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Anti-vascular therapies in ovarian cancer: moving beyond anti-VEGF approaches

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Abstract

Resistance to chemotherapy is among the most important issues in the management of ovarian cancer. Unlike cancer cells, which are heterogeneous as a result of remarkable genetic instability, stromal cells are considered relatively homogeneous. Thus, targeting the tumor microenvironment is an attractive approach for cancer therapy. Arguably, anti-vascular endothelial growth factor (anti-VEGF) therapies hold great promise, but their efficacy has been modest, likely owing to redundant and complementary angiogenic pathways. Components of platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), epidermal growth factor (EGF), and other pathways may compensate for VEGF blockade and allow angiogenesis to occur despite anti-VEGF treatment. In addition, hypoxia induced by antiangiogenesis therapy modifies signaling pathways in tumor and stromal cells, which induces resistance to therapy. Because of tumor cell heterogeneity and angiogenic pathway redundancy, combining cytotoxic and targeted therapies or combining therapies targeting different pathways can potentially overcome resistance. Although targeted therapy is showing promise, much more work is needed to maximize its impact, including the discovery of new targets and identification of individuals most likely to benefit from such therapies.

Keywords

Ovarian cancer; targeted therapy; angiogenesis; anti-vascular agent; resistance to anti-VEGF therapy

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1. Introduction

The evolution of surgical techniques and chemotherapy regimens over the past three decades has resulted in improvements in the survival of women with ovarian cancer [1, 2]. Debulking surgery remains a cornerstone of ovarian cancer treatment, and the platinum–paclitaxel combination regimen is established as a first-line treatment for advanced ovarian cancer that yields response rates of over 80% and complete response rates of 40–60% [1, 3–6]. However, most of the patients who respond to treatment eventually experience a relapse, with a median progression-free survival (PFS) of 18 months [7]. At relapse, patients with platinum-sensitive disease might be treated with the same drugs when the treatment-free interval is greater than 6 months. Patients who develop platinum-resistant or refractory disease are treated with a range of other drugs [8]. However, improving cure rates remains a critical unmet need.

Improvements in the understanding of cancer biology and the underlying mechanisms governing the cancer process have facilitated the development of targeted therapies, including smallmolecule inhibitors and monoclonal antibodies (MoAbs). These agents target tumor cells, surrounding stroma, tumor vasculature, and aberrant cellular signaling mechanisms. However, because of the lack of predictive markers, identifying individual patients who are most likely to benefit from specific targeted drugs has had limited success. Moreover, cancer cells can adapt to various therapies due to their remarkable genetic instability. This trait is especially important for ovarian cancer therapy. In contrast, stromal cells are non-malignant and thought to be genetically stable. Some studies, however, do suggest possible adaptive mechanisms in stromal populations as well [9–11].

Efforts to target tumor angiogenesis have focused on the VEGF pathway. Angiogenesis is one of the hallmarks of cancer. This feature contributes not only to tumor growth but also to tumor cell invasion [12]. Indirectly killing tumors by compromising their vasculature is an attractive anticancer treatment approach because resistance is theoretically less likely to appear in endothelial cells (ECs). Bevacizumab, a MoAb targeting vascular endothelial growth factor-A (VEGF-A), is a good example of a tumor vasculature-targeting agent. Bevacizumab has been approved by the Food and Drug Administration (FDA) for treating colon, lung, kidney, and brain cancers. Anti-VEGF therapy has shown potential for the treatment of some cancers but has not been as efficacious as expected [13]. Moreover, resistance to anti-VEGF treatment has been observed in tumor cells and components of the tumor microenvironment.

Besides VEGF, several other growth factors have a significant proangiogenic effect, including platelet-derived growth factors (PDGF), epidermal growth factor (EGF), fibroblast growth factor (FGF), hepatocyte growth factor (HGF), and angiopoietins [14]. These pathways are taken into consideration when developing combination therapies to overcome resistance to anti-VEGF therapy. In this article, we will review the basic mechanisms of tumor microenvironment interactions in ovarian cancer angiogenesis and ongoing clinical trials of second-generation vascular targeting drugs that target pathways other than VEGF.

2. Vascular disrupting agents (VDAs)

VDAs target ECs and pericytes of the resident or established tumor vasculature, which results in tumor ischemia and necrosis. Selective vascular shutdown suggests a structural difference between the endothelium of tumor vessels and that of non-tumor vessels. Indeed, tumor vasculature is marked by a high rate of EC proliferation, a reduction in the extent of pericyte coverage, abnormalities in the basement membrane, and often, increased vascular permeability. VDA treatment results in structurally disorganized, tortuous, thin-walled vessels that lack smooth muscle and have reduced physiological regulation [15]. VDAs can be divided into two categories: tubulin-destabilizing agents and flavonoids.

2. A. Tubulin destabilizers

ECs are highly dependent on their tubulin cytoskeleton for their function [16]. Most VDAs induce changes in EC shape by disrupting the cytoskeleton and cell-to-cell junctions. This results in increased permeability to proteins and increased interstitial fluid pressure, which can be sufficient to reduce vessel diameter. Plasma leakage also leads to increased blood viscosity, which results in decreased blood flow and rouleaux formation. Another factor contributing to vascular shutdown is the activation of platelets through contact with basement membrane components, which are exposed. This cascade of events results in vascular occlusion more selectively in tumor endothelium than in normal endothelium [17].

Combretastatins, structurally related to colchicine, destabilize the endothelial cytoskeleton by binding to tubulin and induce microtubule depolymerization. Combretastatin A4 phosphate (CA4P) is a lead compound in its class. It has antivascular and antitumor activities in preclinical models [18]. Animal studies have revealed that CA4P induces a high level of blood flow reduction in tumors compared to its effects in normal organs such as the spleen, skeletal muscle, and brain; and causes no significant decrease in heart, kidney, and intestine[19]. However, preclinical studies suggest that following exposure to a VDA, only the center of the tumor becomes necrotic, with a viable rim remaining in the periphery. This rim of viable tumor cells is highly proliferative and has potential for tumor growth [20]. This phenomenon provides the rationale for developing combination therapy with VDAs and anti-angiogenesis or conventional cytotoxic drugs [21]. Both CA4P and bevacizumab can cause hypertension, but a significant increase in blood pressure was not observed when the drugs were used in combination. Other combretastatin derivatives include the serine-linked amino-derivative AVE8062 and the combretastatin A-1 derivative OXi4503.

Bevacizumab and CA4P combination therapy was tested in advanced solid tumor patients (63 mg/m^2 CA4P + 10 mg/kg bevacizumab q14) [21]. A total of 15 patients were enrolled. Nine of 14 patients experienced disease stabilization. A patient with ovarian cancer had a CA125 response lasting for more than a year. Dynamic contrast-enhanced magnetic resonance imaging showed statistically significant reductions in tumor perfusion/vascular permeability, which reversed after CA4P alone but which were sustained following bevacizumab. A randomized phase II trial of CA4P plus bevacizumab versus bevacizumab alone has completed accrual in patients with recurrent, persistent ovarian cancer (NCT01305213). CA4P is also being tested in combination with paclitaxel and carboplatin in phase II trials. Patients with ovarian cancer that had relapsed and who could start trial

therapy within 6 months of their last platinum chemotherapy were given 63 mg/m^2 CA4P at a minimum of 18 hours before 175 mg/m^2 paclitaxel and carboplatin area under the concentration curve (AUC) 5, repeated every 3 weeks. Six (13.5%) of the 44 patients had disease response by Response Evaluation Criteria in Solid Tumors criteria, and 15 (34%) by Gynecologic Cancer InterGroup CA 125 criteria. Hypertension (23% of patients) was controlled by glyceryl trinitrate or prophylactic amlodipine. CA4P followed by paclitaxel and carboplatin is well tolerated and appears to produce a higher response rate than chemotherapy alone group.[22]

2. B. Flavonoids

5, 6-Dimethylxanthenone-4-acetic acid (ASA-404) is a flavonoid derivative that damages DNA and induces apoptosis in ECs in preclinical models. The exact mechanism that leads to tumor cell death remains unknown but involves nuclear factor kappa B (NF-κB), serotonin, tumor necrosis factor alpha (TNF-α), and nitric oxide [23]. To our knowledge, no clinical studies of flavonoids for ovarian cancer therapy have been carried out.

3. PDGF receptor (PDGFR) pathway

PDGF molecules are key regulatory molecules in oncogenesis and angiogenesis and play an important role in ovarian cancer. Four isoforms of the PDGF molecule have been identified: PDGF A-D [24, 25]. PDGF is a dimeric molecule composed of two disulfide-bound chains [26], and it binds to specific receptor isoforms to exert their effects. PDGF-A and PDGF-C bind to PDGFR-α, whereas PDGF-B and PDGF-D bind to PDGFR-β [27]. Thus, PDGF-BB can bind PBGF-β, and PDGF-AB can bind both PDGFR-α and PDGFR-β [27]. At the site of vessel sprouting, ECs secrete PDGF-BB as a chemoattractant for surrounding pericytes to stabilize endothelial channels. Newly formed vessels must be mature and covered by pericytes to function properly. Several growth-factor families, such as PDGFs, angiopoietins, and TGF-β, contribute to this maturation process [28]. Secreted PDGF-BB interacts with heparan sulfate at the EC surface or in the periendothelial matrix. This deposition creates a concentration gradient of PDGF-BB, which, in turn, is critical for the correct investment of pericytes in the vessel wall [29]. Disruption of endothelial-pericyte associations results in excessive regression of vascular loops and abnormal remodeling [30].

Pericytes respond to stimulation created by PDGF-BB concentration gradients and are activated by the dimerization of PDGFR-β [31, 32]. Dimerization of PDGFR leads to autophosphorylation of tyrosine residues in the intracellular domain [25]. Upon activation of the PDGF pathway, signaling occurs *via* the phosphatidylinositol 3-kinase/protein kinase-B (PI3K/Akt) pathway, and mitogen-activated protein kinase (MAPK) molecules are involved alongside proteins of the Src family and phospholipase C-γ [33]. Other molecules related to PDGF signaling include Ras [34], signal transducer and activator of transcription (STAT), and guanine-5'-triphosphatase (GTPase) activating protein [35]. PDGF also induces cell growth and survival [36], transformation [37], migration, vascular permeability, and wound healing [38]. In the tumor vasculature, pericytes express PDGFRs, which play an important role in angiogenesis by recruiting more pericytes and also influence resistance to anti-VEGF therapy. PDGF-BB chemoattracts pericytes that express PDGFR-β [39, 40]. Therefore,

pericyte deficiency after PDGF-B ablation causes vessel leakage, tortuosity, microaneurysm formation, and bleeding [41].

The PDGF/PDGFR axis contributes to resistance to anti-VEGF therapy through several mechanisms. Pericytes support EC survival during anti-VEGF therapy in a paracrine manner. PDGF-BB-related activation of PDGFR-β can stimulate pericytes to produce VEGF [32], and VEGF production from pericytes can protect ECs from VEGF withdrawal and confer resistance to VEGF blockade by close EC–pericyte interaction. PDGF-BB also acts on pericytes that express PDGFR-β to expand the stromal compartment and activate erythropoietin expression, which leads to enhanced tumor angiogenesis [42]. Increased expression of PDGF-CC by tumor-associated fibroblasts can also confer resistance against anti-VEGF treatment. PDGF-CC stimulates vessel growth and maturation and attenuates the response to anti-VEGF therapy [43]. The effect on tumor angiogenesis of PDGF-CC is mediated by its receptors, PDGFR-α and PDGFR-β, which are expressed by ECs, tumor-associated fibroblasts, and bone marrow-derived cells [43].

PDGFR inhibition decreases tumor growth by causing pericyte detachment, which leads to immature vessels that are prone to regression [44]. Anti-PDGF/PDGFR drugs (e.g., imatinib, an anti-PDGFR antibody and aptamers) are largely ineffective in tumors as monotherapy because these drugs can potentially make the tumor vasculature more immature, a state that is characterized by decreased pericyte coverage [32]. PDGFR inhibitors are shown in Tables 1–7. However, these drugs might enhance the efficacy of anti-VEGF drugs by making the ECs more sensitive [44–46]. Initial studies using multitargeted receptor tyrosine kinase inhibitors (TKIs) showed that blocking PDGF-BB increased sensitivity to anti-VEGF therapy by depleting the mature vessels of pericytes [39]. In xenograft models of melanoma and pancreatic cancer, VEGFR and PDGFR inhibition by tyrosine kinase resulted in detachment of pericytes and decreased tumor burden and vascularization [45, 47]. However, there are also potential disadvantages to PDGFR blockade for cancer therapy. Inhibition of vessel maturation can promote malignancy. In primary tumors, pericytes are a barrier to cancer cell intravasation. Because leaky vessels that are not covered by pericytes are not sufficient barriers, tumor cell dissemination can be facilitated by inhibiting PDGFR [48]

Phase II trials using imatinib, c-Abl, Abl-related gene (Arg/Abl2), PDGFR, and c-kit inhibitors all showed minimal activity in ovarian cancer patients [49–51]. Because of its limited effect on ovarian cancer, imatinib was tested with cytotoxic agents. Combining imatinib with docetaxel did not improve efficacy over expected outcomes with docetaxel alone but the toxicity of that regimen was tolerable. Another study of imatinib in combination with weekly paclitaxel demonstrated 50% of patients were free of disease progression at 12 weeks and 5 of 12 patients had a PFS of more than 6 months, including 2 of the 12 with a PFS of more than 12 months [52]. Again, the improvement in clinical activity over weekly paclitaxel alone remains to be determined. (Tables 1, 2)

Multiple TKIs besides imatinib are used to target the PDGFR pathway. Cediranib is a TKI of VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-α and c-kit. In a phase II study of cediranib monotherapy for recurrent epithelial ovarian cancer(EOC), primary peritoneal cancer(PPC),

and fallopian tube cancer(FC), partial responses were documented in 17%, and 13% of patients had stable disease; there were no complete responses [53]. Median PFS was 5.2 months, and 17% of patients were free of progression at 6 months. At the dose administered in this trial (initially 45 mg orally, daily, reduced to 30 mg orally, daily), 11 patients (23%) were removed from the study because of toxicities before 2 cycles. Grade 3 toxicities (>20% of patients) included hypertension (46%), fatigue (24%), and diarrhea (13%). Grade 2 hypothyroidism occurred in 43% of patients. Grade 4 toxicities included central nervous system hemorrhage (n = 1), hypertriglyceridemia/hypercholesterolemia (n = 1), and dehydration/elevated creatinine (n = 1). No bowel perforations or fistulas occurred [53]. In a designed phase III trial (ICON6) [54], cediranib was investigated in combination with platinum-based chemotherapy. The three-arm trial randomized platinum-sensitive patients 2:3:3 to chemotherapy plus placebo followed by 18 months of placebo maintenance (reference arm), chemotherapy plus cediranib followed by 18 months of placebo maintenance (concurrent arm) and chemotherapy plus cediranib followed by 18 months of cediranib (maintenance arm). Acceptable chemotherapy regimens included single agent carboplatin, carboplatin/paclitaxel or carboplatin/gemcitabine for 6 cycles followed by regular monitoring for at least 18 months or until progression of daily cediranib for recurrent platinum-sensitive ovarian cancer. The stage I analysis of ICON6 demonstrated that it is feasible to add cediranib (initially 30 mg orally, daily) to platinum-based therapy but was better tolerated at 20 mg orally, daily, used in the randomized phase II stage II to evaluate the treatments' effects of the trial. Due to a decision to suspend development of cediranib, the phase III program was halted and the trial data based on 456 patients was recently reported. The primary endpoint was changed from OS to PFS and the primary analysis was the maintenance arm *versus* the reference arm. Approximately 70% of the treatment cohort had a platinum-free interval of at least 12 months and 90% of patients received one of the two allowable combination platinum regimens. The primary endpoint (PFS) was significantly longer in the maintenance arm (median 11.1 vs. 8.7 months, HR: 0.57, 95% CI: 0.45–0.74). Surprisingly, OS was also significantly longer in this arm relative to reference, at a median 26.3 months *versus* 20.3 months (HR: 0.70, 95% CI: 0.51–0.99). Hypertension, nausea and diarrhea were each experienced more frequently in the cediranib arms relative to placebo, but only the latter was significant more commonly in the maintenance setting. Grade 3 and grade 4 events were uncommon. [54] (Table 3)

Sorafenib is an inhibitor of VEGFR-1, VEGFR-2, and VEGFR-3, PDGFR-β, and Raf-1 tyrosine kinase activity [55]. It is approved for the treatment of unresectable hepatocellular carcinoma and advanced renal cell carcinoma by the FDA [56, 57]. Matei and colleagues evaluated sorafenib alone (400 mg orally twice daily) in patients with recurrent ovarian cancer or primary peritoneal cancer; 24% of the patients had stable disease for 6 months, and 3.4% of patients had a partial response [58]. This modest response was further hindered by substantial toxicity. Sorafenib has been evaluated in a phase II trial in combination with chemotherapeutic agents (gemcitabine and topotecan) in recurrent ovarian cancer and showed modest effect [59, 60]. Currently, a phase II trial of sorafenib in combination with carboplatin and paclitaxel for first-line treatment of ovarian cancer and in combination with bevacizumab for refractory ovarian cancer is under way (Table 4). A double-blind, randomized, placebo-controlled, phase II study to assess the efficacy and safety of

maintenance therapy with sorafenib was performed. In this trial, 246 patients were randomized 1:1 to receive either sorafenib or placebo; the primary endpoint was PFS. There was no significant difference between sorafenib and placebo arms for PFS (median 12.7 vs. 15.7 months; hazard ratio 1.09; 95% CI 0.72–1.63). More patients receiving sorafenib *versus* placebo required dose reductions of sorafenib (67.5% vs. 30.1%), resulting in a lower than planned median daily dose (median 584.6 vs. 800.0 mg). Treatment with sorafenib was of shorter duration (median 17.6 vs. 51.9 weeks) with more frequent discontinuations due to adverse effects (37.4% vs. 6.5%). Although assessment of efficacy was limited by the high rate of dose reductions and early discontinuations, sorafenib 400 mg BID cannot be recommended as maintenance therapy for patients with OC in complete remission [61].

Nintedanib (BIBF 1120) is a potent inhibitor of VEGFR, PDGFR, and FGFR. In a randomized, phase II, placebo-controlled trial, patients who had just completed chemotherapy for relapsed ovarian cancer with evidence of response but at high risk of early recurrence were treated with Nintedanib. The progression free rates were 16.3% and 5.0% in the nintedanib and placebo groups, respectively (hazard ratio [HR] 0.65; 95% confidence interval [CI], 0.42 to 1.02; P = .06) [62]. This prompted a phase III trial (NCT01015118) in women with newly diagnosed advanced stage (stage II-IV) ovarian cancer following primary cytoreduction (Table 5). The trial randomized 1,366 women at a 2:1 ratio to paclitaxel/carboplatin plus concomitant and 120 weeks of nintedanib maintenance or paclitaxel/carboplatin plus placebo. Approximately 51% of the population had no residual disease after primary debulking. The experimental arm was associated with a 16% reduction in the hazard for progression (primary endpoint measured as RECIST and/or CA125) with a median PFS of 17.3 months *versus* 16.6 months (HR: 0.84 95% CI: 0.72–0.98). The combination was associated with higher frequencies of non-hematologic and hematological toxicity and led to significantly higher rate of treatment discontinuation although the time to treatment discontinuation was not shorter in the experimental arm.

Sunitinib, also a multikinase inhibitor, blocks VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-β, and RET [63]. It is currently FDA-approved for advanced renal cell carcinoma and gastrointestinal stromal tumors [63]. A phase II trial of sunitinib monotherapy for the treatment of patients with recurrent EOC and PPC resulted in a partial response rate of 3.3%; 53% of patients had stable disease [64] (Table 6).

Pazopanib is an inhibitor of VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-α, PDGFR-β, and c-kit. Pazopanib is approved for the treatment of patients with advanced renal cell carcinoma and advanced sarcoma. A phase II trial tested activity in patients with recurrent EOC, PPC, and FC, and the CA-125 response rate was 31%. No patients with measurable disease had a partial or complete response. The PFS at 6 months was 17%. The most common adverse events leading to discontinuation of the study drug were grade 3 alanine aminotransferase (8%) and aspartate transaminase (8%) elevation. Only one grade 4 toxicity (peripheral edema) was reported [65]. Recently, a double-blind, placebo-controlled, phase III clinical study of pazopanib was reported in women with ovarian cancer who achieved a partial or complete response to primary platinum-based adjuvant chemotherapy. In this trial, 940 women (90% stage III-IV) were randomized 1:1 to pazopanib or placebo for up to 24 months. The primary endpoint was PFS. The majority of the women (>85%) had achieved a

complete clinical response prior to enrolling into the study. Pazopanib use significantly reduced the risk of progression (RECIST) by 23% (HR: 0.77, 95% CI: 0.64–0.91) represented by a difference in the median PFS of 4.6 months (12.3 months to 17.9 months). The toxicity assessment was similar to other trials with the agent and was associated with a treatment discontinuation rate of 14%. OS was immature but did not appear to be prolonged at the time of the report. (NCT00866697) (Table 7)

4. EGF receptor (EGFR) pathway

The EGFR family consists of four members: EGFR (erbB1), HER2/*neu* (erbB2), HER3 (erbB3), and HER4 (erbB4). More than 30 ligands to EGFR family proteins have been identified in humans [66]. Dimerization of EGFR proteins is a critical step for transmission of signals, and activation of EGFR and HER2/*neu* induces a cascade of downstream signaling through several pathways (e.g., Ras/Raf/MAPK, PI3K/Akt/mTOR, Src, and JAK/STAT), resulting in cellular proliferation, differentiation, survival, motility, adhesion, and repair [67].

The EGFR pathway has a role in generating resistance to anti-VEGF therapy. Cascone et al. showed that increased activated EGFR was detected on pericytes of xenografts that acquired resistance to anti-VEGF therapy. They also showed that dual targeting of the VEGF and EGFR pathways reduced pericyte coverage and increased PFS in mouse xenograft model of human lung adenocarcinoma [68]. On the other hand, blockade with an anti-EGFR antibody resulted in the selection of tumor cell subpopulations with increased angiogenic potential [69]. Based on this knowledge, a phase II clinical trial was performed in patients with recurrent or refractory EOC, PPC, and FC without any prior treatment with anti-VEGF or anti-EGFR agents [68]. A total of 13 patients were enrolled. Bevacizumab 15 mg/kg was administered intravenously every 21 days, and the EGFR inhibitor erlotinib, 150 mg orally, was given daily. One complete response was observed for more than 16 months, and one partial response was observed for more than 11 months. Seven patients showed stable disease as a best response. Two patients had fatal gastrointestinal perforation, and the study was therefore stopped. [70]. The largest trial of an EGFR inhibitor in ovarian cancer was conducted by the EORTC, which randomized 835 patients 1:1 to erlotinib (150 mg daily for 24 months) or observation. The primary endpoint, PFS was similar between the groups at a median 12.7 months *versus* 12.4 months. Similarly, no difference in OS was observed 51 months *versus* 59 months. Activating EGFR mutations were present in less than 1% of the study population and downstream pathway activators were present in about 7% of cases [70].

Finally, small molecule inhibitors targeting VEGFR and EGFR have been developed and at least one (vandetanib) has been reported in combination with chemotherapy in patients with recurrent platinum-resistant disease. Coleman and colleagues randomized 129 patients with platinum-resistant recurrent ovarian cancer 1:1 to vandetanib in combination with docetaxel *versus* docetaxel alone. Allowance for crossover to single agent vandetanib was optional. The primary endpoint was PFS and was not significantly improved in the combination arm (median 3.0 months *versus* 3.5 months, respectively). Similar findings were observed

relative to OS. The regimen was well tolerated and reflective of the relatively low dose of the agent (100 mg orally, daily). [71].

5. FGF receptor (FGFR) pathway

FGFs that signal through FGF receptors (FGFRs) regulate development, controlling many events from mesoderm patterning in the early embryo [72], all the way to the development of multiple organ systems [73]. FGF signaling extends to many physiological roles in the adult organism as well, including the regulation of angiogenesis and wound healing [74]. The family of FGFs consists of at least 23 secreted glycoproteins, of which 18 are true ligands (FGFs 1–20 and 16–23) [74]. FGFs are sequestered to the extracellular matrix (ECM) by heparan sulphate proteoglycans. Upon release from the ECM by haparanase, proteases, or specific FGF-binding proteins, FGFs bind to FGFRs. The FGFRs comprise the four transmembrane receptor tyrosine kinases FGFR1, FGFR2, FGFR3, and FGFR4 [75]. FGF triggers the autophosphorylation of FGFR at a key tyrosine residue in an activation loop of the tyrosine kinase domain [76]. Activated FGFR phosphorylates FGF receptor substrate 2 to recruit the growth factor receptor-bound protein 2 (GRB2) adaptor molecule [74, 77]. FGF signals can be transduced to the RAS/MAPK or PI3K/Akt signaling cascades, Src tyrosine kinase, and STATs [78]. FGF increases cellular proliferation through the RAS/MAPK pathway, whereas FGF supports cellular survival through the PI3K/Akt pathway [79].

FGFs activate their receptors on ECs or indirectly stimulate angiogenesis by inducing the release of angiogenic factors from other cell types [74]. Among the molecules of the FGF/FGFR pathway, FGF1 and FGF2 are potent proangiogenic factors [80]. FGFR1 and FGFR2 are found in ECs [81]. Released FGFs from ECM stimulate tumor cells in an autocrine manner, whereas ECs are stimulated in a paracrine manner. During tumor angiogenesis, FGFs increase EC proliferation by activation of MAPK and long-lasting activation of protein kinase C, whereas migration is caused by activation of MAPK and downregulation of protein kinase C [82, 83].

The FGF pathway has crosstalk with other angiogenesis pathways, and this crosstalk may confer resistance to anti-VEGF therapy [84]. FGF2 shows synergistic effects with VEGF and PDGF-BB [85–87]. FGF2 upregulates the expression of PDGFR to increase responsiveness to PDGF-BB; likewise, PDGF-BB-treated vascular smooth muscle cells may lead to upregulation for FGFR1 to increase responsiveness to FGF2 [88]. FGF2 also increases the expression of other proangiogenic factors including angiopoietin-2 and VEGF [89, 90]. In the clinical setting, a study of cytokine and growth factor profiles at response and upon progression after a single dose of bevacizumab-containing therapy demonstrated that FGF2 levels were elevated after tumor progression in patients with colorectal cancer and glioblastoma [91, 92]. Pazopanib and nintedanib inhibit FGFR's role as a small molecule tyrosine kinase inhibitor, however other agents with selective FGFR targeting are under development.

6. Angiopoietin/Tie pathway

The angiopoietin/Tie family is an on/off switch for angiogenesis. The angiopoietin family consists of two receptors, Tie1 and Tie2, and three ligands, Ang1 and Ang2 and the orthologous Ang3 in mice or Ang4 in humans. Ang1 has agonistic functions to Tie2, and Ang2 has a competitive antagonist function that is controlled in a context-dependent manner [93]. Because no ligand for Tie1 has been identified, this orphan receptor may act as a negative regulator of Tie2, but its precise role remains elusive [94]. Ang1 is produced by pericytes and smooth muscle cells; it activates endothelial Tie2. Ang1 strengthens interactions between ECs and pericytes in a paracrine manner, is expressed behind the leading edge of angiogenic vessels, and plays an important role in vessel maturation [95]. In contrast, Ang2 is released by angiogenic tip cells. At the cue of angiogenesis, pericytes first detach from the vessel wall (in response to Ang2) and liberate themselves from the basement membrane by proteolytic degradation, which is mediated by matrix metalloproteinases [96]. Ang2 expression is confined to the vascular remodeling area to destabilize the growing edge of ECs and works as a competitive antagonist of Ang1. At this point of EC destabilization, Ang2 binds to Tie2 in an autocrine manner without inducing signal transduction [97, 98]. However, the role of Ang2 appears to be more contextual. When VEGF is absent, Ang2 destabilizes vessels by inhibiting Ang1 signaling, but in the presence of VEGF, Ang2 facilitates vascular sprouting [39]. The relative Ang1:Ang2 ratio may also be important. When Ang1 expression is greater, the vasculature remains quiescent. Conversely, when Ang2 expression is dominant, angiogenesis is favored [99]. Tumor-derived Ang2 promotes angiogenesis by recruiting monocytes expressing Tie2 [100]. Overexpression of Ang1 compared with Ang2 results in dense hypervascularization, with large vessels, and excess Ang2 binding to Tie2 leads to destabilized, leaky vessels [94].

For anti-angiopoietin cancer treatment, selective Ang2-inhibiting agents seem to be more effective and safe. The overall effects of the Ang–Tie system on tumors are context-dependent [94]. Ang1 stimulates tumor growth by promoting EC survival and vessel maturation, but it also inhibits tumor cell migration across vessel walls. These conflicting biological activities warrant caution when considering Ang1 as an anticancer target. Instead, Ang2 may be a more desirable target because it stimulates tumor angiogenesis and recruits proangiogenic monocytes, and Ang2 inhibition promotes vessel regression and normalization [101]. Given that Ang2 and VEGF increase angiogenesis cooperatively, simultaneous blocking of VEGF and angiopoietins is superior to anti-angiopoietin therapy alone for inhibiting tumor angiogenesis, metastasis, and vessel leakage and represents a viable clinical treatment paradigm [102].

Various agents that block either Tie2 or Ang2 are being evaluated in early-phase clinical trials. Among the drugs targeting this pathway, trebananib (AMG386) is a novel, investigational angiopoietin antagonist peptide-Fc fusion protein (peptibody) that selectively binds Ang1 and Ang2, prevents their interaction with Tie2, and inhibits tumor EC proliferation and tumor growth [103]. A randomized, placebo controlled phase II trial of combination weekly trebananib and weekly paclitaxel demonstrated clinical efficacy relative to weekly paclitaxel alone in women with recurrent EOC, FC or PPC. Trebananib was infused at 2 dose levels (3 mg/kg or 10 mg/kg) and was associated with a median PFS of 5.7

months (95%CI: 4.6–8.0 months) and 7.2 months (95%CI: 5.3 to 8.1 months), respectively. This compared favorably to weekly paclitaxel alone (median PFS: 4.6 months, 95% CI: 1.9 vs. 6.7 months). The combined HR of the trebananib arms relative to weekly paclitaxel was 0.76 (95% CI: 0.52–1.12, P=0.165) and further analysis suggested a dose-response effect on PFS [103]. Adverse effects included peripheral edema, hypokalemia, thromboembolic events, and hypertension. One of the two ongoing phase III clinical trials has been reported for the combination of trebananib and paclitaxel in recurrent ovarian cancer. TRINOVA-1, (NCT01204749) mirrored the phase II design and combined weekly paclitaxel with a higher dose (15 mg/kg) of trebananib (or placebo) in patients with up to 3 prior anticancer regimens and a platinum-free interval of 12 months or less. The 919 patients were randomized 1:1 to the treatment arms. The primary endpoint, PFS, was significantly improved in the combination arm (median 7.2 vs. 5.4, HR: 0.66, 95%CI: 0.57–0.77). The effect was persistent, albeit lower, among the 7–8% of patients who were previously treated with bevacizumab. Similarly, approximately half of the treatment cohort had a platinum-free interval between 6 and 12 months but the effect appeared consistent in this stratum. The combination was associated with more edema, like the phase II, but did not reflect other anti-VEGF based agents. TRINOVA-2 is being run in a similar population but in combination with pegylated liposomal doxorubicin (NCT01281254) in patients with recurrent or resistant EOC, FTC, or PPC. Finally, a phase III clinical trial of trebananib in combination with paclitaxel and carboplatin as a first-line chemotherapy (TRINOVA-3, NCT01493505) has completed enrollment. Clinical trials for angiopoietin-based therapies are listed in Table 8.

7. HGF and the c-MET pathway

The HGF/c-MET axis is implicated in a wide variety of epithelial, mesenchymal, and hematological malignancies and angiogenesis [104]. The c-MET proto-oncogene is essential for embryonic development, epithelial–mesenchymal transition, angiogenesis, and wound healing [104, 105]. HGF is the only known ligand for c-MET [106]. Upon HGF binding, c-MET autophosphorylates and recruits several downstream effectors, including Grb2, Gab1, PI3k, phospholipase C-γ, Shc, Src, Shp2, Shp1, and STAT3. Grb2 and Gab1 interact directly with c-MET and are critical in HGF/c-MET signaling [107]. MET is normally expressed by epithelial cells, and it is also seen in ECs, neurons, hepatocytes, hematopoietic cells, and melanocytes. HGF is usually expressed in cells of mesenchymal origin. Because of these characteristics, HGF and MET are the principal mediators of paracrine epithelial-mesenchymal interaction. C-MET receptor expression is regulated by the *MET* proto-oncogene. Dysregulation of HGF/c-MET results from amplification and/or rearrangement of *MET* mutations, ligand and/or receptor overexpression, abnormal paracrine stimulation, or autocrine loop formation [108, 109].

HGF/c-MET also increases angiogenesis by promoting the growth, movement, and morphogenesis of ECs [110, 111]. HGF has a direct effect on ECs *via* enhancement of cancer cell-EC contact induced by focal adhesion kinase (FAK) phosphorylation [112]. HGF also decreases endothelial occludin, a cell–cell adhesion molecule, which results in reduced trans-endothelial resistance of tumor vessels and allows cancer cells to migrate across the EC barrier. Increased expression of HGF/c-MET is related to high vascular density in

tumors, and overexpression of this pathway leads to increased angiogenesis in experimental xenograft models. HGF and c-MET regulate angiogenesis directly or indirectly through VEGF signaling. MET signaling can induce VEGFA expression and angiogenesis through common signaling intermediates such as SRC homology 2 domain-containing proteins (SHCs). HGF/c–MET and VEGF/VEGFR2 cooperate to induce angiogenesis although MET and VEGFR do not physically associate or transphosphorylate each other. They do, however, activate common signaling mediators ERK/MAPK, AKT/mTOR, and FAK [113]. MET kinase inhibitors and a peptide that contained the MET bidentate docking site blocked cancer growth and decreased the number of blood vessels in experimental models [114, 115].

Another interesting aspect of MET biology in tumors is its regulation and activation by hypoxia [116]. Hypoxia induces the expression of the transcription factor hypoxia-inducible factor 1α, and hypoxia-inducible factor-dependent expression of MET occurs in several types of carcinoma cells [117–119]. Anti-angiogenic therapy reduces tumor vascularization, thus causing tumor hypoxia. Anti-angiogenic therapy alone may reduce tumor mass but may also promote MET-dependent spreading of cancer cells, and these observations argue for combination therapies that target both angiogenesis and HGF/c–MET. Preclinical studies with low-molecular-mass compounds that inhibit both VEGFR2 and MET kinases have validated this concept in mouse xenograft models [120, 121], and these inhibitors may prove valuable in controlling metastatic cancer by concurrently blocking angiogenesis and invasion [122].

The HGF/c-MET pathway plays a role in sunitinib resistance by supporting angiogenesis. Sunitinib-resistant tumors show increased HGF expression compared to sunitinib-sensitive tumors, and in these tumors, c-MET expression is elevated in ECs but not tumor cells. Immunohistochemical analysis from tissue that was treated with a combination of sunitinib and c-MET inhibitors revealed significant decreases in microvascular density [123]. Several approaches have been developed to target this pathway, including MoAbs against human HGF (AMG102 or rilotumumab) and NK4 (a four-kringle antagonist). NK4 inhibits not only invasive growth but also tumor angiogenesis [124]. Rilotumumab (AMG102) is a fully human IgG2 MoAb directed against HGF. Rilotumumab suppressed subcutaneous growth of glioblastoma (U-87) in a preclinical model through enhanced apoptosis and reduced mitogenesis [125], but the drug had minimal effect on angiogenesis. Rilotumumab has been tested in patients with persistent or recurrent EOC, PPC, and FC [126]. Single agent rilotumumab showed limited benefit in this patient population in this study. Cabozantinib, a small molecule inhibitor of c-MET, ret, and VEGFR2 has been studied in recurrent ovarian cancer. In a 68 patient, randomized phase II discontinuation trial, women with recurrent platinum sensitive and resistant ovarian cancer were given cabozantinib 100 mg orally, daily for 12 weeks. Patients responding to therapy continued on treatment until progression or intolerance. Patients achieving stable disease were then randomized to either continued cabozantinib or placebo until progression. Fifty-one patients were evaluable for response. The overall response rate was 24%, with 58% having stable disease at 12 weeks. Responses were observed in platinum refractory, resistant and sensitive patients. Toxicities included 10% with grade 3 hand-foot syndrome and 8% with diarrhea. Approximately 10% discontinued treatment due to adverse events, including 2 fatal GI perforations [127]. A

GOG trial randomizing recurrent ovarian cancer patients to either cabozantinib or weekly paclitaxel is ongoing. (NCT01716715)

8. Ephrin/Eph receptor pathway

The erythropoietin-producing hepatocellular (Eph) family of receptor tyrosine kinases regulates various physiologic and pathologic processes, including insulin secretion, bone homeostasis, immune function, blood clotting, pathological forms of angiogenesis, and cancer [128]. The erythropoietin-producing hepatocellular (Eph) family of receptor tyrosine kinases regulates various physiologic and pathologic processes including the regulation of insulin secretion, bone homeostasis, immune function, blood clotting, pathological forms of angiogenesis, and cancer [128]. EphA2 plays a role in axonal migration developmentally and is largely absent from most normal adult tissues except some epithelial cells [129].

EphA2 belongs to the tyrosine kinase Eph receptor family. The Eph receptors can be divided into two subgroups according to their ligands. EphA receptors interact with 5 ligands of the glycosylphosphatidylinostitol-linked ephrin-A subclass, whereas EphB receptors interact with 3 transmembrane ligands of the ephrin-B subclass [130]. Among the various Eph family members, EphA2 is of particular interest because it is overexpressed in ovarian cancer and is related to disease severity and clinical outcome [131].

Several studies have investigated the impact of EphA2 on tumor angiogenesis. EphA2 receptor activation plays an essential role in VEGF-induced EC migration [132]. The EphA2/FAK/paxillin axis has been implicated in vasculogenic mimicry [133, 134], a process by which tumor cells mimic endothelial-derived vasculogenic networks [135]. In ovarian cancer, EphA2 is overexpressed in a substantial fraction of tumor cells as well as the associated vasculature [131]. EphA2 targeting with either a MoAb or small interfering RNA (siRNA) results in anti-tumor effects, mediated by reduced angiogenesis. Some studies have suggested that increased EphA2 expression is associated with resistance to anti-VEGF therapy. Casanova and co-workers showed increased expression of ephrin A1 and EphA2 in a pancreatic cancer xenograft model. Ephrin A1 functions as a proangiogenic factor when blockade of the VEGFR pathway induces tissue hypoxia [84]. EphA2-targeted siRNA incorporated into dioleyol phosphatidylcholine (DOPC) nanoliposomes caused a significant decrease in tumor growth in combination with paclitaxel in an ovarian cancer xenograft model when compared to nonsilencing siRNA [136]. A subsequent clinical study using siRNA-EphA2-DOPC was based on those successful preclinical studies, and a phase I clinical trial is planned to assess the safety of siRNA-EphA2-DOPC in patients with advanced, recurrent cancers (NCT01591356).

9. Delta-like 4 (Dll4)/Notch pathway

The Notch signaling pathway has been implicated in tumor angiogenesis, including vessel maturation, pericyte recruitment, and branching as well as cell differentiation, proliferation, survival, and apoptosis. In mammalian cells, this pathway consists of five transmembrane Notch ligands (Jagged1, Jagged2, and Delta-like ligands [Dll] 1, 3, and 4 [137] and four Notch receptors [Notch 1–4]). Ligand receptor binding leads to cleavage *via* intramembranous proteolysis by γ-secretase and subsequent translocation from the cell

membrane to the nucleus. The Notch intracellular domain interacts with transcription factors to regulate transcription of the basic helix-loop-helix proteins hairy/enhancer of split (Hes) and related proteins (Hey) [138]. ECs express Notch1 and Notch4 receptors and the Jagged1, Dll1, and Dll4 ligands. Among the various Notch ligands, Dll4 is expressed specifically in the endothelium at sites of vascular development and angiogenesis. Experiments involving gene disruption in mice have shown that knockout of only one *Dll4* allele is lethal to the embryo and results in various defects in arterial development and venous circulation, enlargement of the pericardial sac, and failure to remodel the yolk sac vasculature [139]. This suggests that the Dll4/Notch signaling system is a major stimulator of angiogenesis.

VEGF can increase Dll4 expression in the developing ECs, and Dll4 acts as a negative feedback mechanism. Consequently, inhibition of this pathway actually increases angiogenesis, but most of the newly formed vessels are abnormal and functionally compromised. As a result, tumor hypoxia increases, which retards tumor growth [140, 141]. Dll4 expression is also an independent predictor of poor patient survival and a predictor of response to anti-VEGF therapy. Interestingly, tumors that are resistant to anti-VEGF treatment may be sensitive to anti-Dll4 therapy, and combination treatment with anti-VEGF and anti-Dll4 drugs appears to have an additive inhibitory effect on tumor growth [142, 143]. In a mouse model of human glioblastoma, Dll4 targeting along with anti-VEGF therapy resulted in greater inhibition of tumor growth than controls or treatment with an anti-VEGF drug alone [138].

A phase I trial in patients with advanced solid malignancies showed that RO4929097, a γ-secretase inhibitor of Notch signaling, is tolerable in combination with temsirolomus, gemcitabine, and cediranib [144–146]. A phase II study was performed in patients with metastatic colorectal cancer, but single-agent RO4929097 did not show efficacy [147]. A phase II clinical trial of RO4929097 is ongoing in ovarian cancer patients (NCT01195343). Demcizumab (OMP-21M18), monoclonal antibody targeting Dll4, is under phase Ib/II clinical development in ovarian cancer patients (NCT01952249). In this Phase 1b/2 trial, demcizumab is being tested in combination with paclitaxel in patients with platinum-resistant EOC, PPC and FC. Following a phase 1b safety evaluation, a Phase 2 clinical trial will proceed in these patients.

10. Src family kinases (SFKs)

SFKs are a family of nonreceptor protein tyrosine kinases that are around 60 kD in weight and include 9 genes: *Src*, *Blk*, *Fgr*, *Fyn*, *Hcy*, *Lck*, *Lyn*, *Yes*, and *Yrk*. *Src* is rarely mutated in human tumors, and amplifications and rearrangements of the gene in tumors are even rarer[148]. Src mediates mitogenic signals between growth factor receptors like VEGF, EGFR, c-MET and insulin-like growth factor 1R and downstream signaling cascades such as FAK, MAPK, and PI3K/AKT/mTOR [149]. Accumulating data suggest that Src plays an important role in many steps in malignancy, including cancer cell mitosis, adhesion, invasion, motility, survival, angiogenesis, and progression [150].

The antiangiogenic effect of Src is mediated by interleukin 8 (IL-8) and VEGF [151]. Src is associated with VEGF signaling in two aspects. One aspect is as a regulator of activation of the VEGFR pathway upstream; the other is as a signal transduction molecule downstream of VEGFR2. SFKs can control the expression of angiogenic growth factors and cytokines, including VEGF, by regulating their gene expression [150, 152]. Src activation also leads to increased IL-8 expression, and Src inhibition can reduce IL-8 expression levels [151]. SFKs also mediate ligand-dependent VEGFR2 signal transduction. SFKs can cooperate with angiogenic growth factor receptors, such as VEGFR, to elicit signaling in ECs or tumor cells [152]. VEGF-induced Src phosphorylation can promote formation of the FAK/$\alpha_v\beta_5$ signaling complex and caveolin/VEGFR2 complex [153], which are required for vascular permeability response and neovascularization. In c-Src-deficient mice, there was reduced vascular permeability in response to VEGF, suggesting an important role for Src in VEGF-induced angiogenesis [154]. Src is also required for either VEGF-induced ERK1/2 or FAK activation, which leads to increased cell proliferation. Inhibition of Src kinase activity can suppress cell proliferation and migration in human umbilical vein ECs [155].

There are several Src-targeted inhibitors in clinical development. Dasatinib (BMS-354825) is an orally available Src and Abl kinase inhibitor with antiproliferative activity against a broad spectrum of hematological and solid cancer cell lines [156]. As a multikinase inhibitor, dasatinib is being evaluated in breast, lung, colorectal, pancreatic, uterine and ovarian cancers. Bosutinib (SKI-606) is another potent oral Src inhibitor with anti-Abl activity. This compound demonstrated antitumor activity in preclinical models, and clinical development in hematological and solid malignancies is under way. The Src inhibitors AZD-0530, XL-999, and XL-228 are also undergoing early-phase testing. One randomized phase II trial in combination with paclitaxel and carboplatin has been conducted with saracatinib in recurrent platinum sensitive patients [157] and a second in combination with weekly paclitaxel (platinum-resistant patients) is completed [158]. In those two randomized phase II trial, the addition of saracatinib to chemotherapeutic agents did not improve response rate or PFS in ovarian cancer patients. Most of these small molecules have activities against other kinases as well [159] (Table 10).

11. PI3K/AKT/mTOR pathway

PI3K is a lipid kinase that generates 3′-phosphoinositides at the cell membrane when activated by receptor kinases [160]. This leads to recruitment of phosphoinositide-dependent kinase 1 (PDK1) and Akt to the cell membrane. The generation of 3′-phosphoinositides is negatively regulated by phosphatase and tensin homologue. Akt is activated by several enzymes, including PDK1, mTORC2, and IRS-1, and this activation allows Akt to then inhibit tuberous sclerosis protein 2. The PI3K/Akt/mTOR pathway is responsible for survival of ECs during stimulation with VEGF. The binding of VEGF to VEGFR results in dimerization of the receptor followed by activation of the PI3K/Akt/mTOR pathway, which leads to increased EC survival.

Akt is also important for EC survival when new blood vessels are being formed. During new vessel formation, angiogenic cells need to degrade the extracellular matrix. ECs must therefore reinforce the mechanisms of apoptosis inhibition to avoid the risk of anoikis,

apoptosis induced by lack of adhesion to the substrate [161]. ECs repress their apoptogenic program through two main signaling pathways initiated from integrin-mediated attachment to the extracellular matrix and from survival factors such as VEGF and FGF2. Akt is a convergence point for both pathways [162]. Increased expression of Akt-1 in ECs phosphorylates apoptogenic proteins such as Bad, Bax, and caspase-9 [162, 163], which induces apoptosis. At the same time, it increases the levels of the antiapoptotic proteins A1 and Bcl-2 [162]. Other tyrosine kinase receptors (FGFRs, Tie2, insulin receptor, insulin-like growth factor receptor, and MET) and integrins can also activate the PI3K pathway in ECs [164].

Rapamycin analogues inhibit downstream mTOR signaling. Everolimus (RAD001), an oral rapamycin analogue, has been approved for progressive neuroendocrine pancreatic cancer treatment, subependymal giant cell astrocytoma, hormone receptor positive-HER2 negative breast cancer, and advanced renal cell carcinoma. Everolimus showed anti-angiogenic effects in EGFR-resistant cancer cell lines and everolimus partially restored the ability of EGFR inhibitors of EGFR-related signaling effectors and VEGF production, which inhibits proliferation and capillary tube formation of ECs, both alone and in combination with gefitinib [165]. Another mTOR inhibitor, temsirolomus, is approved for renal cell carcinoma.

12. Integrins/focal adhesion-associated proteins

ECs express at least 11 integrins. Integrins are heterodimeric cell surface adhesion receptors for the ECM comprising an α subunit and a β subunit [166]. Among them, $\alpha_5\beta_1$ and $\alpha_v\beta_3$ are upregulated during angiogenesis [167]. VEGFA expression in ECs is regulated in an α3β1-dependent manner [168]. Integrin α_v supports EC survival in tumors by pericyte-induced control of autocrine VEGFA. PDGFR also interacts with integrins, which enhances cell proliferation, migration, and survival [161, 169]. However, integrins lack intrinsic enzymatic activity. The proteins transduce proliferative, survival, migratory, and angiogenic signals by clustering together with kinases and adaptor proteins to form focal adhesion complexes. Focal adhesions are the origin of signals that activate or inhibit cellular processes such as proliferation, survival, and migration of ECs. For example, shear stress induces endothelial migration through a signal initiated by $\alpha_5\beta_1$ binding to fibronectin and involving the adaptor proteins Shc, PI3K, and ERK-MAPK1/2 [170]. Integrin $\alpha_v\beta_3$ promotes adhesion, migration, and phosphorylation of Akt, MAPK, and FAK.

FAK, a non-receptor cytoplasmic tyrosine kinase, and can be activated by VEGFR2. FAK regulates the organization of the cytoskeleton and activates diverse signaling pathways involved in the localized adhesion of the cell surface and in cell motility [171]. Activated FAK recruits SH2 domain-containing proteins such as Src, which phosphorylates FAK at additional sites; this phosphorylation induces the association between signaling molecules (such as the Ras-activating protein Sos, PI3K, p130Cas, and paxillin) and focal adhesions. FAK also activates ERK-MAPK and the PI3K/Akt pathways. Intracellular activation of the RAF/MEK/MAPK pathway induces subsequent initiation of DNA synthesis and cell growth. VEGF/VEGFR2 signaling and integrin signaling converge to RAF/MEK/MAPK through FAK.

Endostatin binds to the $\alpha_5\beta_1$ integrin, which leads to focal adhesion and actin stress fiber disassembly mediated by Src and dependent on tyrosyl phosphatase [159]. Interestingly, the inhibition of EC migration occurs without interference with pathways mediated by PLCγ, Akt, MAPK, Rac, or Pak [160], which implies that there is a specific integrin signaling pathway involved in migration and mediated by Src. However, endostatin blocks VEGF binding, VEGFR2 phosphorylation, and ERK, p38 MAPK, and FAK activation in ECs, which suggests a direct interaction between endostatin and VEGFR2 [161].

Integrins $\alpha_v\beta_3$ and $\alpha_v\beta_5$ are upregulated in both tumor cells and angiogenic ECs, making them attractive therapeutic targets. They are involved in angiogenesis and expressed in malignancies such as melanoma, gliomas, and cancers of the breast, prostate, and colon. Function-blocking MoAbs were among the first integrin antagonists developed and showed considerable anti-angiogenic activity in preclinical models [172, 173]. Cilengitide (EMD-121974) is a synthetic cyclic pentapeptide small-molecule inhibitor of $\alpha_v\beta_3$ and $\alpha_v\beta_5$ integrins [174].

Integrin $\alpha_5\beta_1$ is expressed mainly on vascular ECs and upregulated together with fibronectin in tumor neovasculature. In ovarian cancer, peritoneal dissemination is facilitated by $\alpha_5\beta_1$ through increased expression of MMP-9 and fibronectin [175]. It was shown that upregulated $\alpha_5\beta_1$ expression was also related to poor prognosis [176]. Strategies that target β_1 integrins, particularly $\alpha_5\beta_1$, have shown efficacy in reducing tumor burden in preclinical models. An integrin β_1 inhibitory antibody significantly affected the *in vitro* and *in vivo* growth of human breast cancer tumor cells [177]. Volociximab is a chimeric human immunoglobulin G4 and a function-blocking MoAb against integrin $\alpha_5\beta_1$ [178, 179]. It inhibits angiogenesis independently of VEGF/VEGFR and induced apoptosis in proliferating, but not quiescent, ECs in preclinical experiments [180]. A multicenter phase II study tested volociximab in 16 patients with platinum-resistant ovarian cancer or primary peritoneal cancer. There was one patient with stable disease out of 14 evaluable patients, and weekly volociximab was well tolerated [181]. A phase I clinical trial using volociximab in combination with liposomal doxorubicin (NCT00635193) has just been completed.

13. Inflammatory cytokines

13. A. TNF-α

One of the most prominent cytokines implicated in inflammation is TNF-α, which is constitutively expressed in ovarian cancer tumors and stromal cells such as macrophages [182]. TNF-α plays a multifaceted role in cancer by stimulating other cytokines and angiogenic factors by paracrine and autocrine signaling [183, 184]. TNF-α induces angiogenic factors, including chemokine (C-C motif) ligand 2 (CCL2), IL-6, chemokine (C-X-C motif) ligand 12 (CXCL12), VEGF, IL-8, bFGF, and migration inhibitory factor, and their receptors [184]. TNF-α is an inducer of VEGF, and VEGF in turn induces CXCL12 [185, 186]. TNFα also directly induces CXCL12, and CXCL12 and VEGF synergize in the stimulation of blood vessel formation in ovarian cancer [187, 188]. TNFα-depleted cancer cells showed reduced tumor growth and vascularization [184]. TNFα regulates IL-8 transcriptionally *via* NF-κB, regulates VEGF *via* Sp1 and NF-κB, and regulates bFGF *via* c-Jun[188]. Administration of anti-IL-8, anti-VEGF, and anti-bFGF antibodies abrogates EC

function. In another study, TNF-α signaling was responsible for tumor growth. TNF-α/TNF receptor-1 signaling in CD4+ cells is essential for tumor growth and was linked to increased IL-17 levels in malignant ascites. In a mouse ovarian cancer model, TNF-α neutralizing antibody treatment resulted in decreased tumor burden and leukocyte infiltration. The concentration of IL-17 in ascites and the levels of IL-6 in plasma were decreased as well [189].

Infliximab, a chimeric MoAb against TNF-α, led to decreased levels of CXCL12 and IL-6 and resulted in reduced tumor growth, vascularization, and infiltration of myeloid cells [190]. A TNF-α antagonist, etanercept, which is a soluble p75 TNF receptor that inhibits the TNF-α pathway by competitive binding, was also assessed in a phase I trial to evaluate its efficacy in treating recurrent ovarian cancer. In that study, two cohorts of 17 and 13 patients were treated with a dose of 25 mg twice a week (cohort 1) or 3 times a week (cohort 2) [191]. Six of 18 patients who received a minimum of 12 weeks of therapy reached disease stabilization. The trial demonstrated the feasibility of anti-TNF-α therapy for epithelial ovarian cancer treatment.

13. B. Other inflammatory cytokines

In addition to TNF-α, high levels of several other proinflammatory cytokines have been identified in ascites fluid from ovarian cancer patients, including IL-6, IL-8, CCL2, and macrophage inflammatory protein-1β [192, 193]. IL-6 induces VEGF to increase angiogenesis; VEGF also increases IL-6 in a positive feedback loop [194]. IL-6 also activates STAT3 and MAPK in ECs [195]. It is believed that STAT3 upregulates MMP-9 in these cells, thus contributing to angiogenesis and metastasis [196]. To evaluate the prognostic significance of IL-6 and IL-8 levels in ascites, Lane and colleagues related those levels to a number of clinical measures, including PFS. Using multivariate analyses, the authors concluded that high levels of IL-6 could be related to shorter PFS [193]. Similarly, in another study, high serum IL-6 levels were also correlated with poor prognosis [197].

Blockade of IL-6 using an antibody, siltuximab, was shown to effectively block IL-6 signaling pathways by suppressing Stat3 phosphorylation, which led to decreases in downstream antiapoptotic factors [198]. Siltuximab enhanced paclitaxel sensitivity and cytotoxicity in a paclitaxel-resistant cell line, SKOV3-TR; however, these observations require additional work [198]. The therapeutic efficacy of this agent was assessed in a phase II clinical trial with 20 patients who had advanced platinum-resistant ovarian cancer [199]. One of the patients had a partial response, whereas seven patients experienced disease stabilization in addition to exhibiting decreased plasma levels of several cytokines including CCL2, CXCL12, and VEGF, which suggests that these cytokines are regulated by IL-6 [199].

14. RNA interference

The discovery of RNA interference (RNAi), including miRNA and siRNA-mediated gene silencing, is considered one of the most important advancements in biology in the last decade [200–202]. A specifically designed siRNA can bind the target gene (mRNA) in a sequence-specific manner and induce degradation of mRNA translation [202]. SiRNA is

now commonly used as a powerful tool for silencing post-transcriptional gene expression and investigating gene function.

The main issues related to systemic use of siRNA-based therapeutics are development of an efficient delivery system to enhance the stability of siRNA and avoid unintended effects like immune response and off-target effects. Early studies with siRNA-based therapies relied on local administration for specific diseases, such as age-related macular degeneration, diabetic macular edema, respiratory virus infection, and pachyonychia congenita [203, 204]. To overcome obstacles to the systemic use of siRNA-based therapeutics, various nanoparticles made of biodegradable nanomaterials such as natural or synthetic lipids (*e.g.*, liposomes and micelles) and polymers (*e.g.*, chitosan, poly(lactic-co-glycolic) acid [PLGA], polylactic acid [PLA], polyethilenimine [PEI], and atelocollagen), carbon nanotubes, quantum dots, gold nanoshells, or magnetic iron oxide have been used [205–210]. Chemical modification to increase stability have also been tested [211].

An RNAi approach can also be used to target tumor angiogenesis. Several clinical trials based on systemic delivery of siRNA therapies have progressed into the clinic and are currently being tested in phase I/II clinical trials for viral diseases (hepatitis B) and acute renal failure. Currently, there are eight RNAi-based clinical trials in solid tumors and chronic myeloid leukemia in the United States. The first demonstration of siRNA-mediated effects in a clinical trial was for melanoma in 2008; this study targeted ribonuclease reductase using a cyclodextrin-based polymer-conjugated siRNA following a study in non-human primates [212, 213]. Preliminary data showed that this approach was well tolerated, although dose-limiting toxicity was observed in several patients. Targeting EphA2 using siRNA-DOPC showed antitumor activity *via* antiangiogenic effects in ovarian cancer xenografts [142]. As mentioned above [136], a phase I clinical trial will be started to target EphA2 using neutral nanoliposomal EphA2 siRNA at the University of Texas MD Anderson Cancer Center (NCT01591356).

15. Conclusions

Recurrent and refractory ovarian cancer remains a significant clinical challenge. Even though tumor stromal cells are more stable compared to tumor cells, stromal cells can still adapt. Furthermore, pathways related to angiogenesis are redundant and complementary. These characteristics enable tumors and their supportive vasculature to develop resistance to antiangiogenic therapy. Growing understanding of the mechanisms underlying such resistance is leading to new anti-angiogenesis strategies. Maintenance of complete remission and overcoming chemoresistance in patients who do not achieve complete remission are important goals for targeted therapy in ovarian cancer. Combination therapies that target multiple pathways relevant for tumor angiogenesis have the potential to overcome adaptive resistance and lead to improved patient outcomes

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Table 1

Multiple TKIs and their molecular targets.

Drug	Targets	FDA-approved indication
Cediranib	VEGFR-1, -2 and -3, PDGFR, and c-kit	N/A
Sorafenib	VEGFR, PDGFR, c-kit, FLT-3, and -RAF	HCC, RCC
Imatinib	PDGFRs and c-kit	Leukemia, GIST
Nintedanib	VEGFR, PDGFR, and FGFR	N/A
Sunitinib	VEGFR, PDGFR, c-kit, c-FLT-3, and c-RET	GIST, RCC, HCC, neuroendocrine tumors
Pazopanib	VEGFR, PDGFR, FGFR, and c-kit	Sarcoma, RCC

VEGFR: vascular endothelial growth factor receptor, PDGFR: platelet-derived growth factor receptor, FGFFR: fibroblast growth factor receptor, HCC: hepatocellular carcinoma, RCC: renal cell carcinoma, GIST: gastrointestinal stromal tumor

Table 2

Clinical trial of imatinib (Gleevec) in ovarian cancer.

Treatment	Phase	Indication	Efficacy	Reference
Imatinib+docetaxel	II	Platinum-refractory EOC, FT, or PPC	4PR, 3SD(n=23)	[214]
Imatinib	II	Recurrent resistant EOC, FT, or PPC		Completed(NCT00510653)
Imatinib+gemcitabine	II	Persistent, refractory EOC, FT, or PPC		Completed(NCT00928642)
Imatinib	II	Refractory or relapsed EOC	2DS(n=23)	[51]
Imatinib+paclitaxel	II	Recurrent EOC, Mullerian origin cancer		Terminated(NCT00840450)
Imatinib	II	Progressive refractory non-epithelial ovarian cancer (germ-cell tumor)		Terminated(NCT00042952)
Imatinib	II	Taxane-refractory EOC or PPC		Completed(NCT00036751)
Imatinib	II	Persistent recurrent EOC or PPC		Completed(NCT00041041)
Imatinib + wP	II	Recurrent persistent EOC, FT, or PPC	4PR(n=12)	[52]
Imatinib (maintenance)	II	CR patient		[215]

EOC: epithelial ovarian carcinoma, PPC: primary peritoneal carcinoma, FC: fallopian tube carcinoma, PR: partial response, SD: stable disease, CR: complete response. P: Paclitaxel, wP: weekly paclitaxel

Table 3

Clinical trials of cediranib for ovarian cancer

Treatment	Phase	Indication	Efficacy	Reference
Olaparib±**cediranib**	I,II	Recurrent ovarian or breast cancer		Ongoing (NCT01116648)
Cediranib	I	Recurrent EOC, PPC, or FC	7 PR (n = 20)	[216]
Cediranib	II	Recurrent EOC, PPC, or FC	8 PR (n = 47)	[217]
Cediranib	II	Persistent, recurrent, or refractory EOC, PPC, or FC		Ongoing (NCT00278343)
Cediranib maleate + RO4929097	I	Advanced solid tumors (including ovarian cancer)		Ongoing (NCT01131234)
Cediranib + temsirolimus	I	Advanced gynecologic cancers		Ongoing (NCT01065662)
Cediranib + AZD0530	I	Advanced solid tumors (including ovarian cancer)		Completed(NCT00475956)
platinum based chemotherapy ±**cediranib** ± **maintenance cediranib** (ICON6)	II, III	Platinum sensitive, recurrent EOC, PPC, or FC		Ongoing (NCT00532194)

Table 4

Clinical trials of sorafenib for ovarian cancer

Treatment	Phase	Indication	Efficacy	Reference
Sorafenib + topotecan	I,II	Platinum-resistant EOC or PPC	14 SD, 5 PR (n = 30)	Terminated (NCT00526799) [60]
Sorafenib+topotecan(TRIAS 2009)	I,II	Platinum resistant EOC, PPC or FC		(NCT01047891)
PC±Sorafenib	II	First-line chemotherapy in FIGO stage III-IV EOC, PPC, or FC		Ongoing (NCT00390611)
Sorafenib + gemcitabine	II	recurrent or refractory EOC, PPC	2 PR, 10 SD (n = 33)	[59]
Sorafenib		At least the second remission in EOC, PPC, or FC		Terminated (NCT00522301)
PC ± **sorafenib**	II	Recurrent EOC or PPC		Suspended (NCT00096200)
Sorafenib + bevacizumab	II	Refractory EOC or PPC		Ongoing (NCT00436215)
Sorafenib (maintenance)	II	CR with EOC or PPC	No effect	[61]
Sorafenib	II	Persistent recurrent EOC or PPC	20 SD, 2 PR (n=59)	[58]
Sorafenib	II	Two prior cytotoxic treatments; recurrent, refractory EOC or PPC	4 SD (n = 11)	[218]

PC: paclitaxel and carboplatin

Table 5

Clinical trials of BIBF1120 (vargatef, nintedanib) for ovarian cancer.

Treatment	Phase	Indication	Efficacy	Reference
Cyclophosphamid e±nintedanib	II	Recurrent EOC, PPC, or FC		Not yet recruiting (NCT01610869)
Nintedanib	II	Bevacizumab-resistant, persistent, or recurrent EOC, PPC, or FC		Recruiting (NCT01669798)
Nintedanib+PLD	I,II	Platinum-resistant, refractory EOC		Recruiting (NCT01485874)
Nintedanib+PLD +C	I	Advanced, platinum sensitive relapsed EOC, PPC, or FC		Ongoing (NCT01314105)
Nintedanib B+PLD+C	I	Advanced, platinum-sensitive relapsed		Completed (NCT01329549)
Nintedanib	II	Addition to first-line chemotherapy with interval debulking surgery in patients of EOC, PPC, or FC		Recruiting (NCT01583322)
Nintedanib (maintenance)	II	Following chemotherapy in patients with relapsed EOC, PPC, or FC	PFR: 16.3% (nintedanib) vs. 5.0% (placebo)	[62]
PC±**nintedanib**	III	First-line therapy in advanced EOC, PPC, or FC		Ongoing (NCT01015118)

C: carboplatin, PLD: pegylated liposomal doxorubicin, PFR: progression free survival

Table 6

Clinical trials of sunitinib for ovarian cancer

Treatment	Phase	Indication	Efficacy	Reference
Sunitinib	II	Recurrent ovarian clear cell carcinoma		Recruiting (NCT01824615)
Sunitinib	II	Persistent or recurrent clear cell ovarian cancer		Ongoing (NCT0979992)
Sunitinib	II	Recurrent EOC, FC, or PPC	1 PR, 16 SD (n = 30)	[64]
Sunitinib	II	Refractory or relapsed germ cell tumors		Completed (NCT00453310)
Sunitinib	II	Recurrent and refractory EOC, FC, or PPC	3 PR (n = 36)	[219]
Sunitinib	II	Recurrent platinum-resistant ovarian cancer	Not continuous: 6 PR(n = 36) Continuous: 2 PR (n = 37)	[220]

Table 7

Clinical trials of pazopanib for ovarian cancer

Treatment	Phase	Indication	Efficacy	Reference
PC±pazopanib	I, II	Resistance or refractory EOC, PPC, or FC		Recruiting (NCT01402271)
P±pazopanib	II	Resistance or refractory		Ongoing (NCT01468909)
Pazopanib	II	Recurrent EOC, PPC, or FC	3 PR (CA125 response, n=18)	[65]
Gemcitabine±pazopanib	II	Persistent or recurrent EOC,PPC, or FC		Recruiting (NCT01610206)
wP±papzopanib (MITO-11)	II	Platinum resistance or refractory ovarian cancer		Ongoing (NCT01644825)
Pazopanib+PLD	I, II	Platinum resistance or sensitive EOC, PPC, or FC		Ongoing (NCT01035658)
Pazopanib	II	Platinum-resistant EOC, PPC, or FC		Ongoing (NCT01262014)
Pazopanib+P (PAZPET-1)	I	Platinum resistance ovarian cancer		Recruiting (NCT01608009)
Pazopanib+cyclophosphamide	I,II	Platinum resistance or refractory EOC, PPC, or FC		Recruiting (NCT01238770)
Pazopanib+weekly topotecan (TOPAZ)	I,II	Platinum resistance/intermedia te sensitivity EOC PPC,or FC		Recruiting (NCT01600573)
Pazopanib±Fosbreta bulin (PAZOFOS)	I, II	Recurrent EOC, PPC, or FC		Not yet recruiting (NCT02055690)
Pazopanib(maintenance)	III	After first-line chemotherapy		Ongoing (NCT00866697)

Table 8

Clinical trials of trebananib for ovarian cancer

Treatment	Phase	Indication	Efficacy	Reference
Trebananib	I	Advanced solid tumor (including ovarian cancer)	1 PR(n=3)	[103]
Trebananib +PLD or topotecan	Ib	Advanced recurrent ovarian cancer		Ongoing (NCT00770536)
Trebananib+PC	I	First line chemo therapy in ovarian cancer		Ongoing (NCT01253681)
P±trebananib	II	Advanced recurrent ovarian cancer		Ongoing (NCT00479807)
wP *(a)*±**trebananib**	II	Recurrent ovarian cancer	Arm A: 37% PR Arm B: 19% PR Arm C: 27% PR	[221]
wP±**trebananib**(TRINO VA-1)	III	Recurrent, partially platinum sensitive ovarian cancer		Ongoing (NCT01204749)
PLD± trebananib (TRINOVA-2)	III	Recurrent or resistant ovarian cancer		Ongoing (NCT01281254)
PC± trebananib (TRINOVA -3)	III	First line chemo therapy in FIGO stage III-IV ovarian cancer		Ongoing (NCT01493505)

*(a)*Arm A: QW (3 weeks on/1 week off) plus intravenous trevananib10 mg/kg QW, Arm B: trebananib 3 mg/kg QW, Arm C: placebo QW (QW:paclitaxel (80 mg/m^2) once weekly).

Table 9

Clinical trials with Src-targeted drugs in ovarian cancer

Treatment	Phase	Indication	Efficacy	Reference
Dasatinib+PC	I	Recurrent EOC, PPC, FC	3CR, 5PR, 10SD(n=20)	[222]
Dasatinib	II	Recurrent persistent EOC, PPC, FC	No response	[223]
Dasatinib +carboplatin +ifosfamide +etoposide phosphate	I,II	Young patients(1–25yrs) with Metastatic recurrent solid tumors		Ongoing (NCT00788125)
PC± Saracatinib (OVERT1)	II	Recurrent, resistant ovarian cancer	No additional benefit	[157](NCT00610714)
wP± Saracatinib	II, III	Platinum resistance EOC, PPC, or FC	No additional benefit	[158] (NCT01196741)

Table 10

Drugs targeting the PI3k/Akt/mTOR pathway

mTOR inhibitors	**Temsirolimus, sirolimus (rapamycin), everolimus, deforolimus**
Akt inhibitors	Perifosine, GSK-690693,
PDK1 inhibitor	UCN-01
PI3K inhibitors	PI-103, BGT-226, BEZ-235, XL-765, XL-147

Table 11

Clinical trials of mTOR-targeting for ovarian cancer

Treatment	Phase	Indication	Efficacy	Reference
Everolimus (Certican) + bevacizumab	II	Recurrent EOC, PPC, or FC		Recruiting (NCT01031381)
Sirolimus + ALVAC(2)-NY-ESO-1 (M)/TRICOM vaccine + sargramostim	I	Primary or recurrent EOC, PPC, and FC		Recruiting (NCT01536054)
Deforolimus (AP-23573, MK-8669, ridaforolimus) + carboplatin + paclitaxel	I	Advanced, recurrent solid Endometrial cancer EOC		Recruiting (NCT01256268)
Deforolimus (AP-23573, MK-8669, Redaforolimus) + MK0752 + MK2206		Advanced solid tumors		Ongoing (NCT01295632)
Everolimus + carboplatin + PLD	I	first relapse must occur >= 6 months		Recruiting (NCT01281514)
Everolimus + bevacizumab	II	Recurrent, persistent EOC, PPC, FC		Ongoing (NCT00886691)
Temsirolimus + carboplatin + docetaxel + paclitaxel	II	Stage III-IV ovarian clear cell carcinoma		Recruiting (NCT01196429)
Temsirolimus + PLD	Ib	Refractory Breast cancer, Endometrial, ovarian cancer		Recruiting (NCT00982631)
Temsirolimus	II	refractory or recurrent EOC, PPC, or FC	5 PR,13 SD (n=54)	[224]
Temsirolimus	II	Recurrent EOC, PPC, or FC		
Temsirolimus + topotecan	I	Recurrent, refractory gynecologic cancer	No response	[225]
Temsirolimus + carboplatin + paclitaxel	I	Advanced solid tumor (including ovarian cancer)	1 PR (n=6)	[226]
Temsirolimus + AZD2171	I	Advanced Gynecologic cancer		Ongoing (NCT01065662)
Temsirolimus + PLD	I	Resistant solid tumors		Completed (NCT00703170)
Temsirolimus + docetaxel	I	Resistant solid tumors		Completed (NCT00703625)