Review article
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Tumor angiogenesis and endometrial cancer

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Increasing importance is given to the clinical significance of the new formation of vessels (angiogenesis) in the course of physiological, inflammatory and neoplastic processes. Angiogenesis is best studied in the growth of malignant tumors, since cancer may be regarded as the most important angiogenesis-dependent disease. Vascular endothelial cell proliferation, migration, and capillary formation are stimulated by angiogenic growth factors, which include the proteins vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), and transforming growth factor, and eicosanoids synthesized from n-6 fatty acids. Angiogenesis plays an important role in physiological proliferation of the endometrium and formation of corpus luteum in the second half of menstrual cycle. The present study showed that microvessel counts affect prognosis of patients with endometrial cancer. Analysis of angiogenesis in endometrial cancer may be a useful biologic parameter and additional study of neovascularization is required. Tumor angiogenesis is regulated by the balance of stimulators (e.g., VEGF, bFGF) and inhibitors of angiogenesis (e.g., angiostatin, endostatin, angiostatic steroids). Measuring angiogenesis (blood vessel density) and/or its main regulators such as VEGF and bFGF in solid tumors, or the levels of these growth factors in the serum or urine provides new and sensitive markers for tumor progression, metastasis and prognosis.

KEY WORDS: *Endometrial Neoplasms; Neurovascularization, Pathologic; Neurovascularization, Physiologic; Angiogenesis Factor; Prognosis*

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INTRODUCTION

Tumor angiogenesis is defined as the formation of neovessels from preexisting vascular structures, mainly capillary and venules, under the influence of a malignant tumor (1,2). In 1971, Folkman reported that angiogenesis is mediated by angiogenic molecules, inducing the growth of a close capillary network that surrounds and invades tumors (3,4). This hypothesis has been supported by indirect and direct evidence from many studies (5,8). Angiogenesis are stimulated by the balance of stimulators vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), and transforming growth factor, and eicosanoids synthesized from n-6 fatty acids and inhibitors of angiogenesis (e.g., angiostatin, endostatin, angiostatic steroids) (9,10).

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The "angiogenic switch" and tumor angiogenesis play a critical role in the growth and metastasis of solid tumors. The stimulation of angiogenesis during carcinogenesis is the result of the rupture of the balance between pro- and anti-angiogenic factors. This rupture may be due to the overexpression of angiogenic factors or the loss of local anti-angiogenic factors (11,12). Recent studies show the importance of tumor angiogenesis as an essential factor that affects survival rate and malignant potential of some gynecological malignant tumors. The importance of angiogenesis in gynecological oncology is as follows (13-19):

1) Intratumoral vessel density is an indicator for the emergence and growth of malignant tumors and their precursor lesions,
2) Intratumoral vessel density is an independent prognostic factor for solid malignancies and
3) The inhibition of tumor angiogenesis by means of anti-angiogenetic substances causes suppression of tumor growth.

ANGIOGENESIS IN ENDOMETRIAL CANCER

Angiogenesis plays an important role in the regulation of the female menstrual cycle. That important role is especially

expressed during the second half of menstrual cycle.

The function of angiogenetic factors in the emergence of endometriosis and in female and male infertility is currently under study. In obstetrics, the new formation of blood vessels is significant for the implantation of impregnated blastocysts and for the development and growth of the placenta (20).

Neoangiogenesis in endometrial cancer seems to have important influence on prognosis of patients.

First reports found that high microvessel counts had adverse effect on prognosis in patients with endometrial cancer (21-23).

Mazurek et al. found statistically significant differences in total angiogenic points' density between groups of various clinical FIGO staging, specifically between Ia and Ib, Ic, II. A positive correlation was found between the clinical stage of the disease (according to FIGO) and the total angiogenic points' density, density of endothelial cells and the density of vessels with viable lumen (counts/sq. mm calculated from the central parts of the tumor) (24).

Capillary density in recurrent endometrial cancer also showed neoengiogenesis as factor that correlates with survival. Among patients with recurrent disease, those with a low capillary count had mean survival of 64 months. Patients with recurrent disease with tumors of high capillary density had a mean survival of 45 months ($p = 0.002$) (23).

Obermair et al. show that high intratumor microvessels count is associated with poor survival (25).

Seki N, et al. provide evidence that the expression vascular endothelial growth factor (VEGF) and platelet-derived endothelial cell growth factor (PD-ECGF) are involved in the promotion of angiogenesis in endometrial cancer. In addition, VEGF and PD-ECGF might contribute to the aggressive potential of low-grade tumors or certain histological subtypes with unfavorable prognosis through the induction of angiogenesis (26).

Selvesen et al. reported a 5-year survival probability rates of 57% and 90% for patients with high and low microvessel counts, and in contrast Wagatsuma et al. reported a 0% survival rate in patients with high microvessel counts (27,28).

In endometrial cancer the mean microvessel count per mm^2 varies from $77/mm^2$ to $842/mm^2$ when sections were stained for factor VIII-related antigen and enumerated at 400X magnification (21,22).

A highly sensitive and reliable antigen for highlighting vascular endothelial cells is CD34 (29). By using this marker Obermair et al. found a median microvessel count of $72/mm^2$ in patients with stage I-III endometrial carcinoma. For 5 years, the overall survival probability was 82.2% (+/- 7.6) in 69 patients whose tumors had microvessel counts at or below 100/field, and 52.0%(+/- 13.2) in 24 patients whose primary tumors had microvessel counts above 100/field ($p=0.004$) (25).

Hashimoto et al. reported an influence of tumor- associated macrophages (TAMs) in microvessel density and count. TAMs infiltration was significantly high in tumors with deep myometrial invasion, high grade and elderly patients. Microvessel count strongly correlated with TAMs in tumor stroma ($p=0.0002$). However, associated macrophages may play a crucial role in the promotion of angiogenesis, but cannot be used to predict prognosis of patients with endometrial cancer (30).

Ishiwata I, et al. reported tumor angiogenic activity from tumor angiogenesis factors (TAFs) produced by 25 cell lines that was assayed onto chorioallantoic membranes (CAMs). Neovascularization occurred prominently in such cell lines, as HTBOA (poorly differentiated ovarian carcinoma), HUOCA-II (poorly differentiated clear cell adenocarcinoma), HWUA (poorly differentiated endometrial adenocarcinoma), HKUS (uterine cervical small cell carcinoma), and in HOTHC (anaplastic thyroid carcinoma). The cell lines that secreted TAF showed high heterotransplantability in nude mice and produced rapidly growing tumors, which were rich in blood vessels (31).

The study of tumor angiogenesis is currently one of the leading themes in oncology. This is justified by the importance of tumor angiogenesis in the natural history of cancer, the possible applications of angiogenesis markers as prognostic factors and the emergence of innovative anti-tumor treatments based on anti-angiogenic strategies.

Tumor angiogenesis is not specific for one type of tumor and angiogenetic factors of growth cannot be specific for one type of malignant disease. It is a process that has the major role in developing of many types of tumors and metastasis. Immunohistochemical studies showed importance of angiogenic factors and microvessel density in other cancers such as breast cancer, gastrointestinal cancers, soft-tissue sarcoma and others (32-37).

CONCLUSION

Tumor angiogenesis is one of the important events in the natural history of cancer. Applications of angiogenesis markers as prognostic factors and investigation of anti-tumor treatments based on anti-angiogenic strategies as new type of anti-cancer therapy lead us to the new goals in oncology today.

Proliferation of the endometrium and the formation of the corpus luteum in the second half of the menstrual cycle are examples of angiogenesis in the physiological field.

Neoangiogenesis appear to be important factor in development of endometrial cancer.

High microvessel counts in endometrial carcinoma means poor prognostic factor and decrease in survival rate.

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