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Perspective

Role of Hypoxia and Angiogenesis in Endometrial Cancer Development and Progression

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DESCRIPTION

In developed nations, endometrial cancer is the most prevalent cancer of the female reproductive system. The majority of occurrences of endometrial cancer, or Endometrioid Endometrial Carcinoma (EEC), occur in women. Endometrial hyperplasia, a premalignant lesion, is often the source of EEC. The growth and development of EEC are significantly influenced by hypoxia and angiogenesis.

Hypoxia is a state of low oxygen tension, which is common in solid tumors due to an inadequate blood supply. Hypoxia activates the Hypoxia-Inducible Factor (HIF) pathway, which promotes the survival and growth of tumor cells. HIF is a transcription factor that regulates the expression of genes involved in angiogenesis, metabolism, cell proliferation, and apoptosis HIF-1 and HIF-1 are the two subunits that make up HIF. HIF-1 is rapidly destroyed by the proteasome in normoxic environments. Under normoxic conditions, HIF-1α is rapidly degraded by the proteasome. Under hypoxic circumstances, however, HIF-1 is stabilised and translocates to the nucleus, where it joins forces with HIF-1 to create a heterodimer that binds to target genes' Hypoxia-Responsive Elements (HREs).

Angiogenesis is the process of new blood vessel formation, which is essential for tumor growth and metastasis. Angiogenesis is regulated by a balance between pro-angiogenic and anti-angiogenic factors. Pro-angiogenic factors include Vascular Endothelial Growth Factor (VEGF), Basic Fibroblast Growth Factor (bFGF), angiopoietin-1 (Ang-1), and angiopoietin-2 (Ang-2). Anti-angiogenic factors include Thrombospondin-1 (TSP-1), endostatin, and angiostatin. In tumors, the balance is shifted towards pro-angiogenic factors, leading to the formation of leaky and abnormal blood vessels that promote tumor growth and metastasis.

Hypoxia and angiogenesis are closely interlinked in EEC. Hypoxia promotes angiogenesis by upregulating the expression of pro-angiogenic factors such as VEGF. VEGF is a potent stimulator of angiogenesis that is overexpressed in EEC. VEGF is regulated by HIF-1α, which binds to HREs in the VEGF promoter. In addition to VEGF, HIF-1α regulates the expression of other pro-angiogenic factors, including bFGF, Platelet-Derived Growth Factor (PDGF), and Transforming Growth Factor Alpha (TGF-α).

Angiogenesis, in turn, promotes hypoxia by increasing tumor oxygen consumption and reducing oxygen diffusion distances. Abnormal blood vessels in tumors are often tortuous, dilated, and disorganized, leading to poor oxygen delivery to tumor cells. Hypoxia, in turn, activates HIF-1α and promotes the survival and growth of tumor cells. Hypoxia also induces genetic instability and immune suppression, which promote tumor progression.

The role of hypoxia and angiogenesis in EEC has been studied extensively in animal models and clinical samples. In animal models, hypoxia and angiogenesis are associated with the development and progression of EEC. For example, HIF-1α knockout mice are resistant to EEC development and anti-angiogenic agents such as bevacizumab inhibit tumor growth and angiogenesis in EEC xenografts. In clinical samples, hypoxia and angiogenesis are associated with poor prognosis and resistance to chemotherapy in EEC patients. For example, high expression levels of HIF-1α and VEGF are associated with poor overall survival and disease-free survival in EEC patients.

Recent studies have also investigated the potential use of hypoxia and angiogenesis as therapeutic targets in EEC. One approach involves targeting the HIF-1α pathway directly. Small molecule inhibitors of HIF-1α, such as PX-478 and digoxin, have been shown to inhibit the growth and angiogenesis of EEC cells *in vitro* and in animal models. Clinical trials are currently underway to evaluate the safety and efficacy of HIF-1α inhibitors in cancer patients.

Another approach involves targeting the VEGF pathway, which is a key mediator of angiogenesis in EEC. Several anti-VEGF agents, including bevacizumab, sorafenib, and sunitinib, have been evaluated in clinical trials for the treatment of EEC.

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Bevacizumab, a monoclonal antibody that targets VEGF, has been approved for the treatment of advanced EEC in combination with chemotherapy. However, the use of anti-VEGF agents in EEC is still controversial due to the potential risk of adverse effects, such as hypertension, proteinuria, and gastrointestinal perforation.

In addition to these approaches, several other strategies have been proposed for targeting hypoxia and angiogenesis in EEC. These include targeting the tumor microenvironment, such as stromal cells and extracellular matrix components, which can modulate hypoxia and angiogenesis. Other approaches include targeting the metabolic pathways that are involved in hypoxia adaptation, such as glycolysis and mitochondrial respiration.