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Anti-angiogenesis approach to genitourinary cancer treatment

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ABSTRACT

Angiogenesis plays a crucial role in the survival, proliferation, and metastatic potential of several tumors, including genitourinary (GU) cancers. Over the last decade, increasing basic science and clinical research have led to the approval of several angiogenesis inhibitors. GU tumors are unique in its pathogenesis whereby specific pathways, such as involvement of the Von Hippel-Lindau gene in clear cell renal cell cancer and aberrant overexpression of vascular endothelial growth factor in prostatic cancers and transitional cell bladder cancers, allow for potential targeting using angiogenesis inhibitors. This review discusses the biologic pathways as well as the rationale for using angiogenesis inhibitors in renal cell, prostate, and transitional cell bladder cancers. This review also focuses on pivotal trials and emerging data on the use of these inhibitors.

1. Introduction

The term angiogenesis was coined over a century ago [1], but was not fully elucidated until the 1960s when the late Dr. Judah Folkman found that tiny tumors grew to about 1 mm in size and stopped expanding in the absence of neovascularization [2]. Since then, several investigators have examined various *in vivo* and *in vitro* bioassays, mechanisms of angiogenesis, proangiogenic molecules, and eventually, inhibitors against these molecules, that have been translated into clinical practice [3]. The angiogenic process in the tumor microenvironment involves the complex interplay of free angiogenic growth factors with their cognate receptors, endothelial cell activation, and vascular remodeling. However, as specific angiogenic inhibitors are discovered, unique challenges exist in the application of these inhibitors and how best to measure the effects in a clinically meaningful way. The most impressive anti-cancer results today are with agents targeting vascular endothelial growth factors (VEGF). For instance, bevacizumab, a monoclonal antibody against VEGF, is the first Food and Drug Administration (FDA) approved targeted angiogenesis inhibitor (first and second-line with chemotherapy in metastatic colon cancer) [4]. It has gained approval in combination with cytotoxic agents in several other solid tumors, including lung and breast cancer. This review will discuss key angiogenic pathways and therapeutic strategies involved in common genitourinary (GU) tumors, specifically clear cell renal cell cancer (RCC), prostate cancer, and transitional cell cancer (TCC) of the bladder.

2. Pathways involved in the angiogenic process

Various mechanisms are involved in the angiogenic process with convergence of these signals permitting transduction and subsequent activation of pathways that promote tumor proliferation, migration, invasion, and ultimately, survival and

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metastasis. The disruption of the balance between pro- and anti-angiogenic growth factors, favoring the former; disruption of endothelial cell adhesion, as well as hypoxic regulation of various molecular and cellular systems, contributes to genetic transcription leading to angiogenesis.

2.1. *Pro-angiogenic growth factors*

The family of VEGF has been the most extensively studied proangiogenic factor with more than seven family members described to date [5–7]. VEGF-A is the main ligand involved for tumor angiogenesis [8–10]. Three VEGF receptors have also been described, VEGFR1 (Flt-1: Fms-like tyrosine kinase-1), VEGFR2 (KDR: kinase-insert Domain-containing Receptor in humans; Flk-1: Fetal-liver kinase-1 in mice), and VEGFR3 (Flt4) [11–15]. VEGF-A binds the receptors VEGFR1 and 2, transducing major signals for angiogenesis. VEGF-A is critical in early survival of the embryo [16] and is also known as the vascular permeability factor because of its specific activity [17]. The tumor cell and its supporting infiltrating macrophages and mesenchymal cells have been shown to secrete VEGF-A [18], which contributes to increased tumor growth and metastasis. Other members of the VEGF family bind and activate varying receptors. For instance, the placenta growth factor (PlGF) binds and activates only VEGFR1 [7], while VEGF-C and D binds VEGFR3, which regulates lymphatic growth. Thus, the VEGF system functions in a paracrine manner, where surrounding cells secrete VEGF and VEGF activates its cognate receptors on endothelial cells, to promote angiogenesis.

2.2. *Disruption of endothelial cell adhesion*

Endothelial cells are part of the vascular system responsible for the integrity of the capillary system. Once an angiogenic phenotype is triggered, endothelial cell activation occurs, which describes a series of events that brings about the invasive, migratory, and proliferative capacity of the endothelial cell [19]. Central to these cell adhesion mechanisms is the integrins, which are the cell surface receptors for the extracellular matrix (ECM). Integrins are a family of heterodimer transmembrane glycoproteins consisting of an α and β subunit [20]. Preclinical studies show that genetic ablation or disruption of various integrins result in early embryonic death thought to be secondary to defects in vascular patterning [21]. These integrins bind several natural ligands, including laminin, fibronectin, vitronectin, fibrinogen, fibrin, thrombospondin, matrix metalloproteinase (MMP-2), and fibroblast growth factor 2 [22]. The integrins mediate signaling events by activating the integrin-linked kinase (ILK), protein kinase B (PKB/Akt), mitogen-activated protein kinase (MAPK), Raf or nuclear factor kappa B (NF-κB) pathways [22], in conjunction with other growth factor receptors, resulting in disruption of cell adhesion, tumor proliferation and migration, and survival.

2.3. *Hypoxic regulation of molecular systems*

Variations in oxygen tension result in activation of different genes that are similarly regulated in cancer. One of the important mechanisms involved in the regulation of VEGF is via the Von Hippel-Lindau (VHL) protein-induced degradation of the hypoxia-inducible factor 1 (HIF-1α). HIF is a heterodimeric transcripton factor composed of an alpha and beta 1 subunit with HIF-1α initially identified as a transcription factor regulating erythropoeitin production in the kidney especially during times of hypoxia [23,24]. In normoxic conditions, HIF-1α interacts with the VHL protein, which functions as the recognition site of the E3 ubiquitin ligase, to allow degradation by 26S proteosomes. However, in times of hypoxia, the hydroxylation of HIF-1α is reduced, thereby allowing the 2 subunits to combine at nuclear hypoxic response elements of target genes, which encodes for angiogenesis [25]. In cells that are deficient in VHL, inappropriate accumulation of HIF-1α occurs even in normoxic conditions. In addition, loss of function of the VHL protein leads to avoidance of HIF-1α degradation, thereby leading to constitutive activation of the target genes VEGF, PDGF and transforming growth factor beta (TGF-β) responsible for angiogenesis, proliferation, and survival.

3. Targeting angiogenesis in GU cancers: renal cell carcinoma, prostate cancer, and bladder cancer

Angiogenesis plays a pivotal role in the pathogenesis of GU cancers, thus providing a rational drug target for using angiogenic inhibitors in these tumors. There is a strong biologic basis for targeting angiogenesis in clear cell RCC, the most common histologic type of RCC. In clear cell RCC, at least 60% of tumors have inactivation of the VHL gene [25]. Mechanisms of inactivation of the VHL gene include deletions, methylation, or mutation [26–28]. The resultant mutation of the VHL gene, which functions as a tumor suppressor gene, causes oversecretion of VEGF by clear cell RCC. This mutant VHL gene can be seen not only in hereditary forms, but also in sporadic RCC. With hypoxia, tumor-associated macrophages also migrate towards the hypoxic center of the tumor [29]. Although VEGF-A is the most widely studied ligand in activation of clear cell RCC, other mechanisms may be operative that are independent of the VHL pathway, involving other ligands like VEGF-B and C [30].

Similarly, in prostate and bladder cancer, neovascularization with angiogenesis has been described. Histological studies measuring the microvessel density (MVD) in prostate cancer has been used as a prognostic factor for predicting aggressiveness and metastasis [31]. The same has been shown in bladder cancer with MVD being associated with significant differences in disease-free survival (DFS) and overall survival (OS) [32,33]. Recurrence was also lowest for those with the lowest MVD count and highest for those with the highest MVD. Although MVD is not ideal as a sole prognostic factor [34], there is emerging clinical evidence of the value of using strategies of angiogenesis inhibition in prostate cancer [35–39], either alone or in combination with cytotoxic chemotherapy. In addition, higher baseline urine VEGF levels correlated with worse survival in 100 patients with prostate cancer enrolled in a Cancer and Leukemia Group B (CALGB) study undergoing therapy with suramin, a growth factor antagonist [40].

It is also increasingly being recognized that TCC of the bladder has divergent genetic defects [41]. Non-invasive, low-grade papilloma tumors are characterized by *HRAS* activating muta-