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# Anti-Angiogenesis In Cancer Therapy

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## Basic Concepts in Tumor Angiogenesis

Tumor growth depends on angiogenesis; the recruitment of endothelial cells for the formation of new blood vessels. Angiogenesis normally occurs during development, but, in the adult, it is involved in tissue regeneration and in chronic inflammatory conditions. Like normal tissues, tumors require an adequate supply of oxygen, nutrients, and an effective way to remove waste products. These requirements can vary among tumor types, and change over the course of the disease progression. It is becoming clear that gaining access to the host vascular system and the generation of a tumor blood supply are rate-limiting steps in tumor progression. Without active formation of new blood vessels, tumors cannot grow more than a few millimeters in diameter.

The classical model of tumor angiogenesis regulation can be illustrated as the balance of anti-angiogenic molecules on one side and pro-angiogenic molecules on the other. Induction of the angiogenic switch depends on how heavily that balance tips in favor of pro-angiogenesis. Pro-angiogenic gene expression is increased by physiological stimuli, such as hypoxia, which results from increased relative tumor tissue mass, and by oncogene activation or loss of tumor suppressor genes. The angiogenic switch can be switched on at different stages of tumor progression, depending on the tumor type and the environment. The fact that tumors are dependent on blood supply has resulted in great efforts for development of antiangiogenic molecules and strategies for cancer treatment.

This angiogenic switch is characterized by oncogene-driven tumor expression of pro-angiogenic proteins, such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), interleukin-8 (IL-8), placenta-like growth factor (PLGF), transforming growth-factor--ß (TGF-ß), platelet-derived endothelial growth factor (PD-EGF), and others. Tumor-associated hypoxic conditions also activate hypoxia-inducible factor-1α (HIF-1α), which promotes upregulation of several angiogenic factors. Fibroblasts, in or near the tumor bed, begin to produce pro-angiogenic factors, while progenitor endothelial cells are recruited from the bone marrow. The angiogenic switch also involves downregulation of angiogenesis suppressor proteins, such as thrombospondin, endostatin, and angiostatin.

## Targeting Angiogenesis

Angiogenesis inhibitors are a relatively new class of cancer drugs. These inhibitors can be categorized to two classes; direct and indirect. Direct angiogenesis inhibitors, such as angiostatin, prevent vascular endothelial cells from proliferating, migrating, or avoiding cell death, in response to pro-angiogenic protein stimuli. Direct angiogenesis inhibitors are the least likely to induce acquired drug resistance, because they target genetically stable endothelial cells rather than unstable mutating tumor cells. Indirect angiogenesis inhibitors generally prevent the expression, or block the activity of tumor proteins that activate angiogenesis, or block the expression of receptors on endothelial cells. Many of

these tumor cell proteins are the products of oncogenes that drive the angiogenic switch. The traditional methods of testing cytotoxic chemotherapeutic drugs in cancer patients who have failed conventional therapy do not always apply to the testing of angiogenesis inhibitors. Animal studies reveal that many angiogenesis inhibitors are most effective when administered by a dose and schedule that maintains a constant concentration of the inhibitor in the peripheral blood circulation, rather than a once every few weeks therapy. Cytotoxic drugs, by contrast, are usually administered at maximum tolerated doses followed by off-therapy intervals.

The first anti-angiogenesis clinical trials in human cancer patients have not lived up to their high expectations to significantly reduce tumor burden and prolong life, as observed in various pre-clinical studies. On the other hand, it is not necessarily surprising that the aggressive, therapy-resistant tumors of end-stage patients do not regress when confronted with a single anti-angiogenic agent such as endostatin, VEGF signaling inhibitor, or matrix metalloproteinases inhibitors. Tumors at this stage have already activated various ways that allow them to easily override the angiogenic restrictions of a single pathway.

## Future Directions

There are several challenges that face the application of anti-angiogenic therapy to the clinic. These include the need for surrogate markers of efficacy and the requirement for long-term therapy. Using angiogenesis inhibitors in combination with other therapeutic approaches might increase the efficacy of both, but further research is required to uncover the mechanisms of action of different angiogenesis inhibitors, as well as of combinations of angiogenesis inhibitors with each other and with conventional anticancer therapies.

A promising anti-angiogenic approach that is currently being further explored is the ability of angiogenesis inhibitors not only to reduce tumor growth, but also to block the progression of dormant lesions into aggressive cancers or metastases in high-risk cancer patients. The most successful approaches are likely to involve combinatorial strategies to target cancer cells themselves, along with the tumor stroma (endothelial, perivascular and inflammatory cells). Clinical trials, however, have been hampered, among other reasons, by intellectual property issues that prevent combinatorial testing of agents that are produced by different drug companies. Fortunately, some dual-action inhibitors and multi-targeted kinase inhibitors have emerged that will allow testing this approach, such as drugs that inhibit both PDGF and VEGF receptors.

Finally, an important aspect of angiogenesis research is to use an appropriate experimental setting to study the efficacy of anti-angiogenesis molecules in vivo. Commonly used mice models involve cultured tumor cells that are inoculated into different sites — most frequently subcutaneously, where tumor cells assemble into nodules and grow. Human cancers arise de novo, originating out of once-normal cells in natural tissue microenvironments. So, spontaneous tumor models, in which normal cells become malignant within their natural microenvironments via a multistep pathway, are more likely to recapitulate the human situation. Based on the multistep progression pathway, these models can be used to study the impact of angiogenesis inhibitors on blocking the angiogenic switch in early premalignant lesions or reducing small or bulky late stage tumors. Our specialty has the unique opportunity to offer such spontaneous tumor models in our canine and feline patients, which are in dire need of effective treatments, while offering a model to study cancer biology and test novel treatments that would benefit both animal and human patients.