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THE CONCEPTS OF ANGIOGENESIS FROM ONLY THEORETICAL TO BED SIDE TREATMENT IN THE FIELD OF ONCOLOGY—ORIGINAL ARTICLE

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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 treatment of these diseases. Pathological angiogenesis occurs in major diseases such as cancer, diabetic retinopathies, age-related macular degeneration and atherosclerosis.

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 , the content of above publication were given below , 1-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. 2-up to 2mm size tumor may derived its oxygen and nutrients by passive diffusion. 3-When tumor cell population begins to produce TAF tumor angiogenic factors which creates revascularizations by endothelial cells these endothelial cells of nearby pre existing blood vessels began to migrate ,divide and formed tubular structures to form new blood vessels these blood vessels infiltrate in tumor mass to to established new blood supply for the progress of tumor growth. 4-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, 1-Certain angiogenic drugs seems to have no clinical benefits when used as monotherapy but does have good role when it is combined with chemotherapy drugs. 2-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. 3-Angiogenesis can also contribute in 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. . 4- There are no single TAF, rather large numbers of molecules involved in angiogenesis process

PROCESS OF FORMATION OF NEW BLOOD VESSELS STEP WISE -

There are number of sequential event 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 proangogenic factors Known as Matrix metalloproteinase and urokinase plasminogen activator.(they are basically proteolysis enzymes) This philosophy of above two enzymes (proangiogenic factors) leads to a 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.

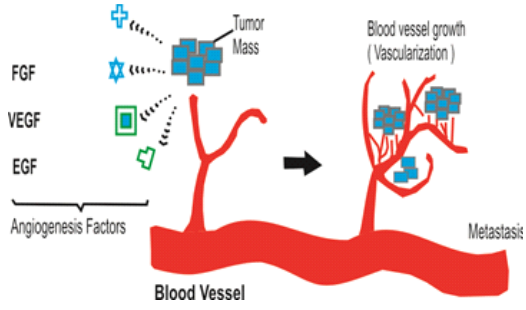

FIG-1- STEPS OF ANGIOGENESIS AND METASTASIS

PERICYTES-

Pericytes is a single layers 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. MOLECULAR MEDIATORS OF TUMOR ANGIOGENISIS - Several angiogenic growth factors found which modulates tumor angiogenesis some working directly some working indirectly thus divided as, A-Directly acting factors B-Indirectly acting growth factors. Directly acting growth factors include VEGF family include Tyrosin kinase, angiopoetine, notch singling receptor specially notch 4, all factors have high degree of specificity for endothelial cells associated neovascularization. Indirectly acting angiogenic factors those who amplify angiogenic process are TNF α and TNF β, 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.

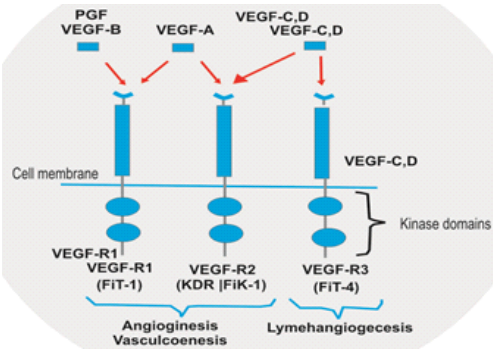

FIG 2- FACTORS WHICH PROMOTES ANGOGENISIS

There are four role of VEGF by which it promotes tumor angiogenisis it can stimulate endothelial cells division and induce endothelial cells migrations also enhanced endothelial cells survival and mobilizes endothelial progenitors cells from bonemarrow 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.

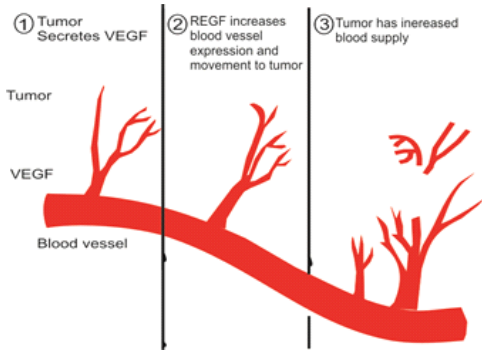

FIG 3–HOW NEW BLOOD VESSELS DEVELOP FOR TUMOR PROGRESSION

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 an stimulation of angiogenic factors VEGF, the Biology of Endogenous angiogenisis 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 doxiycline are known to induce elevated levels of TSP-1.

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 CHEMOTHERAPYAntioangiogenic 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.

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 immunohistochemistary study but the tissue specimen must be from

BENEFITS OF ANTI-VEGF THERAPY-

A- 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.

TOXICITY OF ANTI VEGF THERAPY –

1- Hypertension ,
2- Proptienurea ,
3- Bowel perforation,.
4- Anti thrombotic events Hypertensions do occur due to anti VEGF causes inhibition of endothelial cells derived nitric oxide which is known vasodilator.

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