Angiogenic Factors in Endometrial Cancer

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Endometrial cancer (EC) is the most frequent gynecological malignancy in developed countries and requires a relatively invasive diagnostic evaluation and operative therapy as the primary therapeutic approach. Angiogenesis is one of the main processes needed for cancer growth and spread. The production of angiogenic factors (AFs) appears early in the process of carcinogenesis. The detection of AFs in plasma and tissue and a better understanding of the angiogenic properties of EC may contribute not only to earlier but also more specific diagnosis and consequently tailored and individual therapeutic approaches. AFs and their receptors also have high potential as binding sites for targeted cancer therapy.

Keywords: biomarkers ; angiogenesis ; endometrial cancer ; angiogenic factors ; anti-angiogenic therapy

1. Introduction

Endometrial cancer (EC) is the most frequent gynecological malignancy in the developed world, and its incidence strongly depends on several risk factors [1]. One of the most prominent risk factors is obesity [2][3]. Adipose tissue serves as a storage for hormones that promote the proliferation of endometrial tissue, which leads to malignant alterations. Once endometrial cells become malignant, they obtain the ability of uncontrolled fast growth, which requires a good supply of oxygen and nutrients. Such supply via diffusion is extremely limited and can only support tumors smaller than 1–2 mm in diameter [4]. For larger tumors, EC cells must start to produce angiogenic factors (AFs), i.e., special cytokines, which are secreted into the surrounding tissue and nearby vessels, causing angiogenesis and the delivery of nutrients to the cancerous cells. Elevated AF levels can also be detected in the systemic circulation, indicating a potential non-invasive strategy to detect cancer in its early stages [5].

Altered AF levels in plasma and tissue and understanding of angiogenesis in EC may contribute to not only earlier but also more specific diagnosis. Furthermore, AFs and their receptors are also potential binding sites for targeted cancer therapy and may contribute to more tailored therapeutic approaches to EC.

2. Angiogenesis in Cancer

During the initial stage of tumor growth and development (i.e., before the tumor's size exceeds 1–2 mm3), the tumor is independent of the vascular network, as nutrients and oxygen can be obtained via diffusion. During the later stages of carcinogenesis, such nutrient supply becomes insufficient. Due to rapid tumor growth, high interstitial pressure, and larger distances between cancer cells and capillaries, hypoxia occurs in solid tumors. Hypoxia is an important controller of the angiogenic switch that is mainly regulated by hypoxia-inducible factor-1α (HIF-1α), a transcription factor that activates the transcription of a set of key genes involved in cell survival under hypoxic conditions, e.g., those involved in initiating angiogenesis [22]. In this way, new vasculature is formed in and around the tumor that provides essential nutrients and oxygen for the tumor cells and allows continuous growth and unlimited proliferation. Simultaneously, this vascular network is used for metastatic spread to other organs [4,23]. The density of the capillary network has been shown to be a prognostic factor for EC. Blood microvessel density was associated with deeper myometrial invasion, positive lymphovascular invasion, positive lymph node metastasis, and poor overall survival in EC patients [24].

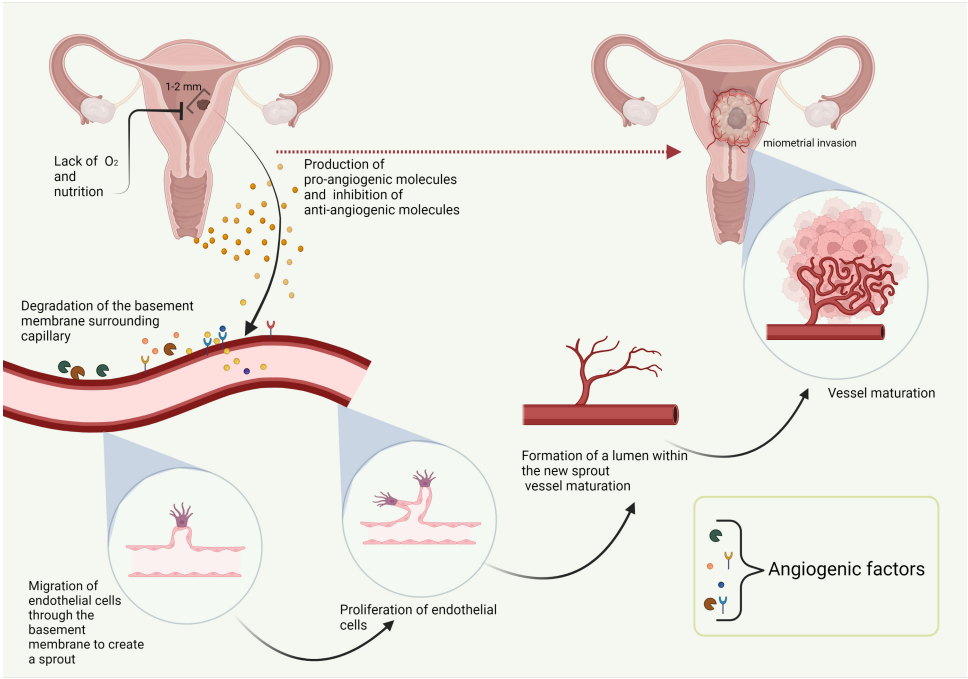

Figure 1. Angiogenesis in endometrial cancer. Created with BioRender.com.

3. Diagnostic Value of AFs

Normal angiogenesis is regulated by both molecular activators and inhibitors. In cancer, the balance between them is disturbed in favor of angiogenic activators. More than a few dozen different proteins have been identified as pro-AFs, including growth factors, cytokines, proteases, protease inhibitors, trace elements, oncogenes, and endogenous modulators [25]. The production of AFs by cancer cells alters AF levels in the surrounding tissue and blood plasma. Altered AF levels may thus represent potential markers that could detect cancer from blood plasma samples in the early and prognostically favorable stages of cancer [26]. AF plasma concentrations could also represent an important additional diagnostic tool for a more precise diagnosis of EC, which could also guide decision-making regarding the extent of surgical treatment.

4. Anti-Angiogenic Treatment of EC

The standard treatment of EC consists of surgery with or without adjuvant radiotherapy and/or chemotherapy, depending on the risk of disease recurrence [6]. EC at the advanced stage has a very poor prognosis under conventional treatment: the 5-year overall survival rate is 40–65% for stage III and 15–17% for stage IV of the disease [7]. Due to the lack of effective treatments, treating patients in an advanced-stage, recurrent, or refractory setting is very challenging. However, advances in our understanding of the molecular mechanisms of EC progression have revealed novel binding sites for targeted therapies, which are emerging as innovative and promising cancer treatment strategies.

Various potential therapeutic approaches are being investigated. Due to the importance of new vasculature for tumor growth, efforts have been made to develop anti-angiogenic therapies for cancer treatment in recent decades. The main classes of anti-angiogenic agents are anti-VEGF monoclonal antibodies (e.g., bevacizumab), soluble VEGFRs (e.g., aflibercept), inhibitors of angiopoietin-Tie2 receptor (e.g., trebananib), and tyrosine kinase inhibitors (e.g., brivanib, cediranib, nintedanib, sunitinib, and lenvatinib) [8].

The earliest exploration of anti-angiogenic agents in EC was a phase-II study of thalidomide in refractory EC performed by the Gynecologic Oncology Group Foundation [9]. It demonstrated an association between elevated plasma VEGF levels and poor prognosis, while thalidomide exhibited limited ability to delay the progression or reduce angiogenic marker levels. Nonetheless, several approaches have been developed to block VEGF action and have achieved good clinical efficacy, including blocking antibodies, decoy receptors, and small interfering RNA against VEGF-A [10][11][12]. The best-known anti-angiogenic agent for gynecological malignancies is bevacizumab, a humanized anti-VEGF monoclonal antibody, currently approved by the FDA as a combination and/or maintenance treatment for certain ovarian and cervical cancer patients. Several phase-II studies have been conducted with bevacizumab in EC patients; however, the results of phase-III studies in EC patients are limited. Although clinically active in various solid cancers, these drugs are associated with typical adverse effects of anti-VEGF treatment, e.g., hypertension, thrombosis, emboli, bleeding, impaired wound healing, proteinuria, bowel perforation, and CNS disorders, which lead to treatment discontinuation in many patients [13]. Furthermore, many tumors are either inherently resistant or gradually develop adaptive resistance to VEGF pathway

inhibition therapies [14]. This dictates the use of anti-VEGF treatments, like other targeted treatments, only according to selected molecular subgroups.

In the GOG-86P trial (NCT00977574, [105]), researchers implemented translational research to examine results for common somatic mutations and microsatellite instability for associations with patients' outcomes in each of three arms, containing either bevacizumab, temsirolimus, or ixabepilone, with standard paclitaxel and carboplatin in advanced or recurrent EC. Progression-free survival and overall survival were not increased in any of the experimental arms. However, in a post hoc analysis of the data, *CTNNB1* mutations (present in up to 20% of EC patients) were associated with a significantly increased PFS in bevacizumab-treated patients. *CTNNB1* mutations may be associated with increased VEGF expression and angiogenesis. They are primarily found in the subset of low-grade endometrioid tumors that have a higher risk of recurrence. The authors conclude that *CTNNB1* mutations may serve as a predictive biomarker for bevacizumab treatment.

Similarly, the assessment of *TP53* mutation status in the same trial showed that women with *TP53* mutant EC had both improved progression-free and overall survival when treated with bevacizumab and chemotherapy, whereas women with *TP53* wild-type tumors showed no difference in outcomes. This might be due to the cell cycle regulation disruption and enhanced angiogenesis in tumor cells due to the loss of wild-type p53 repression of pro-angiogenic factors including the bevacizumab target VEGF-A [15].

Another group of anti-angiogenic agents evaluated in clinical trials for use in EC patients are tyrosine kinase inhibitors of VEGFRs. Nintedanib showed modest activity with an objective response rate (ORR) of 9.4% in the treatment of advanced or recurrent EC and did not meet the study's primary endpoint of efficacy. Nevertheless, preclinical trials on nintedanib suggest that it may be more effective in tumors with loss-of-function *TP53* mutations [16]. Monotherapy with cediranib for recurrent or persistent EC was well tolerated and showed sufficient activity (with a median PFS of 3.7 months and median OS of 12.5 months), which warranted further investigation for recurrent EC [17]. Brivanib was also well tolerated and worthy of further investigation as a single agent in recurrent or persistent EC, based on PFS at 6 months (30.2%). Rates of 6-month PFS were higher for endometrioid carcinoma (31.5%) or mixed epithelial subtypes (50%) compared with serous carcinoma (10%) [18]. The combination of levanitinib and pembrolizumab was assessed in the phase-II KEYNOTE 146 trial (NCT02501096) in advanced EC patients. The EC cohort (n = 108) showed an ORR of 64% in the mismatch-repair-deficient group and 36% in the mismatch-repair-proficient group [19]. In July 2021 (after accelerated approval was granted in 2019), the FDA approved this combination for EC patients with advanced EC that is not microsatellite-instability-high or mismatch-repair-deficient and who exhibit disease progression following prior systemic therapy but are not candidates for curative surgery or radiation [20].

Aflibercept serves as a decoy receptor for VEGF binding at high affinity. In the Gynecologic Oncology Group Phase-II clinical trial, it met pretrial activity parameters but was associated with significant toxicity at the dose and schedule used [21]. Trebananib is an Fc fusion peptibody that prevents Tie2 receptor activation through binding of both Ang-1 and Ang-2. However, a phase-II trial showed an ORR of 3.1% for recurrent or persistent EC, with insufficient single-agent activity to warrant further investigation of trebananib [22].

5. Conclusions

Angiogenesis represents an important step in the pathogenesis of EC development, progression, and metastases and thus an opportunity for better diagnostic and tailored therapeutic approaches. There are conflicting results regarding the role of AFs in EC, and more clinical studies that evaluate circulating AFs are necessary to reach a uniform conclusion regarding the use of AFs as diagnostic and prognostic biomarkers. However, although the results from different studies regarding the use of AFs as biomarkers for gynecological cancer are not conclusive, there is a clear pattern of decreased progression-free survival and overall survival rates when pro-AFs are over-expressed in either serum or EC tissue. Relevant studies concluded that increased AF levels were correlated with worsening in the clinical stage and histological grade of EC and were associated with poorer prognosis.

Molecular changes occur earlier than phenotypic changes, and thus identifying new biomarkers may enable early diagnosis and facilitate decision making regarding the appropriate therapeutic (surgical and/or pharmacotherapeutic) measures. There is a trend toward a combined molecular and histological approach to risk stratification, and the discovery of robust prognostic biomarkers will eventually lead to improved survival outcomes for women with EC.

Anti-angiogenic therapy has already been incorporated into the regular treatment of several types of human cancers, including EC and other gynecological cancers. However, the anti-angiogenic agents in use today are only effective in a

subset of patients, and many initial responders become resistant over time. This emphasizes the urgent need for a better understanding of the molecular and cellular effects of current anti-angiogenic agents as well as the discovery of alternative inhibitors of angiogenesis. As learned from recent clinical trials, proper design and conduct of translational research can yield important findings and allow assessment of treatment efficacy within biologically similar tumors. This may help to stratify patient populations for future treatment options.

References

1. Lortet-Tieulent, J.; Ferlay, J.; Bray, F.; Jemal, A. International Patterns and Trends in Endometrial Cancer Incidence, 1978–2013. J. Natl. Cancer Inst. 2017, 110, 354–361.
2. Arem, H.; Park, Y.; Pelser, C.; Ballard-Barbash, R.; Irwin, M.L.; Hollenbeck, A.; Gierach, G.L.; Brinton, L.A.; Pfeiffer, R.M.; Matthews, C.E. Prediagnosis Body Mass Index, Physical Activity, and Mortality in Endometrial Cancer Patients. J. Natl. Cancer Inst. 2013, 105, 342–349.
3. Freuer, D.; Linseisen, J.; O'Mara, T.A.; Leitzmann, M.; Baurecht, H.; Baumeister, S.-E.; Meisinger, C. Body Fat Distribution and Risk of Breast, Endometrial, and Ovarian Cancer: A Two-Sample Mendelian Randomization Study. Cancers 2021, 13, 5053.
4. Carmeliet, P.; Jain, R.K. Angiogenesis in cancer and other diseases. Nature 2000, 407, 249–257.
5. Roškar, L.; Klančič, T.; Knific, T.; Rižner, T.; Smrkolj, Š. Tie-2, G-CSF, and Leptin as Promising Diagnostic Biomarkers for Endometrial Cancer: A Pilot Study. J. Clin. Med. 2021, 10, 765.
6. Stelloo, E.; Bosse, T.; Nout, R.A.; Mackay, H.J.; Church, D.N.; Nijman, H.W.; Leary, A.; Edmondson, R.J.; Powell, M.E.; Crosbie, E.J.; et al. Refining prognosis and identifying targetable pathways for high-risk endometrial cancer; a TransPORTEC initiative. Mod. Pathol. 2015, 28, 836–844.
7. Lee, Y.C.; Lheureux, S.; Oza, A.M. Treatment strategies for endometrial cancer: Current practice and perspective. Curr. Opin. Obstet. Gynecol. 2017, 29, 47–58.
8. Ferrara, N.; Kerbel, R.S. Angiogenesis as a therapeutic target. Nature 2005, 438, 967–974.
9. McMeekin, D.S.; Sill, M.W.; Benbrook, D.; Darcy, K.M.; Stearns-Kurosawa, D.J.; Eaton, L.; Yamada, S.D. A phase II trial of thalidomide in patients with refractory endometrial cancer and correlation with angiogenesis biomarkers: A Gynecologic Oncology Group study. Gynecol. Oncol. 2007, 105, 508–516.
10. Waldner, M.J.; Neurath, M.F. Targeting the VEGF signaling pathway in cancer therapy. Expert Opin. Ther. Targets 2012, 16, 5–13.
11. Eng, L.; Azad, A.K.; Habbous, S.; Pang, V.; Xu, W.; Der Zee, A.H.M.-V.; Savas, S.; Mackay, H.J.; Amir, E.; Liu, G. Vascular Endothelial Growth Factor Pathway Polymorphisms as Prognostic and Pharmacogenetic Factors in Cancer: A Systematic Review and Meta-analysis. Clin. Cancer Res. 2012, 18, 4526–4537.
12. Ramjiawan, R.R.; Griffioen, A.W.; Duda, D.G. Anti-angiogenesis for cancer revisited: Is there a role for combinations with immunotherapy? Angiogenesis 2017, 20, 185–204.
13. Oza, A.M.; Selle, F.; Davidenko, I.; Korach, J.; Mendiola, C.; Pautier, P.; Chmielowska, E.; Bamias, A.; DeCensi, A.; Zvirbule, Z.; et al. Efficacy and Safety of Bevacizumab-Containing Therapy in Newly Diagnosed Ovarian Cancer: ROSiA Single-Arm Phase 3B Study. Int. J. Gynecol. Cancer 2016, 27, 50–58.
14. van Beijnum, J.R.; Nowak-Sliwinska, P.; Huijbers, E.J.M.; Thijssen, V.L.; Griffioen, A.W. The Great Escape; the Hallmarks of Resistance to Antiangiogenic Therapy. Pharmacol. Rev. 2015, 67, 441–461.
15. Aghajanian, C.; Filiaci, V.; Dizon, D.S.; Carlson, J.W.; Powell, M.A.; Secord, A.A.; Tewari, K.S.; Bender, D.P.; O'Malley, D.M.; Stuckey, A.; et al. A phase II study of frontline paclitaxel/carboplatin/bevacizumab, paclitaxel/carboplatin/temsirolimus, or ixabepilone/carboplatin/bevacizumab in advanced/recurrent endometrial cancer. Gynecol. Oncol. 2018, 150, 274–281.
16. Leslie, K.K.; Filiaci, V.L.; Mallen, A.R.; Thiel, K.W.; Devor, E.J.; Moxley, K.; Richardson, D.; Mutch, D.; Secord, A.A.; Tewari, K.S.; et al. Mutated p53 portends improvement in outcomes when bevacizumab is combined with chemotherapy in advanced/recurrent endometrial cancer: An NRG Oncology study. Gynecol. Oncol. 2021, 161, 113–121.
17. Dizon, D.S.; Sill, M.W.; Schilder, J.M.; McGonigle, K.F.; Rahman, Z.; Miller, D.S.; Mutch, D.G.; Leslie, K.K. A phase II evaluation of nintedanib (BIBF-1120) in the treatment of recurrent or persistent endometrial cancer: An NRG Oncology/Gynecologic Oncology Group Study. Gynecol. Oncol. 2014, 135, 441–445.
18. Bender, D.; Sill, M.W.; Lankes, H.A.; Reyes, H.D.; Darus, C.J.; Delmore, J.E.; Rotmensch, J.; Gray, H.J.; Mannel, R.S.; Schilder, J.M.; et al. A phase II evaluation of cediranib in the treatment of recurrent or persistent endometrial cancer: An

NRG Oncology/Gynecologic Oncology Group study. Gynecol. Oncol. 2015, 138, 507–512.

19. Powell, M.A.; Sill, M.W.; Goodfellow, P.J.; Benbrook, D.M.; Lankes, H.A.; Leslie, K.K.; Jeske, Y.; Mannel, R.S.; Spillman, M.A.; Lee, P.S.; et al. A phase II trial of brivanib in recurrent or persistent endometrial cancer: An NRG Oncology/Gynecologic Oncology Group Study. Gynecol. Oncol. 2014, 135, 38–43.
20. Makker, V.; Taylor, M.H.; Aghajanian, C.; Oaknin, A.; Mier, J.; Cohn, A.L.; Romeo, M.; Bratos, R.; Brose, M.S.; DiSimone, C.; et al. Lenvatinib Plus Pembrolizumab in Patients with Advanced Endometrial Cancer. J. Clin. Oncol. 2020, 38, 2981–2992.
21. Taylor, M.H.; Lee, C.-H.; Makker, V.; Rasco, D.; Dutcus, C.E.; Wu, J.; Stepan, D.E.; Shumaker, R.C.; Motzer, R.J. Phase IB/II Trial of Lenvatinib Plus Pembrolizumab in Patients with Advanced Renal Cell Carcinoma, Endometrial Cancer, and Other Selected Advanced Solid Tumors. J. Clin. Oncol. 2020, 38, 1154–1163.
22. Coleman, R.L.; Sill, M.W.; Lankes, H.A.; Fader, A.N.; Finkler, N.J.; Hoffman, J.S.; Rose, P.G.; Sutton, G.P.; Drescher, C.W.; McMeekin, D.S.; et al. A phase II evaluation of aflibercept in the treatment of recurrent or persistent endometrial cancer: A Gynecologic Oncology Group study. Gynecol. Oncol. 2012, 127, 538–543.
23. Moore, K.N.; Sill, M.W.; Tenney, M.E.; Darus, C.J.; Griffin, D.; Werner, T.L.; Rose, P.G.; Behrens, R. A phase II trial of trebananib (AMG 386; IND#111071), a selective angiopoietin 1/2 neutralizing peptibody, in patients with persistent/recurrent carcinoma of the endometrium: An NRG/Gynecologic Oncology Group trial. Gynecol. Oncol. 2015, 138, 513–518.
