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Bevacizumab and micrometastases: Revisiting the preclinical and clinical rollercoaster

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ABSTRACT

The use of bevacizumab, a monoclonal antibody against vascular endothelial growth factor (VEGF), in combination with standard therapeutic approaches, has offered clinical benefit for patients with advanced colorectal, breast, ovarian, renal, non small-cell lung cancer and glioblastoma. However, the strategy of administering bevacizumab until disease progression has been challenged by certain preclinical evidence, suggesting that prolonged exposure to anti-VEGF treatment may elicit an adaptive–evasive response, resulting in a more aggressive tumor phenotype. Moreover, the use of bevacizumab in adjuvant chemotherapeutic regimens has led to less promising results than expected. Despite our poor understanding of how bevacizumab acts in micrometastatic disease, numerous clinical trials (involving >20,000 cancer patients) are ongoing or are planned to test the therapeutic benefit in the adjuvant setting. The discrepancy of bevacizumab's efficiency in the two settings calls into question the validity of current strategies that use similar treatment regimens for early and advanced diseases. Herein, we review the mechanisms of bevacizumab activity in the macro- as compared to the micrometastatic environment and discuss possible alternative strategies in the adjuvant setting that might spur attention for future clinical trials. Rather than providing an encyclopedic survey of the literature, we highlight exemplary principles.

Contents

Abbreviations: BMDC, Bone marrow-derived cells; CPC, Circulating progenitor cells; DFS, Disease-free survival; GBM, Glioblastoma multiform; mCRC, Metastatic colorectal cancer; mRCC, Metastatic renal-cell cancer; NSCLC, Non small-cell lung cancer; OS, Overall survival; SNP, Single nucleotide polymorphism; TKI, Tyrosine kinase inhibitor; VEGF, Vascular endothelial growth factor; VEGFR, Vascular endothelial growth factor receptor.

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1. The ongoing debate

Four decades after Judah Folkman's postulate that angiogenesis could be a therapeutic target in cancer (Folkman, 1971), anti-angiogenic treatment has now evolved into a widely used, clinically approved strategy for the treatment of multiple solid tumors. The identification of vascular endothelial growth factor (VEGF) as a key effector of endothelial cell growth and tumor vessel formation (Leung et al, 1989) has transformed

the VEGF receptor (VEGFR) signaling pathway to an appealing therapeutic target in preclinical experiments and clinical trials. However, despite initial encouraging signs from preclinical studies that sustainable benefit might be expected in cancer patients by targeting VEGF signaling, recent preclinical reports raised concerns regarding evasive adaptation or even evolution to a more malignant cancer phenotype after prolonged exposure to anti-angiogenic agents (Ebos et al., 2009; Paez-Ribes et al., 2009; Bagri et al., 2010a, 2010b; Carmeliet & Jain, 2011a; De Bock et al., 2011). Moreover, the magnitude of the clinical benefit with those agents has been rather modest across several tumor types.

Bevacizumab (Avastin®, Genentech) is a recombinant humanized monoclonal antibody that neutralizes the biological activity of human VEGF (Fig. 1 for more details on the structure and mechanism of action of bevacizumab). It is the first anti-angiogenic therapeutic agent with demonstrated clinical benefit as first-line therapy in metastatic colorectal cancer (mCRC), metastatic breast cancer (mBC), advanced non squamous, non small-cell lung cancer (NSCLC), advanced epithelial ovarian cancer and metastatic renal-cell carcinoma (mRCC) and as second-line therapy for glioblastoma multiform in large randomized clinical trials (Hurwitz et al., 2004; Sandler et al., 2006; Escudier et al., 2007; Miller et al., 2007; Friedman et al., 2009; Burger et al., 2011). On the other hand, the incorporation of bevacizumab in adjuvant chemotherapeutic regimens for the prevention of relapse of early-stage colorectal cancer (de Gramont et al., 2012; Allegra et al., 2013) or triple negative breast cancer (Cameron et al, 2012) has led to rather disappointing results thus far. The debate has been further fuelled by the high drug costs (Tappenden et al, 2007a, 2007b), its adverse effects and the conflicting preclinical evidence regarding its biological role in the micrometastatic

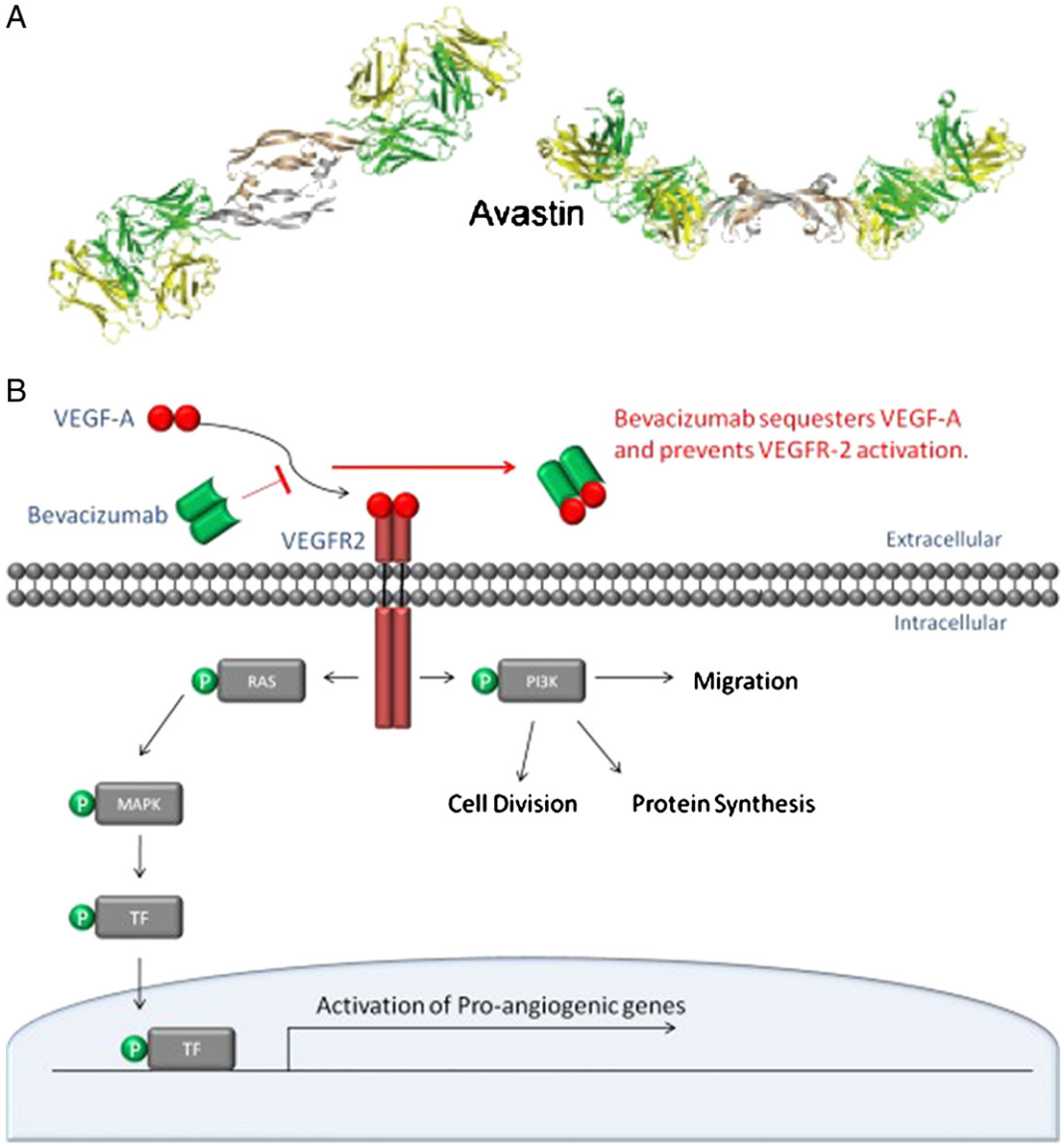

Fig. 1. A. Bevacizumab is a recombinant humanized monoclonal IgG1 antibody that binds to and inhibits the biologic activity of human vascular endothelial growth factor-A (VEGF-A). It contains human framework regions and the complementarity-determining regions of a murine antibody that binds to VEGF-A. Bevacizumab has a molecular weight of approximately 149 kDa. VEGF is colored in gray and pink; the light and heavy chains of the Fab parts of bevacizumab are yellow and light green, respectively. The left side shows the complex in top-down. The right side depicts the same complexes rotated 90° around the y-axis. Reproduced with permission by Fuh et al. (2006). **B**. The majority of VEGF-A effects are mediated through its binding to the VEGFR-2 receptor on endothelial cell surfaces. Upon binding, the receptor autophosphorylates and initiates a signaling cascade, starting with the activation of the proto-oncogene Raf, which subsequently phosphorylates MAP kinase kinase, which phosphorylates MAP kinase. The activated MAP kinase in turn activates numerous transcription factors (TF), which enter the nucleus and stimulate the expression of angiogenic factors. Binding of VEGF to VEGFR-2 also activates PI3K and triggers calcium release from the endoplasmic reticulum. This ultimately leads to the activation of nitric oxide synthase and the production of nitric oxide, which stimulates vasodilation and increases vascular permeability. At the same time PI3K phosphorylation provokes the expression of angiogenic factors resulting in increased cell proliferation, migration, permeability, invasion, and survival. Bevacizumab exerts its effect by binding to extracellular VEGF-A and preventing its binding to receptors on the endothelial cell surfaces. Reproduced with permission.