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Angio-Inhibitors in Ovarian Cancer

Nikos G Gavalas, Sofia-Paraskevi Trachana, Meletios A Dimopoulos and Aristotle Bamias*

Department of Clinical Therapeutics, Medical School, University of Athens, Alexandra Hospital, Athens, Greece

Abstract

Ovarian Cancer represents the most fatal type of gynaecological malignancies. The tumor microenvironment consists the region where a number of processes contributing to the pathogenesis of this deadly disease occur. Except the cell proliferation process itself, processes such as angiogenesis can be held accountable for the progress of disease. More specifically, angiogenesis represents a hallmark phenomenon in cancer and a number of studies have shown that it is responsible for the spread of tumor and metastasis in most types of cancer including ovarian cancer. The process leads to new blood vessel formation and stabilization of the tumor vasculature. In recent years angiogenesis has been given considerable attention in order to identify novel targets for developing effective anti-tumor therapies. Among other families of molecules, growth factors have been identified to play important roles in driving the process of angiogenesis and thus the formation of new blood vessels that play the key role in supplying cancer with appropriate nutrients, hence allowing its spread and metastasis. Such molecules include the vascular endothelial growth factor (VEGF), the platelet derived growth factor (PDGF), the fibroblast growth factor (FGF) and the angiopoietin (Ang)/Tie 2 receptor complex. These proteins are key players in molecular pathways located within the tumor cell and they have been recently under heavy research being in the spotlight of the development of anti angiogenic molecules that may act as stand-alone therapeutics (monotherapy) or in combination with current treatment regimes such as standard chemotherapy. Such molecules include Bevacizumab, Sorafenib, Imatinib mesylate, Sunitinib, Trebananib, Aflibercept, Intedanib, Pazopanib, and Cediranib. There is also a special reference to the possible angio-agenic effect that paclitaxel may confer either in monotherapy or in combination with other agents. The roles of these molecules that have been developed in order to combat angiogenesis are described in this paper.

Keywords: Ovarian; Cancer; Angiogenesis; Pathway; Inhibitors; Molecular

Pathogenesis of Ovarian Cancer

Cancer consists one of the main public health problems globally and it constitutes one of the most frequent causes of death in the Western world. A total of 1,665,540 new cancer cases and 585,720 deaths from cancer have estimated to occur in the United States only in 2014 according to Siegel et al. [1]. On the other hand and in accordance to the increased disease and mortality rates every year, the economic burden of cancer is furthermore associated with costs and expenditure such as prevention, screening and treatment services and the associated lost productivity due to cancer-related death [2,3]. Ovarian cancer consists the most fatal gynecologic type of cancer. In terms of pathology, epithelial ovarian cancers are classified into five main types including Endometroid Carcinomas (EC), High-Grade Serous Carcinomas (HGSC) Clear Cell Carcinomas (CCC), Mucinous Carcinomas (MC) and Low-Grade Serous Carcinomas (LGSC) [4]. It has to be noted that the referred distinct histological sub-types share only few molecular similarities and many of them arise from non-ovarian tissues [5]. To date, contemporary therapeutic approaches are common for all different subtypes of epithelial ovarian cancer. It is of importance to note that the effectiveness of the cytotoxic drugs used (e.g. platinum compounds) has reached a plateau as been indicated by the unaltered 5-year survival of ovarian cancer patients the last 15 years [6]. Ovarian carcinomas have been considered to arise from the epithelium that lines the ovarian surface. The latter is composed from a layer of flat to cuboidal epithelial cells that derive from the embryonic coleomic epithelium [7].

The theory behind the above includes the invagination of the ovarian surface epithelium. The exposure of the invaginated epithelium to stimulation by hormones promotes its malignant transformation [8], with the normal ovary lacking constituents that resemble the ovarian carcinoma subtypes. Furthermore, ovaries develop embryologically from mesodermal epithelium on the urogenital ridge, separate from the müllerian ducts, and although inclusion cysts are frequently encountered in ovaries, there is no histological evidence that these structures could constitute the precursors of high grade serous carcinomas.

Research in the last decade have generalized that fallopian tube is the site that holds the major interest for the pathogenesis of ovarian cancer, especially in High Grade Serous Carcinoma. More specifically, dysplastic lesions in the fallopian tube of women with germline BRCA1 mutation that were subjected to prophylactic salpingoophorectomy were described [9]. These lesions were later characterized as Serous Tubular Intraepithelial Carcinomas (STICs) and were also described in a number of subsequent studies [10-13]. Kindelberger et al. not only recognized STICs after careful examination of the fimbria in a series of serous ovarian carcinomas but they also identified identical *TP53* mutations among STICs and the corresponding invasive carcinomas [14], providing thus the etiological link between these two entities.

Genetic lesions also reflect the heterogenity of epithelial ovarian

***Corresponding author:** Aristotle Bamias, Professor, Department of Clinical Therapeutics, Medical School, University of Athens, Alexandra Hospital, 80 Vas. Sofias Avenue, 115 28, Athens, Greece, Tel: +3-0210-3381-580; Fax: +3-0210-3381-511; E-mail: bamias@med.uoa.gr

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carcinomas. More specifically, Shih and Kurman have proposed the dualistic model for ovarian carcinogenesis [15] having classified epithelial ovarian carcinomas based on the genetic alterations that are implicated in their carcinogenesis into two types.

Type I tumours include low-grade serous carcinomas, mucinous carcinomas, clear cell carcinomas, endometroid carcinomas and malignant Brenner tumours [15]. They are slow growing tumours and are usually detected at a low International Federation of Obstetrics and Gynecology (FIGO) stage, with most of them confined in the ovary [16].

KRAS and *ERBB2* gene mutations that deregulate MAPK signaling pathway drive carcinogenesis in approximately 70% of LSGC [17,18]. In the case of Low Grade Endometroid and Clear Cell Carcinomas similar genetic alterations are detected, such as those that affect the PI3K signaling pathway [19] and genome-wide mutation analysis in such tumours have also shown the implication of tumour suppressor genes in their pathogenesis [20].

Regarding type II tumors, the predominant genetic alteration that drives carcinogenesis is *TP53* mutations. High Grade Serous Carcinomas (HGSCs) and High-Grade Endometroid Carcinomas harbor *TP53* mutations in >95% of cases [21]. Mutations in the *TP53* gene, result in increased genomic instability detected in HGSCs [22,23]. DNA copy number gains or losses have been also detected in genes such as *PIK3CA* [24,25] and mutations in *BRCA1/2* genes that characterize cases of familiar ovarian carcinomas are rarely encountered in sporadic cases.

Although the presence of newly approved molecular therapies for ovarian carcinomas seems to be promising [26-28], the lack of well defined biomarkers that could improve their effective use is a bigger problem. The need to improve our understanding of ovarian cancer at the molecular and cellular level by recognizing the cell of origin, identifying precancerous lesions and delineating the pathogenesis of the disease, is therefore highlighted and processes such as angiogenesis are currently under focus in order for more potent drugs to be discovered.

Angiogenesis in Cancer Pathogenesis

Angiogenesis is the process of new blood vessels formation, and it constitutes a hallmark process of cancer progress. It is a rather complex process and involves a large number of cytokines and corresponding receptors. It occurs during the menstrual cycle and also wound healing in the ovaries and the endometrium, in adult life. In terms of terminology, angiogenesis term was found more than a century ago [29], and its meaning was later fully elucidated by Judah Folkman [30]. Angiogenesis has been shown to be a necessary process for oncogenesis as well as subsequent tumor growth and dissemination through the process of metastasis [29,30].

Microvessel related studies revealed that the initiation of angiogenesis may occur during the growth of human cancers [31,32] and in the case of ovarian cancer, the process has also been associated with the formation of malignant ascites [33,34].

During oncogenesis, tumor endothelial cells, are able to divide up to 50 times faster than normal endothelial cells, providing them with a significant growth advantage over normal counterparts. The architecture of the tumor blood vessels exhibits differences to the architecture of normal blood vessels, thus showing rather abnormal in shape. Tumor vessels exhibit high vascular permeability, poor blood flow, and a rather irregular shape when compared to normal ones [35] and the elimination of the angiogenic process may result in the inability of the tumor to grow further.

The angiogenesis detailed mechanism is quite complex and it is yet to be fully elucidated. In general, cancer cells release pro-angiogenic factors such as the Vascular Endothelial Growth Factor (VEGF) [36,37]. These factors activate endothelial cells, leading to new blood vessel formation, and angiogenesis is initiated. The angiogenic process within the tumor microenvironment includes the interaction of angiogenic growth factors with corresponding receptors, this leading to endothelial cell activation, and vascular remodeling.

Pro-angiogenic factors action is counterbalanced by anti-angiogenic action by numerous other factors such as thrombospondin [38] and this balance has been termed the angiogenic switch [36,38]. In the case of normal tissues, the angiogenic switch is turned off, resulting in a balance between pro- and anti-angiogenic factors. In tumor tissues though balance is leaning towards the pro-angiogenic factors and as a result angiogenesis occurs [36,38]. The pro-angiogenic factors are diffused from the tumor cells, bind onto adjacent endothelial cells in the case of mature blood vessels and trigger a process called sprouting [39]. In this case, switching to the angiogenic phenotype leads to the formation of new blood vessels, a process that occurs from pre-existing vasculature [40-41]. The newly formed vessels act by infiltrating the tumor mass and promote tumor expansion and subsequent metastatic spread, therefore contributing to the pathogenesis of cancer. An overview of the angiogenic process is shown in Figure 1.

Angiogenesis is also involved in the metastasis of the tumor to the peritoneal cavity. At the time of metastasis tumor cells from their organ of origin are secreted and move over to the peritoneum where they eventually reach the innermost layer of the peritoneum that is the mesothelium. The mesothelium forms a cellular monolayer supported by a basement membrane. Tumor cells then adhere to the mesothelium followed by penetration of the mesothelium so tumor cells gain access to the submesothelial connective tissue. Invasion of the connective tissue provides the scaffold for further tumor proliferation, thereby establishing a metastatic deposit. The final step in this process is the induction of angiogenesis for sustainability of the tumor proliferation potential and also the achievement of further metastatic growth.

Peritoneal mesothelial cells have been shown to secrete angiogenic factors such as VEGF and Fibroblast Growth Factor (FGF) [42,43]. IL-1β and TNF-α have been shown to facilitate an increase in the expression of pro-angiogenic factors whereas proteins such as IL-2 inhibited secretion of such pro-angiogenic proteins [42]. IL-1β has been shown to act in a similar way in ovarian cancer [43]. In ovarian cancer, the peritoneum seeding which is observed in these cases results also in ascites formation [44], and VEGF seems to act as an important mediator of neovascularisation and metastasis [45-47]. Therefore there is a strong indication that angiogenesis may play a role in cancer metastasis in the peritoneum with mesothelial cells playing significant role in the process.

Angiogenesis plays an important role in all types of cancer including gynaecological ones [48,49], thereby a role for angiogenesis in the pathophysiology of ovarian cancer has now been established. We will further refer to inhibitors of this process as have been reviewed in the literature.

Angiogenesis Inhibitors in Ovarian Cancer

Angiogenesis poses an important process for ovarian cancer dissemination, therefore it is of significance to attempt to come up with

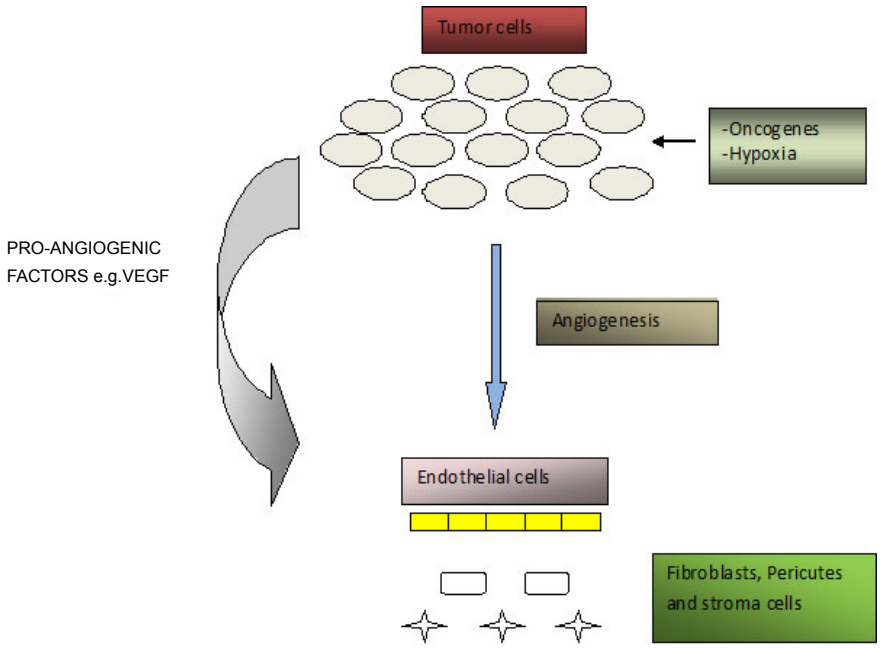

Figure 1: An overview of the angiogenic process. The figure shows briefly components of the angiogenesis process. As tumors grow the necessity for oxygen and nutrients becomes greater. Hypoxia then stimulates cancer cells to produce and secrete growth factors that act on endothelial cells and pericytes, thus stimulating angiogenesis.

strategies that target angiogenesis pathways. Such agents have been now developed that act alone or in combination with chemotherapy in order to confer a substantial effective treatment [50,51].

Bevacizumab

The rationale for the usage of agents such as Bevacizumab is targeting the VEGF pathway, a molecular cascade of signaling events that plays a crucial role in angiogenesis [36,37]. VEGF plays an important role in the angiogenic process itself but also in the survival of immature blood vessels before they reach maturation [52].

The VEGF pathway includes the seven members of the VEGF family, namely VEGF A-E and PIGF 1 and 2 (Placental Growth Factor 1 and 2) that act as ligands and bind onto corresponding receptors on the target cell surface, namely VEGFR 1-3 [53,54]. As in the case of other tumors, the isoform $VEGFA_{165}$ is the main functional molecule in the pathogenesis of ovarian cancer [55,56].

VEGF expression has been shown to be regulated by factors such as the Insulin Growth Factor 1 (IGF-1) and IL-6 [57,58] and by mutations in genes such as p53, *ras*, *src*, vhl [50,59] Functionwise, VEGFR2 is the main receptor isoform through which VEGF mediates its effects directly related to angiogenesis [60,61]. VEGFR1 has a less defined role but it may play a role as a decoy receptor for VEGFR2 [62].

VEGF is produced by cancer cells and relates to the metastatic potential of a number of different types of tumors as in the case of ovarian cancer as well [51,63] and it constitutes an important mediator of ascites formation in the latter stages of the disease [64,65]. Intracellular signaling molecules that comprise the cascade of events that lead eventually to angiogenesis include molecules of the JAK and STAT pathway, PI-3 kinases, and MAP kinases [51,66,67]. The activation of the JAK-STAT pathway has been correlated with the upregulation of VEGF and intracellular signaling in angiogenesis, especially the upregulation of STAT3 and STAT5 [67]. MAP kinases are also involved in an interplay with VEGF levels [67,68]. An autocrine loop of VEGF/VEGFR has been indicated to be responsible for the initiation of signaling [54,67].

Except the referred molecules, there are other proteins that have been lately studied and shown to be involved in a signaling interplay with the VEGF/VEGFR complex. These include the Src kinases, [69], and phospholipase C that may interact with Erk/MAPK molecules enhancing the VEGF effect on vascular permeability and vessel formation [70].

Bevacizumab, is an anti-VEGF monoclonal antibody that has exhibited satisfactory action as a single phase treatment agent in phase II trials in recurrent epithelial ovarian cancer [50,71]. In general, it is a humanized monoclonal antibody that binds the VEGF molecule, especially the VEGF-A isoform, thus neutralizing the VEGF activity. Bevacizumab has also been used in combination with other therapeutic agents such as platinum compounds e.g. carboplatin, and other agents such as paclitaxel, topotecan, docetaxel [72-76]. Pre-clinical studies include those from Mesiano et al. that tested Bevacizumab's activity in immunodeficient mice and showed that the drug inhibited subcutaneous tumor growth, and completely abrogated ascites formation [77]. Similar results showing synergistic effects of the drug alongside paclitaxel were also shown [78]. The role of Bevacizumab in ovarian cancer has been further established, showing that it increases the efficacy of chemotherapy in the initial management of the disease [79,80] but also in relapsed platinum- sensitive [81] and platinum-resistant [82] phases of the disease. The continuous administration of bevacizumab could also significantly prolong survival in vivo [79]. Finally, the effect of bevacizumab on patients maintenance after been treated with a combination of chemotherapy and bevacizumab has recently been shown [26].

Aflibercept (VEGF-Trap)

Aflibercept, or VEGF-Trap as it is commonly called, consists

another possibly potent anti-angiogenic agent. Aflibercept, structure-wise, is a fusion protein combined from different protein domains, including the domain 2 of VEGFR1, the domain 3 from VEGFR2 and these two domains are then attached to the Fc hinge region of a human IgG1 [83]. VEGF-Trap binds all isoforms of VEGF (including PIGF1 and 2) with a picomolar affinity for VEGFA and confers a neutralizing effect [83,84].

Research is ongoing concerning the efficacy of the agent. Pre-clinical data on Aflibercept on ovarian cancer xenografts has shown that it is able to inhibit the effect of angiogenesis by narrowing of vessels, endothelial cell apoptosis and the subsequent stop of blood flow and finally reduction of tumor burden and formation of ascites [85,86]. VEGF-Trap has also been used in combination with other therapeuting agents such as docetaxel and cisplatin [87,88]. Results reported from a phase 1/phase 2 trial of aflibercept in combination with docetaxel in patients with recurrent gynecologic malignancies, including ovarian cancer, reported promising preliminary findings [88]. It has to be noted here also that a recent study by Tew et al. [89] with the drug being administered in a combination with topotecan and pegylated doxorubicin to platinum resistant patients, shows though that there is still a necessity for ongoing trials of the drug.

Intedanib (BIBF 120)

The rationale for using BIBF 1120 (Intedanib) is that it is an agent that blocks the activity of VEGFR 1-3, but also blocks the signaling of other angiogenesis related molecules such as Platelet Derived Growth Factor Receptor a and b (PDGFRa and PDGFRb), and also targets the Fibroblast Growth Factor receptors (FGFRs) [90].

PDGF is an essential protein to pericyte recruitment which is a critical aspect of blood vessel maturation. When the PDGF receptor is activated it leads to upregulation of angiogenic events [91,92]. PDGF has also been shown to interact with VEGF in two ways: either by their signaling cascades being converged or the PDGF pathway may be activated in response to resistance to VEGF inhibition [92, 93]. The importance of PDGF in angiogenesis and in tumor progress is highlighted by the correlation of its expression with ovarian cancer patients' prognosis [94]. The PDGF family contains four isoforms namely PDGF A-D and two receptor isoforms PDGFR-α and PDGFR-β [95,96]. In the case of ovarian cancer, PDGF has been recorded in a large number of samples, PDGFR is also expressed in ovarian carcinomas and it is also present in malignant ascites [97-100].

In the case of FGF, there are 23 FGF isoforms identified, and five receptor molecules (FGFR) have also been described [101]. Upon binding of the ligand onto the receptor, the receptor molecules tend to dimerise leading to the initiation of the intracellular signaling to occur. Disruption of the dimerisation due to events such as alternative splicing may result in inability or increased sensitivity of the ligand to bind the receptors in an effective manner [102-104]. In the case of ovarian cancer, FGF may be also secreted into ascites alongside other angiogenic factors such as VEGF, and it may be contributing to cancer progression and angiogenesis [105,106], so the expression of FGF may also be associated with prognosis [107].

Pre clinical data from mouse models shows that BIBF 1120 exhibits high activity in decreasing vessel density and reducing tumor growth [108]. BIBF 1120 has been used as a single agent but in combination with carboplatin/paclitaxel in epithelial ovarian cancer patients [109]. More studies are necessary in order to establish the full effect of this agent as different side effects have been observed via its use in clinical trials.

Pazopanib

Pazopanib is a tyrosine kinase inhibitor that inhibits the activity of VEGFR 1-3 but it also aims to deactivate PDGFRa and PDGFRb and FGFR -1 and FGFR-3 [110]. In the case of Pazopanib the available pre-clinical data in mouse models showed that the drug may inhibit VEGF- and FGF- induced angiogenesis and the tumor volume may be decreased at a percentage rate of 79%-84% [111,112]. When cell lines were used and Pazopanib was administered, there was a decrease in the VEGFR2 phosphorylation within 4 hours [112]. Clinical studies using Pazopanib as a single agent are currently undergoing in order to establish the time point of intervention, the duration of the treatment and the efficacy of combination therapy alongside other chemotherapy and anti-angiogenic compounds [110].

Cediranib

Cediranib consists another multiple tyrosine kinase inhibitor, and it imposes its effects by neutralizing the effect of molecules such as VEGFR 1-3, FGFR-1 and PDGFRa and PDGFRb [113,114]. In the case of cediranib, the available pre clinical data has shown that the drug inhibits angiogenesis in ovarian cancer in a dose dependent manner [115]. Clinical trials are currently undergoing in phase 2, and it seems that there is a necessity for trials including combinations between cediranib and chemotherapeutic agents.

Sorafenib

Sorafenib is another tyrosine kinase inhibitor that neutralises the effect of VEGFR molecules such as VEGFR-2 and VEGFR-3 and also PDGFRb and other angiogenic factors [116,117]. Studies are ongoing and results for some of them are currently in the process of being reported [117]. In the case of Sorafenib, relevant pre-clinical data has shown that the drug may inhibit tumor growth in nude mice and reduced tumor growth was observed at a significant level [118]. Safety data from recent cinical studies preclude a necessity for continuation of the trials by using Sorafenib as a monotherapy agent in recurrent ovarian cancer [116]. Finally, the combination of Sorafenib alongside the administration of topotecan in platinum resistant ovarian cancer patients seems also to be a promising regime [119].

Sunitinib

Sunitinib is a another angiogenesis inhibitor mainly exerting its effects on VEGFR-2 and PDGFRB among other such molecules. Pre-clinical data in mouse models concerning Sunitinib has shown also that it can inhibit tumor growth and has as an effect the observation of a reduced microvessel density count [120]. Some clinical studies exhibit modest efficacy results e.g. Campos et al. have shown the effect of Sunitinib in women with platinum refractory ovarian cancer [121] whereas modest activity has been shown in other trials [122].

Trebananib (AMG-386)

Trebananib, otherwise called AMG-386, is a peptide-Fc fusion protein that inhibits elements of the angiopoeitin (Ang) pathway and especially the binding of both Ang-1 and Ang-2 onto the Tie-2 receptor [123,124].

By interacting with Tie-2, both Ang-1 and Ang-2 facilitate new vessel production [125]. Moreover, Ang-1 acts also via the use of the Akt/survivin pathway stabilizing the newly produced vessels [126]. Ang-2 may act alone or in combination with other pro-angiogenic factors such as VEGF to establish and enhance vasculature and it also promotes endothelial cell migration by blocking the vessel stabilizing action of angiopoietin 1 [127].

Trebananib pre-clinical data in mouse models shows that it is directly involved with intracellular signaling [128]. Clinical studies using AMG-386 as a single agent or in combination with other agents such as bevacizumab are currently under way and results are awaited [129].

Imatinib mesylate

Imatinib mesylate is a molecule that prevents binding of PDGF onto its corresponding receptor and inhibits subsequent downstream signaling via the use of Akt [130]. Pre-clinical data has been very encouraging in terms of the efficacy of the molecule [131], whereas clinical studies have also shown promising preliminary efficacy in ovarian cancer [132].

Paclitaxel as an Anti-Angiogenesis Agent

There is a hypothesis stating that paclitaxel may indeed play an antioangiogenic role. Paclitaxel is currently used as a monotherapy or in combination with other anti-angiogenic agents such as Bevacizumab. The actual mechanism of its anti-angiogenic effect has not been elucidated yet. Hypotheses on that particular effect include the inhibition of endothelial *in vitro* [133], and also the antiangiogenic effect being exerted due to a possible increased uptake of paclitaxel by endothelial cells [134]. Paclitaxel has been also shown to increase Cox-2 mRNA expression which is a molecule that enhances angiogenesis. Further investigation is necessary in order to shed more light into such mechanisms.

Conclusion

Ovarian cancer represents one of the most fatal types of gynaecological cancer in the world. Angiogenesis is a process that represents a hallmark in cancer progression and metastasis. The angiogenic effects are conferred from specific pro-angiogenic molecules that exert their actions via molecular pathways that occur downstream of the binding of these molecules such as VEGF, PDGF, FGF and Ang with their corresponding receptors. By studying these pathways, new molecular targets for developing novel therapeutic regimes have emerged. Using knowledge that is produced from these studies, new anti-angiogenic molecules have been developed and many clinical trials are underway. Results in many cases are promising, therefore the importance for angiogenesis research to continue in the case of ovarian cancer is high, as it may lead to the discovery of new potent therapeutic regimes but also enhance the efficacy of those currently used in clinic.

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