Tumor Angiogenesis: Clinical Implications

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Tumor angiogenesis is the formation of new blood vessels from the preexisting vessels, which is normally initiated by the dissolution of the parent vessel basement membrane and endothelial migration into the stroma, forming the angiogenic stimulus. This process is crucial for the progression of solid tumors as well as hematogenous malignancies. The induction of angiogenesis is mediated by several angiogenic molecules released by both tumor and host cells. The prevascular stage of the tumor is associated with local benign behavior, whereas the vascular stage is associated with rapid tumor growth and eventual metastases. Tumor angiogenesis has both predictive as well as therapeutic implications. Several clinical studies have correlated the extent of angiogenesis with prognosis of cancer patients. An assessment of tumor microvessel count in biopsy specimens can be useful prognostically. Inhibition of angiogenesis prevents the growth of tumor cells at the primary as well as secondary sites. Anti-angiogenic therapy may provide a novel approach to the management of various cancer patients. Angiogenesis inhibitors can be co-administered with cytotoxic chemotherapy or radiotherapy to achieve synergistic antitumor effects.

This paper will highlight the key principles of tumor angiogenesis. An overview of predictive as well as therapeutic implications will also be provided.

Key words: angiogenesis inhibitors, combination therapy, microvessel count, tumor angiogenesis

Angiogenesis is the process of vascularization of a tissue involving the development of new capillary blood vessels from pre-existing blood vessels. It occurs as a normal biological process in the female reproductive cycle, in response to ischemia and in wound healing.[8,14,27] Many non-malignant diseases of unknown cause are associated with angiogenesis. For example, angiogenesis associated with retrolental fibroplasias or with diabetic retinopathy may lead to blindness in both cases. Neovascularization may invade the joints in arthritis.[14] Solid tumors induce angiogenesis, which is different from the physiological angiogenesis. The physiological control of angiogenesis involves a complex interplay between endogenous positive and negative regulators of blood vessel growth. Angiogenic growth factors comprise various peptides that stimulate vascular proliferation through binding to specific endothelial cell receptors.[21] The degree of angiogenesis and expression of angiogenic factors have been associated with prognosis in several human cancers. In addition, angiogenesis offers a theoretically selective target for anticancer therapy.

Tumor Angiogenesis

Abnormal angiogenesis is particularly implicated in tumor growth and the progression of the tumor to a metastatic phenotype. This hypothesis was first proposed by a Harvard surgeon, Judah Folkman in 1971.[11] This theory has now matured into a detailed molecular understanding of how tumors induce their vasculature. Virtually all tumors begin their existence as small clusters of avascular cells that cannot grow beyond 2-3 millimeter in diameter until a new blood supply can be recruited.[20] The period between the prevascular state (carcinoma *in situ*) and the vascular state (invasive carcinoma) may last for decades.[10] Over time, cancer cells produce and release angiogenic growth factors at levels that overwhelm the suppressive effects of endogenous inhibitors. This process triggers the cascade of events of tumor angiogenesis **(Figure 1)**.

Clinical Implications

Surgeons have long realized that malignant tumors bleed easily and, are hypervascular. In general, this vascularity due to increased blood vessels was thought to be the result of the response to tumor metabolites and necrotic tumor products.[9] Subsequently, it was found that these vessels were essential for tumor growth.[13] These angiogenic vessels provide tumor cells with oxygen and take away metabolic waste. Once angiogenesis occurs, tumors enter an exponential phase of growth.[12] Peri-tumoral inflammation amplifies neovascularization via angiogenic stimuli released by monocytes and macrophages. Central tumor hypoxia generates angiogenic signals, which

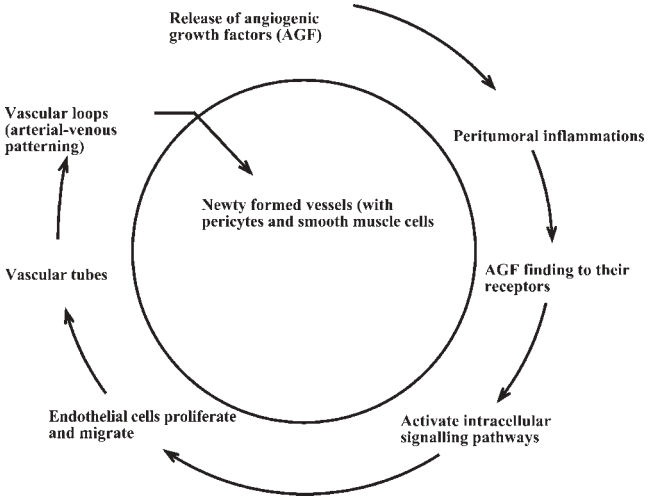

Figure 1. The angiogenesis cascade.

upregulate secretion of vascular endothelial growth factors (VEGF). VEGF is a dimeric glycoprotein that exerts its biologic effect through interaction with VEGF receptors present on the endothelial cell surface, leading to endothelial cell migration, proliferation and vascular permeability. Therapeutic inhibition of VEGF has thus led to angiogenesis inhibition.

Predictive Implications

Tumor angiogenesis provides channels through which cancer cells can metastasize. A 1 centimeter ^{3} tumor contains approximately 10^9 cancer cells, which, in turn, are supported by 10^7-10^8 vascular endothelial cells. Experimental studies have shown that this co-population sheds between $1x10^6$ – $2\ x10^6$ cancer cells per 24 hours into the circulation.[7] While most circulating cancer cells are eliminated by host defense systems, a few survive after lodging in distant organs, remaining dormant until angiogenesis takes place.

Depending on the experimental evidence of tumor angiogenesis, numerous clinical studies were conducted in the early 1990s to correlate the prognostic role of tumor vasculature in human cancers. The extent of angiogenesis was first correlated with metastasis in human breast carcinoma in 1991.[28] Subsequently, many other studies including ours have shown a significant association of high microvessel count (MVC) with metastasis and survival in breast cancer cases.[4,17,23,26] A high MVC was correlated in many solid tumors including brain tumors.[5] Therefore, assessment of the MVC in biopsy specimens from various cancer patients can be a useful predictive tool. Moreover, anti-angiogenic therapy may be more effective in hypervascular tumors. An elevated level of angiogenic protein in serum or urine of cancer patients may suggest its usefulness for follow-up or monitor of the response of treatment.[19]

Therapeutic Implications

Numerous studies including ours have demonstrated that angiogenesis inhibition can suppress tumor growth and metastasis.[1,24] Intervention with angiogenesis inhibitors early in tumorogenesis significantly diminishes both tumor burden and tumor size.[2] Moreover, these agents can be co-administered with cytotoxic chemotherapy or radiotherapy to achieve synergistic anti-tumor effects.[15] As a rule angiogenesis inhibitors exert a cytostatic effect, acting to stabilize disease rather than shrinking tumors. This is an important distinction to make in understanding how anti-angiogenic therapy differs from chemotherapy. Furthermore, a specific anti-angiogenic therapy can be administered for a long period without any interruptions. Drug resistance is not a problem in anti-angiogenic therapy, because it is directed towards the endothelial cells rather than the tumor cells.[3]

The development of anti-angiogenic therapy began during the late 1980s following the discovery of the first angiogenesis inhibitors from natural and endogenous sources. The early inhibitors are recombinant human platelet-factor 4 (from platelets), AGM-1470 (from Aspergillus fumigatus fresnius), cartilage-derived inhibitor (from bovine and marine cartilage), tetrahydrocortisol-S (a natural steroid metabolite) and interferon alpha2a (secreted by monocytes).[1] In 1992, TNP-470 (formerly AGM-1470) became the first anti-angiogenic agent to enter human clinical studies. By 2001, more than 60 anti-angiogenic agents were in clinical trials, including endostatin and angiostatin.[18] Recently there are numerous molecules that have been designed to target VEGF; many are in clinical trials. The furthest along, however, is bevacizumab, a human monoclonal antibody targeting circulating VEGF. Preclinical models support its potential use as a single agent therapy for cancer and also suggest that the combination of bevacizumab and chemotherapy might improve drug delivery to tumors. In view of targeting growth and angiogenic pathways from bench to bedside, two crucial pathways for the growth of carcinoma have been identified: 1) Epidermal growth factor (EGF) receptor pathway which controls proliferation, migration, and survival of tumor cells, and 2) VEGF receptor pathway, which controls vascularization in advanced tumors.[18] **Table 1** describes the biological targets of anti-angiogenic therapy.

Biological Targets
• Growth factors and growth factor receptors
• Signal transduction pathways
• Tumor associated antigens/markers
• Proteasome
• Cell-survival pathways
• Extracellular matrix/angiogenic pathways
• Nuclear target

Table 1. Biological targets of antiangiogenic therapy.

In Nepal, we have only one angiogenesis inhibitor (Thalidomide) available for restricted use.[22] Experimental studies have demonstrated that thalidomide, a drug developed as a sedative, has anti-tumoral effects through angiogenesis inhibition and immunomodulation. Multiple myeloma is so far the most responsive malignancy to

thalidomide singly or in combination.[25] In addition to its approved indication for erythema nodosum leprosum, thalidomide has beneficial effects in certain solid tumors; glioblastoma multiforme, renal cell carcinoma, malignant melanoma, epithelial ovarian cancer and hepatocellular carcinoma. Moreover, thalidomide has beneficial effects in cancer cachexia, which is common in elderly patients with advanced cancers.[6]

Conclusions

Tumor angiogenesis presents a promising opportunity for the development of prognostic factors and novel anti-cancer agents in the modern era. The concept of anti-angiogenesis is now shaping a worldwide effort to control cancer growth by molecular targeting of the tumor vasculature.

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