

# Multifactorial Epidemiology and Etiology of Cancer Microenvironment Induced Angiogenesis

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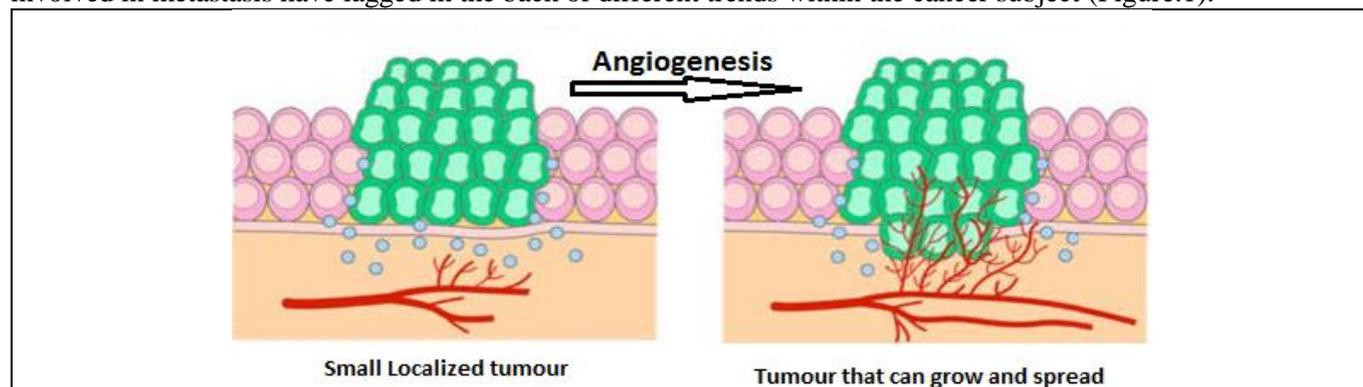
## ABSTRACT

The incidence and mortality of cancer are decreasing, due not only to scientific and clinical improvements in care, but also as a result of the dissemination of information concerning the prevention, the diagnosis, and the coordinated multimodality approach to cancer treatment that is required to optimize patient outcome. Research is in well progress since half century but it failed to give a right solution to fight against it. However, the developments in science and technology facilitated scientists to develop new methods of treatment, which can eventually lead to the development of improved therapies tailored to take into account the cytogenetic and molecular characteristics of specific human cancers. This review provides an overview that summarizes the current state of research on micro metastatic state with solid tumors.

**KEY WORDS:** Etiology, Epidemiology, Cancer, Angiogenesis, MMP, Hypoxia.

## 1. INTRODUCTION

Many chemical and bodily cancer agents can set off one or extra of a variety of mutations in cells when given chronically (Oshimura and Barrett, 1986). A desirable variety of most cancers causing chemical substances are man-made and used either as business dealers, insecticides, pharmaceutical chemical substances or as meals components (Hueper, 2013). Carcinogens are extremely diverse systems and include each natural and synthetic product. All chemical carcinogens are surprisingly reacting electrophiles that react with the electron wealthy atoms like RNA, DNA and protein (Miller and Miller, 1981). Metals inclusive of arsenic and arsenic compounds, chromium, nickel, cadmium and beryllium can result in the improvement of lung cancer and prostate most cancers (Romaniuk, 2017). Physical carcinogens along with X-ray and UV ray may additionally purpose the formation of pyrimidine dimmers, apurinic web sites with consequent smash in DNA and formation of loose radicals, which motive destroy, leading to somatic mutations (Pitot, 1993). A big number of DNA and RNA viruses have proved to be oncogenic in animals, while only some viruses were connected with human cancer. The most lifestyles-threatening aspects of the oncogenic procedure is metastasis (Kumar, 2010). Even although the clinical significance of such expression of the malignant phenotype has been well appreciated, advances in know-how the molecular mechanisms involved in metastasis have lagged in the back of different trends within the cancer subject (Figure.1).



**Figure.1. Tumors induce blood vessel growth in promoting angiogenesis, Image courtesy of the National Cancer Institute**

**Matrix Metalloproteinases:** Matrix metalloproteinases (MMPs), are a family of related zinc metalloendopeptidases that function in the turnover of components of the extracellular matrix (Tetlow, 2001). These enzymes play a central role in the normal embryogenesis and tissue remodeling and in many diseases such as arthritis, cancer, periodontitis, glomerulonephritis, encephalomyelitis, atherosclerosis and tissue ulceration. Tissue inhibitors of metalloproteinases (TIMPs) are the principle physiologic inhibitors of the MMPs. TIMPs are secreted proteins that complex with character MMPs and regulate the pastime of person MMPs. Together, the MMPs and TIMPs shape a complex organic gadget strictly controlling degradation of extracellular matrix (Gomez, 1997). The MMPs and TIMPs have an extensive position in facilitating tumor invasion and metastasis, no longer most effective through their direct function

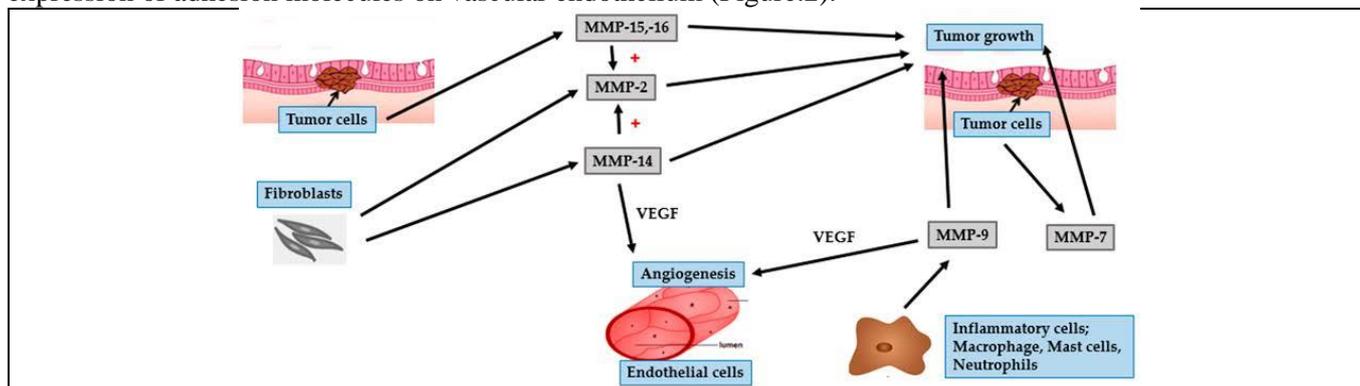
in degrading extracellular matrix but also by way of interaction with other biological structures implicated in tumor invasion, such as cell adhesion molecules, cytoskeletal proteins and boom elements (Bodiga, 2014).

**TIMP-1 AND 2:** TIMP-1 mRNA expression is up-regulated in many human cancer sorts and in a few instances correlates with greater severe clinical outcome e.g., colorectal carcinoma, non-small cell lung carcinoma and breast carcinoma. Studies in experimental mouse fashions have revealed sarcastically that TIMP-1 can show off proneoplastic and antineoplastic effects at some stage in number one and metastatic tumor improvement. TIMP-2 is a multifunctional inhibitor of angiogenesis, tumor boom and tumor invasion. These techniques involve not handiest tumor cells themselves however additionally the modulation of complex tumor-host interactions. Because the host reaction to the tumor microenvironment can act both to facilitate and to inhibit tumor invasion and spread, manipulating those host reaction elements has grown to be a prime focus of novel anticancer strategies. Although TIMP-2 can block the action of MMPs, it is able to also depend on MMP-unbiased mechanisms that modulate tumor-host interactions. TIMP-2 has an immediate position in regulating tyrosine kinase-type growth issue receptor activation (Ylisirnio, 2000).

**Angiogenesis:** Angiogenesis, the formation of new capillaries, is many of the key occasions in numerous detrimental pathologic procedures, inclusive of tumor growth, metastasis, arthritis and so on as well as in physiologic tactics, like organ growth and development, wound recovery and reproduction (Carmeliet and Jain, 2000). Blood vessels represent the first organ in the embryo and form the biggest network in our body however unluckily also are often lethal. When disregulated, the formation of recent blood vessels contributes to severe malignant, ischemic, inflammatory, infectious and immune disorders. Molecular insights into these procedures are being generated at unexpectedly increasing pace, imparting new therapeutic opportunities which are currently being evaluated (Nishida, 2006).

**Tumor growth and Metastasis:** Angiogenesis is needed for invasive tumor growth and metastasis and constitutes a vital point within the manipulate of cancer development. For tumors to broaden in length and reach metastatic ability they have to make an angiogenic switch via perturbing the nearby stability of proangiogenic and antiangiogenic factors (Ribatti and Crivellato, 2012). Tumors that have become neovascularized frequently express increased ranges of proangiogenic proteins, along with vascular endothelial increase factor (VEGF) and simple fibroblast boom factor (bFGF). The expression of proangiogenic proteins may be brought on by numerous elements, including hypoxia, activation of oncogenes or inactivation of tumor suppressor genes. In some tumors, the angiogenic transfer is the end result of down law of antiangiogenic elements. In most grownup tissues, the stability between proangiogenic and anti-angiogenic signaling favors vasculature. In a few instances, however, proangiogenic activities prevail, ensuing inside the tumor vascularization and metastatic growth. Two general techniques have been used inside the development of antiangiogenic dealers: inhibition of proangiogenic issue and therapy with endogenous inhibitors of angiogenesis (Ellis and Fidler, 1996).

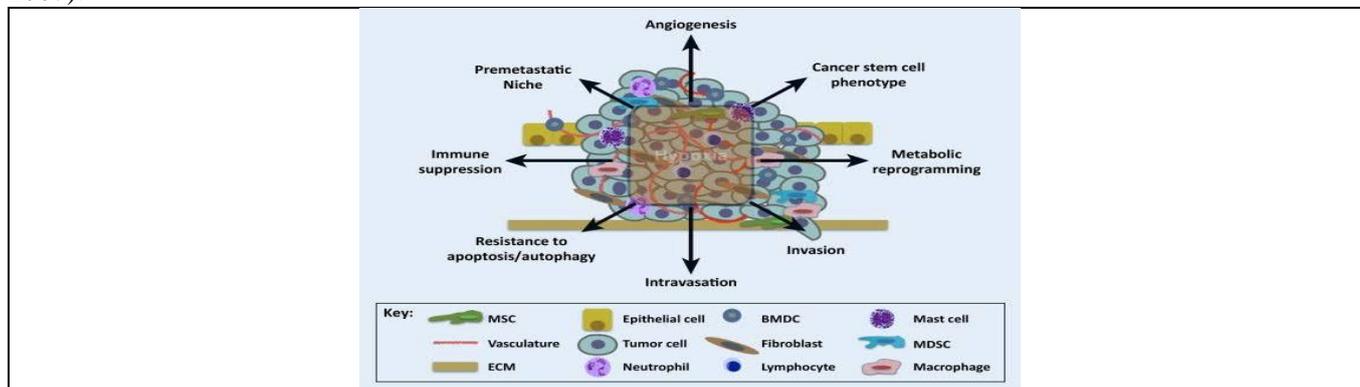
**Vascular Endothelial growth element:** Solid tumors are multi compartmentalized systems, consisting of three major compartments: cancer and stromal cells, the extracellular matrix (ECM), and the vasculature. The volumes of each of these components vary relying at the foundation and length of the tumor and the organ in which primary tumor develops. Tumors require vasculature to benefit get entry to oxygen and other nutrients, permitting boom and metastasis. VEGF (vascular endothelial growth factor) has been shown to be one of the most potent angiogenic factors produced through tumor cells. It binds to endothelial cell surface receptors and turns on numerous functions of the mobile, which includes angiogenesis (Tammela, 2005). VEGF, also referred to as vascular permeability element (VPF or VEGFA) is the critical and significant regulator of angiogenesis. The other participants of the VEGF own family, VEGF-B, VEGF-C, VEGF-D and PIGF also play a position in angiogenesis. It can up-modify expression of adhesion molecules on vascular endothelium (Figure.2).



**Figure.2. Role of MMPs in tumor growth and progression to angiogenesis**

**Role of Hypoxia:** Beyond a certain length, easy diffusion of oxygen to metabolizing tissues turns into inadequate. Tumor improvement paperwork, the growing metabolic demands of the developing mass of cells. Many tumors

broaden a critically hypoxic microenvironment and secrete angiogenesis-stimulating elements such as platelet-derived growth factor and VEGF. In tumors, VEGF expression is enhanced in zones surrounding necrotic foci, suggesting a mechanism by way of which a hypoxic microenvironment may stimulate tumor angiogenesis. By activation of the hypoxia-inducible factor (HIF) family of genes, which code for heterodimeric fundamental helix-loop-helix proteins composed of  $\alpha$  and  $\beta$  subunits. HIF-1 $\alpha$ : is synthesized inside the cytoplasm of cells but is swiftly degraded under normoxia, however, the intracellular content of HIF-1 $\alpha$  increases straight away after a lower oxygen anxiety. HIF-1 $\beta$  is a transcription component that mediates hypoxia-induced responses, consisting of apoptosis and VEGF gene expression. Hence; the oxygen availability is an essential regulator of tumor angiogenesis (Brahimi-Horn, 2007).

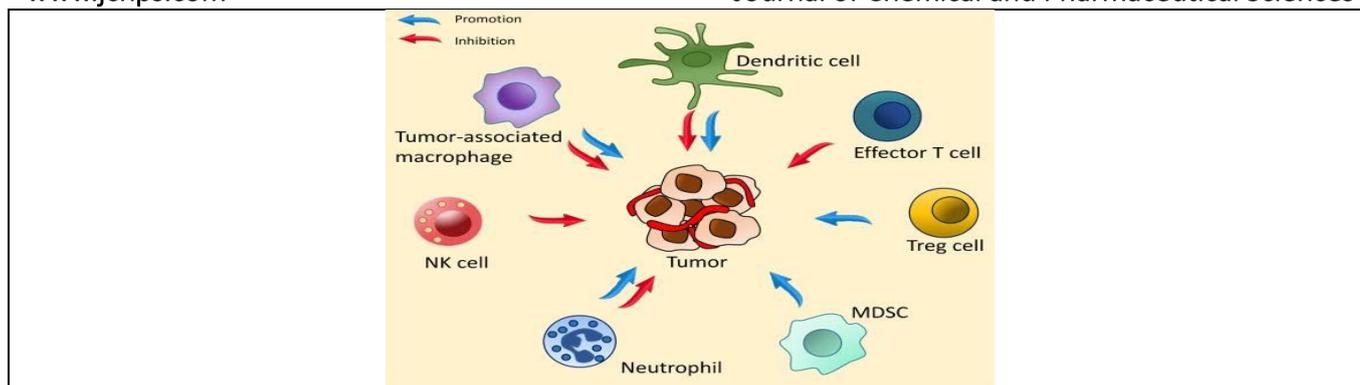


**Figure.3. Role of hypoxia in cancer, Image adopted from Trends in Cancer**

**T-Lymphocytes:** CTLs offer effective antitumor immunity in host. CTLs may additionally carry out a surveillance characteristic by using spotting and killing doubtlessly malignant cells that express peptides which might be derived from mutant mobile or oncogenic viral proteins which are presented in affiliation with class I MHC molecules. Role of NK cells and macrophages NK cells can be activated through direct recognition of tumor or on account of cytokines produced by way of tumor-particular T lymphocytes. Recognition of tumor cells by means of NK cells is not MHC constrained. In some cases, Fc receptors on NK cells can bind to antibody-covered tumor cells main to antibody dependent mobile cytotoxicity (ADCC). Numerous observations suggest that activated macrophages additionally play a giant role inside the immune responses to tumors by means of releasing lysosomal enzymes, reactive oxygen metabolites or with the aid of generating TNF- $\alpha$ . Macrophages additionally specific Fc receptors permitting them to mediate ADCC. Activated macrophages secrete TNF- $\alpha$ , that has powerful antitumor interest. Role of immune device in tumor improvement- immune surveillance Host affords both humoral and cellular mediated immune responses to tumor antigens and tested to be effective inside the immune destruction of tumors (Bronte, 2005). A range of tumors have been shown to induce tumor-unique cytotoxic-T lymphocytes (CTLs). The essential effectors consist of herbal killer cells, macrophages and tumors unique antibodies. T-Lymphocytes CTLs provide effective antitumor immunity in host. CTLs may additionally perform a surveillance characteristic through spotting and killing probably malignant cells that specific peptides that are derived from mutant cell or oncogenic viral proteins which can be offered in association with elegance I MHC molecules (Coulie, 2014).

**Role of NK Cells and Macrophages:** NK cells can be activated through direct popularity of tumor or as a result of cytokines produced by means of tumor-unique T lymphocytes. Recognition of tumor cells by way of NK cells isn't MHC restricted. In some instances, Fc receptors on NK cells can bind to antibody-covered tumor cells leading to antibody based cellular cytotoxicity (Wu and Lanier, 2003). Numerous observations imply that activated macrophages additionally play a considerable function in the immune responses to tumors via releasing lysosomal enzymes, reactive oxygen metabolites or by means of producing TNF- $\alpha$ . Macrophages also specific Fc receptors enabling them to mediate ADCC. Activated macrophages secrete TNF- $\alpha$ , that has potent antitumor pastime (Whitworth, 1990).

**ADCC:** In Antibody Dependent Cell Cytotoxicity (ADCC), the goal tumor cells, which might be coated with IgG antibodies, are selectively lysed by using killer cells, a unique sort of lymphomonocytic cellular. Several one-of-a-kind leukocyte populations like neutrophils, eosinophils, mononuclear phagocytes and NK cells are able to lysing the target cells. Recognition of certain antibody takes place thru a low affinity receptor for Fc $\gamma$  on the leukocyte, referred to as Fc $\gamma$ RIII or CD16. The antibody molecule presents the specific popularity signal whilst the in any other case quiescent and nonspecific effector cells are directed to the goal cells to offer the cytotoxic occasion (Natsume, 2009).



**Figure.4. Role of immune cells in promotion and inhibition of cancer, Image adopted from AJPS**

**Tumor Escape Mechanism:** Malignant tumors may also specific protein antigens that are diagnosed as overseas by way of the tumor host, and even though immune surveillance may also restrict the outgrowth of some tumors, it is clean that the immune gadget frequently does no longer save you the incidence of human deadly cancers (Nagaraj and Gabrilovich, 2008). It can be because of the rapid growth and spread of a tumor overwhelms the effector mechanism of the immune responses. The lack of ability of the host to expand an effective immune reaction has additionally been proven in several classes. The method of tumor breaks out may be a result of numerous mechanisms as given below. A) Class I MHC expression can be down regulated on tumor cells, that is required for CTL recognition. B) Tumor products might also suppress antitumor immune responses (e.g. TGF-P). C) Loss of floor expression of tumor antigens. D) Tumor surface antigens can be hidden from the immune machine (Lauritzen, 1998).

**Cytokines:** Cytokines are small secreted proteins which mediate and regulate immunity, infection, and hematopoiesis. They are small, structural proteins with molecular weights starting from 8 KD to forty KD. They act via binding to unique membrane receptors, which then sign the cellular via 2nd messengers, regularly tyrosine kinases, to regulate its conduct (gene expression). Responses to cytokines include growing or reducing expression of membrane proteins (along with cytokine receptors), proliferation, and secretion of effector molecules. Cytokines are endogenous immune stimulatory proteins. Cytokines play a critical position in tumor metastasis. Some of the cytokines may additionally inhibit tumor increase through interfering with host tumor dating for example by means of inhibiting tumor angiogenesis and modulation of greater cellular matrix (Kumar, 2011).

## 2. CONCLUSION

In maximum instances, physiological cellular dying happens via apoptosis in preference to necrosis. Abnormalities in this technique are implicated as cause or contributing thing in a variety of diseases. Inhibition of apoptosis can promote neoplastic transformation, mainly in mixture with disregulated cellular cycle manipulate, and may have an impact on the reaction to tumor cells to anti-cancer therapy. Diverse regulators of the caspases, inclusive of activators and inhibitors of mobile loss of life proteases are also observed. It is an important procedure in controlling tissue homeostasis in multicellular organisms. Apoptosis is occasionally called programmed cellular loss of life (PCD) due to the fact it is a crucial part of the developmental software and is frequently the cease end result of temporal direction of cell occasions. Apoptosis may be caused with the aid of a variety of stimuli together with ionizing radiations, gluco-corticoids chemotherapeutic dealers, lymphokines deprivation and diverse oxidants. Although the stimuli which set off apoptosis range markedly, the morphological functions of the manner are but conserved in special mobile sorts. It includes chromatin condensation, nuclear fragmentation, Plasma membrane blebbing, mobile shrinkage and formation of apoptotic bodies.

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