Synopsis of Angiogenesis Inhibitors in Oncology

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Angiogenesis is a dynamic process essential for primary tumor growth and metastases. New insights into the basic understanding of the biologic processes responsible for angiogenesis have led to the characterization of potential therapeutic targets. Several strategies for the development of antiangiogenic therapeutic modalities have been employed, including agents that (1) decrease the activity of specific angiogenic factors, (2) decrease the activity of endothelial survival factors, (3) increase the activity of naturally occurring antiangiogenic agents, or (4) indirectly downregulate angiogenic and survival factor activity.

By definition, angiogenesis is the establishment of a neovascular blood supply derived from preexisting blood vessels, whereas vasculogenesis is the embryonic establishment of a blood supply from mesodermal precursors such as angioblasts or hemangioblasts. Tumor angiogenesis more accurately refers to a combination of angiogenesis and vasculogenesis in which the main blood supply to a tumor is derived from preexisting blood vessels, although circulating endothelial cell precursors may contribute to the growing endothelial cell mass.

Numerous investigators have established the association of tumor angiogenesis with metastasis.[1] Indeed, it is thought that tumor angiogenesis is essential for the growth of both primary and metastatic tumors,[2,3] and provides both nutrients and oxygen to the growing tumor mass. A neovascular blood supply is also essential for increasing the chance that tumor cells will gain access to the circulation and subsequently begin the process of forming metastases at different sites. Once a tumor establishes an invasive phenotype in the organ of metastasis, it must then establish its own neovascular blood supply in order to grow.

This process, more complex than was previously thought, requires the coordinated activities of multiple factors and cell types. For tumors to develop a neovascular blood supply, tumor and host cells must secrete proangiogenic factors that offset the activities of inhibitory angiogenic factors. In addition, the newly derived tumor endothelium must respond to and survive in a relatively caustic microenvironment; thus, endothelial cell-survival factors are essential in the maintenance of this neovasculature. Nevertheless, because the process of angiogenesis is regulated by redundant factors and pathways, inhibition of any single pathway is unlikely to lead to prolonged response in most patients with solid malignancies.

More than 1,700 papers were published on aspects of tumor angiogenesis in 2001. This field of research is closely scrutinized by scientists, clinicians, patients, and the media. However, data from phase I and II antiangiogenic trials have only been reported in abstract form; most of the data is too preliminary to draw meaningful conclusions. Further, phase III trials, even if they have reached their target accrual, are several years away from maturity with appropriate follow-up. The published reports available on clinical trials have thus far produced little more than information on the toxicity and tolerability of angiogenesis inhibitors.

Given the complexity of angiogenesis, the basic biology of this process must be better understood before effective antiangiogenic therapy can be developed. Herein, we review recent advances in the basic understanding of angiogenesis and the role of angiogenic factors in tumorigenesis. Further, we will discuss overall strategies, expectations, and future directions of antiangiogenesis therapy.

The Angiogenic Switch in Tumor Progression

Under normal physiologic conditions, the activity of endogenous pro-angiogenic factors equals that of antiangiogenic factors, leading to a homeostatic balance that prevents the uncontrolled growth of tissues. Pathologic angiogenesis occurs when the effect of stimulatory molecules outweighs the effect of inhibitory molecules (Table 1).[4] Intensive study of the angiogenic process led to the realization that this process involves more than simple proliferation of endothelial cells. This process
also requires endothelial cells to divide, invade the basement membrane, migrate, and undergo differentiation and capillary-tube formation (Figure 1).[4] This process is driven not only by angiogenic molecules, but also by other factors, such as degradative enzymes, that mediate the above processes. Interestingly, the processes of tumor angiogenesis (as noted above) and the processes of tumor-cell invasion are very similar.

**Vascular Endothelial Growth Factor**

The best characterized of the stimulatory angiogenic factors is vascular endothelial growth factor (VEGF), which has also been associated with an aggressive phenotype in numerous solid malignancies.[5-10] Vascular endothelial growth factor is a 32- to 44-kDa protein secreted by nearly all cells.[4] At least four isoforms of VEGF, derived from alternate splicing of the mRNA, have been characterized.[4,11] The smaller isoforms, VEGF-121 and VEGF-165 (the numbers denote the number of amino acids), are secreted from cells. The larger isoforms, VEGF-189 and VEGF-205, are cell associated, and their functions are currently being investigated.

One distinguishing factor of VEGF is its ability to induce vascular permeability. In fact, this factor was originally named vascular permeability factor (VPF) and was subsequently found to be homologous to VEGF.[12-14] The extent of vascular permeability induced by VEGF is 50,000 times that of histamine, which was historically the gold standard for induction of permeability. This action by VEGF allows proteins to diffuse into the interstitium and to form the lattice network onto which endothelial cells migrate.

In the past, it was believed that receptors for VEGF were expressed predominantly on endothelial cells. Recently, the VEGF receptors have also been found on cells of neural origin, Kaposi’s sarcoma cells, hematopoietic precursor cells, certain leukemias, and selected epithelial tumors.[15,16] The current nomenclature for the three known VEGF receptors is VEGFR-1(Flt-1), VEGFR-2 (KDR/Flik-1), and VEGFR-3 (Flt-4). These tyrosine kinase receptors require dimerization to induce intracellular signaling following specific ligand binding. The receptors for VEGF may mediate distinct functions within the endothelial cell. For example, VEGFR-1 may be important in migration, whereas VEGFR-2 may be important in the induction of permeability, endothelial cell proliferation, and survival.

Neuropilin, a receptor involved in neuronal guidance, has been identified as a coreceptor for VEGF-165 and may enhance angiogenesis.

Recently, the angiopoietin family of ligands has been found to play an important role in the homeostasis of the tumor vasculature. The angiopoietins are proteins involved in angiogenesis that bind to the endothelial-cell-specific tyrosine kinase receptor Tie-2. Angiopoietin-1 (Ang-1) acts as an agonist and is involved in endothelial-cell differentiation and stabilization.[17] In contrast, Ang-2 binds to Tie-2 and blocks the binding of Ang-1 to this receptor.[18,19] This blockade leads to endothelial-cell destabilization and vascular regression.[20]

**Angiogenesis Hypotheses**

It has been hypothesized that tumor angiogenesis involves the co-option of preexisting blood vessels in addition to vascular regression and subsequent neovascularization.[20] This theory suggests that tumors initially co-opt existing blood vessels within an organ for their nutrient blood supply. Shortly thereafter, the existing vasculature becomes destabilized, most likely through the release of Ang-2 by endothelial cells. This loss of vascular integrity leads to relative hypoxia within the tumor, which in turn leads to upregulation of VEGF in the tumor cells. These events then lead to a robust angiogenic response. At that stage, the newly developed endothelial cells require stabilization, which is achieved through release of Ang-1 by endothelial cells and possibly through continued response to VEGF. Thus, the process of angiogenesis depends on the temporal coordination of factors that regulate pathways in the establishment of stable conduits that provide a nutrient blood supply to the tumor.

In vitro, Ang-1 has been shown to be angiogenic, inducing tube formation of endothelial cells growing on extracellular matrix components. However, recent in vivo studies have demonstrated that Ang-1 may in fact be antiangiogenic. We have shown that overexpression of Ang-1 in human colon cancer cells leads to decreased angiogenesis and tumor growth, whereas overexpression of Ang-2 leads to an increase in tumor growth and angiogenesis.[21] This finding is consistent with immunohistochemical studies that demonstrate that colon cancers express Ang-2 but do not express Ang-1. This suggests that the imbalance of Ang-2 over Ang-1 may be an initiating factor in tumor angiogenesis. Others have also confirmed the above findings in breast and gastric cancer tumor cells and cell lines.[22,23]

Numerous nonspecific angiogenic factors affect the growth of cell types other than endothelial cells. These factors include the fibroblast growth factors (acidic and basic), transforming growth factor-alpha, and epidermal growth factor (EGF), both of which bind to the EGF receptor;
platelet-derived growth factor (PDGF); platelet-derived endothelial-cell growth factor (PD-ECGF); angiogenin; and the CXC chemokines interleukin-8, macrophage inflammatory protein 1, platelet factor 4, and growth-related oncogene alpha (Table 1).[24]

These factors are known to be angiogenic in in vivo models but are not specific for endothelial cells. However, as noted earlier, a single molecule or family of molecules does not drive angiogenesis; rather it depends on the cooperation and integration of various factors leading to endothelial cell proliferation, migration, invasion, differentiation, and capillary-tube formation. It has yet to be determined whether inhibiting the activity of a single angiogenic factor will lead to vascular compromise of significant duration. More likely, the redundancy in the angiogenic process will select for other angiogenic factors when a specific angiogenic factor is targeted.

Upstream Regulation of Angiogenic Factor Expression in Tumors

Tumors may constitutively express high levels of angiogenic factors or may express high levels of angiogenic factors in response to the tumor microenvironment. Signals that upregulate angiogenic factors include extracellular signals, intrinsic upregulation of signal transduction activity, and loss of tumor suppressor genes (Table 2).

Extracellular Signals

Extracellular signals that lead to the induction of angiogenic factor expression include environmental stimuli such as hypoxia or a decrease in pH.[25-27] In fact, hypoxia is the most potent stimulus for inducing angiogenic factors, especially VEGF. Hypoxic induction of VEGF is probably mediated through Src kinase activity, which then leads to downstream induction of signaling cascades and eventually to an increase in the activity of hypoxia-inducible factor-1 (HIF-1) alpha.[28,29] This factor then increases the transcription of the VEGF gene, which in turn leads to the induction of angiogenesis. Recent evidence suggests that activation of growth factor receptors may also increase HIF-1 alpha activity.[30]

Cyclooxygenase-2 is an enzyme constitutively overexpressed in colon cancer and other solid malignancies.[31] Its overexpression may play a role in malignant cell survival. In addition, elegant studies from Dubois and others have demonstrated that COX-2 can regulate VEGF expression and angiogenesis.[31-33] Thus, COX-2 inhibitors may provide a means of indirectly inhibiting angiogenesis with minimal toxicity.

Several studies have shown that activation of the EGF receptor (EGF-R) can lead to induction of angiogenic factors in tumor cells.[34-36] In orthotopic models of bladder and pancreatic cancers, treatment of mice with an anti-EGF-R antibody led to a decrease in VEGF and interleukin-8 expression that was associated with a decrease in tumor growth and vascularity.[36,37] Other cytokines and growth factors such as insulin growth factors (IGF)-I and -II, hepatocyte growth factor, interleukin-1, and platelet-derived growth factor have all been shown to upregulate VEGF. Thus, antiangiogenic therapy could involve downregulation of upstream mediators of the angiogenic factors rather than targeting the angiogenic factors themselves.[28,38]

Intrinsic Upregulation of Signal Transduction

Once a growth factor or a cytokine binds to its receptor, a cascade of intracellular signaling events is initiated. Two specific signal transduction pathways are well known to mediate the upregulation of angiogenic factors: the phosphatidylinositol 3 (PI3)-kinase/Akt signal transduction pathway, which eventually leads to stabilization of HIF-1 alpha,[39,40] and the mitogen-activated protein kinase (MAPK) pathway, in which phosphorylation of Erk-1/2 activates factors that increase transcription of the VEGF gene.[41] Activated ras and Src have also been shown in in vivo models to be associated with increased VEGF production and angiogenesis.[42] Again, therapeutic strategies that target the upstream effector molecules in angiogenesis may be a rational means of preventing angiogenesis. Indeed, inhibitors of signal transduction molecules have been shown to inhibit angiogenesis in in vivo tumor models.[28]

Loss of Tumor Suppressor Genes

Protein products of tumor suppressor genes such as the von Hippel-Lindau (VHL) or p53 genes also regulate angiogenesis. The wild-type VHL protein represses transcriptional regulation of the VEGF gene by facilitating degradation of HIF-1.[43-45] A loss of heterozygosity with a mutation in the remaining VHL allele leads to loss of transcriptional control of the VEGF gene and overexpression of VEGF. Mutant p53 has also been associated with an increase in angiogenesis.[46] Reinsertion of the wild-type p53 gene into cells with mutant p53 can downregulate VEGF expression and angiogenesis. Thus, the process of angiogenesis is driven by external forces (including environmental stimuli), aberrations in internal signaling, and alterations in tumor suppressor gene function.
Effective Antiangiogenic Therapy

Overall Expectations
The knowledge that angiogenesis is essential for tumor growth and the formation of metastases has led to a large research effort in an attempt to discover effective antiangiogenesis compounds. However, angiogenesis not only is a pathologic process but also is essential for homeostasis. Physiologic angiogenesis is important in reproduction, wound healing, and menses, as well as a compensatory response to ischemia in coronary-artery and peripheral vascular diseases. Thus, therapeutic efficacy of antiangiogenesis therapy requires a balance where angiogenesis in tumors is inhibited without disrupting physiologic angiogenesis.

For example, controversy exists regarding the effects of antiangiogenic therapy and wound healing.[47-50] Because of the need for neovascularization in wound healing, one would expect that an effective antiangiogenic agent would inhibit healing similar to its antiangiogenic effect on tumor growth. However, treatment with endostatin did not significantly decrease the breaking strength of cutaneous wounds in mice,[49] and although it decreased functional blood vessels and matrix density in granulation tissue in another mouse model, endostatin did not significantly affect overall wound healing.[50] Interestingly, wound angiogenesis is being used as a surrogate marker of drug activity.

In addition to potential effects of antiangiogenic therapy on homeostasis, duration of antiangiogenic therapy and criteria for efficacy are other issues to be considered. Because most antiangiogenic therapies are intended to decrease the development of new blood vessels, the traditional end points for tumor treatment success or failure must be redefined. For example, a desirable response for standard chemotherapy is a 50% decrease in the cross-sectional area of a tumor; however, the desired end point after antiangiogenic therapy might be inhibition of further tumor growth (ie, tumor stabilization or prolongation of time to progression). Thus, the criteria for the effectiveness of antiangiogenic therapy (whether in the clinic or in the laboratory) must be considered from a new perspective relative to conventional therapies.

Although some reports exist of tumor regression in experimental models of angiogenesis,[51,52] such findings are rare; the vast majority of studies in this field demonstrate that antiangiogenic therapy leads to an inhibition of tumor growth rather than a regression of established tumors.[53,54] Therefore, the ability to appropriately interpret the results from experimental models is critical to ensure that extrapolations to the clinical setting are not fraught with unrealistic expectations.

For example, a typical growth curve for a subcutaneously implanted tumor may demonstrate that antiangiogenic therapy significantly decreases tumor growth rate. In this preclinical model, this "positive" result may lead to clinical trials of that same agent. In the clinic, however, inhibition of tumor growth can be interpreted as "progressive disease" and the therapy thus considered a failure, particularly if tumor-imaging studies are done at short intervals. Therefore, longer periods of antiangiogenic therapy administration may be required to fully characterize the efficacy of antiangiogenic therapy (assessed by the inhibition of tumor growth rate and reduced metastases) compared with chemotherapy (assessed by decreases in tumor size).

Effective antiangiogenic therapy will probably need to be delivered on a chronic basis. Chronic administration will require that the agent be delivered easily (perhaps by the oral route) and have few cumulative long-term effects. As previously noted, the effect of antiangiogenic therapy may require longer evaluation intervals. One must also consider that the goal of standard antiangiogenic therapy is intended to decrease blood vessel formation and prevent further tumor growth, not cause tumor regression. Therefore, uniform response criteria should be developed for determining the effectiveness of antiangiogenic therapy (eg, time to progression, survival, quality of life); these criteria will probably differ from current criteria for tumor response to cytotoxic agents that include reductions in tumor size.

Overall Strategies
Despite the simplified view that antiangiogenic therapy simply interferes with the blood supply to a tumor, the strategies in the development of antiangiogenic therapies are quite diverse and distinct. Antiangiogenic strategies can be classified under four major categories: (1) those that decrease the activity of specific angiogenic factors; (2) those that decrease the activity of endothelial survival factors; (3) those that increase the activity of naturally occurring antiangiogenic agents, such as angiostatin, endostatin, thrombospondin; and (4) those that indirectly downregulate activity of angiogenic and survival factors.

Decreased Activity of Angiogenic Factors
In the following discussion, VEGF will be the prototype molecule used to describe strategies to
increase the activity of angiogenic factors because it has been linked to the angiogenesis and aggressiveness of many disease types. Anti-VEGF strategies include the use of neutralizing antibodies to VEGF or its receptors, ribozymes targeted to receptor mRNA, and tyrosine kinase inhibitors that block downstream signaling. All the above-mentioned strategies have shown promise in preclinical trials and are now in clinical development.

One of the earliest strategies used to inhibit VEGF activity involved the use of a neutralizing antibody to VEGF where the antibody is a hybrid of a variable region that recognizes the epitope and a humanized Fc region that is not recognized as foreign by the human host. This latter region should also interact with human Fc-receptor-bearing effector cells and/or complement. A similar strategy is utilized for anti-VEGF receptor antibodies. Antibodies must be delivered intravenously, although the long half-life may allow administration once every 2 or 3 weeks.

The other commonly used strategy for inhibiting VEGF activity is the use of tyrosine kinase inhibitors.[55] These are small molecules that prevent kinase activation on binding of the ligand to a tyrosine kinase receptor. Although these compounds are claimed to be relatively selective for their specific targets, these tyrosine kinase inhibitors actually do have some cross-reactivity with other receptors, albeit requiring a much higher dose to achieve an effect. These inhibitors are delivered intravenously or orally.

**Anti-VEGF and Increased Apoptosis**

Studies from our laboratory have examined anti-VEGF receptor antibodies and tyrosine kinase inhibitors in mouse models of colon cancer and liver metastasis.[54,56] Interestingly, these agents demonstrated similar efficacy, leading to a decrease in hepatic tumor burden, vessel count, and proliferative index of the tumor cells. Surprisingly, we found an increase in the number of tumor cells undergoing apoptosis. We further investigated this phenomenon to determine if endothelial cell apoptosis was the preemptive cause of tumor cell apoptosis. We established a technique of double-staining whereby we could first identify endothelial cells and then identify those endothelial cells undergoing apoptosis using the terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate nick-end labeling (TUNEL) assay.[54]

We found that a wave of endothelial cell apoptosis preceded a wave of tumor cells undergoing apoptosis.[56] This suggests that endothelial cell apoptosis occurs prior to tumor cell apoptosis, demonstrating that VEGF is a survival factor for tumor endothelial cells and further supporting the hypothesis that maintenance of the integrity of the tumor vasculature is required for tumor survival. Because anti-VEGF therapy leads to an increase in tumor and endothelial cell apoptosis, one would surmise that this therapy could lead to a decrease in tumor size. There are reports of studies in subcutaneous xenograft models where tyrosine kinase inhibitors to the VEGF receptor and other angiogenic factor receptors can cause regression of established tumors.[55] However, in our model of colon cancer liver metastasis, while tumor growth was inhibited, the growing cancer, albeit at a slower rate, eventually led to the demise of the animals. This is likely due to the fact that there are redundant mechanisms for angiogenesis within tumors and that antiangiogenic therapy directed at a specific factor may lead to selection of cells whose angiogenesis is driven by a different factor.[3,57]

**Decreased Activity of Endothelial Survival Factors**

A second antiangiogenic strategy involves agents that decrease the activity of endothelial cell survival factors (Figure 2).[58] Typically, angiogenesis is simply thought of as the development of a new vasculature within tumors where endothelial cells migrate, proliferate, invade the basement membrane, and differentiate to form a primitive capillary network. However, the tumor microenvironment is a caustic one with low pH and low oxygen tension. Therefore, for these fragile endothelial cells to survive, they must be exposed to endothelial cell survival factors that prevent apoptosis in these adverse conditions.

Endothelial cell survival factors include pericytes that may stabilize endothelium, either by cell-to-cell contact or by secretion of endothelial cell survival factors such as VEGF or Ang-1. Vascular endothelial growth factor and Ang-1 are two endothelial cell survival factors that are necessary for endothelial cell survival in the absence of pericytes.[20] These factors can be secreted by endothelial cells, tumor cells, or nonmalignant cells within the microenvironment. Vascular endothelial growth factor has been shown to inhibit endothelial cell apoptosis by activation of various intracellular signaling proteins, including the Akt pathway, IAP, A1, and the MAPK pathway.[59] Angiopoietin-1 binds to the specific endothelial cell receptor, Tie-2, and activates the Akt pathway, a pathway that mediates survival in many cell types.[60]

Another very important mechanism for endothelial cell survival is the binding of integrins located on the endothelial cell surface to the extracellular matrix. At first, integrins were thought to be important only in cell-to-cell contact and binding to the extracellular matrix, but it is now known that
integrins may mediate intracellular signaling, either alone or in combination with other receptors.[61] The integrins alphav beta 3, alphav beta 5, alphav beta 1 have been shown to act as survival factors for endothelial cells, and disruption of the binding between the integrins and the extracellular matrix may lead to endothelial cell death (Figure 3).[61-63] It is likely that integrin engagement with the extracellular matrix leads to integrin aggregation and activation of focal adhesion kinase. As a result, downstream signaling is activated, initiating endothelial cell survival mechanisms.[64]

Specific small molecules have been developed that may inhibit integrin activation, and antibodies have been synthesized that block integrin binding to the extracellular matrix.[65,66] Numerous agents are in preclinical evaluation or early clinical testing.

**Increased Activity of Naturally Occurring Antiangiogenic Agents**

Another antiangiogenic strategy is one that increases the activity of naturally occurring antiangiogenic agents. These agents include thrombospondin, angiostatin, and endostatin. A great deal of publicity has surrounded the discovery of angiostatin and endostatin, as these agents were first discovered as fragments of larger molecules (angiostatin is a fragment of plasminogen, and endostatin is a fragment of collagen XVIII).[51,67,68] The exact mechanism by which these two compounds lead to a decrease in angiogenesis is not clearly understood. Thrombospondin, a naturally occurring angiogenic antagonist, is also being evaluated in preclinical trials.

The interferon family of proteins, although better known for other activities, also has antiangiogenic properties.[69-76] These cytokines, specifically interferon-alpha, were shown to cause regression of life-threatening childhood hemangiommas in a study published in the early 1990s.[72] Further investigation has demonstrated that interferon-alpha and interferon-beta can downregulate basic fibroblast growth factor levels in various tumor systems.[76] More recently, reports have demonstrated the efficacy of interferon-alpha in regression of tumors in children.[65] The efficacy of interferon therapy may be dependent on chronic low-dose therapy because higher dose therapy is often associated with intolerable side effects.

**Indirect Downregulation of Angiogenic and Survival Factor Activity**

The last antiangiogenic strategy is one that indirectly downregulates the activity of angiogenic factors. Vascular endothelial growth factor and other angiogenic factors are oftentimes unregulated in response to stress, such as hypoxia, low pH, or cytokines. Strategies that downregulate the upstream signaling pathways to VEGF and other angiogenic factors may indirectly downregulate VEGF activity and angiogenesis. Our laboratory, as well as others, has demonstrated that several growth factor receptors are involved in induction of VEGF on binding of its ligand to its receptor (EGF-R, IGF-receptor I).[36,77] Strategies to inhibit the activity of these receptors may lead to a decrease of in vivo VEGF production and angiogenesis, which in turn leads to a decrease in tumor growth.

It is also known that tumor suppressor genes, such as p53 and VHL, repress transcription of VEGF. We have shown that in a colon cancer cell line with a mutated p53 gene, infection of a wild-type p53 gene can lead to downregulation of VEGF and decrease angiogenesis in vivo.[38] It is possible that anti-VEGF therapy may be beneficial in patients with the VHL syndrome, which is almost certainly due to overexpression of VEGF in the formation of multiple vascular tumors.[43]

**Future Directions in Antiangiogenic Therapy**

Most local tumors can be adequately treated by surgery and/or radiation. However, the true challenge in oncology lies in treating metastatic cancers. The host microenvironment plays a major role in modulating gene expression in tumors growing at different sites, and this holds true for angiogenic factor expression as well. In our laboratory, we have found that VEGF expression is actually higher in primary tumors than it is in liver metastases. Therefore, it would be naive for oncologists to think that antiangiogenic activity would be equally efficacious in different tumors growing at different sites. In addition, the endothelium is phenotypically distinct at different sites and, therefore, each tumor may not only express different angiogenic factors, but the endothelium may have different angiogenic factor receptors.[78]

**Selection of Appropriate Therapy**

It is foreseeable that in the future we will need to obtain biopsies of tumors growing at various metastatic sites and analyze expression of various genes within these biopsies. The revolution of microarray technology may allow us to rapidly identify angiogenic factors that may be driving angiogenesis in specific tumors at specific sites. At that point, we may then be able to direct appropriate antiangiogenic therapy toward specific targets. It is also possible that continued
antiangiogenic therapy against a specific target may lead to selection of clones whose angiogenesis is driven by a different tumor. Therefore, it may be important to "restage" patients with repeat biopsy of these tumors to adequately determine the angiogenic profile of tumors within the course of their growth and, hopefully, response to antiangiogenic regimens. Clearly, inhibition of angiogenesis will play a substantial role in the future of oncology.

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