suppression
miR-204-5p	Thrombospondin 1 (THBS1)	induction

CONCLUSION

Angiogenesis and vasculogenic mimicry play a key role in the development and progression of OC. The knowledge of the factors influencing these processes may contribute to increasing the effectiveness of OC therapy. Due to the participation of both angiogenesis and VM in cancer development, both angiogenesis inhibitors and VM inhibitors should be considered in the treatment of OC. In cases of developing resistance to anti-angiogenic drugs, treatment aimed at inhibiting the formation of vessels in the mechanism of vasculogenic mimicry opens up the possibility of an effective OC therapy.

References

Alitalo K., Carmeliet P. **Molecular mechanisms of lymphangiogenesis in health and disease**. Cancer Cell. 2002; 1:219-227.

Awasthi N., Schwarz R.E. **Profile of nintedanib in the treatment of solid tumors: the evidence to date**. Onco Targets Ther. 2015; 8:3691-3701.

Bellon G., Martiny L., Robinet A. **Matrix metalloproteinases and matrikines in angiogenesis**. Critical reviews in oncology/hematology. 2004; 49(3): 203-220.

Benedito R., Rocha S.F., Woeste M., Zamykal M., Radtke F., Casanovas O., et al. **Notch-dependent VEGFR3 upregulation allows angiogenesis without VEGF-VEGFR2 signalling**. Nature. 2012; 484:110-114.

Cao Z., Bao M., Miele L., Sarkar F.H., Wang Z, Zhou Q. **Tumour vasculogenic mimicry is associated with poor prognosis of human cancer patients: A systemic review and meta-analysis**. European Journal of Cancer. 2013; 49(18):3914-3923.

Chelariu-Raicu A., Coleman R.L., Sood A.K. **Anti-Angiogenesis Therapy in Ovarian Cancer: Which Patient is It Most Likely to Benefit? Oncology**. Williston Park. 2019; 33(7):629378.

Chen X., Mangala L.S., Mooberry L., Bayraktar E., Dasari S.K., Ma S., et al. **Identifying and targeting angiogenesis-related microRNAs in ovarian cance**r. Oncogene. 2019; 38:6095-108.

Chen Y., Zhang L., Liu W.-X., Wang K. **VEGF and SEMA4D have synergistic effects on the promo-tion of angiogenesis in epithelial ovarian cancer**. Cellular & Molecular Biology Letters. 2018; 23(1).

Chen Y.S., Chen Z.P. **Vasculogenic mimicry: a novel target for glioma therapy**. Chin J Cancer. 2014;33(2):74-9.

Cooke V.G., LeBleu V.S., Keskin D., Khan Z., O'Connell J.T., Teng Y. et al. **Pericyte depletion results in hypoxia-associated epithelial-to-mesenchymal transition and metastasis mediated by met signalling pathway**. Cancer Cell. 2012; 21(1):66-81.

Cortez A.J., Tudrej P., Kujawa K.A., Lisowska K.M. **Advances in ovarian cancer therapy**. Cancer Chemother Pharmacol. 2018; 81:17-38.

Dhani N.C., Oza A.M. **Targeting Angiogenesis: Taming the Medusa of Ovarian Cancer**. Hematol Oncol Clin North Am. 2018; 32(6):1041-1055.

du Bois A., Floquet A., Kim J.W., Rau J., del Campo J.M., Friedlander M. et al. **Incorporation of pazopanib in maintenance therapy of ovarian cancer**. J Clin Oncol. 2014; 32:3374-3382.

du Bois A., Kristensen G., Ray-Coquard I., Reuss A., Pignata S., Colombo N., et al. **Standard first-line chemotherapy with or without nintedanib for advanced ovarian cancer (AGO-OVAR 12): a randomised, double-blind, placebo-controlled phase 3 trial**. Lancet Oncol. 2016; 17:78-89.

Ferrara N., Kerbel R.S. **Angiogenesis as a therapeutic target**. Nature. 2005; 438:967-974.

Floquet A., Vergote I., Colombo N., Fiane B., Monk B.J., Reinthaller A. et al. **Progression-free survival by local investigator versus independent central review: comparative analysis of the AGO-OVAR16 Trial**. Gynecol Oncol. 2015; 136:37-42.

García García Y., Marín Alcalá M., Martínez Vila C. **Anti-angiogenic therapy for ovarian cancer**. European Journal of Cancer Supplements. 2020; 15:77-86.

Gao S., Fan C., Huang H., Zhu C., Su M., Zhang Y. **Effects of HCG on human epithelial ovarian cancer vasculogenic mimicry formation in vivo**. Oncol Lett. 2016 ;12(1):459-466.

Garrido M.P., Torres I., Vega M., Romero C. **Angiogenesis in Gynecological Cancers: Role of Neurotrophins**. Front Oncol. 2019; 9:913.

Gavalas N.G., Liontos M., Trachana S.P., Bagratuni T., Arapinis C., Liacos C. et al. **Angiogenesis-Related Pathways in the Pathogenesis of Ovarian Cancer**. Intern. J. Mol. Sci. 2013; 14(8):15885-15909.

Gupta N., Duda D.G. **Role of stromal cell-derived factor 1alpha pathway in bone metastatic prostate cancer**. J Biomed Res. 2016; 30(3):181-185.

Hughes G., Toellner H., Morris H., Leonard C., Chaudhuri N. **Real World Experiences: Pirfenidone and Nintedanib are Effective and Well Tolerated Treatments for Idiopathic Pulmonary Fibrosis**. J Clin Med. 2016; 5:78-89.

Jiang J., Chen Y., Zhang M., Zhou H., Wu H. **Relationship between CD177 and the vasculogenic mimicry, clinicopathological parameters, and prognosis of epithelial ovarian cancer**. Annals of Palliative Medicine. 2020; 9(6):3985-3992.

Kurnit K.C., Fleming G.F., Lengyel E. **Updates and New Options in Advanced Epithelial Ovarian Cancer Treatment**. Obstet Gynecol. 2021; 137(1):108-121.

Ledermann J.A., Embleton-Thirsk A.C., Perren T.J., Jayson G.C., Rustin G.J.S., Kaye S.B. et al. **Cediranib in patients with relapsed platinum-sensitive ovarian cancer (ICON6): a randomised, double-blind, placebo-controlled phase 3 trial**. Lancet. 2016; 387:1066-1074.

Li X., Yang Z., Han Z., Wen Y., Ma Z., Wang Y. **Niclosamide acts as a new inhibitor of vasculogenic mimicry in oral cancer through upregulation of miR-124 and downregulation of STAT3**. Oncol Rep. 2018; 39(2):827-833.

Liang J., Yang B., Cao Q., Wu X. **Association of Vasculogenic Mimicry Formation and CD133 Expression with Poor Prognosis in Ovarian Cancer**. Gynecologic and Obstetric Investigation. 2016; 81(6):529-536.

Lim D., Do Y., Kwon B.S., Chang W., Lee M.S., Kim J., Cho J.G. **Angiogenesis and vasculogenic mimicry as therapeutic targets in ovarian cancer**. BMB Rep. 2020; 53(6):291-298.

Liu W., Lv C., Zhang B., Zhou Q., Cao Z. **MicroRNA-27b functions as a new inhibitor of ovarian cancer-mediated vasculogenic mimicry through suppression of VE-cadherin expression**. Rna. 2017; 23(7):1019-27.

Liu Y., Luo Y., Cai M., Shen P., Li J., Chen H. et al. **Anti-angiogenic therapy in ovarian cancer: current situation & prospects**. Indian J Med Res. 2021; 154(5):680-690.

Luo Q., Wang J., Zhao W. et al. **Vasculogenic mimicry in carcinogenesis and clinical applications**. Journal of Hematology & Oncology. 2020; 13(1).

Markowska A., Sajdak S., Markowska J., Huczynski A. **Angiogenesis and cancer stem cells: New perspectives on therapy of ovarian cancer**. Eur J Med Chem. 2017; 142:87-94.

Monk B.J., Poveda A., Vergote I., Raspagliesi F., Fujiwara K., Bae D.S. et al. **Anti-angiopoietin therapy with trebananib for recurrent ovarian cancer (TRINOVA-1): a randomised, multicentre, double-blind, placebo-controlled phase 3 trial**. Lancet Oncol. 2014; 15:799-808.

Orecchia P., Balza E., Pietra G., Conte R., Bizzarri N., Ferrero S. et al. **L19-IL2 Immunocytokine in Combination with the Anti-Syndecan-1 46F2SIP Antibody Format: A New Targeted Treatment Approach in an Ovarian Carcinoma Model**. Cancers. 2019; 11:1232.

Qi H., Sun B., Zhao X., Du J., Gu Q., Liu Y. et al. **Wnt5a promotes vasculogenic mimicry and epithelial-mesenchymal transition via protein kinase Cα in epithelial ovarian cancer**. Oncology Reports. 2014; 32(2):771-779.

Quintero-Fabián S., Arreola R., Becerril-Villanueva E., Torres-Romero J.C., Arana-Argáez V., Lara-Riegos J. et al. **Role of Matrix Metalloproteinases in Angiogenesis and Cancer**. Front Oncol. 2019; 9:1370.

Reinthaller A. **Antiangiogenic therapies in ovarian cancer**. Memo. 2016; 9:139-143.

Saharinen P., Eklund L., Alitalo K. **Therapeutic targeting of the angiopoietin-TIE pathway**. Nat Rev Drug Discov. 2017; 16(9):635-661.

Salinas-Vera Y.M., Gallardo-Rincon D., Garcia-Vazquez R., Hernandez-de la Cruz O.N., Marchat L.A., Gonzalez-Barrios J.A., et al. **HypoxamiRs profiling identify miR-745 as a regulator of the early stages of vasculogenic mimicry in SKOV3 ovarian cancer cells**. Front. Oncol. 2019; 9:381.

Saman H., Raza S.S., Uddin S., Rasul K.. **Inducing Angiogenesis, a Key Step in Cancer Vascularization, and Treatment Approaches**. Cancers (Basel). 2020;12(5):1172.

Sestito R., Cianfrocca R., Rosanò L., Tocci P., Di Castro V., Caprara V. et al. **Macitentan blocks endothelin-1 receptor activation required for chemoresistant ovarian cancer cell plasticity and metastasis**. Life Sci. 2016;159:43-48.

Shibuya M.. **Vascular endothelial growth factor (VEGF) and its receptor (VEGFR) signalling in angio-genesis: a crucial target for anti- and pro-angiogenic therapies**. Genes Cancer. 2011; 2:1097-1105.

Sicard A.A., Dao T., Suarez N.G., Annabi B. **Diet-Derived Gallated Catechins Prevent TGF-β-Mediated Epithelial-Mesenchymal Transition, Cell Migration and Vasculogenic Mimicry in Chemosensitive ES-2 Ovarian Cancer Cells**. Nutr Cancer. 2021;73(1):169-180.

Singh N., Badrun D., Ghatage P. **State of the art and up-and-coming angiogenesis inhibitors for ovarian cancer**. Expert Opin Pharmacother. 2020; 21(13):1579-1590.

Sobocińska A., Czarnecka A., Szczylik C. **Mechanizmy angiogenezy w nowotworzeniu** Postepy Hig Med Dosw. 2016; 70:1166-1181.

Su M., Feng Y.J., Yao L.Q., Cheng M.J., Xu C.J., Huang Y., et al. **Plasticity of ovarian cancer cell SKOV3ip and vasculogenic mimicry in vivo**. Int J Gynecol Cancer. 2008; 18(3):476-486.

Sun Q., Zou X., Zhang T., Shen J., Yin Y., Xiang J. **The role of miR-200a in vasculogenic mimicry and its clinical significance in ovarian cancer**. Gynecol Oncol. 2014; 132(3):730-8.

Tang J., Wang J., Fan L., Li X., Liu N., Luo W. et al. **cRGD inhibits vasculogenic mimicry formation by down-regulating uPA expression and reducing EMT in ovarian cancer**. Oncotarget. 2016; 7: 24050-24062.

Torre L.A., Trabert B., DeSantis C.E., Miller K.D., Samimi G., Runowicz C.D. et al. **Ovarian cancer statistics, 2018**. CA: A Cancer Journal for Clinicians. 2018; 68(4):284-296.

Valdivia A., Mingo G., Aldana V., Pinto M.P., Ramirez M., Retamal C. et al. Fact or Fiction, **It Is Time for a Verdict on Vasculogenic Mimicry?** Front Oncol. 2019; 9:680

van Beijnum J.R., Nowak-Sliwinska P., Huijbers E.J., Thijssen V.L., Griffioen A.W. **The great escape; the hallmarks of resistance to antiangiogenic therapy**. Pharmacol Rev. 2015; 67:441-461.

Viallard C., Larrivée B. **Tumor angiogenesis and vascular normalization: alternative therapeutic targets**. Angiogenesis. 2017; 20(4):409-426.

Wang Y., Liu P., Wang X., Mao H. **Role of Xlinked inhibitor of apoptosisassociated factor1 in vasculogenic mimicry in ovarian cancer**. Mol Med Rep. 2017; 16(1):325-330.

Wechman S.L., Emdad L., Sarkar D., Das S.K., Fisher P.B. **Vascular mimicry: Triggers, molecular interactions and in vivo models**. Adv Cancer Res. 2020;148:27-67.

Wei X., Chen Y., Jiang X., Peng M., Liu Y., Mo Y. et al. **Mechanisms of vasculogenic mimicry in hypoxic tumor microenvironments**. Molecular Cancer. 2021; 20(1).

Wu S.Y., Rupaimoole R., Shen F., Pradeep S., Pecot C.V., Ivan C. et al. **A miR-192-EGR1-HOXB9 regulatory network controls the angiogenic switch in cancer**. Nat Commun. 2016; 7:11169.

Xie H.J., Zhao J., Zhuo-Ma D., Zhan-Dui N., Er-Bu A. **Tsering T. Inhibiting tumour metastasis by DQA modified paclitaxel plus ligustrazine micelles in treatment of non-small-cell lung cancer**. Artif Cells Nanomed Biotechnol. 2019; 47(1):3465-77.

Xu Y., Li Q., Li X.Y., Yang Q.Y., Xu W.W., Liu G.L. **Short-term anti-vascular endothelial growth factor treatment elicits vasculogenic mimicry formation of tumors to accelerate metastasis**. J Exp Clin Cancer Res. 2012; 31(1):16.

Yang C., Xia B.R., Zhang Z.C., Zhang Y.J., Lou G., Jin W.L. **Immunotherapy for Ovarian Cancer: Adjuvant, Combination, and Neoadjuvant**. Front Immunol. 2020; 11:577869.

Yousif L.F., Di Russo J., Sorokin L. L**aminin isoforms in endothelial and perivascular basement membranes**. Cell Adh Migr. 2013; 7(1):101-10.

Zhang S., Li M., Gu Y., Liu Z., Xu S., Cui Y., et al. **Thalidomide influences growth and vasculogenic mimicry channel formation in melanoma**. J Exp Clin Cancer Res. 2008; 27:60.

Zhang X., Zhang J., Zhou H., Fan G., Li Q. **Molecular Mechanisms and Anticancer Therapeutic Strategies in Vasculogenic Mimicry**. J Cancer. 2019; 10(25):6327-6340.

Zhu M., Fejzo M.S., Anderson L., Dering J., Ginther C., Ramos L. et al. **Periostin promotes ovarian cancer angiogenesis and metastasis**. Gynecologic oncology. 2010; 119(2), 337-344.

Zimna A., Kurpisz M. **Hypoxia-Inducible Factor-1 in Physiological and Pathophysiological Angiogenesis: Applications and Therapies**. Biomed Res Int. 2015; 2015:549412.