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# Angiogenesis in Gynaecological Cancers and Anti-angiogenesis Therapy Options

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## ABSTRACT

Angiogenesis is required for the growth of primary tumours and secondary metastases in cancer, including gynaecological cancers. The development and improvement of anti-angiogenesis therapy in gynaecological cancers has been a major focus of fundamental and clinical research. Current anti-angiogenic agents, such as bevacizumab, have modest survival benefits in patients with gynaecological cancer. As a result, a better understanding of angiogenesis and the tumour microenvironment in gynaecological cancers is critical for developing more effective antiangiogenic therapies, whether alone or in combination with other therapeutic approaches. We discuss the molecular aspects of (tumour) blood vessel formation and the tumour microenvironment, as well as a comprehensive clinical review of current anti-angiogenic therapies for gynaecological cancers.We discuss the various phenotypes of angiogenic endothelial cells as potential therapeutic targets, as well as strategies for intervening in their metabolism and approaches for targeting their (inflammatory) tumour microenvironment.

**Keywords:** Angiogenesis; Anti-angiogenic therapy; Endothelial cells; Endothelial cell metabolism

## INTRODUCTION

Gynecological cancers, such as ovarian cancer, cervical cancer, and endometrial cancer, have a global incidence of one million cases and a mortality rate of 500,000 deaths per year. Each of these cancers is distinct, with distinct epidemiologic and genetic risk factors, symptoms, prognoses, and therapeutic responses. However, they all have one thing in common: curative options are limited. As a result, novel molecular and cellular insights are required to improve and personalise treatment strategies. Understanding that vascularization is required for tumour growth has resulted in the development of therapeutic approaches targeting tumour vasculature. Although anti-angiogenic therapy has become part of first-line maintenance treatment in several types of human cancers, including gynaecological cancers, anti-angiogenic agents currently in use are only effective in a subset of patients, and many patients who respond to these drugs initially develop resistance over time.

These disappointing results in cancer patients highlight the critical need for new insights at the molecular and cellular levels into the effects of current angiogenesis inhibitors and/or the discovery of alternative anti-angiogenic agents. For example, bevacizumab produces a radiographic response in recurrent glioblastoma but does not improve patient survival. Throughout adulthood, the healthy endothelium remains dormant and is only activated during physiological processes such as wound healing and the female reproductive cycle. During angiogenesis, endothelial cells rapidly activate and begin to form new blood vessels. This process is tightly controlled by pro- and anti-angiogenic factors. Angiogenesis is essential in the female reproductive system for monthly ovulation and successful pregnancy, but it also plays a role in the pathogenesis of cancer by promoting tumour growth and metastatic spread.

## LITERATURE REVIEW

Cancers with a high microvessel density frequently

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have a poor prognosis and a higher risk of recurrence. The female reproductive system and its cancers have such an angiogenic molecular signature that anti-angiogenic therapy is theoretically promising. The current review describes the process of angiogenesis and its role in cancer in general, as well as the genetic and metabolic regulators of angiogenesis in the context of the female reproductive system and their role in ovarian cancer, cervical cancer, and endometrial cancer. We highlight existing and novel therapeutic strategies for targeting angiogenesis in these types of cancers and discuss the benefits and drawbacks of these approaches.

Angiogenesis is the process by which growing tissues become vascularized. Cells grow along existing vessels in vessel co-option, a type of passive angiogenesis. Splitting of existing blood vessels characterises intussusceptive angiogenesis. The most efficient type of vascularization is sprouting angiogenesis. Vasculogenic mimicry is a tumour cell-organized form of vascularization that results in vascular networks composed of transdifferentiated cancer cells with an EC phenotype. During the sprouting angiogenesis process, developing capillaries are guided by specialised ECs located at the top of growing vessels, known as tip cells. Tip cells proliferate slowly, have stress fibres with probing filopodia, and migrate into the extracellular matrix towards an angiogenic growth factor gradient. As a result, tip cells absorb directional cues from their surroundings.

## DISCUSSION

Furthermore, tip cells actively recruit pericytes and non-vascular cells, most likely through the secretion of platelet-derived growth factor-B. Pericytes share a basal lamina with the ECs of capillaries and post-capillary venules in resting vessels and are involved in vessel wall stabilisation and EC proliferation control. Pericytes in sprouting angiogenesis live outside the capillary wall, which is known as 'extramural,' and migrate alongside the angiogenic sprout. Tip cells are followed by stalk cells, which, in contrast to tip cells, are highly proliferative, produce fewer filopodia, form a vascular lumen, and form adherens and tight junctions to keep the new sprout stable. Tubulogenesis, the process by which ECs form lumens, is a critical step in angiogenesis that involves interactions with the ECM and cytoskeletal reorganisation.

The phalanx cells, the third known specialised EC, tightly align and form a smooth internal monolayer of the newly formed blood vessel. Phalanx cells have a dormant phenotype, do not proliferate, and can live for many years. These specialised ECs have tight junctions and help to normalise and stabilise the vasculature through increased cell adhesion. Finally, a new vascular loop is formed by connecting two sprouts of endothelial tip cells, resulting in a continuous lumen, a process known as anastomosis. Angiogenesis performs physiological functions in the female reproductive system that other organs do not. The ovaries and endometrium go through cyclical changes that are associated with angiogenesis and subsequent blood vessel loss. As a result, the ovaries and endometrium produce both pro- and anti-angiogenic factors. In fact, both basic FGF, the first proangiogenic growth factor discovered, were discovered in human ovaries. ANG2 was the first anti-angiogenic factor discovered to function as an endogenous regulator of blood vessel regression, and it is abundant in the ovarian corpus luteum during luteolysis, a process that involves the structural and functional degradation of the corpus luteum and its associated vasculature at the end of the ovarian cycle [1-5].

Angiogenesis is one of the most important processes in the development of primordial follicles into ovulatory follicles and, eventually, a corpus luteum in the ovaries. The cyclic growth and maturation of primordial follicles, as well as luteal regression, are dependent on angiogenesis and the subsequent breakdown of blood vessels. Primordial follicles lack their own vascular network and rely on blood vessels in the surrounding stroma for maintenance. An antrum develops in the follicles as they grow, and ECs of blood vessels in the adjacent stroma are activated for sprouting angiogenesis into the thecal layer [6].

## CONCLUSION

The prognosis for recurrent and advanced epithelial ovarian cancer, cervical cancer, and endometrial cancer is poor, and current systemic therapies are ineffective. Anti-angiogenic agents, of which bevacizumab is the most widely used in gynaecological cancers, have also been FDA approved. The survival benefit for patients with ovarian cancer, cervical cancer, and endometrial cancer, on the other hand, is disappointing. In patients with gynaecological cancers, other strategies, such as dissociating pericytes from the tumour vasculature and targeting both ECs and pericytes to overcome anti-VEGF therapy resistance, show more promising results. However, these strategies have unintended consequences because capillary pericyte coverage disrupts systemic endothelial integrity, resulting in vessel leakage, edoema, and cancer cells entering the vascular system to metastasize more easily.

Several tyrosine kinase inhibitors, administered as single agents or in combination with chemotherapy, demonstrated only modest efficacy in ovarian cancer, cervical cancer, and endometrial cancer. VDAs targeting established vasculature have only been tested in clinical trials for ovarian cancers, in combination with chemotherapy or other anti-angiogenic compounds. Again, patient survival was only marginally extended. As a result, new avenues must be explored in order for anti-angiogenesis agents such as VDA to be successful. Combinationtherapies with metabolism-targeting therapeutics, ECM-targeting agents, and antiinflammatory agents are appealing options that merit further investigation.

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## CONFLICT OF INTEREST

There are no conflicts of interest by author.

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