Cancer Therapy & Oncology
International Journal
ISSN: 2473-554X

Juniper Publishers
key to the Researchers

Review Article
Volume 22 Issue 5 - December 2022
DOI: 10.19080/CTOIJ.2022.22.556100

Cancer Ther Oncol Int J

The concepts of Angiogenesis and its implications in oncology!

Major Dr M Q Baig*

Professor, Radiation Oncology, J K Cancer Institute, India

Submission: December 07, 2022; **Published:** December 22, 2022

***Corresponding author:** Major Dr M Q Baig, Professor, Radiation Oncology, J K Cancer Institute, Kanpur UP, India

Abstract

Angiogenesis is the growth of new blood vessels and is a key process which occurs during both physiological and pathological disease processes. Knowledge of the mechanisms through which this process is initiated and maintained will have a significant impact on the many of the solid tumors in field of medical oncology . Pathological angiogenesis occurs in major diseases such as cancer, diabetic retinopathies, age-related macular degeneration and atherosclerosis.

Keywords: Angiogenesis; Medical oncology; Solid tumors

Introduction

Approval of several antiangiogenesis drugs for systemic therapy for several malignances have been developed, like bevacizumab a humanized monoclonal antibody to vascular endothelial growth factor VEGF, however the success of bevacizumab in combination with chemotherapy in metastatic breast cancer and metastatic colorectal cancer is well established and as monotherapy of bevacizumab in case of metastatic renal cancer approved till date. Era of antiangiogenic drugs began with the landmark article published in 1971 in NEW ENGLAND JOURNAL OF MEDICINE by Folkman [1], the content of above publication was given below,

i. Solid tumors will not grow beyond 2mm in size unless they induce and sustain new blood supply to provide oxygen and nutrients for their growth of tumor mass.

ii. Up to 2mm size tumor may derive its oxygen and nutrients by passive diffusion.

iii. When tumor cell population begins to produce TAF tumor angiogenic factors which creates revascularizations by endothelial cells these endothelial cells of nearby preexisting blood vessels began to migrate, divide and formed tubular structures to form new blood vessels these blood vessels infiltrate in tumor mass to established new blood supply for the progress of tumor growth.

iv. Administration of antiangiogenesis agents for example Anti TAF tumor angiogenesis factor specific neutralizing antibodies will block tumor angiogenesis process , but such tumor shrinkage would never be completely because microscopic tumor which size 2mm or less can survive without new vessels so this type of therapy never be called curative Dr Folkman further described in his reports following- He described nature of angiogenic switch present in tumors ,first stimulator of angiogenesis, are Basis fibroblast growth factor and discovery of several endogenous antiangiogenesis inhibitors, after so many twist and turns ,the concepts of therapeutic role of angiogenesis has been finally formulated,

a. Certain angiogenic drugs seems to have no clinical benefits when used as

b. monotherapy but does have good role when it is combined with chemotherapy drugs.

c. In addition to stimulators of angiogenisis process there are number of endogenous antiangiognisis factors down regulatory effect on them can lead to progress of tumors.

d. Angiogenesis can also contribute to growth of liquid tumors like hematological malignancies not just for only solid tumors due to expression of number of growth factors like

cytokines, cytokinines by activated endothelial cells at newly formed blood vessels sites, as well as bone marrow which promote survival and growth of tumor cell populations [2].

e. There are no single TAF, rather large numbers of molecules involved in angiogenesis process (Figure 1).

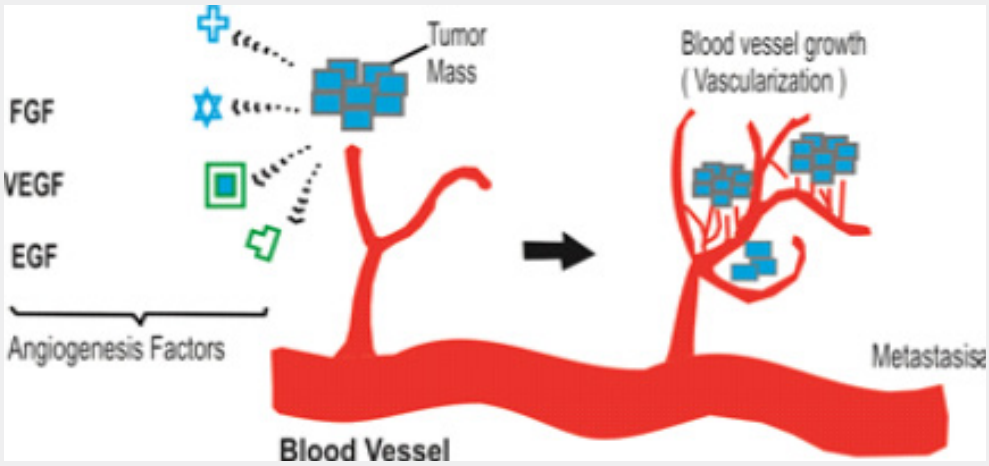

Figure 1: Steps of Angiogenesis and Metastasis.

Discussion

A-Process of formation of new blood vessels:

There are number of sequential events involved in the development of new capillary blood vessels in ongoing tumor mass. The first step in the formation of new blood vessels is breaking of basement membrane of parental venule (pre-existing small blood vessels) that create moment of endothelial cells towards adjacent tumor cells this process stimulated by proangiogenic factors secreted by tumor cell mass, these proangiogenic factors Known as Matrix metalloproteinase and urokinase plasminogen activator. (They are basically proteolysis enzymes) This philosophy of above two enzymes (proangiogenic factors) leads to research to form drugs which inhibit such enzyme. Second step in formation of new blood vessels is migration of endothelial cells as well as division of these mature endothelial cells adjacent to tumor moss and finally formation of new basement membrane of juvenile blood vessels these new angiogenic blood vessels of tumor cells established the further growth of tumor cells populations , apart from this some endothelial proginator cells formed in bone marrow from here these goes to main blood vessels supply via this these proginators reaches to tumor cell mass to stimulate division of mature endothelial cells in order to form new blood vessels.

B- Pericytes

Pericytes is a single layer of periendothlial smooth muscle cells which modulate endothelial cell functions and critical for the development of mature vascular network since role of pericytes in helping survival of endothelial cells thus pericytes emerged as an important therapeutic target for antiangiogenic therapy [3].

C-Molecular Mediators of Tumor Angiogenisis

Several angiogenic growth factors found which modulates tumor angiogenesis some working directly some working indirectly thus divided as,

i. Directly acting factors

ii. Indirectly acting growth factors.

Directly acting growth factors include VEGF family include Tyrosin kinase, angiopoetine, notch singling receptor specially notch 4, NOTCH 4? is a member of notch family is basically a TRANS MEMBRANE RECEPTOR express primarily on endothelial cells of blood vessels .All factors have high degree of specificity for endothelial cells associated neovascularization. VEGF another name is VPF vascular Permeability factor, VEGF produced by primary tumor cells, macrophages , platelets cells , VEGF also plays role in normal physiological functions such as bone marrow formation, Haemopoiesis, wound healing not only limited to solid tumors but also hematological malignancies leukemia's and lymphomas [4]. Types OF VEGF -VEGF 1,VEGF 2 ,VEGF3 OUT OF THAT VEGF 1 AND 2 regulate angiogenesis and VEGF regulate lymph angiogenesis, . VEGF is protein with vascular permeability that is secreted by tumor cells**.** Indirectly acting angiogenic factors those who amplify angiogenic process are TNF a and TNF b, Transforming growth factors, Inflammatory cytokinines such as IL6 and IL8, Granulocyte stimulating factor, PDGF platelet derived growth factor, estrogen and androgen hormone as well. VGEF was discovered in 1989 and replaced to be highly specific and potent mitogen for vascular endothelial cells (Figure 2).

How to cite this article: Major Dr M Q B. The concepts of Angiogenesis and its implications in oncology!. Canc Therapy & Oncol Int J. 2022; 22(5): 556100. DOI: 10.19080/CTOIJ.2022.22.556100

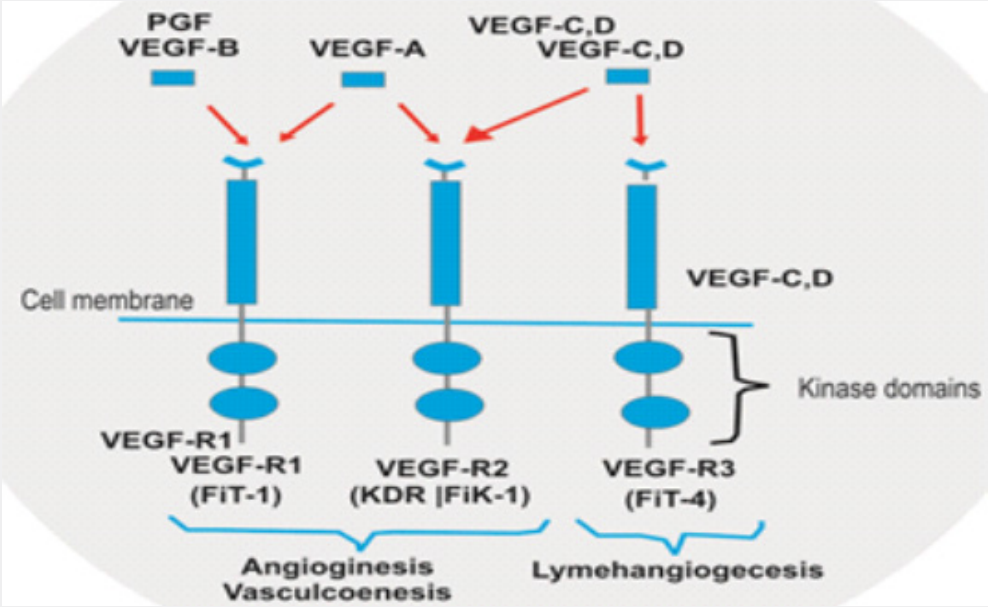

Figure 2: Factors which Promotes Angogenisis.

There are four roles of VEGF by which it promotes tumor angiogenesis it can stimulate endothelial cells division and induce endothelial cells migrations also enhanced endothelial cells survival and mobilizes endothelial progenitors cells from bone marrow to the site of tumorogenesis, elevated expression of VGEF commonly associated with tumor hypoxia so hypoxia in tumor cells leads to over expression of VGEF thus leads to neovascularization of tumor cell mass [5] (Figure 3).

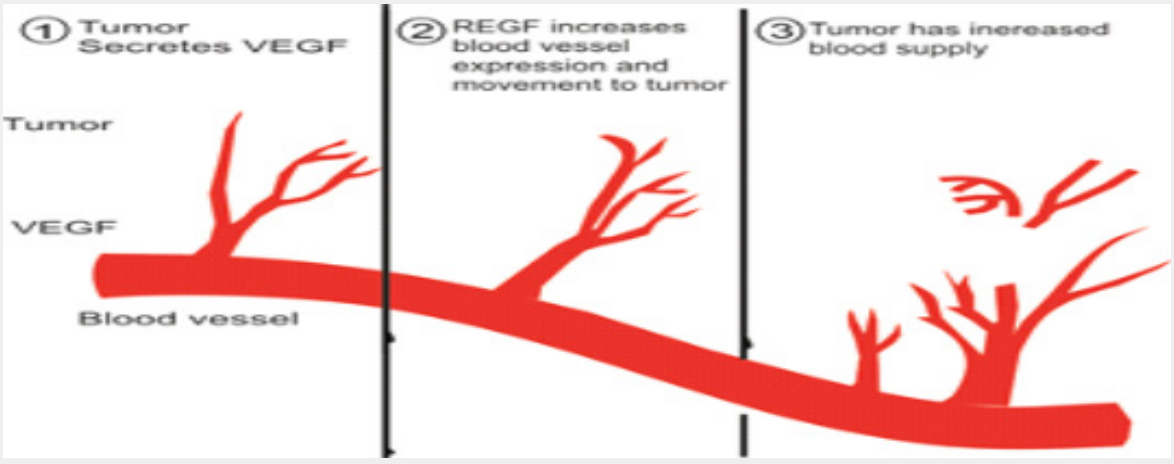

Figure 3: How New Blood Vessels Develop for Tumor Progression.

D-Endogenus Inhibitors of Tumor Angiogenisis

In addition to multiple factors stimulating the angiogenesis there are inhibits molecules of angiogenesis process as well that inhibitor is a large glycoprotein molecule present in Extracellular matrix named Trombospondin-1 (TSP-1) P53 gene was found to regulate TPS-1 level, loss of P53 gene associated with down regulation of TSP-1 expression. Second inhibitor is VASOINHIBIN a protein which is secreted by Endothelial cells and stimulation of angiogenic factors VEGF, the Biology of Endogenous angiogenesis inhibitors is that they maybe induce by other cancer therapy to have added effect for example some antiangiogenic treatment strategy such as low dose metronomic chemotheraphy or doxycycline are known to induce elevated levels of TSP-1 [6].

How to cite this article: Major Dr M Q B. The concepts of Angiogenesis and its implications in oncology!. Canc Therapy & Oncol Int J. 2022; 22(5): 556100. DOI: 10.19080/CTOIJ.2022.22.556100

E-Strategies for Development of Antiangiogenic Drugs

Most obvious strategy would be development of drugs that neutralize proangiogenic growth factors such as VEGF. All approved antiangiogenic drugs either block VEGF or VEGF tyrosin kinase receptor example Bevacizumab drug developed to neutralize VEGF in addition to antibody/protein therapy a large number of small molecule and receptor tyrosin kinase inhibitors have been developed to block VEGF receptor phosphorylation such drugs are SUNITINIB and SORAFENIB these drugs action is not only inhibition of angiogenesis but also, they directly act by inhibition of tumor cell. Bevacizumab when bevacizumab treatment would be more helpful, use alone not effective but when use along chemotherapy drugs they prove to have good results, other mode of treatment and drugs those having antiangiogenic effect or example radiation treatment, Cetuximab or Transtuzumab (targeting Her-2 antibody) do have down regulatory effect on VEGF and up regulatory effect on TSP-1. How antioangiogenic drugs enhanced the effects of radiation and chemotherapy? Antioangiogenic drugs actually increase tumor oxygenation and blood supply thus increase intratumor level of chemotherapy as well as increase oxygen level also increases the effects of radiotherapy [7].

F-Markers of Tumor Angiogenisis

Possible markers of tumor angiogenesis are circulatory blood proteins VEGF, Proangiogenic growth factors, circulatory endothelial progenitors cells . Biomarkers are elevated levels of VEGF are associated with poor prognosis, thus if high levels of VEGF, bevacizumab treatment would be more helpful , VEGF receptors diagnosis and test require tissue specimen for immunohistochemistry study, but the tissue specimen must be from

Benefits of Anti-Vegf Therapy

Inhibit the new vessels growth in tumor tissue.

B- Blockade OF development of endothelial progenitor cells

C- Normalization of vasculature thus decrease permeability of and increase chemotherapy drug delivery to tumor tissue.

D- Direct effect on tumor as antitumor effect.

E- E-Inhibition of damage of endothelial cells by chemotherapy drugs.

F- F-Immunomodulatory effect. For the tumors other than renal cell carcinoma anti VEGF therapy only provide benefits when it given in combination with chemotherapy drugs ,Tyrosin kinase inhibitors in metastatic colorectal cancer enhanced its effect when given with chemotherapy drugs like metastatic breast cancer bevacizumab augments the effects of paclitaxil based chemotherapy [8,9].

Toxicity of Anti Vegf Therapy

i. Hypertension,

ii. Proptienurea,

iii. Bowel perforation,

iv. 4- Anti thrombotic events Hypertensions do occur due to anti VEGF causes inhibition of endothelial cells derived nitric oxide which is known vasodilator. Why cause protein urea because it causes damage to vascular endothelial cells of glomeruli which leads to protein urea Gastro intestinal perforation do occur in 1.5 to 5.5 % patients receiving bevasuzimab , because it causes GI ulceration which further leads to gastrointestinal perforations Bevasuzimab induces VEGF inhibition which results in cholesterol emboli syndrome CES (HTN, GI PERFORATION, ESIONOPHELIA) which leads to mesenteric vessels ischemia which further leads to perforation.

Conclusion

Basis of angiogenesis within the tumor ecosystem cellular and molecular components is provided. Clinical evidence has demonstrated the effectiveness of traditional vessel-directed antiangiogenics, stressing on the important role of angiogenesis in tumor establishment, dissemination, and growth. Particular focus is placed on the interaction between tumor cells and their surrounding ecosystem, which is now regarded as a promising target for the development of new antiangiogenics drugs which having proving benefits in colorectal cancer , breast cancer as well as in lung cancer (NSCLC) Non-small cell lung carcinomas.

References

1. Folkman J (1971) Tumor angiogenesis: therapeutic implications. N Engl J Med 285(21): 1182-1186.
2. Mark Slevin, Yihai Cao, Jan Kitajewski (2009) Welcome to Journal of Angiogenesis Research. J Angiogenes Res 1: 1.
3. Kerbel R S (2006) Antiangiogenic therapy: a universal chemosensitization strategy for cancer? Science 312(5777): 1171-1175.
4. Khosravi P (2006) Angiogenesis y neoplasias. Ann Med Interna 23(8): 355.
5. Risau W (1997) Mechanisms of angiogenesis. Nature 386(6626): 671-674.
6. Ferrara N, Gerber H P, LeCouter J (2003) The biology of VEGF and its receptors. Nat Med 9(6): 669-676.
7. Veikkola T, Karkkainen M, Claesson-Welsh L, K Alitalo (2000) Regulation of angiogenesis via vascular endothelial growth factor receptors. Cancer Res 60(2): 203-212.
8. Winston S N Shim , Ivy A W Ho, Philip E H Wong (2007) Angiopoietin A. TIE(d) Balance in Tumor. Angiogenesis. Mol Cancer Res 5(7): 655-665.
9. Kumar R, Yoneda J, Bucana C D, I J Fidler (1998) Regulation of distinct steps of angiogenesis by different angiogenic molecules. Int J Oncol 12(4): 749-757.

How to cite this article: Major Dr M Q B. The concepts of Angiogenesis and its implications in oncology!. Canc Therapy & Oncol Int J. 2022; 22(5): 556100. DOI: 10.19080/CTOIJ.2022.22.556100

DOI: 10.19080/CTOIJ.2022.22.556100

How to cite this article: Major Dr M Q B. The concepts of Angiogenesis and its implications in oncology!. Canc Therapy & Oncol Int J. 2022; 22(5): 556100. DOI: 10.19080/CTOIJ.2022.22.556100