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Angiogenesis: types, factors and significance

Sonia Sharma.

University of Jammu, Jammu

Abstract

Angiogenesis is the generation of the new blood vessels from the existing blood vessels. It is complex physiological process regulated by the various endogenous angiogenic factors. These factors maintain the balance in angiogenesis and anti-angiogenesis. When physiological angiogenesis regulation fails pathological angiogenesis starts as in cancer and some other diseases like neurodegenerative diseases and arteriovenous malformations etc. Sustained angiogenesis is also the one of the hallmarks of cancer as it promotes both tumor growth and metastasis which is main cause of deaths in cancer patients. Angiogenesis is multistep process consists of various steps. Hypoxia, HIF-1α is the main stimulus for angiogenesis in cancer as it upregulates the expression of the angiogenesis factor. VEGF (vascular endothelial growth factor) is the principle pro- angiogenesis factor since it directly activates the endothelial cells and forms the linings of the blood vessels. VEGFs factors bind to tyrosine kinase vascular endothelial growth factor receptors, VEGFR-1, 2 and 3 receptors present on the surface of normal endothelial cells. VEGFR-2 plays an important role in cancer angiogenesis since it further up regulates the pathways like PI3K/Akt/mTOR, ERK and MAPK and mediates the HIF-1α/VEGF mediated angiogenesis. Anti-angiogenesis therapy is FDA approved validated anticancer therapy it has also already increased the life span of many cancer patients. In comparison to other anticancer therapies, it is less toxic since it targets the normal endothelial cells and has low risk of resistance. Anti- angiogenic therapy also has some complication like they increased aggressiveness of cancer by increasing metastasis, cancer stem cell germination through hypoxia induction etc. Most efficient way of use of the anti-angiogenesis therapy is use of angiogenesis inhibitors in combination with the conventional cytotoxic drugs.

Introduction

Cancer is defined as group of related diseases caused by uncontrolled cell division. Cancer produces the mass of tissue in solid tumors. Lung, breast, prostate and skin cancer are the most common cancers. Cancer is a genetic disease caused by mutation in genes normally controlling cell division and is the leading cause of death globally. Under normal physiological body conditions cells grow, multiply and ultimately die. But in cancer an abnormal mutated cell divides continuously and produces more and more abnormal cells which damages the surrounding healthy cell and then invade and migrates to other essential body organs and ultimately death in cancer because of metastasis.

Types of cancers

1. Carcinoma: cancer of skin or tissue lining the organs like kidney and lung. Carcinoma is most common types of cancer in humans. E.g. of carcinoma are breast, lung and liver

2. Sarcoma: is rare kind of cancer that occurs in connective tissue. Tumor of muscles, tendons, fat is sarcoma. Sarcomas are cured by removal of tumor by surgery.

3. Lymphoma: cancer of immune system or lymphocytes infection fighting cells. These cells are present in spleen, bone marrow, thymus and other parts of body. It is treatable form of cancer

4. Leukemia: occurs in blood forming cells in bone marrow, cancer of WBC. Lymphoma and leukemia are different in cells of their origin.

5. Brain and spinal cord: Cancer of Central Nervous System. Begins in normal cells of brain or spinal cord. It can be benign or metastatic

6. Melanoma: most dangerous form of skin cancer and less common also as compared to other cancers

Causes of cancer

Mutation change in the genetic material is defined as mutation. Mutation is of two types acquired mutations and inherited mutations. Acquired mutations are those which are develop during the life span of an individual by certain external factors like, tobacco alcohol, sun rays etc. Inherited mutations are that which runs in family and passed from parents to offsprings. Breast cancer and colorectal cancer are hereditary. Mutations in gene controlling normal cell division like tumor suppressor genes, oncogenes and DNA repair enzymes BRAC1, BRAC2, p53, RAS and HER 2 causes cancer. Single mutation cannot cause cancer because cancer requires multiple mutations to develop.

Life style**:** life style is also an important cause of cancer like, smoking; about 85 % of lung cancers are because of tobacco. Tobacco smoke has harmful chemicals like carbon monoxide, hydrogen cyanide, toluene, ammonia etc about 30 % death in cancer is because of tobacco smoking. Smoking increases the risk of oral cancer, kidney and bladder. Alcohol is also carcinogen and classified as group 1 carcinogen by WHO. Alcohol consumption is one of cause of cancer-like mouth, lyrnax, throat and breast. Lack of physical activity, high fat diet, and intake of packed food, intake of high salt and artificial sweeteners also develops the risk of cancer. Obesity increases the risk of thyroid, kidney, collateral and pancreatic cancer.

Environmental factors: like harmful sun radiations ionizing x-rays and non-ionizing UV sunlight can damage the skin and causes early signs of aging and skin cancer, basal cell carcinoma, sqauamous carcinoma and melanoma are few of examples. Water and air pollution also causes cancer. Presence of harmful chemicals like asbestos, benzene, formaldehyde monoxide minerals

oils, soot and radon and ammonia hydrocarbons in water and air cause cancer. Chemicals causing cancer are called as carcinogens.

Biological factors: certain biological factors like bacteria and viruses also cause cancer. Bacterium likes salmonella typi and streptococcus bovis cause gall bladder and colon cancer respectively. Mycobacterium Tuberculosis causes lung cancer. Helicobacter pylori cause gastritis. Human hepatitis B (HBV) Human papillomavirus (HPV), cause cervical cancer and hepatitis C virus (HCV) are also cancer-causing viruses cause hepatitis cause lung cancer. Epstein –Barr virus the herpes virus cause lymphoma and cancer of nose and throat.

Age: with the increasing age the risk of certain cancers is increased as with increasing age the time of exposure to certain chemicals and radiations are also increased and thus risk of mutation is also increased. Like DNA mutation of TERC and TERT in cancer cell increases the activity of telomerase enzyme in cancer cell. In the normal cells with age the telomeres get shorten with every cell division but in cancer cell because the telomerase enzyme is mutated and there is no shorting of telomeres and thus cancer cell keeps on dividing and becomes immortal.

Hormones: high levels of certain hormones like estrogen, progesterone and testosterone increases the risks of breast cancer and prostate cancer. Women who receive menopausal hormonal therapy also have increased risk of endometrial cancer.

Occupational risk factors: cancer causing factors related to work and living environments like asbestos fibrestar and pitch polynuclear hydrocarbons (e.g. benzopyrene) increases the occupational risk of cancer. Some metal compounds some plastic chemicals (e.g. Vinyl chloride) present in work and living environments causes cancer.

Inflammation: physiological inflammation starts with the injury and ends with repair but in certain conditions inflammation starts its own without the injury and increases the rate of DNA mutations and causes cancer. Inflammation increases the rate of cell division angiogenesis and metastasis. Colon cancer is because of pathological inflammation

Before cancer actually develops normal cell follows the following phases like hyperplasia, dysplasia and then cancerous. In hyperplasia phase cell in tissue and organ starts dividing more than normal cells and number of cells in tissue and organ gets increased but there is no change in morphology of tissue or organ. In dysplasia morphology of organ or tissue changes. Hyperplasia and dysplasia phases may or may not be cancerous. Third stage is cancerous. Thus, normal cell passes through hyperplasia, dysplasia and then becomes cancerous.

Cancer angiogenesis

In 1971, Folkman first proposed that cancer growth is angiogenesis dependent. Later this was proved and leads to new field of science called as angiogenesis. Importance of tumor angiogenesis is that like a normal cell, tumor is also dependent upon the blood supply for nutrients and growth.

Tumor cannot grow without angiogenesis and with advanced angiogenesis can grow up to 10 mm. Sustained angiogenesis is also the one of the hallmarks of cancer. Angiogenesis plays an important role in solid tumor progression along with this angiogenesis increase the aggressiveness of cancer by increasing cancer cell migration and invasion.

Tumor angiogenesis factor (TNF): Solid tumor passes from avascular to vascular stage. Avascular stage is in which the tumor is dormant less than 1 mm and vascular stage in which tumor is vascularized with newly formed blood capillaries from existing blood vessels, developed under the influence of tumor angiogenesis factor secreted by tumor itself. With advanced angiogenesis the tumor can grow up to 10 mm in diameter.

Vasculogenesis and angiogenesis are the two basic fundamental physiological processes by which new blood vessels are formed in the body. Vasculogenesis is the process by which new blood vessel arises during embryonic developments from angioblasts or hemangioblasts. It involves the development of primitive vascular system including the heart. Whereas the angiogenesis is the formation of the new blood vessels from the pre-existing blood vessels for repair, expansion and remodeling of existing blood vascular system. New blood vessels in angiogenesis are formed by the two processes first by sprouting of endothelial cells, sprouting angiogenesis is deeply studied and second by intussusceptive angiogenesis means by splitting of existing blood vessels. The stimulus for both vasculogenesis (through eNOS) and angiogenesis is hypoxia. Arteriogenesis is the formation of medium sizes arteries containing tunica media adventiata and the stimulus for arteriogenesis is stress.

S.No	*Types*		*Stimulus*
1)	Vasculogenesis	The generation of new blood vessels during embryonic development.	Hypoxia
2)	Angiogenesis	The generation of new blood vessels from existing blood vessels for repair and expansion of blood vascular system.	Hypoxia
3)	Arteriogenesis	The generation of medium sized arteries.	Stress

Table-1: Types of angiogenesis.

Angiogenesis the generation of the new blood vessels from the existing blood, vessels play an important role in embryogenesis, bone formation, repair, female reproductive cycle and wound healing. Physiological angiogenesis is complex process and highly regulated by various angiogenic factors like pro-angiogenic activators like EGF, FGF, PDGF, VEGF and, IL-8 etc and anti-angiogenic inhibitors like endostatin, angiostatin and retinoids, IL-12 and α, β and γ

interferons etc. When physiological angiogenesis regulation fails pathological angiogenesis occurs as in cancer and some other diseases like neurodegenerative diseases and arteriovenous malformations. VEGF (vascular endothelial growth factor) as is the principle angiogenic factor as it specifically activates endothelial cells. VEGF family of angiogenic factors consists factors like A, B, C, D, E and PGF These angiogenic factors bind to transmembrane tyrosine kinase receptors VEGFR-1, 2 and 3. Phosphorlyation of VEGFR-2 play an important role in angiogenesis as it further activates various downstream pathways like, PI3K/Akt/mTOR pathway, HIF-1α/VEGF, MAPK pathway, and thus neoangiogenesis in cancer which contributes to cancer cell survival, proliferation, migration, invasion and metastasis. Angiogenesis stimulates both tumor growth and cancer cell metastasis.

Angiogenesis factor	*Anti-angiogenesis factor*
VEGF (Vascular endothelial growth factor)	Endostatin
bFGF(Fibroblast growth factor)	Angiostatin
TGF-β(Transforming growth factor-Beta)	IL-12(Interleukin-12)
IL-8(Interleukin-8)	Thrombospondin
PDGF (platelet derived growth factor)	Interferon-α, β and γ
EGF	
PGF	

Table -2: List of angiogenesis factor and anti-angiogenesis factor.

Angiogenesis is a continuous process which starts in embryo and is continuous throughout the life of an individual. New blood vessels arise either by sprouting of endothelial cells from existing vessels towards the signal VEGF-A, Delta –notch signaling is main signaling pathway involved in the sprouting angiogenesis or by splitting of the existing blood vessels. Both these types of angiogenesis can occur at almost any stage of life and in almost in any organ of the body. Other tumor vasculaization modes are vascular mimicry in which tumor cell line into tumor vessel in this cancer cell expresses the cancer stem cell phenotype and contributes to the cancer growth. Hypoxia is stimulus for vascular mimicry. Vasculogenesis involves the differentiation of (EPCs) endothelial progenitor cells into (ECs) endothelial cells at the site of tumor development. Vessel cooption is another way of tumor vascularization in which cancer cell can opt the preexisting vasculature for the nutrients supply. Vessel's cooption can be one of way by which cancer cell survives whereas angiogenesis is responsible for exponential growth of the cancer, vessel cooption is alternative to cancer angiogenesis, and mediated by VEGFs.

HIF: uncontrolled cell division results in irregular blood supply and less oxygen condition which is known as hypoxia. Hypoxia is a characteristic feature of solid tumors .HIF- 1is a transcription factor (HIF-2 and HIF-3 are the other analogs of HIF-1) which regulates the syntheses of various angiogenic proteins, principles among them is VEGF (vascular endothelial growth factor).HIF -1 complex consists of HIF- 1α and HIF-1β.At high oxygen level HIF-1α is continuously degraded in the cytoplasm and at low oxygen condition HIF-1α is stabilized and migrates into the nucleus forming complex with HIF- β, that is HIF-1 complex and stimulates the expression of hypoxia responsive genes. Under high oxygen condition HIF-1α have short life span of half-life of 5 mins. Hypoxia induced angiogenic factors further activates the endothelial cell proliferation, migration and sprouting, vasodilatation, ECM, degradation, vessel maturation and smooth muscle

recruitment thus neo angiogenesis in cancer. Without angiogenesis tumor cannot grow and either go apoptosis or necrosis. Other roles played by hypoxia in the cells are cell metabolism, erythropoiesis and cell proliferation and cell survival.

HIF-1 α under high oxygen conditions goes protosomal degradations by Von Hippel-Lindau (VHL) degradation pathway. Two proline amino acids acts as substrate for two hydrolases named hydrolyasaes prolyl -4- hydrolases (PHDs) and HIF1 prolyl hydrolyses (HPH).Hydroxylation degradation of proline reside require sufficient oxygen only then PHDs can degrade the HIF-1α subunit of HIF-1.PHD modify proline 402 and 546 in the odd domain in HIF-1α residues in the HIF-1α and directs towards the VHL. , PHD family has 3 PHD 1, 2 and 3.PHD 2 is most active for VHL degradation of HIF-1α. Hypoxia is also responsible for resistance in chemotherapy and radiotherapy

HIF-1α upregulates the expression of VEGF and its receptors. VEGF activates the endothelial cells (which lines the inner wall of blood vessel) to release the matrix metalloproteinases (MMPs), these are the group of calcium dependent zinc containing endopepetidases which degrade almost all the components of extracellular matrix in cancer (ECM) like gelatin, collagens, elestins, glycoprotein and proteoglycan and promotes metastasis and invasion. MMPs levels are often elevated in the most of the cancers and cause the migration and proliferation of the endothelial cells. Soon activated endothelial cells start forming the hallow tubes and integrin α and β matures these tubes into mature blood vessels. These mature blood vessels are stabilized by the angiogenic factors Angiotensin-1, -2, and their receptor Tie-2. VEGF proteins are the most powerful and principal angiogenic proteins. VEGF plays an important role in the stimulation of the migration of endothelial progenitor cells from bone marrow to the tumor sites VEGF family consists of proteins like VEGF-A, B, C, D, E, and PGF. Which binds to the VEGFRs on the surface of the normal endothelial cells, and cause the proliferation of endothelial cells and supports the growth of new blood vessels and thus angiogenesis. VEGF -A, B and C cause generations of blood vessels, angiogenesis and C and D promotes lymphogenesis. VEGF-A is coded by gene on long arm of chromosome 6,6q21.3 and has 6 isoforms 121,145,165,183,189 and 206. Most frequent isoform is 165 VEGF- A (vascular permeability factor) (45 kDa). VEGF-B has 2 isoforms VEGF-B 167 and VEGF-B 186.

S.NO	*Types*	*Function*	*Receptor*
1)	VEGF-A (45 kDa) (Vascular permeability factor)	Angiogenesis	R1 and R2
2)	VEGF-B (48 kDa)	Embryonic Angiogenesis	R1
3)	VEGF-C (24 kDa)	Lymphogenesis	R2 and R3
4)	VEGF-D (16 kDa)	Lymphogenesis	R2 and R3
5)	VEGF-E		R2
6)	PGF (placental growth factor) (50 kDa)	Angiogenesis, Lymphogenesis and repair and diseases like, inflammation, cancer	R1

Table -3: VEGF Family, types and receptors.

Vascular endothelial growth factor (VEGFs): factors play an important role in angiogenesis, vascular permeability, survival, stimulation and proliferation of endothelial cells, and prevents the apoptosis of endothelial cells by binding to transmembrane tyrosine kinase receptors present on the surface of the endothelial. VEGFR-2(vascular endothelial growth factor receptor-2) is principal receptors as it is earliest marker of endothelial cells and plays an important role in tumor progression. Angiogenesis is mainly by binding of VEGF -A to VEGFR-2 rests all signaling factors plays secondary role in angiogenesis. HIF is major inducer of VEGF other angiogenic factors and induce the expression of factors like are EGF, TGF-α and β, PDGF and FGF

Vascular endothelial growth factor receptors (VEGF Receptors): There are three VEGF receptors, VEGFR-1.R-2and R-3 .VEGFR-1(FLT1) is activated by VEGF-A and B, stimulates the activation of macrophages and thus promotes the migrations and metastasis of tumor cells, the receptor VEGFR-2(KDR) is activated by VEGF-A, C and E and stimulates angiogenesis, VEGFR-3(FLT4) activated by C and D and stimulates angiogenesis in embryonic life and lymphogenesis. VEGFR-1 and VEGFR-2 are expressed on the endothelial cells. All the three vascular endothelial growth factor receptors (VEGF receptors) differ by their signaling properties. Kinase activity of VEGFR-2 is 10 folds high as compared to VEGFR-1. VEGF can also bind to NPR and regulates angiogenesis and endothelial cell migration without tyrosine kinase activity.

S.No	*Types*	*Function*
1)	VEGFR-1 (FLT-1)	Stimulation of Macrophages
2)	VEGFR-2 (KDR)	Angiogenesis
3)	VEGFR-3 (FLT-4)	Lymphogenesis and Embryonic Angiogenesis

Table-4: VEGF Receptors, types and function.

The VEGFs proteins phosphorylate transmembrane tyrosine kinase VEGFR receptors and activate the induction of the HIF-1α/VEGF mediated angiogenesis pathway leading to tumor growth, proliferation, invasion, migration, and metastasis

Other angiogenesis factors

Angiopoietins proteins bind to receptors Tei-1 and plays an important role in vessels maturation and stabilization of newly formed blood vessels.

EGF (epidermal growth factor) and TGF-α (transforming growth factor-α): both binds to EGF receptors and cause proliferation of the endothelial cells.

bFGF (basic-fibroblast growth factors or FGF-2): family of FGF consists of at least 20 proteins the first pro-angiogenic factor to be discovered it binds to tyrosine kinase FGFR receptors 1, 2, 3, and 4. It also cause proliferation of the endothelial and fibroblasts cells and stimulates the secretion

of VEGF and other proteases. The stimulus for FGF is the wound and it cause repair and healing by sprouting angiogenesis.

Targets in angiogenesis pathway: HIF- 1α, Angiogenesis factors, receptors, invasion, migration and proliferation, tube formation, and vessel maturation.

Angiogenesis factors

Lists of angiogenesis factors: VEGF (vascular endothelial growth factor) ,bFGF(fibroblast growth factor-1and 2, hepatocyte growth factor (HGF), platelet derived growth factor (PDGF),transforming growth factor alpha and beta (TGF-α and β), tumor necrosis factor alpha (TNF-α), ,interleukin- IL-1,6, and 8, and platelet derived growth A,B,C and D factor,HIF-1,2, and 3,endothelin, angiogenin, Ang-1 and,2,NO,insulin and integrin, CXC chemokines,leptin, follistatin, erythropoietin, fibrinogen, placental growth factor(PGF), epidermal growth factors (EGF), progranulin,proliferin and vitronectin.

Lists of antiangiogeneic factors: the first naturally occurring angiogenic inhibitor is thrombospondin, angiostatin (38 kDa) and endostain (20 kDa), vasostatin, platelet factor 4,prolactin (16 kDa),fibronectin fragment ,tumstatin, interferon α, β, and γ, interleukins (IL-4,12) , PEX, TIMP2/3, endogenous antiangiogenesis, and glioma-derived angiogenesis inhibitor factor, canstatin, Gro beta, proliferin related protein, heparinases , human chronic gonadotropin, pigment epithelium derived factor, and canstatin.

Antiangiogenic factors like endosatin, angiostatin and thrombospondin cause the apoptosis of the endothelial cells and inhibits the proliferation and migration of the endothelial cells.

Antiangiogeneic foods: green tea, lemon, dark chocolate, garlic, red grapes, oranges, ginger, blackberries, red wine, soy beans, pineapple, apple, tomatoes, lavender, pumpkin and cherries these are foods rich in anti-angiogeneic properties.

Matrix metalloproteinases (MMPs) are the protolytic enzymes which play an important role in organogenesis and wound healing secreted by the activated endothelial cells. These are the Ca dependent and Zn containing endopeptidases their levels is often increased in the most of cancer and promotes metastasis by digesting the essential components of the extracellular matrix (ECM).MMPs family includes the collgenases (MMPs -1,8 and 13, gelatinasaes (MMPs -2 and 9 , steromelysins (MMPs -3,10, 11and 12 , metrilysins (MMPs-7 and 26), membrane type (MMP 14,15,16,17 24,and 25) and other MMPs (MMP-20 and 23).Their activity is regulated by tissue inhibitors of metalloproteinases (TIMPs) .MMPs play an important role in repair, angiogenesis, invasion and migration

Extracellular matrix (ECM) in cancer plays an important role in angiogenesis by providing mechanical support and cell adhesion. They support endothelial cell proliferation, migration, stabilization. All stages of angiogenesis involve the interaction of cytokines and ECM where ECM

not only supports but also controls the steps involved in angiogenesis like morphonris and maturation of the new bloods vessels

In-vivo Angiogenesis assay: Matrigel plug assay, corneal angiogenesis, CAM chick chorioallantois membrane, and hindlimb ischemia assay.

In-vitro Angiogenesis assay: endothelial proliferation assay, endothelial migration assay, and endothelial differentiation assay.

Ex -vivo assay: organ Culture: rat and chick aorta ring assay.

Breast cancer angiogenesis: Breast cancer is the second leading cause of death in the world. Breast tumor angiogenesis involves the vasculogenesis which involves the proliferation of endothelial progenitors' cells (EPCs) at the site of tumor and angiogenesis which involves the development of the new vasculature by sprouting of endothelial cells and by intussusceptive angiogenesis. Breast cancer angiogenesis involves the endothelial cells from different origins. Breast cancer stem cell (BCSCs) derived endothelial cells modify into vascular endothelial cells in breast cancer and cause tumor angiogenesis. VEGF expression is also increased in breast cancer. Anti-VEGF therapy has already increased in the life span of many Breast cancer patients.

New blood vasculature developed in cancer is heterogenic as newly formed blood vessels are immature, leaky, structurally and functionally abnormal, of small diameter, have increased permeability of molecules across blood vessels. This further results in unstable cancer micro environment and increased hypoxia condition which, reduces the vascular supply of drugs to cancer cell, thus resistance to therapies like chemotherapy and radiotherapy.

Cancer statics

According to GLOBOCAN 2018, Global cancer incidence is 18.1million new cancer cases and Global cancer mortality is 9.6 cancer deaths in both the sexes and for all cancers among all the ages worldwide. Global cancer incidence 2018 in females is as 1) thyroid 2) lung 3) breast,4) colorectal and 5) and Global cancer morality by sex in females is as 1) breast 2) lung 3) colorectal 4) cervix and 5) stomach. Global cancer incidence 2018 in males is as 1) lung 2) stomach) coleratal4) liver and 5) prostate. Global cancer morality by sex in males is as 1) lung 2) liver 3) stomach, 4) colorectal 5) prostate. According to GLOBOCAN the five most commonly diagnosed cancer types in incidence wise are 1) lung 2) breast 3 colorectal 4) prostate 5) stomach for both the sexes all ages worldwide 2018. According to the five most commonly diagnosed cancer type mortality wise are1) lung 2) colorectal 3) stomach 5) stomach. 5) Breast for both sexes and all ages worldwide 2018.

Antiangiogenic therapy is validated anticancer therapy, most effective when used in combination with other conventional cytotoxic anticancer therapies. Angiogenic inhibitors have two advantages

1) They are less toxic as they target only normal endothelia cells.

2) Less risk of resistance as compared to other conventional anticancer therapies.

In 2004 US FDA approved the first antiangiogenesis drug Avastin (Bevacizumzb) recombinant humanized monoclonal antibody against VEGF-A for metastatic colorectal cancer in combination with the chemotherapy, with carboplatin and paclitaxel as first line treatment for cancer. FDA has approved the three types of antiangiogenic therapies for cancer

1) Those drugs which inhibits the VEGF or any other angiogenic factors.

2) Those drugs which neutralize the VEGF or any other angiogenic factors and

3) Drugs that block the binding of angiogenic factors to their receptors.

As antiangiogenesis therapy targets only the endothelial cells it is specific and has lesser side effects when compared to other anticancer therapies. The combination of antiangiogenic therapy and other chemotherapies has already increased the life expectancy in many cancers patients' Antiangiogenic therapy has its own complications like resistance to antiangiogenic therapy, induction of hypoxia, increase in cancer stem cell population and metastasis. Therefore, there is need for screening of novel antiangiogenic inhibitors.

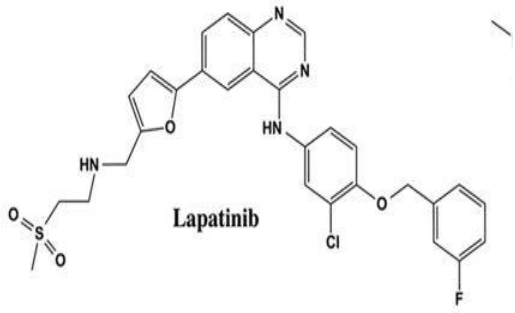
U.S FDA approved inhibitors: FDA has approved many angiogenic inhibitors: Bevacizumab 2005, Sorafinib 2006, Sunitinib 2009, and Pazopainib 2011, Vandetaninib 2012, Axtinib 2014, Ramcucmab 2015, Lenvatinib. Sunitinib inhibits VEGF, PDGFR and FLT3, Axitinib inhibits all VEGFRs, Avastin inhibits VEGF -A, lenvatinib inhibits all VEGFRs, Sorafenib inhibits VEGF, PDGFR and RAF, Vandetanib inhibits all VEGFRs, Pazopanib inhibits all VEGFRs, Ramucirumab inhibits VEGFR-2, and Cabozantinib inhibits all VEGFRs, Everolimus,, Thalidomide, Lenalidomide,

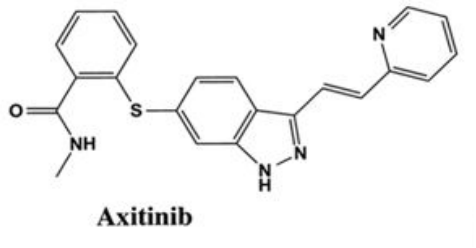
S.No	*FDA Approved Drugs*	
1)	Monoclonal Antibodies	FDA indications
	Bevacizumab	Glioblastoma, Metastatic breast cancer and Colorectal carcinoma, renal carcinoma and non-squamous NSCLC
	Cetuximab	Colorectal carcinoma
	Panitumumab	Colorectal carcinoma
	Trastuzumab	Metastatic breast cancer
2)	Small molecules RTK inhibitors	FDA indications
	Erlotinib	Pancreatic cancer and NSCLC
	Sorafenib	Advanced Renal cell carcinoma and hepatocellular carcinoma
	Sunitinib	Advanced renal carcinoma and GIST
	Gefitinib	NSCLC
	Lapatinib	Metastatic breast cancer
	Pazopanib	Renal cell carcinoma
3)	mTOR inhibitor	FDA indications

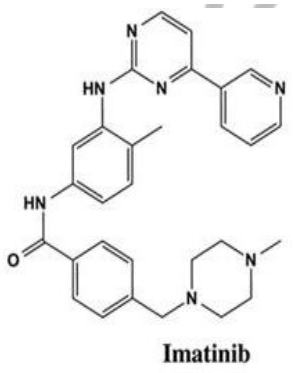
	Temsirolimus	Advanced renal carcinoma
	Everolimus	Advanced renal carcinoma
4)	Other Anti-angiogenesis Agents	FDA indications
	Bortezomib	Mental cell lymphoma and Multiple myeloma.
	Thalidomide	Multiple myeloma

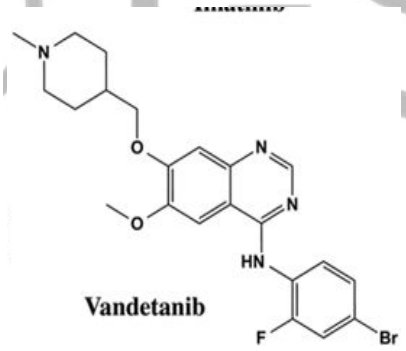
Table -5: List of angiogenic inhibitors approved by FDA.

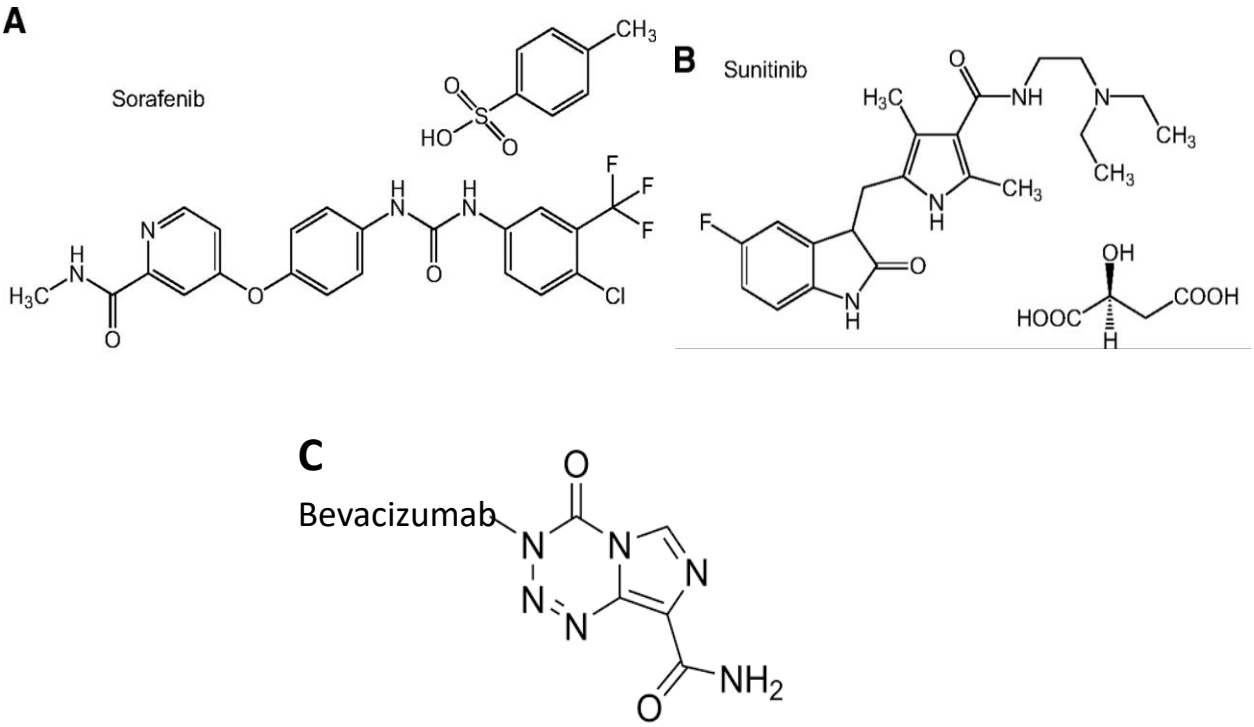
Antiangiogenic therapy: plays an important role in cancer treatment as most of the angiogenic proteins and receptors are over expressed and active in cancer. Along with the inhibition of angiogenesis these angiogenic inhibitors also inhibit the lymphatic system which promotes cancer metastasis.











Complications of antiangiogenic therapy: include the decreased chemo perfusion as antiangiogenic therapy cause vascular trimming and thus, they reduce the vascular supply of cytotoxic drugs to cancer. Another drawback of antiangiogenic therapy is cancer stem cell generations because of induction of hypoxia and HIF-1 signaling. Antiangiogensis therapy cause metastasis and increase the aggressive nature of cancer also by activation of HIF-1α downstream effectors and pro-invasive pathway. Acquired resistance is also one of complication of antiangiogenic therapy as antigiogenic inhibitor also shows adaptive resistance. Because of alternate angiogenesis pathway like vessel cooption. Intrinsic resistance because of generation of tumor resistant clones.

For maximum benefit of antiangiogenesis therapy we need combined application of physiological, molecular and statically understanding of angiogenesis pathway.

Other side effects of anti VEGF therapy include bleeding, hypertension, thrombotic, cardiac failure, hair changes, hypothyroidism, low blood count, diarrhea, bleeding, delay healing and skin problems.

S.No	*Three major Antiangiogenic therapies are*	
1)	True angiogenesis inhibitors	Drugs which inhibit the new blood formation.
2)	Vascular targeting agents	Dugs that inhibit the established vascular system.

3)	The double barred approach	Drugs that inhibit the inhibits blood vessels and cancer cell.

Table-6: Three major Antiangiogenic therapies.

Angiogenesis depends upon the physical activity. Exercise increases the angiogenesis. Diseases like cancer, ophthalmic conditions, rheumatoid arthritis have stimulation of angiogenesis and angiogenesis inhibitors can be therapeutic in these diseases. Whereas diseases like ischemic heart diseases, wound healing and peripheral arterial diseases have decrease angiogenesis in these cases stimulation of angiogenesis can be therapeutic.

Future perceptive

Antiangiogenic therapy is FDA approved and has improved outcomes of the cancer treatment. It also has increased the life span of the many cancer patients but its benefits are modest. There is need of search of predictive markers which will predictive whether will patents will benefit from this therapy or not. Chemotherapies often result in resistance in cancer because cancers are heterogeneous and have genetic insatiability. Combination of conventional therapies and antiangiogenic therapies can reduce both tumor size and vascularization also.

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