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TUMOR ANGIOGENESIS

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Abstract: Angiogenesis was first identified as an important process in tumor survival and sustenance in the 1980's, but the therapeutic potential of anti-angiogenic agents was only realized and implemented into clinical practice in early 2000. It is well recognized that tumors selectively recruit vasculature which serves to provide a survival advantage, while also permitting escape from natural defense mechanisms. Research into modification of this process of neovascularization, using anti-angiogenic agents, has shown that tumor cell death can be significantly accelerated, especially in combination with cytotoxic chemotherapy. We discuss the research that has been conducted in elucidating the process of angiogenesis in the tumor micro-environment, and the possible pharmacological interventions to achieve clinical benefit with tumor responses.
Keywords: Angiogenesis, Tumor, Vasculature.

Introduction

Angiogenesis (*angio* = blood vessels, *genesis* = creation) refers to the formation of new blood vessels from pre-existing blood vessels. [(1)] It is a normal process in growth and development as well as wound healing. Tumor angiogenesis, a perversion of the normal process of angiogenesis, is a series of sequential events resulting in the formation of a neovascular blood supply to the tumor. The biological capability of inducing angiogenesis is one of the hallmarks of cancer contributing to creating the tumor microenvironment. [(2)] Like normal cells, neoplastic cells need oxygen and other nutrients for their survival and growth. Solid tumors require a vascular system to grow beyond about 1-2 mm in diameter to support their metabolic requirements since this is the diffusion limit for critical nutrients, oxygen and for waste disposal. [(3, 4, 5)] Angiogenesis is also an important factor in the metastasis of malignant cells by permitting these cells access to abnormal vessels. [(6)] Multiple studies have shown that the levels of angiogenic factors in tumors are indicative of the aggressiveness of the tumors and their potential for metastasis. [(7, 8, 9, 10)]

Mechanisms of Tumor Vascularization

The major cellular mechanisms involved in the vascularization of tumors are:

1. Vasculogenesis [(11)] – This mechanism involves the differentiation of vascular endothelial precursors called angioblasts into endothelial cells and de novo formation of a vascular network. [(12)] Precursor cells home to the tumor site from the bone

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marrow or blood. [13, 14, 15] The recruitment and integration of EPCs is a complex multistep process, including chemoattraction, active arrest and homing within angiogenic vasculature, transmigration to the interstitial space, incorporation into the microvasculature and differentiation into mature endothelial cells. [3]

2. Sprouting Angiogenesis [16] – This process is characterized by vascular endothelial cell proliferation and migration towards the angiogenic factor. [17] Tumor cells and tumor-associated stromal cells secrete growth factors such as VEGF that bind to endothelial cells and initiate a signaling cascade. MMPs break down the ECM and basement membrane, thus promoting migration of the endothelial cells. [18, 6] Following this, there is reorganization of the endothelial cells into tubules with a central lumen resulting in sprouting of new branches from pre-existing vessels. Maturation of these new vessels occurs by organization of pericytes and smooth muscle cells around the endothelial tubule. [3]
3. Intussusception or Splitting Angiogenesis – This is the division of existing vessels into multiple independent vessels. The endothelial cells proliferate or re-arrange resulting in a core of cells in the lumen of a pre-existing vessel. The cells then form a trans-vascular tissue pillar between two lumens and thus, divide the original vessel into two new vessels. [19]
4. Vascular Co-option [20] – Co-option is the growth of a tumor around existing vessels forming perivascular cuffs. This limits the tumor size since the cells are dependent on diffusion of oxygen and nutrients from the existing vessel.
5. Vascular mimicry – Mimicry is the phenomenon of cancer cells forming vascular tubes that resemble endothelial cell-lined tubes. Some malignant cells have also been shown to have the capability of differentiating into endothelial cells. [21, 22]

The degree of contribution of these various mechanisms to the vascularization of different tumors is controversial.

Regulators of angiogenesis

A dynamic balance between the positive and negative regulators of angiogenesis governs the process of neovascularization. In normal adult tissues, the inhibitors predominate blocking angiogenesis. This balance is highly regulated under physiological conditions, so that the "angiogenic switch" is "off" and angiogenesis occurs only when needed (e.g., during embryonic development, wound healing, and menstruation).

Stimuli for angiogenesis: In the setting of malignancy, positive angiogenic regulators are induced by hypoxia (due to increasing tumor size), inflammatory cytokines, loss of tumor suppressor genes and activation of oncogenes. [23, 24]

- A hypoxic tumor microenvironment activates the *hypoxia stress response* and induces the expression of the *Hypoxia Inducible Factor* HIF. The transcription factor HIF in-turn induces synthesis of angiogenic promoters such as VEGF. [25, 26]
- Activated oncogenes in tumors (e.g., *Ras* and *Myc*) upregulate the production of proangiogenic factors such as VEGF. [27]

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- In normal tissues, *p53* stimulates the expression of anti-angiogenic factors. Loss of *p53* function thus causes a fall in levels of anti-angiogenic factors, especially Thrombospondin-1. [28]

Angiogenic signaling in tumors is dysregulated as a result of oncogene activation and tumor suppressor loss.

- Immune inflammatory cells may also produce such inductive signals for angiogenesis indirectly.

Upregulation of the stimulators accompanied by downregulation of the inhibitors leads to a change in the local balance between the stimulators and inhibitors of angiogenesis and tips the balance toward angiogenesis, turning "on" the "angiogenic switch". [28, 29, 30] This angiogenic switch produces a signaling cascade and activates genes promoting angiogenesis.

A compelling body of evidence indicates that the angiogenic switch is governed by a large number of pro-angiogenic factors and angiogenic inhibitors that are activated and repressed, respectively. [29]

Stimulators of angiogenesis:

VEGF – primary pro-angiogenic factor; induces endothelial cell activation, proliferation and migration [31]
bFGF, PDGF – recruitment of perivascular cells [32]
Integrins – In contrast to normal endothelium, angiogenic endothelium over-expresses specific members of the integrin family of ECM binding proteins that promote EC adhesion, migration and survival. [33]
Angiogenin
EGF
MMP 2, MMP 9 – basement membrane and ECM degradation
IL-1 beta, IL-6, IL-8
G-CSF
Placental GF
HGF
TNF-alpha

Inhibitors of angiogenesis:

Thrombospondin – primary anti-angiogenic factor; inhibits growth and migration of endothelial cells; also induces apoptosis in endothelial cells through activation of caspases. [34]
Angiostatin (fragments of plasmin)
Endostatin (type 18 collagen)
Tissue inhibitor of metalloprotease (TIMPs)
Anti-thrombin III fragment
Platelet Factor-4
Interferon alpha and beta

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Interferon inducible protein 10
Maspin
Meth 1 and 2
Prolactin fragment
Vasostatin
VEGF inhibitor
Pigment Epithelium Derived Factor (PEDF)

Tumor vasculature

Compared to normal tissues, the vasculature of tumors is extremely disorganized characterized by tortuosity, uneven diameters, excessive vessel branching and precocious sprouting, haphazard interconnections/shunting, increased permeability, and chaotic blood flow. [35, 36] This abnormal vasculature in tumors is believed to be a result of the dysregulated angiogenic signaling. The chaotic blood flow in tumor vasculature may be partially responsible for the poor interaction of leukocytes with endothelial cells and may help tumor cells avoid immune surveillance. The pericytes surrounding tumor vasculature are loosely arranged with wide inter-endothelial junctions and incomplete basement membranes causing the vessels to be abnormally leaky. [37] This, in combination with the lack of functional lymphatics within tumors as well as the pressure generated by proliferating cancer cells, leads to an increased interstitial pressure within the tumor. All these factors contribute to the abnormal microenvironment of the tumor and impede its blood supply. Thus, the tumor vasculature is often insufficient to sustain the tumor's oxygen and nutrient requirements. This causes focal death of tumor resulting in areas of necrosis. The tumor microenvironment is usually acidic due to accumulation of wastes and CO2 from the inadequate blood supply.
Three zones can be found in tumors: [38]

- Avascular necrotic zone
- Stable quiescent zone
- Proliferative zone

Anti-angiogenic therapy

Anti-angiogenic therapy targets vascular growth within tumors, with the aim of suppressing tumor growth and metastasis. [39] In 1971, Judah Folkman proposed a hypothesis that tumor growth is dependent on angiogenesis. [40] He first introduced the concept that tumor growth might be inhibited, or even reversed, by blocking tumor angiogenesis. He became known as the "father of tumor angiogenesis'. This led to tremendous research and, in 2004, the U.S. Food and Drug Administration (FDA) approved the first anti-angiogenic monoclonal antibody Bevacizumab as a first-line treatment for metastatic colorectal cancer. [41] Thereafter, the use of bevacizumab and other targeted agents e.g., sorafenib, sunitinib, pazopanib was approved for various types of cancers including metastatic non-squamous non-small cell lung cancer, metastatic breast cancer, recurrent glioblastoma multiforme and metastatic renal cell carcinoma.

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Classification of potential targets and anti-angiogenic agents: [42]

- Endothelial growth factors inhibitors
- EC signal transduction inhibitors
- Inhibitors of EC proliferation
- Inhibitors of MMPs
- Inhibitors of EC survival
- Inhibitors of bone marrow precursor cells

Three classes of agents that target VEGF: [42]

- Monoclonal antibodies - Bevacizumab
- VEGF decoy receptor - Aflibercept
- Small molecule tyrosine kinase inhibitors – Sorafenib, Sunitinib, Pazopanib, Axitinib

Recent work has shown that inhibiting tumor angiogenesis increases the effectiveness of coadministered chemotherapy and radiotherapy. [43] Anti-angiogenic therapy leads to 'normalization' of the abnormal tumor vasculature and better efficacy of other therapy due to improved delivery of the drug to the tumor cells. This explains the synergy of VEGF inhibitors with chemotherapy. [44]
However, limited efficacy and resistance remain outstanding problems. [45]

Adverse Effects

Hypertension and asymptomatic proteinuria are associated with bevacizumab therapy. Hypertension and proteinuria were found to uniformly decrease after the cessation of therapy. [46] Anti-angiogenic drugs are also associated with adverse thromboembolic events including strokes, myocardial infarctions, transient ischemic attacks and angina. [47]
Data demonstrates that tight regulation of VEGF-A signaling is critical for establishment and maintenance of the glomerular filtration barrier and strongly supports a pivotal role for VEGF-A in renal disease. Dysregulation of VEGF-A is not only associated with but also plays a pathogenic role in initiating glomerular injury. [48]
A study described a regulatory loop by which VEGF controls survival of haematopoietic stem cells (HSCs). They observed a reduction in survival, colony formation and *in vivo* repopulation rates of HSCs after ablation of the VEGF gene in mice. This may be the explanation for their association with leukopenia and lymphopenia. [49]

Resistance

In both preclinical and clinical settings, the benefits of anti-angiogenic therapy are at best transitory and are followed by a restoration of tumour growth and progression. Emerging data support a proposition of two modes of unconventional resistance:

- evasive resistance, an adaptation to circumvent the specific angiogenic blockade
- intrinsic or pre-existing non-responsiveness (absence of a discernable (even transitory) beneficial effect of an angiogenesis inhibitor).

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The emergent mechanisms of evasive resistance include revascularization consequent to upregulation of alternative pro-angiogenic signals; protection of the tumour vasculature either by recruiting pro-angiogenic inflammatory cells or by increasing protective pericyte coverage; accentuated invasiveness of tumour cells into local tissue to co-opt normal vasculature; and increased metastatic seeding and tumour cell growth in lymph nodes and distant organs. [50] Compensatory pro-angiogenic signals include PIGF, FGFs, Angiopoietins, PDGF. [51, 52, 53, 54, 55] These factors are potential targets for future anti-angiogenic therapy.

Animal studies demonstrated that interrupting VEGF blockade induces rapid vascular regrowth in tumors because the persisting empty sleeves of the basement membrane provide a scaffold for rapid revascularization. [56]

The hypoxia and acidosis in malignant tissue results in selection of tumor cell lines, the so-called cancer stem cells, that are resistant to hypoxia-induced apoptosis and render the cancer more invasive and metastatic. [57]

These are some of the many proposed mechanisms of resistance to anti-angiogenic therapy.

Conclusions:

A better understanding of the pathophysiology of the angiogenic process, in the tumor micro-environment, has enabled scientists to develop pharmacological agents with activity in several tumor types. There are several available anti-angiogenic agents, and although there is significant overlap in their pharma logical activity, there are also mechanisms unique to each agent, which allow for a broader spectrum of activity, especially with the 2nd and 3rd generation agents. Further research is exploring the clinical utility of combining anti-angiogenic agents with immunotherapy.

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