REVIEW ARTICLE

Tumor Angiogenesis – An updated Review

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ABSTRACT

Angiogenesis is a fundamental process of formation of new blood vessels. This highly synchronized process occurs during human development, reproduction, wound repair and is also a fundamental pathogenic process in cancer and several other diseases. The inhibition of angiogenesis has been a subject of comprehensive research for years. Several studies have found reasonable improvement in considering angiogenesis inhibitors and its success in its use as a traditional form of therapy. This review summarizes several important angiogenic factors, the mechanism of angiogenesis at molecular level and various drugs used for the treatment. The aim of this review was to discuss the various factors involved in angiogenesis so as it can be applied in the battle against cancer and other angiogenic-related diseases.

Keywords: Angiogenesis, Anti-angiogenic therapy, Cancer.

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INTRODUCTION

A cancer cell progresses through a series of mutations which is accompanied by activation of certain specific genes and loss of suppressor genes which makes the tumor cells independent in growth signals, insensible to antigrowth signals and indifferent to apoptotic signals. This make tumor cell capable of limitless replicative potential and also tumorigenic. But the question arises whether these neoplastic properties are necessary and sufficient enough for a cell to expand into a population which becomes clinically detectable, symptomatic or lethal. The answer is that these neoplastic processes may only be necessary but not sufficient enough for the cancer to become metastatic and lethal. The literature review suggests that it is the microvascular endothelial cell dictating a cancer cell that it can grow into a tumor and comes to a size which becomes clinically detectable, can kill the host or can metastasize to distant organs. This implies that for any tumor to metastasize or to develop into a lethal phenotype, it must first employ and then sustain its own private blood supply which is called as Tumor angiogenesis. Tumors which cannot induce angiogenesis remain quiescent at a microscopic in situ size and such non-angiogenic cells produce lesions which are usually non-detectable and so are called "No takes".[1-5]

Concepts of Tumor Angiogenesis

The previous concepts of tumor angiogenesis involved simple dilatation of existing blood vessels and an inflammatory reaction which is more precisely a side effect of tumor growth. But it was *Sir Judah Folkmann* who proposed a visionary hypothesis stating that the most primary solid tumors are those which undergo a prolonged state of avascularity and apparently latent growth in which the maximum size attainable is only 1-2 mm in diameter. Up to this size, the tumor cells obtain the necessary oxygen and nutrient supplies which they require for growth and survival and this is achieved by simple passive diffusion. These microscopic tumor masses in due course toggle on angiogenesis by conscripting surrounding mature host blood vessels to commence sprouting new blood vessel capillaries which nurture toward and ultimately permeate the tumor mass, thus providing the potential for unrelenting expansion of the tumor mass and also hematogenous metastatic spread. He also proposed that the angiogenic switch was initially hypothesized to set off by the ectopic production

and elaboration of a growth factor called "tumor angiogenesis factor" (TAF) by the tumor cells. Lastly it ought to be possible to affect tumor growth by jamming tumor angiogenesis by somehow preventing TAF production. This kind of therapeutic approach can be successful in curative sense also. [4, 5]

Phases of tumor angiogenesis

The process includes two major phases; namely activation phase and formation phase. After the formation of capillaries, maturation and stabilization of blood vessels takes place by pericyte recruitment, vessel sprouting and vessel stabilization. It adapts the same molecular mecha- nism in both physiological and pathological angiogenesis. The decisive role is of the mesenc- hymal cells because it releases Angiopoetin -1 which binds to Tie-2 receptors expressed on endothelial cells directing them to recruit pericytes and stabilize. These Tie receptors are tyrosine kinases whose expression follows VEGFR expression.[4, 5]

Characteristics of tumor blood vessels

The capillaries are characterized by an irregular diameter and are dilated. The endothelial cells are overlapped with each other and are organized in a chaotic way. These vessels have abnormal branching pattern leading to abluminal sprouts. They lack smooth muscle coat because the pericytes are absent or detached. These blood vessels have very weak interconnections and focal intercellular openings between the endothelial cells and scanning electron microscopy reveals that the openings are less than 2 micron meters in diameter making them extremely leaky. The leakiness can result in extravasation of plasma proteins and even erythrocytes and it may also lead to traffic of tumor cells into the blood stream and formation of metastases. The tumor vessels have an irregular basement membrane regarding the matrix protein composition, assembly and structure. In addition there is no division between arterioles and venules among tumor vessels; so the blood flow is chaotic leading ta poorly oxygenated tumor tissue. [4, 5]

Different Mechanisms of Tumor Vascularization

Six different mechanisms have been hypothesized, namely

- Sprouting angiogenesis
- Intussusceptive angiogenesis
- Recruitment of endothelial progenitor cells
- Vessel cooption
- Vasculogenic mimicry
- Lymphangiogenesis

Sprouting Angiogenesis – Refers to the growth of new blood capillary vessels from pre-existing vessels. These blood vessels endow with oxygen and nutrients to the expanding tissues and also remove the metabolic waste.

Intussusceptive microvascular growth - It is a rapid process in which endothelial cells are remodeled by increasing the volume of vessel but decreasing the diameter of vessel. This process takes place usually after vasculogenesis and does not need proliferation of endothelial cells.[4,6]

Vessel cooption - Tumor cells exit from microvessels present in the target organ, which begin to grow around these blood vessels causing the endothelial cells to undergo apoptosis, and finally stimulate neovascular sprouts from neighboring vessels. This process, called "cooption," may represent an intermediate or alternative step in the switch to the angiogenic phenotype.

Vasculogenic mimicry - The term "vasculogenic mimicry" illustrates the pretense of tumor cells as endothelial cells. This process usually occurs in aggressive tumors wherein the tumor cells dedifferentiate to an endothelial phenotype and make tube-like structures. These mechanisms endow the tumor cells with a secondary circulation system which works independently of angiogenesis.

Lymphangiogenesis - Lymphatic vessels are also part of the vascular circulatory system. The lymphatic system is a network of capillaries, collecting vessels and ducts that drain most of the organs. In contrast to the blood vascular network, the lymphatic network is an unrestricted transport scheme, without a driving force which drains extravasated fluid, collects lymphocytes and returns it to circulation. This proves the role of

lymphatic system in tumor progression.[4, 6]

The Angiogenic Switch[7- 9]

After understanding the different mechanisms of angiogenesis the next question arises about when angiogenesis is activated during the development of cancer. Whether angiogenesis is simply an inevitable consequence of limited vascularization in tumor cells or is the angiogenic switch – an important part of the repertoire of qualities that a tumor acquires to be successful. This is an endless debate which is to be answered. The literature suggests that there are 4 different mechanisms of angiogenic switch. They are

1. Prevascular tumors recruit their own blood supply.
2. Circulating endothelial cells in tumor angiogenesis are responsible for activating angiogenic switch.
3. Non endothelial cells may amplify tumor angiogenesis.
4. Process of Vessel cooption

Prevascular tumors recruit their own supply

The recruitment of blood supply is the most common mechanism of the angiogenic switch. Majority of carcinomas originate as microscopic lesions in an avascular epithelial layer. These microscopic lesions are separated by a basement membrane from the underlying vasculature in submucosa/dermis. The basement membrane act as a temporary physical barrier but as the basement membrane gets breached by the new vessel sprouts; tumor cells form multiple cell layers around each new capillary blood vessel and provide nutrients to the tumors. But these microcylinders are restricted to the oxygen diffusion limit for each specific tumor. [7- 9]

Circulating endothelial cells in tumor angiogenesis.

Recent experimental and clinical evidence reveals that circulating endothelial progenitor cells derived from stem cell reservoirs in the postnatal bone marrow can be recruited to the vascular bed of tumors and can thus contribute to tumor growth. VEGF elaborated by a variety of tumor signals through both VEGFR-1 and VEGFR-2 can mobilize progenitor endothelial cells (since endothelial cells contain VEGFR) into the circulation where they are recruited into the vascular bed of certain tumor types, but not in all tumors.[7- 9]

Non endothelial cells may amplify tumor angiogenesis

In addition to recruiting vascular endothelium from the host, certain tumors may also attract mast cells, macrophages and inflammatory cells. These cells can amplify tumor angiogenesis by releasing proangiogenic molecules such as bFGF, or by releasing metalloproteinases that can mobilize VEGF and other angiogenic proteins. The tumor cells may also trigger host stromal cells in the tumor microenvironment to overexpress the angiogenic protein VEGF.[7- 9]

Vessel cooption

Tumor cells sometimes exit from microvessels in the target organ, begin to grow around these vessels thus causing the endothelial cells to undergo apoptosis, and finally induce neovascular sprouts from neighboring vessels. This process, called "cooption," was so considered an intermediate or in some cases as an alternative step in the switch to the angiogenic phenotype.[7- 9] (As described previously)

Molecular components of the angiogenic switch-The angiogenic switch is regulated by two components, promoters and inhibitors.

Promoter – VEGF- The most potent angiogenic factor is VEGF. Alternative splicing of human VEGF mRNA gives rise to different isoforms of 121, 145, 165, 189, 206 amino acid residues. It has four types of receptor - Neuropilin, VEGFR1 (Flt1), VEGFR2 (KDR/Flk1), VEGFR3 (Flt4). The majority of effects of VEGF are exerted through activation of VEGFR2 such as proliferation and migration. VEGF stimulâtes micro vascular endothelial cell proliferation. It also involves endothelial cell migration and sprouting by inducing tyrosine phosphorylation of VE – cadherins which is a component of adherens type cell to cell junctions responsible for endothelial cell migration. VEGF mediates

cell matrix interactions by the expression of 11 and 20 integrin. It inhibits endothelial cell apoptosis and increases endothelial cell permeability. It is possible that certain other positive regulators of angiogenesis may operate through VEGF or be VEGF-dependent. For e.g. the high angiogenic activity of bFGF, which is related because of the following observations: First, bFGF induces the expression of VEGF2; Second, the two endothelial mitogens act synergistically to stimulate capillary tube formation in vitro; Third, systemic administration of a soluble receptor for VEGF (Flk-1) partially blocks cornea angiogenesis induced by implanted bFGF.[10] The molecular mechanism of VEGF as promoter of angiogenesis is depicted in the Table-1. The other promoters with their respective function is illustrated in the Table-2

Balance Hypothesis of Angiogenic switch

The normally quiescent vasculature can be activated to sprout new capillaries (angiogenesis), a morphogenic process controlled by an angiogenic switch mechanism. The prevailing evidence suggests that changes in the relative balance of inducers and inhibitors of angiogenesis can activate the switch. In some tissues, the absence of angiogenesis inducers may keep the switch off, while in others the angiogenesis inducers are present but held in check by higher levels of angiogenesis inhibitors. Thus, either reducing the inhibitor concentration, e.g., for TSP-1, by loss of a tumor suppressor gene; or increasing the activator levels, e.g., for induction of VEGF, by hypoxia, can each change the balance or activate the switch, leading to the growth of new blood vessels.[5, 10, 11]

Molecular origins of tumor angiogenesis [5, 10, 11]

After understanding the pathophysiology tumor angiogenesis, the authors worked on the molecular aspects of process of angiogenesis. The 3 basic molecular pathways involved in tumor angiogenesis are

1. The VEGF and VEGF- receptor family in tumor angiogenesis.
2. The Notch Delta-like ligand 4 signaling pathway.
3. Angiogenesis and circulating bone marrow derived cells.

1. *The VEGF and VEGF- receptor family in tumor angiogenesis*- Induction of or an increase in VEGF expression in tumors can be caused by numerous environmental (epigenetic) factors such as hypoxia, low pH, inflammatory cytokines (e.g., interleukin-6), growth factors (e.g., basic fibroblast growth factor), sex hormones (both androgens and estrogens), and chemokines (e.g., stromal-cell–derived factor 1). Other causes include genetic inductive changes such as activation of numerous different oncogenes or loss or mutational inactivation of a variety of tumor-suppressor genes. This molecule is only one member of a family of proteins that also comprises VEGF-B, VEGF-C, VEGF-D, VEGF-E and PlGF. These proteins interact with three major tyrosine kinases: VEGFR1, VEGFR2 and VEGFR3 and two non-receptor tyrosine kinases; neuropilin 1 and neuropilin 2 that also bind to other ligands. The binding of VEGF to VEGFR 2 leads to a cascade of different signaling pathways, the main being-

a. Up regulation of genes involved in mediating the proliferation and migration of endothelial cells and migration of endothelial cells.

b. Promoting their survival and vascular permeability.

2. *The Notch Delta-like ligand 4 signaling pathway* - The interaction of Dll4 and notch receptors through the contact of adjacent endothelial cells leads to a series of proteolytic events whereby a notch intracellular signaling domain is cleaved and released by a γ-secretase; the domain then translocates to the nucleus. There it interacts with transcription factors and induces the expression of various target genes. The induction of Dll4–notch signaling is thought to act as a damping mechanism to prevent excessive angiogenesis and to promote the orderly development of new blood vessels.

3. *Circulating bone marrow derived cells in angiogenesis* – Promoters and guardians of tumor angiogenesis

a. Myeloid cells in the tumor microenvironment
b. Tumor associated macrophages
c. Mast cells
d. Platelets – Guardians of Tumor vasculature

Myeloid cells in tumor microenvironment[12] - Myeloid cells are derived from bone marrow which plays an important role in the growth and metastasis. These cells are easily recruited to the tumor environment and stimulate tumor angiogenesis. Besides promoting tumor angiogenesis, myeloid cells suppress the tumor immunity and also promote metastasis to distant and distinct sites.[12]

Pro-tumorigenic myeloid subpopulation - The pro-tumorigenic subpopulation contribute to tumor angiogenesis which are enlisted in Table-3.

Clinical implication of myeloid cells - Several myeloid subpopulations may play roles during neovascularization of tumors, mediating refractiness to anti-angiogenic therapies or the escape from tumor surveillance. Myeloid cells represent novel targets for therapeutic strategies. The mobilization and recruitment of myeloid cells by the tumor defines them as a potential delivery system to target the tumor environment. [12,13]

Mast cells and angiogenesis- Mast cells derived components are -

1. Act as effective pro-angiogenic factors such as VEGF, bFGF, TGF-beta, TNF-alpha and IL-8.
2. Proteinases and heparin derived from mast cells release heparin-binding pro-angiogenic factors which are blocked on cell surfaces and also in the extracellular matrix (ECM) promoting angiogenesis.
3. Mast cells release histamine and VEGF, which induce microvascular hyperpermeability thus showing pro-angiogenic effects.
4. Mast cells also promote chemotactic recruitment of monocytes/macrophages and lymphocytes making them capable of contributing to angiogenesis by releasing angiogenesis modulating molecules.[13]

Platelets – the guardians of tumor angiogenesis: Platelets promote angiogenesis by releasing certain soluble factors which may regulate the endothelial stability of the angiogenic tumor

Action	Molecular Mechanism
Endothelial cell migration	VEGF induced tyrosine phosphorylation of VE – cadherins which is a component of adherens type cell to cell junctions are responsible for endothelial cell migration.
Cell – Matrix interactions	VEGF enhances the expression of 11 and 20 integrins which is responsible for cell-matrix interactions.

Table-1: Mechanism of VEGF In Tumor Angiogenesis (VEGF – Vascular endothelial growth factor; VE cadherin – vasculo endothelial cadherin)

Fibroblast Growth factor	• Stimulates EC proliferation. • Promotes microvessel tube formation • Promotes EC migration. • Important promoter of blood vessel remodeling after tissue injury.
Platelet growth factor	• Increases capillary wall stability. • Stimulates the proliferation of cultured pericytes • Increases DNA synthesis on capillary. • Stimulate formation of angiogenic sprouts in vitro.
Angiogenin	• Promotes angiogenesis in vivo • Assists EC adhesion and spreading in vitro
Angiotropin	• Helps activate microvascular ECs during wound healing • Stimulates angiogenesis in vivo • Randomly induces capillary EC migration
Matrix metalloproteinase-9 (MMP-9)	• Thought to help mobilize EPCs by cleaving ECM
Stromal-cell-derived factor-1 (SDF-1)	• Helps guide EPCs to ischemic areas during angiogenesis
Tumor necrosis factor-*α* *(TNF-α)*	• Stimulates angiogenesis in vivo. • Stimulates EC tube formation in vitro.
Transforming growth factor-*α* *(TGF-α)*	• Promotes EC proliferation • Stimulates angiogenesis in vivo

Angiopoietin-1 (Ang-1)	• Recruits pericytes to recently created blood vessels. • Helps promote EC survival and sprout formation. • Increases the diameter of blood vessels endothelium.
Angiopoietin-2 (Ang-2)	• Antagonist of Tie-2 receptor, reduces levels of pericytes. • Increases plasticity of newly formed blood vessels.

Table-2: Promoters of Angiogenesis (EC–Endothelial cell; ECM – Extracellular matrix)

vessels. They prevent vascular damage induced by the tumor cells. Moreover these soluble factors diminish the injuries produced by inflammation.[13,14]

Clinical importance of platelets: Interference in platelet-tumor vessel cross-talk represents an interesting and challenging approach for manipulating tumor vasculature to improve anticancer therapies[13,14]

Tumor associated macrophages (TAM's)- Macrophages, the eminent cells of wound healing provide aid for tissue growth, remodel the tissue matrix and also promote angiogenesis.

Bone Marrow derived myeloid cells	**Function**
Macrophages	Promotes angiogenesis
Myeloid derived suppressor cells	Suppresses immunity
Protumorigenic myeloid subpopulations	Promoting metastasis
Pro tumorigenic cell type	**Function**
Neutrophils	Promote angiogenesis by releasing potent angiogenic factors such as VEGF that are usually sequestrated in the ECM.
Eosinophils	Eosinophils in their secretory granules contain VEGF
Mast cells	Express pro angiogenic factors like VEGF, bFGF, TGF beta, TNF alpha and MMP -9
Dendritic cells	Immature dendritic cells upregulate proangiogenic factors like VEGF on exposure to hypoxia.
Tie 2 expressing monocytes TEMs	Promote angiogenesis by expressing the potent proangiogenic molecule bFGF.

Table-3: Meloid Cells In Tumor Angiogenesis (VEGF Vascular endothelial growth factor; bFGF – Fib- roblast growth factor; MMP – Matrix metallopro- teinases; TNF – Tumor necrosis factor)

Group of drug	**Action**	**Examples**
Group I	Prevents secretion of angiogenic facrors from tumor cells	Interferons
Group II	Increase the secretion of anti angiogenic molecules by the tumor cells or normal cells	Retinoids
Group III	Prevents the tumor cells from stimulating and activating macrophages or endothelial cells to secrete any angiogenic molecules	
Group IV	Neutralizes biological activity of angiogenic factors.	Marimastat and Neovastat
Group V	Cause endothelial cells to become refractory to inducers of angiogenesis secreted by both the tumor cells and surrounding normal cells.	Endostatin Thalidomide

Table-4: Antiangiogenic Drugs

The literature review suggests that macrophages proliferation, tumor cell migration, invasion and also tumor angiogenesis.[14]

Applications of tumor angiogenesis

The tumor cells attract monocytes activating them to secrete angiogenic factors in HNSCC. In addition to them macrophages produce cytokines that act in paracrine fashion on the tumor cells and stimulate them to secrete VEGF. So it is believed that these cells may have an indirect role in the induction of angiogenesis in tumors

(including HNSCC). Beyond its effects on tumor expansion, the most important way in which angiogenesis can facilitate tumor metastasis is by providing an efficient route of exit for tumor cells. Angiogenesis enhances entry of tumor cells into the circulation by providing an enhanced density of young, permeable blood vessels which possess little basement membrane and less intercellular junction complexes than normal mature blood vessels. Moreover the number of metastasis formed is proportional to the number of tumor cells shed. A very imperative finding which fascinated the field of interest came out in a study reported by Weidner et al in 1991 who found that in the primary tumor which have a higher degree of angiogenesis have worse prognosis proving that there is a direct relationship between angiogenesis and metastasis. Besides understanding the prognostic implication of tumor angiogenesis, it also served to highlight the extent to which a tumor mass can become contaminated by blood vessels.[5, 15, 16]

Anti Angiogenic therapy

Anti-angiogenic substances can be divided in two categories, directly acting like endostatin, targeting endothelial cell recruitment, endothelial cell proliferation as well as tube formation, whereas indirect inhibitors like Iressa which target tumor cells production of pro-angiogenic growth factors or interfere with their receptors or intracellular signaling pathways (Table 4).[17, 18]
Advantages of anti-angiogenic therapy over conventional chemotherapy: They are not restricted to a certain histologic tumor entity as all solid tumors depend on angiogenesis. In contrast to chemotherapy, no endothelial barrier has to be crossed by the therapeutic substances. The endothelial cell targeted is genetically stable and therefore subjected to be less prone to development of drug resistance. Moreover, antagonism of angiogenesis is a highly selective therapy promising less serious side effects.[17-24]

CONCLUSION

Cancer cells are like teenagers and all they want to do is consume and nurture. To streamline the progress of consumption, these cells send chemical messages that cause blood vessels to fabricate themselves wherever they are. This creation of new blood vessels is called angiogenesis. It is now concluded that without angiogenesis, a tumor cannot grow to a significant size because the growth rate of malignant tissue will surpass the capacity of the normal blood supply in a given region to support malignant growth.

Abbreviations – HNSCC – Head and neck squamous cell carcinoma, VEGF – Vascular Endothelial growth factor, TAM – Tumor Associated Macrophages

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