

## INTRODUCTION

# Translational Research: The Role of VEGF in Tumor Angiogenesis

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Angiogenesis is defined as the formation of new blood vessels from preexisting vasculature. Preclinical studies have shown the major role of angiogenesis in tumor growth and metastasis formation, and therefore, inhibiting tumor angiogenesis may be a promising therapeutic modality [1, 2]. Paracrine stimuli derived from tumor cells are the main promoters of angiogenesis. Once activated by these stimuli, endothelial cells begin to proliferate and migrate, subsequently resulting in new tube formation and blood flow. This complex process involves numerous biological activities. Vascular endothelial growth factor (VEGF) is one of the most potent and specific angiogenic factors of tumor-induced angiogenesis [3, 4]. Originally identified for its ability to induce vascular permeability and stimulate endothelial cell growth, VEGF is now recognized as a key factor required for growth of tumors [5]. The clinical importance of VEGF for tumor growth is supported by the fact that most tumors produce VEGF and that inhibition of VEGF-induced angiogenesis significantly inhibits tumor growth in vivo [6-8]. In addition to decreasing the number of vessels, antiangiogenic drugs may also decrease the interstitial tumor pressure. This reduction in interstitial pressure may result from the ability of these agents to block VEGF-induced permeability. VEGF expression has been shown to correlate with microvessel density in a number of solid malignancies including carcinomas of the breast, and tissue concentrations of this growth factor appear to be predictive of mortality associated with breast cancer [9, 10]. Similar results have been obtained in studies of solid malignancies in various organs including the lung, prostate, and colon [11-13]. These preclinical and clinical findings support VEGF as a promising target for anticancer therapy.

In patients with cancer, antiangiogenic agents, used alone or combined with chemotherapy, may inhibit tumor growth, reduce metastasis formation, prolong survival, and improve quality of life. Clinicians need to make a major shift in their thinking if the beneficial effects of these novel agents are to be recognized. Appropriate schedules of such combinations need to be developed so that the mechanism of action (i.e., antiangiogenic or cytotoxic) is fully considered. The concern that concomitant administration of antiangiogenic drugs and chemotherapy will impair cytotoxic drug delivery is precluded by evidence from animal studies. *Teicher et al.* [14-16] clearly demonstrated that combination therapy with angiogenesis inhibitors has synergistic antitumor effects in the Lewis lung carcinoma xenograft model. In these studies, addition of the antiangiogenic agents to the cytotoxic therapies reduced not only the number of lung metastases formed from the primary tumor but also the number of large metastases. These results provide evidence that antiangiogenic therapies can potentiate the efficacy of standard anticancer therapies.

This special issue of *The Oncologist* presents a diversity of preclinical and clinical studies about anti-VEGF strategies for cancer treatment. *McMahon* gives an excellent overview of the role of VEGF tyrosine kinase receptors in tumor angiogenesis and the strategies being developed to inhibit this signaling pathway. Subsequently, *Ellis* presents preclinical data that show the role of VEGF in the growth and metastasis of colon cancer. He also presents evidence that antiangiogenic therapy with VEGF receptor inhibitors SU5416 and SU6668 inhibits the growth of liver metastases. The study by *Vajkoczy* and coworkers strongly supports the idea that regional differences in Flk-1 activity in vivo may significantly affect tumor

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susceptibility to compounds that target the VEGF-Flk-1/KDR. Their study evaluated regional VEGF-Flk-1/KDR activities in vivo using SU5416 as measured by intravital fluorescence videomicroscopy. *Rosen* presents an overview of clinical studies of antiangiogenic therapy. *Arastéh* and *Hannah* review evidence that anti-VEGF treatment might also benefit patients with AIDS-related Kaposi's sarcoma. This is followed by an overview by *Harris* on the role of the von Hippel-Lindau (VHL) tumor-suppressor gene in regulating VEGF expression

and the rationale for the use of SU5416 treatment in VHL patients. *Gasparini* reviews the importance of VEGF tissue levels in treatment planning for breast cancer. Another promising application for anti-VEGF treatment is presented by *Verheul* and coworkers, who propose SU5416 as a treatment for ascites and pleural effusion formation in patients with advanced-stage cancer. Finally, *Carter* addresses the challenging question of the selection of strategies for clinical development of angiogenesis inhibitors.

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