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Review

Angiogenesis in gynecological cancers and the options for anti-angiogenesis therapy

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ABSTRACT

Angiogenesis is required in cancer, including gynecological cancers, for the growth of primary tumors and secondary metastases. Development of anti-angiogenesis therapy in gynecological cancers and improvement of its efficacy have been a major focus of fundamental and clinical research. However, survival benefits of current anti-angiogenic agents, such as bevacizumab, in patients with gynecological cancer, are modest. Therefore, a better understanding of angiogenesis and the tumor microenvironment in gynecological cancers is urgently needed to develop more effective anti-angiogenic therapies, either or not in combination with other therapeutic approaches. We describe the molecular aspects of (tumor) blood vessel formation and the tumor microenvironment and provide an extensive clinical overview of current anti-angiogenic therapies for gynecological cancers. We discuss the different phenotypes of angiogenic endothelial cells as potential therapeutic targets, strategies aimed at intervention in their metabolism, and approaches targeting their (inflammatory) tumor microenvironment.

1. Introduction

Gynecological cancers, such as ovarian cancer, cervical cancer, and endometrial cancer, have an estimated worldwide incidence of one million cases and an estimated mortality rate of 500,000 deaths every year [1]. Each type of these cancers is unique with different epidemiologic and genetic risk factors, symptoms, prognoses, and responses to therapy. However, what they have in common is that curative options are limited [2–6]. Therefore, novel insights at the molecular and cellular level are needed to improve and personalize treatment strategies.

The understanding that vascularization is essential for tumor growth

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has led to the development of therapeutic approaches directed against the tumor vasculature [7,8]. Although anti-angiogenic therapy has become part of first-line maintenance treatment in several types of human cancers, including gynecological cancers, anti-angiogenic agents in use today are only effective in a subset of patients, and many patients who initially respond to these drugs develop resistance over time. These disappointing results in cancer patients emphasize the urgent need for new insights at the molecular and cellular levels of the effects of the current inhibitors of angiogenesis and/or for discovering alternative anti-angiogenic agents. For example, recurrent glioblastoma shows a

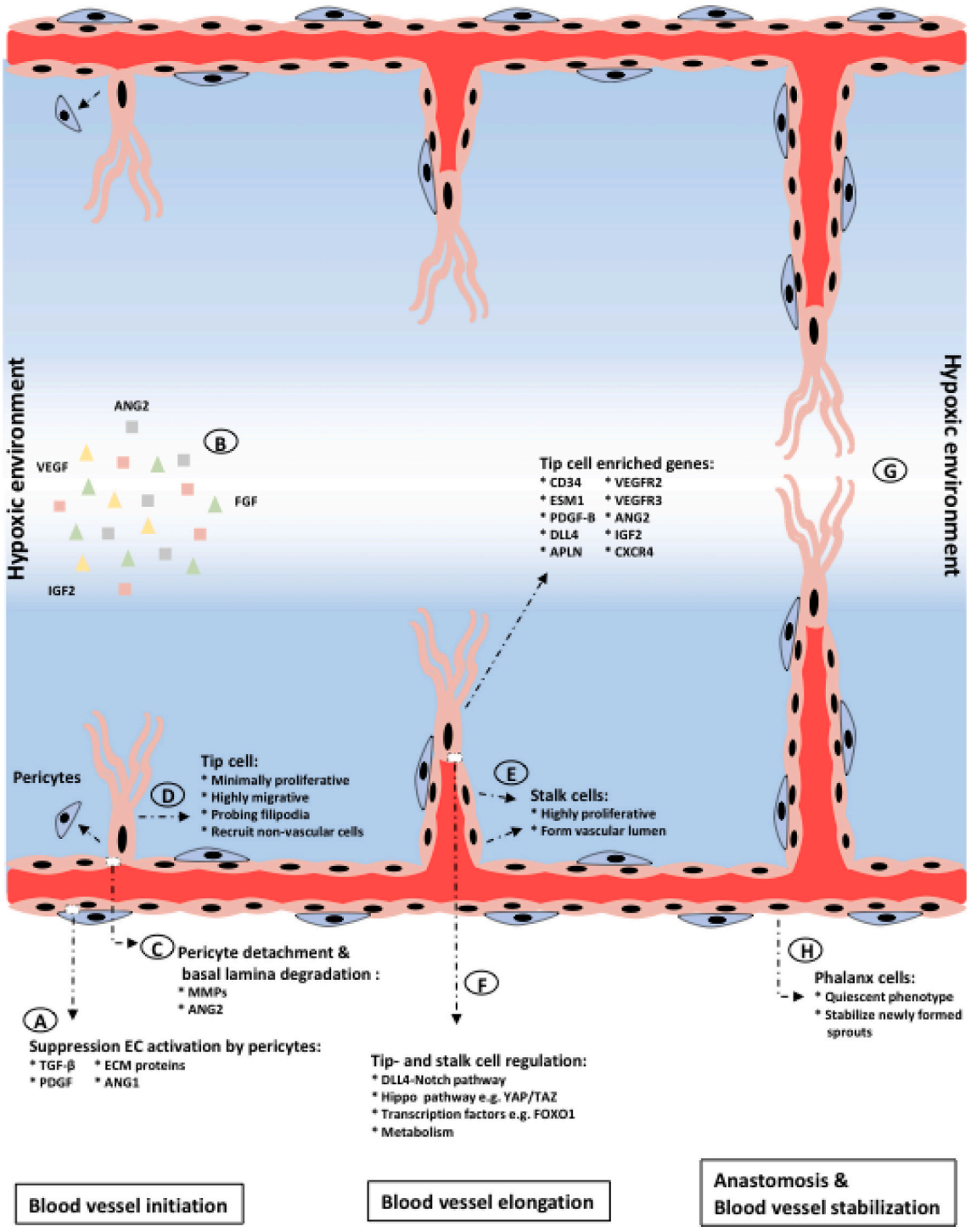

Fig. 1. Endothelial cell differentiation: tip cell, stalk cell, and phalanx cell phenotypes. (A) Quiescent ECs form a monolayer of cells that are surrounded by pericytes, which suppress EC activation and stabilize the quiescent vessel. (B) During angiogenesis, a single leading tip cell is attracted by microenvironmental signals and (C) breaks down the basal lamina and migrates into the extracellular matrix. (D) Tip cells possess actin stress fibers with probing filopodia and are characterized by their low proliferation activity, high migratory capacity, and their ability to recruit non-vascular cells. (E) The highly proliferative stalk cells follow the tip cell, form a vascular lumen, and ensure vessel elongation. (F) Tip cell and stalk cell phenotype regulation involves several factors, including growth factors, transcription factors, and metabolism. (G) A new vascular loop is established by connecting two sprouts of endothelial tip cells, thereby forming a continuous lumen, also known as anastomosis. (H) The phalanx cell phenotype is eventually acquired by differentiated ECs once the new vessel is formed.

radiographic response to bevacizumab, but patient survival is not improved [9–12]. Below in chapter 6, we show that also in gynecological cancers bevacizumab therapy has disappointing effects on patient survival.

The healthy endothelium remains quiescent throughout adulthood and is only activated during physiological processes such as wound healing and the female reproductive cycle. During angiogenesis, endothelial cells (ECs) rapidly switch to an activated state and start to form new blood vessels. This process is tightly regulated by pro-angiogenic and anti-angiogenic factors [13,14]. Angiogenesis is important in the female reproductive system to allow monthly ovulation and successful realization of pregnancy, but also has a critical role in the pathogenesis of its cancers, by promoting tumor growth and metastatic spread. High microvessel density of cancers is often associated with poor prognosis and a greater risk of recurrence [15–24]. The female reproductive system and its cancers have such an angiogenic molecular signature that anti-angiogenic therapy theoretically is promising.

In the current review, we describe the process of angiogenesis and its role in cancer in general, the genetic and metabolic regulators of angiogenesis in the context of the female reproductive system, and their role in ovarian cancer, cervical cancer, and endometrial cancer. We highlight existing and novel therapeutic strategies for targeting angiogenesis in these types of cancers and discuss the advantages and drawbacks of these approaches.

2. Angiogenesis

2.1. Endothelial cell differentiation: Tip cell, stalk cell, and phalanx cell phenotypes

Growing tissues become vascularized via different types of angiogenesis [25]. Vessel co-option is a type of passive angiogenesis where cells grow along existing vessels [26]. Intussusceptive angiogenesis is characterized by splitting of existing blood vessels [27]. Sprouting angiogenesis (Fig. 1) is the most efficient type of vascularization [28,29]. In cancer, there is also a tumor cell-organized form of vascularization called vasculogenic mimicry, leading to vascular networks made up of transdifferentiated cancer cells that have an EC phenotype [30,31].

Throughout the process of sprouting angiogenesis (Fig. 1), developing capillaries are guided by specialized ECs, located at the top of growing vessels, the tip cells [32–34]. Tip cells have a low proliferative activity, possess actin stress fibers with probing filopodia and migrate into the extracellular matrix (ECM) (Fig. 1) towards a gradient of angiogenic growth factors. Consequently, tip cells assimilate directional cues from the environment and thereby determine the direction in which the new sprout grows [32]. Additionally, tip cells actively recruit pericytes and non-vascular cells, likely by platelet-derived growth factor-B (PDGF-B) secretion. In resting vessels, pericytes share a basal lamina with the ECs of capillaries and post-capillary venules (termed ' intramural' pericytes) and are involved in the stabilization of the vessel wall and control EC proliferation [14,35–38]. In sprouting angiogenesis, pericytes reside outside the capillary wall, which has been termed 'extramural', and migrate alongside the angiogenic sprout [35]. Tip cells are followed by stalk cells, which in contrast to tip cells are highly proliferative, produce less filopodia, form a vascular lumen (Fig. 1) [40–42], and establish adherens and tight junctions to maintain the stability of the new sprout [43]. Tubulogenesis, the process of lumen formation by ECs, is an essential step of angiogenesis and involves interactions with the ECM and cytoskeletal reorganization [14,36,44]. The third known specialized ECs are the phalanx cells, which tightly align and form a smooth internal monolayer of the newly formed blood vessel (Fig. 1). Phalanx cells have a more dormant phenotype, they do not proliferate. These specialized ECs express tight junctions and are involved in the normalization and stabilization of the newly formedvasculature through increased cell adhesion [45,46]. Finally, a new vascular loop is established by connecting two sprouts of endothelial tip cells, thereby forming a continuous lumen, also known as a process called anastomosis [14,47–49].

2.2. Genetic control of EC differentiation and new developments in sprouting angiogenesis

Quiescent ECs form a monolayer of cells that is surrounded by pericytes, which provide cell-survival factors and anti-proliferative factors (e.g. transforming growth factor (TGF)-β) that suppress EC activation and stabilize the quiescent vessel [50]. The recruitment and maintenance of pericytes requires growth factors such as PDGF and angiopoietin 1 (ANG1) [51]. Endothelial cells and pericytes share a lamina basalis consisting of ECM proteins that prevent ECs from leaving their position. The need for oxygen and nutrients in surrounding tissues initiates sprouting angiogenesis by inciting the production of pro-angiogenic signals, such as vascular endothelial growth factor (VEGF), angiopoietin 2 (ANG2), fibroblast growth factor (FGF), epidermal growth factor (EGF), and insulin-like growth factor 2 (IGF2) [52–54]. In response to these angiogenic cues, the basal lamina of the quiescent EC monolayer is degraded by matrix metalloproteases (MMPs), pericytes detach from the vessel wall, and ECs of the quiescent vessel loosen their junctions. Detachment of pericytes is stimulated by ANG2 that is produced and stored by ECs for rapid release when needed [55–58].

VEGF-A is the most important angiogenic factor that controls vessel formation. VEGF-A expression is regulated by several factors including hypoxia (hypoxia-inducible factor 1 (HIF1), growth factors, cytokines (e.g. TGF-β), hormones (e.g. estrogen and progesterone), and expression of oncogenes and tumor-suppressor genes [50,59,60]. Both tip cells and stalk cells are stimulated by VEGF-A, but they have differential transcriptional signatures [14,32,46,61]. VEGF binds to its receptor VEGFR2 on the ECs of the preexisting vessel and a single tip cell migrates into the ECM and senses microenvironmental signals for guidance [32,46]. To prevent excessive tip cell formation and movement towards the angiogenic signal, the selection of a tip cell from a population of quiescent ECs is tightly regulated. The selected tip cell itself prevents neighboring ECs to become a tip cell via the delta-like 4 (DLL4)-Notch signaling pathway [14,41,62–65]. The VEGF-VEGFR2 interaction induces upregulation of DLL4 expression in tip cells and then DLL4 is transported to the cell membrane to bind to Notch receptors on adjacent ECs causing the Notch intracellular domain (NICD) to be released from the membrane. NCID translocates to the nucleus and drives the expression of VEGFR1, while it reduces the expression of VEGFR2 [66]. Soluble VEGFR1 acts as a decoy receptor and limits the activity of VEGF and imposes a stalk cell phenotype [40]. By lowering extracellular VEGF levels, soluble VEGFR1 modulates the signaling via VEGFR2 [67].

Besides their morphological characteristics, tip cells express tip cell-specific genes (Fig. 1) that are much lower expressed by the other EC subtypes [34,53,68]. Del Toro et al. identified tip cell-specific genes by laser-capture analysis of ECs that were isolated from *DLL4*$^{+/-}$ mouse retinas compared to wild-type retinas [69]. Previous studies reported that some of these genes are upregulated by VEGF stimulation (*Dll4* and *endothelial cell-specific molecule 1* (*Esm1*)) [62,70] and under hypoxic conditions (*Esm1*, *Pdgf-b*, and *apelin* (*Apln*)) [34]. Recombinant ESM1 protein promotes VEGF-induced EC migration and proliferation in vitro [70] and induces endothelial tube formation [71]. Although ESM1 was previously described to be specifically expressed in tip cells in the developing mouse retina [69,72], in tumor blood vessels ESM1 expression was not restricted to sprouting cells, but can be detected throughout the vasculature [73]. Recently, it has been shown that the VEGF-activated transcription factor forkhead box 01 (FOXO1) inhibits tip cell formation by inhibiting DLL4 expression [74]. FOXO1 is activated via the protein kinase mammalian sterile 20-like kinase 1 (MST1), a core kinase of the hippo pathway, under hypoxia. This results in the nuclear import of FOXO1 in endothelial tip cells, thus increasing its transcriptional regulation of genes associated with tip cell function and polarity.

Consequently, MST1- or FOXO1-deficient mouse models showed loss of tip cell polarity and impaired sprouting angiogenesis [75]. Furthermore, knockdown of these genes in human umbilical vein endothelial cells (HUVECs) reduced migration activity and inhibited the expression of migration-associated genes [75]. Like MST1, yes-associated protein (YAP) and its paralog transcriptional co-activator with PDZ-binding motif (TAZ) are also core molecules of the hippo pathway [76]. YAP/TAZ acts downstream of the hippo pathway and regulates key events in angiogenesis. *Yap/Taz* knockout in mice reduced the number of proliferating ECs and the number of tip cells and decreased filopodia density on these cells [77]. In contrast, endothelial YAP/TAZ hyperactivation in mice induced excessive filopodia on tip cells at the retinal vascular front [78]. These findings suggest that YAP/TAZ is involved in the morphogenesis and abundancy of tip cells and in the proliferation of stalk cells during sprouting angiogenesis. The 6 CCN family members, secreted matricellular proteins that are associated with the ECM [79], are involved in angiogenic processes, such as EC proliferation, migration, and differentiation [37,80]. One of its members, cysteine-rich protein 61 (CYR61, also known as CCN1), is a target of the YAP/TAZ signaling molecules [81,82], and regulates the tip cell phenotype through interplay with integrin αvβ3 and VEGFR2 [83].

The sialomucin CD34 is another tip cell marker that has been used to study tip cell biology and function in vitro (Fig. 2). $CD34^+$ tip cells are present in all EC cultures and show increased abundance of the mRNA of tip cell-specific genes. Genome-wide mRNA profiling of these cells demonstrated enrichment for functions related to angiogenesis and migration as compared to $CD34^-$ non-tip cells [84]. Furthermore, $CD34^+$ tip cells demonstrated a much lower proliferation rate [84] and a higher migratory capacity [85] compared to $CD34^-$ non-tip cells. Several other tip cell and stalk cell regulators and markers have been reviewed recently [53,86,87].

3. Angiogenesis in the female reproductive system

Angiogenesis has physiological functions in the female reproductive system which do not occur in other organs. Ovaries and endometrium undergo cyclic changes that are associated with angiogenesis and subsequent loss of blood vessels. Therefore, ovaries and endometrium produce both pro-angiogenic and anti-angiogenic factors. In fact, both basic FGF (bFGF), the first pro-angiogenic growth factor discovered, as well as VEGF, were initially characterized in human ovaries [88–90]. ANG2 was the first anti-angiogenic factor found to function as an endogenous regulator of blood vessel regression, and is highly expressed in the ovarian corpus luteum during luteolysis, a process involved in the structural and functional degradation of the corpus luteum and its associated vasculature at the end of the ovarian cycle [91,92]. In the following sections, we describe the dynamics of angiogenic processes in the ovary and endometrium. The blood supply of the female reproductive system and its histology are shown in Fig. 3.

3.1. Angiogenesis in ovaries

In the ovaries, angiogenesis is one of the most important processes in the development of primordial follicles into ovulatory follicles and subsequently into a corpus luteum. The cyclic growth and maturation of primordial follicles and luteal regression depend on angiogenesis and subsequent breakdown of blood vessels [93,94]. Primordial follicles do not have a vascular network of their own and their maintenance relies on blood vessels in the surrounding stroma [95]. As follicles continue to grow, an antrum develops in the follicles and ECs of blood vessels in the adjacent stroma are activated for sprouting angiogenesis into the thecal layer. A vascular sheath, consisting of two capillary networks in the theca interna and externa, is formed. The newly formed vessels are separated from the avascular granulosa cells by the membrana granulosa. Angiogenesis into the developing follicles increases steadily and the newly-formed blood vessels provide oxygen, nutrients, and hormones (e.g., gonadotropins), which are essential for the maturation of follicles during the ovarian cycle [96–101]. Angiogenesis becomes even more intense after ovulation, during the development of the corpus luteum [96,102]. After enzymatic breakdown of the membrana granulosa, ECs from the theca interna rapidly migrate into the avascular granulosa layer, and theca capillaries expand by angiogenesis to form a dense sinusoidal capillary network [99,103–105]. Maturation of the transient vascular bed of the corpus luteum is characterized by the recruitment of pericytes that cover the capillaries to ensure vessel stabilization [106]. Remarkably, the corpus luteum is so well vascularized

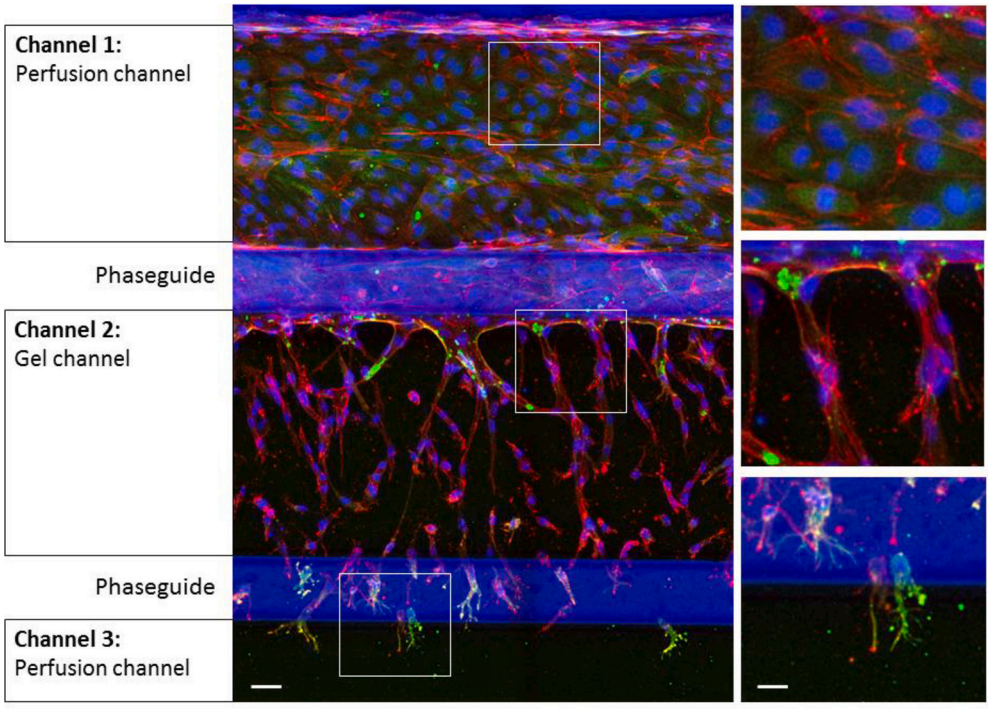

Fig. 2. $CD34^+$ tip cells in a 3D angiogenic sprouting model. In channel 1 of an OrganoPlate® (Mimetas), a confluent layer of ECs has formed a vessel on an ECM gel containing collagen 1 (channel 2). Out of the vessel, sprouts are formed that grow towards channel 3 that contains angiogenic factors. Immunofluorescent staining was performed of CD34 (green), F-actin (red) and nuclei (blue). ECs in the vessel show a luminal staining of CD34. In addition, CD34 staining was present on the tips of EC sprouts that have a tip cell morphology including filopodial extensions. Magnifications are shown and indicated in the overview image. Scale bars, overview, 100 μm; higher magnifications, 50 μm.

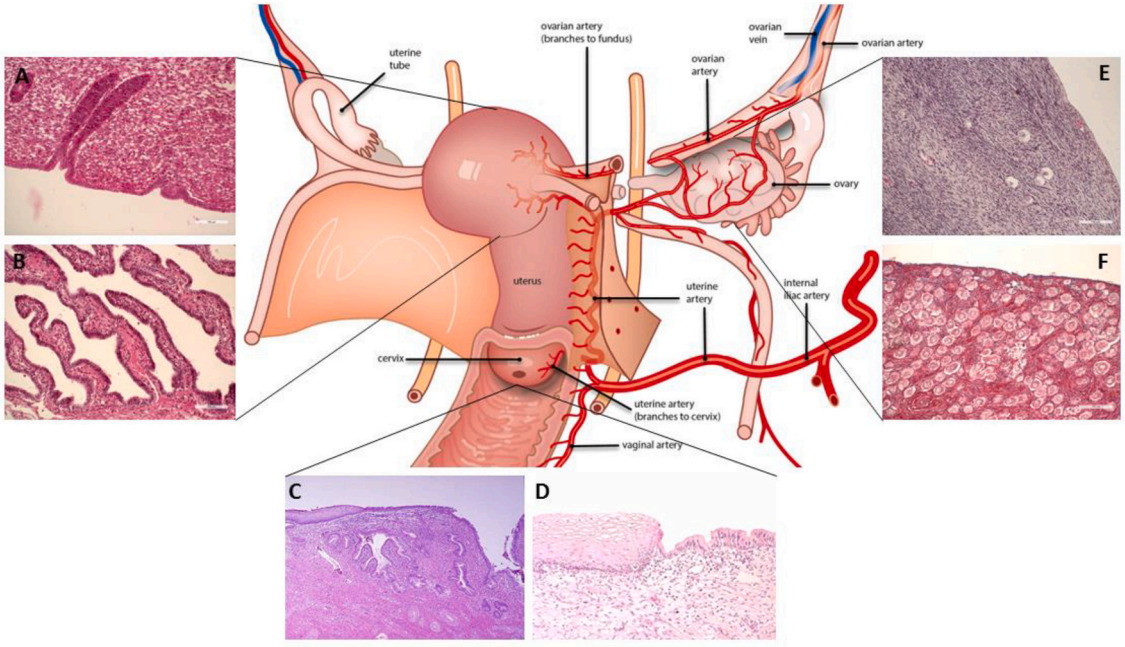

Fig. 3. Anatomy, histology and the blood supply of the female reproductive system showing the locations where the largest part of gynecological cancers occur: endometrium (**A**; proliferative endometrium and **B**; secretory endometrium), transformation zone of stratified squamous epithelium of the exocervix and columnar mucus secreting epithelium of the endocervix (**C** and **D**) and cubic ovarian surface epithelium in **E** and **F**. Scale bars, A, B, C, 100 μm; D, 25 μm; E,F, 50 μm.

that ECs are its most abundant cell type, with the majority of the parenchymal cells in close contact with one or more capillaries [99,102,107,108]. The mature corpus luteum has one of the highest blood supplies per unit mass [109]. When fertilization and intra-uterine implantation do not occur, the corpus luteum and the newly formed vessels regress at the end of the ovarian cycle [100].

3.2. Angiogenesis in the endometrium

In the endometrium, vascular growth starts in the proliferative phase and continues throughout the secretory phase of the menstrual cycle [110,111]. The spiral arteries lengthen and have a coiled appearance during the post-ovulatory phase of the menstrual cycle [112]. Long straight pre-capillaries connect the coiled spiral arteries with the sub-epithelial capillary plexus which matures below the epithelium [111,113]. In the absence of an embryo, the functional layer of the endometrium is shed and the superficial layer of the remaining basal layer is repaired by angiogenesis [114]. Vascular sprouts have not been found in the endometrium whereas proliferating ECs have been identified within existing endometrial vessels. In addition, EC proliferation and capillary density in the endometrium does not change significantly during the menstrual cycle [115–117]. These findings suggest that vascular expansion in the endometrium does not occur as sprouting angiogenesis but rather by elongation [118] and intussusceptive angiogenesis [113,119–121]. In contrast to sprouting angiogenesis, intussusceptive angiogenesis occurs rapidly within minutes or hours and does not rely on EC proliferation [122].

4. Angiogenesis in gynecological cancers

The growth of primary tumors and secondary metastases depends on angiogenesis as solid tumors and their metastases cannot grow beyond 1–2 mm^3 without additional vasculature, because of the lack of sufficient nutrients and oxygen that are required for the growing tumors [123–126]. Furthermore, unlike after physiological angiogenesis, tumor blood vessels remain structurally and functionally abnormal. Tumor angiogenesis takes place by uncontrolled proliferation of ECs that have a different phenotype than ECs in non-cancer physiological conditions [39,127]. Consequently, the tumor vasculature is irregularly shaped, dilated, tortuous, and disorganized [126,128,129] which is associated with high expression levels of pro-angiogenic factors, including VEGF, bFGF, neuropilin 1 (NRP1) [130,131], TGF-β [132] andneurotrophins [133]. Interestingly, it is also becoming evident that microRNAs (miRs) play a major role in the viability, proliferation and integrity of the tumor vasculature [134,135]. Examples here are miR125-a [136] that regulates the VEGF signaling pathway, and miRs 7, 141, 153 and 221 [137–140] that each intervene in critical stages of tumor angiogenesis. The density of the capillary network is inversely associated with overall survival and progression-free survival of women with gynecological cancers [15–24,141,142], at least partly due to increased metastatic spread.

4.1. Angiogenesis in ovarian cancer

The majority of ovarian cancers are epithelial ovarian cancers (EOCs), and high grade serous carcinoma (HGSC) is the most prevalent subtype (70–80%) [143]. Other subtypes of EOCs are low-grade serous carcinoma (<5%), endometrioid carcinoma (10%), clear cell carcinoma (10%) and mucinous carcinoma (3%) [144]. Most women with EOC are diagnosed in an advanced stage of the disease, when metastases are manifest on the peritoneum (also called peritoneal carcinomatosis often accompanied by calcifications that are called psammoma bodies) (Fig. 4) [145], in lymph nodes and/or in other organs [146–148]. The peritoneal cavity has no anatomical barriers and allows cancer cells to spread relatively easily. Metastatic spread primarily occurs by shedding of the EOC cells from the ovary into the peritoneal cavity. In the peritoneal cavity, EOC cells are transported passively by the physiological movements of peritoneal fluid and attach to the peritoneal mesenchymal cells to form small superficial tumors [149–151].

In general, EOC tumors are well vascularized. However, recently we have shown that the circulation in the vessels is poor [126]. Fig. 4E shows that the vasculature towards carcinomatosis on the peritoneum of ovarian cancer is dense, but insight the metastasis the flow in the blood vessels is poor (Fig. 4E) promoting edema formation and inflammation.

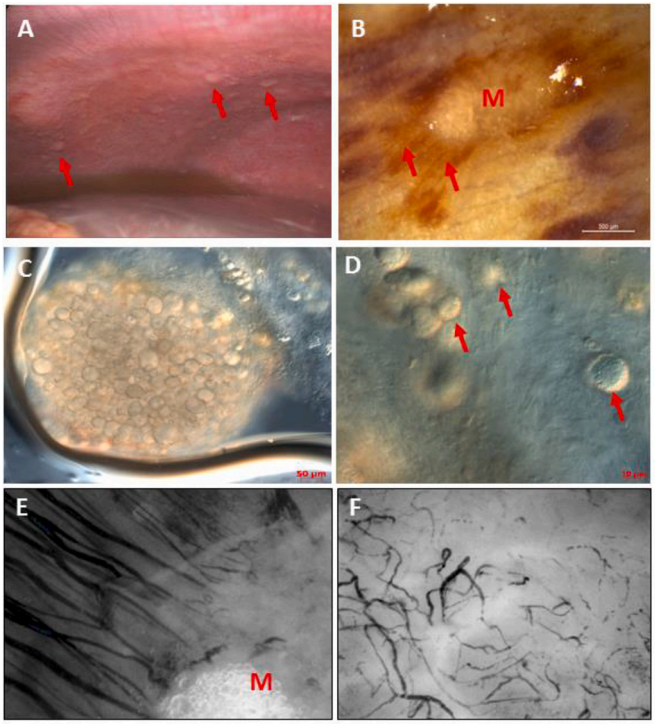

Fig. 4. Human peritoneum with peritoneal carcinomatosis (PC; metastases of epithelial ovarian cancer (EOC)). A Laparoscopy image of the peritoneum of the anterior abdominal wall in a patient with PC of EOC. Numerous metastases are present on the peritoneum (red arrows). B Microscopic image of a metastasis (M) showing capillaries running from the normal peritoneal microvasculature towards the metastasis (arrows), bar = 500 um. C Differential interference contrast (DIC) microscopical image of a metastasis, bar = 50 um. D DIC microscopical image of calcium phosphate calcifications called psammoma bodies (arrows) attached to the peritoneum besides a metastasis, which are characteristic for carcinomatosis, bar = 10 um. E Incident dark field (IDF) image of capillaries running from the normal peritoneal microvasculature towards the metastasis (M), the image represents a field of view of 1.55 × 1.16 mm. F IDF image of the microvasculature of a metastasis, the image represents a field of view of 1.55 × 1.16 mm. Images E and F are from Kastelein et al. in Clinical Experimental Metastasis [126], with permission under the Creative Commons License (http://creativecommons.org/licenses/by/4.0/). No changes were made to the original images.

Besides the intraperitoneal dissemination of EOC cells, progression of EOC and its metastases depends on the nature of the intra-tumoral stroma. The stromal tumor microenvironment consists of ECM and a variety of cell types, including ECs, cancer-associated fibroblasts (CAFs), pericytes, mesenchymal stem cells, and white blood cells, such as cancer-associated macrophages [152–155]. These cells may also be involved in the interactive signaling with EOC cells and may promote or inhibit metastasis [156–158]. CAFs often form the majority of stromal cells in several types of human cancers and contribute to vascular stabilization in EOC and other types of human cancers [158]. CAFs have a different gene expression profile than normal fibroblasts, and mediate paracrine or autocrine signaling in and between cancer cells and stromal cells [159–162]. Tumor-derived pro-angiogenic growth factors, such as PDGF, bFGF, TGF-β, and VEGF activate CAFs, demonstrating a close interaction between CAFs and angiogenesis [163,164]. On the other hand, CAFs promote angiogenesis by recruiting endothelial progenitor cells to the tumor stroma, mediated by secretion of stromal cell-derived factor-1α (SDF-1α). In addition, CAF-secreted SDF-1α stimulates tumor growth directly by signaling through the receptor CXC chemokine receptor type 4 (CXCR4), which is expressed by cancer cells [165–167]. The SDF-1α/CXCR4 axis also plays a role in the interactions between cancer cells, immune cells and mesenchymal stem cells and in the homing of cancer stem cells in their niches [154].

Cancer stem cells (CSCs) have been described in EOC [168–170]. Non-cancerous stem cells and CSCs are protected in their niches (their microenvironment) against radiotherapy and chemotherapy. This microenvironment enforces stem cells and CSCs not to proliferate and thus render them protected against therapy. CSCs are considered to be a cause of recurrence of tumors and, therefore, are in focus of cancer research in recent years [154,167–169,171,172]. Krishnapriya et al. have reported that ovarian CSCs can contribute to angiogenesis on the basis of in vitro experiments with the use of human ovarian CSCs harvested from ascites and grown in spheroids [168]. Under specific conditions, the spheroids gave rise to EC-like cells that expressed EC markers and nitric oxide synthase and formed tube-like structures in the spheroids. The anti-VEGF antibody bevacizumab inhibited differentiation into EC-like cells in the spheroids. These EC-like cells may be transdifferentiated CSCs involved in a process called vascular mimicry [173], which has been found frequently in tumors [174]. Vessel co-option also occurs when cancer cells are invasive along existing blood vessels [175,176]. An association between ovarian CSCs and angiogenesis, on the basis of similar signaling pathways, such as VEGF, Wnt, Notch, and Sonic hedgehog was also noted by Markowska et al. [177], who listed clinical trials with anti-angiogenic agents. These clinical trials are discussed below.

4.2. Angiogenesis in cervical cancer

The most common cervical cancers are squamous cell carcinoma and adenocarcinoma [4,178]. Precursor lesions include cervical intraepithelial neoplasia (CIN) in squamous epithelium and adenocarcinoma in situ (AIS) in columnar epithelium [179]. High grade CIN (or HSIL), AIS and cervical cancer are characterized by a dense capillary network [180], and neovascularization and increased capillary density have also been demonstrated directly underneath precursor and malignant lesions of the cervix [181–183]. There is an inverse correlation between the density of the capillary network and the prognosis of cervical cancer [184,185]. More specifically, the density of the capillary network correlates inversely with pelvic lymph node metastases, disease-free survival and overall survival [24,186–188]. Expression of VEGF has been found to be directly correlated with the density of the capillary network and the degree of dysplasia [185,189]. The oncoproteins E6 and E7 that are encoded by human papillomavirus genes play a distinct role in this phenomenon. E6 induces degradation of the tumor suppressor protein p53 and E7 activates HIF1α and inactivates retinoblastoma protein (pRb), which ultimately leads to upregulation of VEGF expression and consequently tumor angiogenesis [190–192]. Furthermore, ANG1 and ANG2 and their Tie receptors are upregulated in cervical cancer cells in vitro.

4.3. Angiogenesis in endometrial cancer

Endometrial cancers are broadly classified in two major types based on clinicopathological features (type 1 low grade and type 2 high grade) and can be further subdivided into POLE ultra-mutated, microsatellite instability hypermutated, copy-number low, and copy-number high [193]. High expression levels of pro-angiogenic factors including VEGF, platelet-derived EC growth factor (PD-ECGF) and FGF2, have been recognized as an essential characteristic of endometrial cancer growth, survival, and metastasis and these high levels inversely correlate with survival of patients with endometrial cancer [194–199]. The density of the capillary network increases progressively from benign to malignant tumors [22]. However, there are conflicting results with respect to the prognostic relevance of the expression of VEGF and its receptors in endometrial cancer [200–203]. In contrast, the density of the capillary network has been shown to be a prognostic factor for endometrial cancer [23,195,204]. VEGF expression is high in endometrial cancer, whereas it is hardly expressed in healthy endometrium [200]. HIF1α and HIF2α are

active as transcription factors in endometrial cancer cells and induce expression of VEGF [205,206]. Hypoxia is an important controller of the angiogenic switch that is mainly regulated by HIF1α. HIF1α and HIF2α are transcription factors with slightly different roles [154] that each activate transcription of a set of key genes that are involved in cell survival in hypoxic conditions such as those that are involved in the initiation of angiogenesis [207,208]. Hypoxia is a general phenomenon in solid tumors [209,210] due to their rapid growth, on the one hand, the high interstitial pressure [211], and the too large distances between cancer cells and capillaries on the other hand.

5. Therapeutic targeting of angiogenesis in gynecological cancers

5.1. VEGF-targeted therapy in gynecological cancers

Current treatment of gynecological cancers includes surgery, radiotherapy, and chemotherapy, and combination therapy with angiogenesis inhibitors [150,177,212–215]. Although in general the treatment of low stage gynecological cancers is often successful, with many patients achieving a long term survival, success of treatment of advanced or recurrent disease is disappointing. Compensatory mechanisms and/or escape mechanisms allow cancer cell survival leading to progression of disease and recurrence [178]. Recent developments in molecular biology of gynecological cancers have led to the development of agents that target signaling pathways of ECs of the tumor vasculature.

In contrast to chemotherapy, targeted therapy interferes with specific molecular mechanisms and should take advantage of molecular differences between cancer cells and non-cancer cells. Targeted therapy can be divided into two major categories: monoclonal antibodies and small-molecular compounds. Monoclonal antibodies do not enter cells due to their size but target ligands in the extracellular environment of tumors or receptors on the surface of cells. Small-molecular compounds can enter cells, in particular when they have lipophilic moieties, to interfere specifically with target molecules that are essential for cancer cells and preferably not for non-cancer cells [216]. Anti-angiogenic therapies are tested in gynecological cancers because of the importance of angiogenesis in gynecological cancers and the need for new treatment strategies [152,217].

VEGF has emerged as a major therapeutic target in several types of cancers [156,157,218,219] and other pathological conditions [35,220–222]. Currently, three VEGF-targeting monoclonal antibodies, bevacizumab, ramucirumab, and aflibercept, have been approved for the treatment of various types of cancer [223,224]. Bevacizumab is a recombinant antibody that impedes blood vessel formation and the growth of tumor tissue by preventing the binding of VEGF-A to its receptors by neutralizing circulating VEGF. It has been approved by the Food and Drug Administration (FDA) for the treatment of ovarian and cervical cancer [216,225–227].

For ovarian cancers, bevacizumab treatment in combination with chemotherapy (carboplatin/paclitaxel), followed by single-agent bevacizumab, was approved by the European Medicines Agency (EMA) in 2011 and by the FDA in 2018 as a first-line treatment for stage III and IV epithelial ovarian, fallopian tube, and primary peritoneal cancers after initial surgical resection. This approval was based on the GOG-0218 randomized phase III trial which demonstrated that patients treated with this combination have a longer progression-free survival than patients treated with chemotherapy alone (14.1 versus 10.3 months) [228]. However, a follow-up study showed no differences in overall survival among patients receiving bevacizumab in combination with chemotherapy as compared to patients receiving chemotherapy alone [229].

In recurrent ovarian cancer, three phase III trials were conducted to evaluate the use of bevacizumab. Both the AURELIA study [230], which included platinum-resistant recurrent patients, and the OCEANS study [231], which included platinum-sensitive recurrent patients, demonstrated a longer progression-free survival in the groups treated with bevacizumab-combined chemotherapy as compared to chemotherapy alone (6.7 versus 3.4 months and 12.4 versus 8.4 months, respectively). Again, no significant differences in overall survival were found in these studies [230,231]. However, recently, the randomized phase III GOG-0213 trial with platinum-sensitive recurrent epithelial ovarian, fallopian tube or primary peritoneal cancers demonstrated an improved overall survival in the group of patients treated with bevacizumab in combination with chemotherapy as compared to the group of patients treated with chemotherapy alone (42.2 versus 37.3 months). Progression-free survival was longer with the addition of bevacizumab to chemotherapy than chemotherapy alone (13.8 versus 10.4 months) [232]. On the basis of these studies, bevacizumab treatment has been approved in both primary and recurrent ovarian cancer, although the clinical benefit for patients is still modest and overall survival seems unaffected.

In metastatic and recurrent cervical cancer, the combination treatment of bevacizumab and chemotherapy was approved by the FDA in 2014 on the basis of the results of the Gynecologic Oncology Group (GOG)-240 phase III trial [227,233]. The GOG-240 trial demonstrated that patients treated with bevacizumab in combination with chemotherapy (topotecan/paclitaxel or cisplatin/paclitaxel) showed an improved overall survival (17 versus 13.3 months), progression-free survival (8.2 versus 5.9 months) and higher response rate (48% versus 36%) as compared to patients treated with chemotherapy alone [233].

The clinical trials of bevacizumab to treat ovarian cancer and cervical cancer argued for testing of bevacizumab therapy to treat endometrial cancer. Bevacizumab-combined chemotherapy or bevacizumab as a single agent therapy for metastatic and recurrent endometrial cancer have been tested in phase II studies, but these studies showed only modest efficacy [234–237].

The overall positive effects of anti-VEGF therapy in gynecological cancers are limited and subgroups of patients that would benefit most have not yet been defined, as biomarkers of response are lacking [226]. The strict inclusion criteria that have been applied in the GOG-240 trial [233] would exclude patients with metastatic or recurrent cervical cancer from receiving bevacizumab treatment on the basis of the occurrence of bleeding, poor renal function or poor performance status [225]. In addition, there are still pending issues with respect to side effects, such as hypertension [238,239] and therapy resistance [152,217]. Adaptive resistance and intrinsic resistance, the upregulation of alternative pro-angiogenic pathways and expression of pro-angiogenic factors are considered to be mechanisms of bevacizumab resistance [240]. However, predictive biomarkers for drug resistance have not yet been identified [241,242]. Because the target cells (ECs) were considered to be genetically stable, it was assumed that ECs would not develop bevacizumab resistance. However, the study of Krishnapriya et al. (2019) has shown that bevacizumab inhibits the differentiation of ovarian CSCs into ECs (vascular mimicry as described in chapter 4.1) [168]. As a consequence, it cannot be excluded that the therapy-resistance of the ECs of the tumor vasculature is caused by the fact that these ECs have the genetic makeup of the ovarian CSCs and are in fact genetically-instable cancer cells. Identifying alternative anti-angiogenic therapeutic strategies and/or targeting multiple angiogenic pathways may increase the therapeutic benefit for gynecological cancers and may overcome drug resistance by compensatory escape mechanisms. A summary of ongoing clinical trials investigating anti-angiogenic drugs in ovarian cancer, cervical cancer, and endometrial cancer is listed in Table 1.

5.2. Targets within the tumor microenvironment: Pericyte-endothelial interactions in tumor angiogenesis

Cancer cells may become resistant to anti-VEGF therapy because of their genetic instability as discussed above, and due to alterations in the microenvironment of cancer cells in response to anti-VEGF therapy

Table 1
Summary of ongoing trials registered as 'recruiting' in clincicaltrials.gov investigating anti-angiogenic drugs in ovarian cancer, cervical cancer and endometrial cancer in September 2020.

No	Identifier	Trial phase	Short study title	Anti-angiogenic intervention Drug(s)/ Biological(s)	Tumor type
1	NCT03737643	Phase 3	Durvalumab treatment in combination with chemotherapy and bevacizumab, followed by maintenance durvalumab, bevacizumab and olaparib treatment in advanced ovarian cancer patients	Bevacizumab	Advanced ovarian cancer
2	NCT02399592	Phase 2	Bevacizumab and tocotrienol in recurrent ovarian cancer	Bevacizumab	Ovarian cancer
3	NCT03353831	Phase 3	Atezolizumab with bevacizumab and chemotherapy vs. bevacizumab and chemotherapy in early relapse ovarian cancer	Bevacizumab	Ovarian cancer
4	NCT02759588	Phase 1b Phase 2	GL-ONC1 oncolytic immunotherapy in patients with recurrent or refractory ovarian cancer	Bevacizumab	Ovarian cancer
5	NCT03740165	Phase 3	Study of chemotherapy with pembrolizumab followed by maintenance with olaparib for the first-line treatment of women with BRCA non-mutated advanced epithelial ovarian cancer	Bevacizumab	Advanced epithelial ovarian cancer
6	NCT02884648	Phase 2	Bevacizumab in ovarian cancer patients with disease at second-look surgery	Bevacizumab	Ovarian cancer
7	NCT01932125	Phase 4	An interventional study of avastin (bevacizumab) in patients with advanced/metastatic epithelial ovarian cancer, fallopian tube cancer or peritoneal cancer	Bevacizumab	Advanced epithelial ovarian cancer, fallopian tube cancer, peritoneal carcinoma
8	NCT03363867	Phase 2	BEACON - ABC in recurrent platinum resistant HGSOC (BEACON)	Bevacizumab	Ovarian cancer, fallopian tube cancer, peritoneal carcinoma
9	NCT02584478	Phase 1 Phase 2	Phase 1/2a evaluation of adding AL3818 to standard platinum-based chemotherapy in subjects with recurrent or metastatic endometrial, ovarian, fallopian, primary peritoneal or cervical carcinoma	AL3818	Recurrent or metastatic endometrial, ovarian, fallopian, primary peritoneal or cervical carcinoma
10	NCT02873962	Phase 2	A phase II study of nivolumab/ bevacizumab/ rucaparib	Bevacizumab	Peritoneal cancer, ovarian cancer, fallopian tube cancer
11	NCT03587311	Phase 2	Bevacizumab and anetumab ravtansine or paclitaxel in treating participants with refractory ovarian, fallopian tube, or primary peritoneal cancer	Bevacizumab	Fallopian tube cancer, ovarian cancer, primary peritoneal carcinoma
12	NCT02839707	Phase 2 Phase 3	Pegylated liposomal doxorubicin hydrochloride with atezolizumab and/or bevacizumab in treating patients with recurrent ovarian, fallopian tube, or primary peritoneal cancer	Bevacizumab	Fallopian tube cancer, recurrent ovarian cancer, primary peritoneal cancer
13	NCT02312245	Phase 2	Avatar-directed chemotherapy in treating patients with ovarian, primary peritoneal, or fallopian tube cancer	Bevacizumab	Recurrent fallopian tube carcinoma, recurrent ovarian carcinoma, recurrent primary peritoneal carcinoma
14	NCT03239145	Phase 1	Pembrolizumab (Anti-PD-1) and AMG386 (Angiopoietin-2 (Ang-2) in patients with advanced solid tumor	Trebananib (AMG386)	Advanced solid tumors Gynecological: ovarian cancer
15	NCT04121975	Phase 2	CCRT combined with endostar for the treatment of locally advanced cervical cancer	Endostar	Cervical cancer
16	NCT03622827	Phase 2	Postoperative concurrent chemoradiotherapy combined with endostar for high-risk early stage cervical cancer	Endostar	Cervical cancer
17	NCT03786081	Phase 1 Phase 2	Safety and efficacy of tisotumab vedotin monotherapy & in combination with other cancer agents in subjects with cervical cancer	Bevacizumab	Cervical cancer
18	NCT03367871	Phase 2	Combination pembrolizumab, chemotherapy and bevacizumab in patients with cervical cancer	Bevacizumab	Cervical cancer
19	NCT03912415	Phase 3	Efficacy and safety of BCD-100 (Anti-PD-1) in combination with platinum-based chemotherapy with and without bevacizumab as first-line treatment of subjects with advanced cervical cancer (FERMATA)	Bevacizumab	Cervical cancer
20	NCT03912402	Phase 2	Efficacy and safety of BCD-100 (Anti-PD-1) in combination with platinum-based chemotherapy and bevacizumab in patients with recurrent, persistent or metastatic cervical cancer (CAESURA)	Bevacizumab	Cervical cancer
21	NCT04138992	Phase 2 Phase 3	A study on the efficacy and safety of bevacizumab in untreated patients with locally advanced cervical cancer	Bevacizumab	Cervical cancer
22	NCT03556839	Phase 3	Platinum chemotherapy plus paclitaxel with bevacizumab and atezolizumab in metastatic carcinoma of the cervix	Bevacizumab	Cervical cancer
23	NCT03526432	Phase 2	Phase II study of atezolizumab + bevacizumab in endometrial cancer	Bevacizumab	Endometrial cancer
24	NCT03694262	Phase 2	The EndoBARR trial (Endometrial bevacizumab, atezolizumab, rucaparib)	Bevacizumab	Endometrial cancer
25	NCT01552434	Phase 1	Bevacizumab and temsirolimus alone or in combination with valproic acid or cetuximab in treating patients with advanced or metastatic malignancy or other benign disease	Bevacizumab, Temsirolimus	Malignant female reproductive system neoplasm

[240]. Cancer cells do not act alone in tumor progression and metastatic spread as these processes require remodeling of their microenvironment by communication between cellular and non-cellular components [156]. Unlike the heterogeneity of cancer cells, common features are found in the pro-angiogenic tumor microenvironment that supports vessel formation and maturation [240]. Cancer progression creates hypoxia, acidity, and oxidative stress within the tumor microenvironment, which increases stiffness of the ECM and induces angiogenesis, and a metabolic switch towards aerobic glycolysis [156]. As tumor growth and resistance to anti-angiogenic therapy is associated with the (adapting) tumor microenvironment, targeting of the tumor microenvironment offers new therapeutic opportunities to treat gynecological cancers.

During angiogenesis, pericytes in their intramural form are considered to play an important role in the final stabilization and maturation of the newly-formed vessels [14]. Vascular maturation and pericyte coverage of the tumor vasculature also induce resistance to anti-

angiogenic therapy [240]. However, in most tumors, blood vessels are covered by high numbers of pericytes [127], which may be 'extramural'. In the literature, there are conflicting reports on the presence and role of pericytes in tumor vasculature, which is probably due to the use of different pericyte markers, some of which, like smooth muscle actin, stain only highly differentiated pericytes [243]. Anti-VEGF therapy inhibits development of new vessels, but vessels that are already covered by mural pericytes are mature, functional and not responsive to VEGF anymore. In addition, blocking of VEGF signaling in human tumors increases the number of vessels covered with mural pericytes [244–246]. Therefore, dual targeting of tumor-associated ECs and pericytes may be an attractive approach for the treatment of gynecological cancers.

Recruitment of pericytes to the endothelium and their crosstalk with ECs is mediated by multiple ligand-receptor complexes, including PDGF-B/PDGF receptor-β (PDGFR-β), ANG1/Tie2, TGF-β/TGF-β receptor (TGF-βR), and heparin-binding EGF (HB-EGF)/EGF receptor (EGFR). During angiogenesis, PDGF-B is released by endothelial tip cells and binds to its receptor PDGFR-β expressed on pericytes. PDGF-B/PDGFR-β interaction is essential for vascular maturation, and blocking of either PDGF-B or PDGFR-β induces pericyte deficiency and vascular dysfunction [51]. Whereas PDGF-B/PDGFR-β signaling is EC-to-pericyte signaling, pericytes-to-EC signaling occurs through the ANG1/Tie2 system [51,247]. ANG1 and ANG2 are both ligands for the endothelial Tie2 receptor, but have opposite effects on Tie2 activation and signaling. ANG1 is mainly expressed by pericytes and is considered to be an agonistic ligand for Tie2, whereas ANG2 is predominantly expressed and stored by ECs [55–58] and is an antagonistic ligand for Tie2 [91,248,249]. ANG1/Tie2 binding promotes pericyte adhesion and vessel stabilization and is widely expressed in adult tissues, whereas ANG2/Tie2 binding disrupts blood vessel formation and is only expressed at sites of vascular remodeling [57,91].

TGF-β signaling induces the differentiation of myeloid progenitor cells into pericytes, but is also involved in endothelial stalk cell proliferation and differentiation [250,251]. TGF-β signaling is complex [252] which is shown by the fact that both ECs and pericytes produce TGF-β and TGF-βR and the effects of TGF-β signaling is a result of the interactions between the two cell types [253]. In addition, crosstalk between TGF-β and Notch regulates the expression of N-cadherin, a transmembrane protein that mediates cell-cell adhesion in junctional adhesion plaques of ECs and pericytes [254,255].

HB-EGF belongs to the EGF family of growth factors and is expressed in various types of cells, including ECs and pericytes [256,257]. Phosphorylation of EGFR on pericytes by EC-derived HB-EGF stimulates pericyte proliferation, motility and recruitment to ECs [257,258]. The observed increased activation of EGFR on pericytes in mouse xenografts that acquired resistance to bevacizumab treatment, suggests that HB-EGF/EGFR signaling plays a role in resistance to anti-VEGF inhibitors [259].

Clinical trials of combined therapies against pericytes and ECs are described in the following sections.

5.3. Clinical anti-angiogenesis trials in ovarian cancer

5.3.1. Targeting the VEGF/VEGFR, PDGF/PDGFR, and EGF/EGFR axes

Several pericyte-endothelial combined targeted therapies in gynecological cancers have been evaluated in clinical phase II/III trials. Pazopanib, a non-specific tyrosine kinase inhibitor with activity against VEGFR1, VEGFR2, VEGFR3, PDGFR-α, PDGFR-β, and c-Kit [260], showed prolonged progression-free survival in women with stages II-IV ovarian, fallopian tube, or peritoneal cancer, as compared to patients treated with placebo (17.9 versus 12.3 months) in the AGO-OVAR 16 phase III trial [261]. Pazopanib in combination with paclitaxel treatment showed prolonged progression-free survival in platinum-resistant ovarian cancer patients as compared to the placebo group (6.4 versus 3.5 months) in the MITO-11 phase II trial [262]. Overall survival data of the AGO-OVAR 16 and MITO-11 trials were not different with or without pazopanib treatment. Moreover, secondary endpoint measurements in the AGO-OVAR 16 trial did not show differences in health-related quality of life of patients treated with pazopanib as compared to the placebo group [263]. Clinical trials with erlotinib, a tyrosine kinase inhibitor of EGFR, as monotherapy or in combination with bevacizumab did not show effects in patients with ovarian cancer [264,265].

5.3.2. Targeting the ANG/TIE axis

The TRINOVA-1 double-blind phase III clinical trial investigated the combination of paclitaxel with placebo or with trebananib, an ANG1- and ANG2-neutralizing peptibody that prevents their binding to the Tie2 receptor. A peptibody is the fusion protein of a peptide and an antibody to prolong its biological activity [266]. Treatment of patients with recurrent ovarian cancer with the combination of paclitaxel and trebananib showed minimal prolonged progression-free survival as compared to patients treated with paclitaxel and placebo (7.2 versus 5.4 months), whereas overall survival did not differ (19 versus 17.3 months). In the combined paclitaxel/trebananib patient group, treatment was discontinued more often and there was a higher incidence of edema (17% versus 6% and 64% versus 28%, respectively) [267]. On the other hand, treatment with paclitaxel/trebananib did not compromise quality of life of the patients [268].

5.3.3. Targeting the TGF-β/TGF-βR axis

Tasisulam, a TGF-β/TGF-β type I receptor kinase (ALK5) inhibitor, has been tested in two phase I clinical trials in patients with refractory or malignant solid tumors, including ovarian cancer, to determine the recommended dose for phase II trials [269,270]. Following these trials, the multi-arm phase Ib study determined the maximum tolerated dose for safety of tasisulam combined with standard chemotherapy in patients with advanced solid tumors. This study included ovarian, cervical, uterine and endometrial cancer, which comprised only 6% of the total number of patients [271]. The phase II single-arm study of tasisulam in patients with platinum-resistant ovarian cancer demonstrated a progression-free survival of 1.9 months and an overall survival of 12.9 months [272].

Trabedersen, a specific phosphorothioate antisense oligodeoxynucleotide that binds to TGF-β2 mRNA and thereby inhibits TGF-β2 protein synthesis, has been studied in phase I/II clinical trials in various types of cancers, including brain, prostate, pancreatic, and colorectal cancers [273]. To date, trabedersen and several tyrosine kinase inhibitors against the TGF-β pathway have been studied only in preclinical ovarian cancer models [132,274].

5.4. Clinical anti-angiogenesis trials in cervical cancer

5.4.1. Targeting the VEGF/VEGFR, PDGF/PDGFR, and EGF/EGFR axes

Pazopanib, lapatinib (a tyrosine kinase inhibitor with activity against EGFR and HER2/neu) or the combination of pazopanib and lapatinib treatment, were studied in the VEG105281 phase II open-label study in women with primary stage IVB or recurrent cervical cancer. Patients treated with pazopanib showed prolonged progression-free survival and significantly improved overall survival as compared to patients treated with lapatinib (18.1 versus 17.1 weeks and 50.7 versus 39.1 weeks, respectively). Combined therapy of pazopanib and lapatinib was excluded from the analysis because of the ineffectiveness and higher toxicity compared to monotherapy [275].

5.4.2. Targeting the ANG/TIE axis

To the best of our knowledge, clinical trials with inhibitors against the ANG/TIE axis have not been performed yet in patients with cervical cancer.

5.4.3. Targeting the TGF-β/TGF-βR axis

Tasisulam treatment in cervical cancer was tested in one phase I

clinical trial, which included only 1 patient with cervical cancer [269], and one phase Ib clinical trial, which included 13 patients with ovarian, uterine, endometrial, or cervical cancer. The exact number of patients with cervical cancer was not indicated in this study [271]. As far as we know, other clinical trials of inhibitors against the TGF-β/TGF-βR axis have not been performed in cervical cancer patients.

5.5. Clinical anti-angiogenesis trials in endometrial cancer

5.5.1. Targeting the VEGF/VEGFR, PDGF/PDGFR, and EGF/EGFR axis

Elevated VEGF expression is an independent prognostic factor for poor prognosis in endometrial cancer [276,277]. However, carboplatin-paclitaxel-bevacizumab treatment of advanced and recurrent endometrial cancer in a randomized phase II trial (the MITO END-2 trial) did not affect progression-free survival significantly in comparison to carboplatin-paclitaxel [277,278]. Only one study of pazopanib monotherapy to treat endometrial cancer has been reported so far. This PAZEC phase II non-randomized open-label study in chemotherapy-resistant patients or patients with a contraindication for chemotherapy, included a case report of a 57-year-old patient with FGF receptor 2 (FGFR2)-positive recurrent metastatic endometrial cancer demonstrating a positive response to pazopanib monotherapy [279]. The patient, who suffered from abdominal wall metastasis, was free from metastases of the abdominal wall and intestines after pazopanib treatment and was still in complete remission 30 months after pazopanib discontinuation [279]. Data of the PAZEC study has not been published yet.

5.5.2. Targeting the ANG/TIE axis

Trebananib treatment has been evaluated in a single-arm clinical trial including 32 persistent/recurrent endometrial cancer patients. The progression-free survival and overall survival were 2.0 and 6.6 months, respectively. One patient showed a partial response, 8 patients had stable disease and 5 patients had 6 months event-free survival. Unfortunately, trebananib monotherapy was not efficacious enough to warrant further studies [280].

5.5.3. Targeting the TGF-β/ TGF-βR axis

Tasisulam treatment of endometrial cancer was tested in only a small number of patients with cervical cancer. Tasisulam treatment in endometrial cancer was tested in two phase I clinical trials, which included 1 patient with endometrial cancer [269,270], and one phase Ib clinical trial, which included 13 patients with ovarian, uterine, endometrial, and cervical cancer. The exact number of patients with endometrial cancer was not indicated [271]. As far as we know, other trials with inhibitors against the TGF-β/TGF-βR axis have not been performed in patients with endometrial cancer.

6. Targeting the established tumor vasculature with vascular disrupting agents

Vascular disrupting agents (VDAs) are a new class of anti-blood vessel drugs that are aimed to target ECs of established tumor vasculature. Structural and functional differences between tumor vessels and non-tumor vessels allow selective vascular targeting. In contrast to non-tumor vessels, the tumor vasculature is often fragile, leaky, and has an abnormal blood flow [126,281]. Two types of VDAs have been tested [282]. The first types are VDAs such as combretastatin A4-phosphatase (CA4P) that disrupt the microtubular cytoskeleton and endothelial cell-cell junctions in tumors by targeting the colchicine-binding domain of β-tubulin, which leads to rounding up of ECs and a collapse of the immature tumor vasculature. This deprives the tumor of oxygen and nutrients and ultimately leads to ischemia and necrosis of the tumor mass [283]. Given the fact that the cytoskeleton is vital for EC functions such as proliferation, migration, and barrier function, treatment with VDAs may be successful in the treatment of (advanced) cancers [284–286]. The second type of VDAs are flavonoids [282] that target ECs in tumors via DNA-damaging effects and induce EC apoptosis. The exact mechanism of action that leads to EC apoptosis is not known [287].

The efficacy of VDA treatment has limitations because mature blood vessels in the periphery of tumors are not affected by VDAs. In contrast to immature vessels in the center of the tumor mass, ECs of mature vessels in the tumor periphery have a tight pericyte coverage, ensuring vessel stabilization [39,127,288,289]. ECs in the periphery are less dependent on the tubulin cytoskeleton for their structure and function, but are rather dependent on actin filaments to support their cytoskeleton [283,290]. Consequently, cancer cells in the periphery of tumors are still provided with oxygen and nutrients and remain viable after VDA treatment. Several attempts have been made to overcome tumor resistance against EC-targeting VDAs. Chen et al. described the pericyte-targeting VDA called *Z*-GP-DAVLBH, which is activated by fibroblast activation protein α (FAPα). FAPα is specifically expressed on the plasma membrane of CAFs and pericytes of epithelial cancers and has low or undetectable expression in normal adult tissues [291,292]. Z-GP-DAVLBH has been proposed as a VDA that selectively destroys the cytoskeleton of FAPα-expressing tumor pericytes, disrupting the blood vessels in both center and periphery of tumors. This was confirmed in multiple lines of xenografts [293]. In addition, it was shown by Foley et al. that the VDA called (*S*)-2-amino-N-(2-methoxy-5-(5-(3,4,5-trimethoxyphenyl)isoxazol-4-yl)phenyl)-3-phenylpropanamide hydrochloride (STA-9584), targets vessels in both center and periphery in tumor xenografts in vivo, but this study did not have a follow-up yet [294].

Combination treatment of VDAs with anti-angiogenesis compounds, pericyte- and EC-targeting VDAs, or of VDAs and conventional chemotherapeutic agents may be an efficient treatment option [295]. Combination treatment of VDA and the mammalian target of rapamycin (mTOR) inhibitor temsirolimus may be an option to delay tumor recurrence after VDA treatment due to upregulation of HIF1α expression as the mTOR inhibitor prevents this [296].

Here, we describe the human clinical trials of VDAs in ovarian cancer and cervical cancer. To date, there are no trials of either type of VDA in endometrial cancer, nor were patients with endometrial cancer part of basket trials for solid tumors.

6.1. Clinical trials of VDAs in ovarian cancer

6.1.1. Combination of VDAs and chemotherapy

The safety of combining CA4P with standard doses of carboplatin and paclitaxel was tested in a three-arm phase Ib dose escalation and pharmacokinetic study. CA4P is the only VDA that has been developed to treat ovarian cancer so far [297]. The combination with carboplatin and/or paclitaxel appeared to be safe. Pharmacological interactions between these drugs were were not found, and 7 out of 18 patients with ovarian, fallopian tube, and peritoneal cancer showed a response according to the Response Evaluation Criteria In Solid Tumors (RECIST) and/or CA-125 criteria [298]. This study was followed by a single-arm phase II trial in which 18 patients with relapsed or platinum-resistant ovarian cancer received CA4P at 18–20 h prior to carboplatin and paclitaxel treatment. The addition of CA4P to carboplatin and paclitaxel treatment resulted in a response rate of 29% of this heterogeneous group of patients according to RECIST and/or CA-125 criteria [299].

6.1.2. Combination of VDAs with anti-angiogenic compounds

The dose escalation and pharmacokinetic study of CA4P in combination with bevacizumab was tested in a single-arm phase I trial in 15 patients with advanced cancer, including 4 patients with ovarian cancer. The combination of CA4P with bevacizumab was safe and well tolerated. Two patients with ovarian cancer exhibited stable disease and 2 patients had progressive disease according to RECIST. Among the patients with ovarian cancer, one patient showed a response by CA-125 criteria that lasted for over a year. The anti-vascular activity of CA4P in the presence

or absence of bevacizumab was analyzed with the use of dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI). DCE-MRI showed that CA4P alone increased vessel density in the tumors whereas anti-vascular effects were found after treatment with CA4P in combination with bevacizumab [300]. The GOG-186-I open-label randomized phase II trial investigated treatment with the single agent bevacizumab as compared to bevacizumab in combination with CA4P in women with persistent or recurrent ovarian, fallopian tube, or peritoneal cancer [301]. Patients treated with the combination of CA4P and bevacizumab showed prolonged progression-free survival as compared to patients treated with bevacizumab monotherapy (7.3 versus 4.8 months). The overall response rate was similar in patients treated with bevacizumab alone and with CA4P and bevacizumab. However, patients treated with the combination of CA4P and bevacizumab developed hypertension more often than patients treated with bevacizumab alone (35% versus 20%). [301]. Hypertension and adverse cardiovascular events are side effects both of CA4P and other anti-angiogenic therapy [302]. No treatment-related deaths were observed in this study.

6.2. Clinical trials of VDAs in cervical cancer

The flavonoid 5,6-dimethylxanthenone-4-acetic acid (DMXAA) is the only VDA that has been tested in patients with cervical cancer [303]. The dose escalation, pharmacokinetics, and anti-vascular effects of DMXAA were investigated in a single-arm phase I trial in 63 patients with solid cancers, including 3 patients with cervical cancer. Tumor responses were analyzed by plain radiographs every 3 weeks and by computer tomography or ultrasound scans every 6 weeks. In general, DMXAA treatment showed anti-tumor activity at well-tolerated doses. One patient with metastatic cervical cancer showed a partial response after 8 courses (1100 mg/m^2) [303]. Other clinical trials with (flavonoid) VDAs have not been reported thus far in patients with cervical cancer, which does not exclude the existence of unpublished negative studies as was indicated recently by Daei Farshchi Adli et al. [304].

Novel microtubule inhibitors are being developed, such as WX-132-18B [305], NOV202 [306], plocabulin [307], vinyl sulfone [308], derivatives of quinaldine and carbazole [309], and ethoxy-erianin phosphate [310], but they have not been tested in clinical trials yet.

7. Targeting the metabolism of the tumor vasculature

7.1. Metabolic adaptation of ECs

Formation of new blood vessels by differentiated endothelial tip cells, stalk cells, and phalanx cells during angiogenesis (Fig. 1) is an energy-demanding process. In addition to genetic signals, a metabolic switch has been associated with EC differentiation [311]. In vitro and in animal models, it has been shown that ECs in general have a relatively high glycolytic activity, which is further increased during angiogenesis [311,312], leading to metabolic characteristics similar to proliferative cancer cells [156,209,313–315]. ECs take up glucose via glucose transporters (GLUT), mainly by GLUT-1, and it has been shown that VEGF increases *GLUT-1* expression via the activation of the PI3K-AKT signaling pathway [316]. In line with these observations, metabolic inhibitors are becoming attractive sensitizers to standard anti-cancer therapy [317–320]. Because angiogenesis depends on metabolism in EC, metabolic inhibitors can be regarded as anti-angiogenic agents as well.

The main limitation of previous studies on EC metabolism is that the models employed in these studies did not allow for appropriate discrimination between tip cells and other angiogenic phenotypes [311,312,321]. The relative contribution and regulatory functions of metabolic pathways in tip cells and non-tip cells, respectively, were not determined in these studies. Therefore, we studied metabolism in isolated fractions of tip cells and non-tip cells in more detail with the use of an in vitro approach to identify and isolate CD34$^+$ tip cells and CD34$^-$ non-tip cells in EC cultures using flow cytometry [85,322]. These studies have shown that both endothelial tip cells and non-tip cells use glycolysis as well as mitochondrial respiration for their energy demand, but that tip cells are less glycolytic as compared to non-tip cells [85]. Although glycolysis is significantly lower in tip cells, glycolysis is essential to maintain the tip cell phenotype and for the differentiation of tip cells from non-tip cells [322]. It has been postulated that ECs increase their glycolytic flux when switching from quiescence to proliferation [321], but we found that glycolysis as well as mitochondrial respiration are necessary for the proliferation of non-tip cells [85].

Although ECs are considered to be glycolytic, studies have suggested that mitochondrial respiration is essential for homeostasis and angiogenic capacity of the endothelium [323–325], indicating metabolic flexibility in the pathways to generate adenosine triphosphate (ATP) [209,314,315,326]. ECs are able to switch to mitochondrial respiration for their energy demand when anaerobic glycolysis is impaired, a condition referred to as the Crabtree effect [327]. For example, it has been shown that inhibition of glycolysis in ECs induces a switch to mitochondrial respiration, inhibits cell proliferation, and enhances the oxidation of mitochondrial fuels (pyruvate, fatty acids, amino acids) [85,322,327,328]. Differentiated ECs and in particular tip cells are known to exhibit metabolic flexibility that is characterized by the ability to reversibly shift between substrates and/or metabolic pathways to respond or adapt to conditional changes that may occur during sprouting angiogenesis [85,322,329,330].

Hypoxia triggers angiogenesis, but it is also known as a biologically unbalanced status, referred to as cycling hypoxia [331,332]. During angiogenesis, migrating tip cells and proliferating stalk cells are both exposed to various microenvironmental conditions, such as areas with hypoxia or normoxia and areas with or without growth factors. In addition, ECs are well-equipped to metabolize mitochondrial-oxidizable substrates such as fatty acids and glutamine [333,334]. Adaptations to such varying conditions in the microenvironment of the growing vessel requires the differentiated ECs to have a flexible metabolism that can meet such fluctuations, and in vitro studies have shown that this is the case [85,322]. The dynamic nature and the complexity of the metabolic networks in differentiated EC types (tip cells, stalk cells, and phalanx cells) during sprouting angiogenesis challenge/hamper the development of new effective anti-angiogenic therapy-based on targets of the metabolic pathways, either or not in combination with standard therapies.

7.2. Clinical trials of metabolic targeting in ovarian cancer

Lonidamine is applied as an inhibitor of glycolysis in cancer cells, likely by inhibition of hexokinase [335]. Hexokinase is a rate-limiting glycolytic enzyme that converts glucose into glucose-6-phosphate and is found in several cellular compartments, including the outer mitochondrial membrane and in mitochondria. Interestingly, lonidamine elevates aerobic glycolysis in healthy cells, whereas in cancer cells lonidamide inhibits glycolysis [335]. Although the exact mechanism of metabolic lonidamine effects remains unclear, lonidamine has been shown to be tolerated well in a single-arm phase II study when combined with paclitaxel and cisplatin in patients with advanced ovarian cancer [336]. In the group of women with measurable disease (patients with a tumor size between 2 and 5 cm or >5 cm) a complete or partial response was found in 80% of patients, and in the group of women with evaluable disease (patients with a tumor size of <2 cm, no evidence of disease, or microscopic disease only) 16% of the patients showed clinical progression according to WHO criteria [337].

Metformin is widely prescribed for type 2 diabetes and is considered to be an anti-hyperglycemic drug as it lowers blood glucose levels. The use of metformin is associated with a reduced risk of cancer in patients with type 2 diabetes [338,339]. Although the exact mechanism of action on cancer cells is unclear, the use of metformin in cancer treatment has gained a huge interest. Metformin inhibits complex I of the mitochondrial respiratory chain and thereby suppresses mitochondrial coupled

ATP production [320,339]. In addition, metformin has been reported to inhibit the glycolytic enzyme hexokinase by mimicking glucose-6-phosphate as a competitive inhibitor [340]. The dose escalation and pharmacokinetic study of the anti-cancer effects of metformin in combination with temsirolimus was tested in a phase I trial including 21 patients with advanced or refractory cancers, including 2 patients with ovarian cancer and 4 patients with endometrial cancer [341]. Temsirolimus is an inhibitor of mTOR, which is an enzyme that is regulated by upstream receptor tyrosine kinases such as the IGF-1 receptor (IGF-1R) and is involved in the regulation of cell growth, proliferation, and apoptosis [342]. The combination of metformin and temsirolimus appeared to be well tolerated. Tumor progression and response rate were evaluated according to RECIST and it appeared that 44% of the patients showed tumor progression and 56% of the patients showed stable disease as their best response. The clinical benefit, described as no evidence of progression during 6 or more treatment cycles, appeared to occur in 22% of patients with advanced or refractory cancers [341].

Sodium phenylbutyrate is a fatty acid compound that has been applied in the clinic for the treatment of children with genetic defects in the urea cycle [343]. The genetic defects in the urea cycle caused impaired conversion of the highly toxic ammonia, a waste product of amino acid catabolism, into urea. The resulting hyperammonemia results in cognitive decline. Phenylbutyrate is oxidized to phenylacetate, which conjugates with glutamine and lowers ammonia levels by preventing glutamine-stimulated ammoniagenesis [344]. The dose escalation and pharmacokinetic study of phenylbutyrate was tested in a phase I trial in 21 patients with advanced solid tumors, including 1 patient with ovarian cancer. Phenylbutyrate monotherapy was well tolerated. However, the clinical response rates were moderate because 4 patients developed rapid progression of their disease and were withdrawn from therapy and only 3 patients (2 patients with anaplastic astrocytoma and 1 patient with glioblastoma) showed stable disease which lasted for 5, 7, and 4 months, respectively, according to the standard National Cancer Institute tumor response criteria [345].

7.3. Clinical trials of metabolic targeting in cervical cancer

The association between the use of metformin and survival of women with cervical cancer has been tested in a retrospective study [346]. This study included 70 patients that had been treated with metformin and 715 non-users of metformin. The percentages of patients with a 5-year progression-free survival and overall survival were similar between patients treated with metformin and patients not treated with metformin (57.3% versus 61.8% and 71.7% versus 70.7%, respectively). Patients treated with radiotherapy as primary therapy either or not in combination with metformin therapy also did not show significant differences in 5-year progression-free survival and overall survival. The use of metformin monotherapy does not appear to be associated with an improved clinical outcome in cervical cancer patients [346].

The dose-escalating and pharmacokinetic study of the glucose analog 2-deoxyglucose (2-DG), an inhibitor of the glycolytic pathway by its interaction with the first glycolytic enzyme hexokinase, was tested in a phase I trial in 12 patients with advanced cancer, including 1 patient with cervical cancer. The uptake of 2-DG was assessed with fluorodeoxyglucose-positron emission tomography (FDG-PET) scanning. Monotherapy with 2-DG appeared to be well tolerated by patients with advanced cancer [347]. However, a clinical outcome of treatment of patients with gynecological cancer is not available yet.

7.4. Clinical trials of metabolic targeting in endometrial cancer

A translational pre-operative prospective trial of metformin treatment showed reduced cancer cell proliferation in patients with endometrial cancer. Immunohistochemical analysis of endometrial cancer tissues showed reduced expression of the proliferation markers Ki-67 and topoisomerase IIα after metformin treatment (in 90% and 80% of patients, respectively) [348]. Several other studies confirmed these findings [349,350]. Following these findings, a phase II trial of metformin was tested in combination with medroxyprogesterone acetate (a synthetic variant of the hormone progesterone) as treatment for fertility preservation and prevention of recurrence of endometrial carcinoma. This study included 17 patients with endometrial hyperplasia and 19 patients with endometrial cancer. Treatment with metformin in combination with medroxyprogesterone acetate appeared to be safe and well tolerated. Within 36 weeks of treatment, 81% of patients showed a complete response (16 patients with endometrial hyperplasia and 13 patients with endometrial cancer) and of these patients 10.3% relapsed in a follow-up study. Partial responses were found in 14% of patients within 36 weeks of treatment. After initial treatment, 2 patients with endometrial cancer showed progression at 12 weeks. In both patients the cancer dedifferentiated from grade 1 endometrioid adenocarcinoma into undifferentiated adenocarcinoma. Despite the promising results, a limitation of this study is that more than 80% of the patients were obese and showed insulin resistance, therefore the effect of metformin in non-obese patients or insulin-sensitive patients remains to be elucidated in future studies [348].

7.5. Therapeutic targeting of tumor metabolism in combination with anti-angiogenesis therapy in gynecological cancers

Cancer cells also have flexible adaptive responses to hypoxia and limited availability of nutrients like ECs during angiogenesis. Metabolic adaptation of cancer cells is required for both malignant transformation and subsequent tumor development. Although aerobic glycolysis has been widely accepted as a common feature of metabolic adaptation of cancer cells, the so-called Warburg effect, recent studies have shown that mitochondrial respiration is also involved in the metabolic adaptation of cancer cells [314,351]. As the tumor microenvironment contributes to adaptation of cancer cell metabolism and tumor vessel abnormalities impair the delivery and efficiency of current chemotherapeutic agents, targeting of the dysregulated metabolism in combination with anti-angiogenesis therapy may be effective to suppress tumor growth and metastasis [352,353].

8. Conclusions

Recurrent and advanced epithelial ovarian cancer, cervical cancer, and endometrial cancer have a poor prognosis, and current systemic therapies have limited effectivity. Alternatively, anti-angiogenic agents have been FDA approved, of which bevacizumab is the most widely used drug in gynecological cancers [354]. However, survival benefit for patients with ovarian cancer, cervical cancer, and endometrial cancer is disappointing. Other strategies, such as dissociating pericytes from the tumor vasculature and targeting both ECs and pericytes to overcome anti-VEGF therapy resistance, show more promising results in patients with gynecological cancers. However, these strategies have unwanted side effects because limited pericyte coverage of capillaries disrupt systemic endothelial integrity, causing vessel leakage, edema, and cancer cells to enter the vascular system to metastasize more easily [240]. Unfortunately, predictive biomarkers identifying the categories of patients who will benefit from targeted therapy against both ECs and pericytes are still missing. Newer anti-angiogenic strategies include tyrosine kinase inhibitors (drugs that target mediators of the signaling cascade of biological processes like cell growth, differentiation, and metabolism) and VDAs (drugs that target ECs of established tumor vasculature). Several tyrosine kinase inhibitors, administered as single agents or in combination with chemotherapy, showed only modest efficacy in ovarian cancer, cervical cancer, and endometrial cancer as well [355,356]. VDAs targeting established vasculature have been tested in clinical trials for ovarian cancers only, in combination with chemotherapy or with other anti-angiogenic compounds. Again, patient survival was only modestly prolonged. Therefore, new avenues have to be

found to render anti-angiogenesis agents including VDA successful. Combination therapies with metabolism-targeting therapeutics, ECM-targeting agents, and anti-inflammatory agents are attractive options that warrant further investigation.

Author's roles

BYA, AWK, and CJFvN: conceptualization and writing. CJFvN: CJFvNC supervision, review, and editing. MT: contributed to Fig. 4, Visualization. ROS: participation in study design and critical discussion. CHJRJ, YPL, AB, KK, AJW, FA, CARL, IK, ROS: review and editing. All authors contributed to the critical revision of the content and approved the final version of the paper.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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