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Study on Molecular Basis of Cancer Induced Angiogenesis

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Cancer is a disease caused by defective cells that have an uncontrollable ability to proliferate without regard for the physiological organ. Cancer is a complicated multi-factorial, multi-staged, and multi-mechanistic disease. Within the initiation and course of manifestation, it comprises the interaction of environmental and host elements. Inherited genetic dispositions have a significant role in 5-10% of breast cancer cases and 5- 13% of colon cancer cases. Viral infections cause about 7% of cancer fatalities in developed countries; 4% are due to occupational hazards; 2% are due to sunlight; 2% are due to pollution of air, water, and soil; and less than 1% are due to food components and business products.

Keywords: Etiology; epidemiology; cancer; angiogenesis; MMP; hypoxia.

1. INTRODUCTION

When fed persistently, several chemical and physical cancer agents can cause one or more of a variety of mutations in cells [1]. A desired array of cancer-causing chemical substances is man-made, pesticides, pharmaceutical chemicals, or food additives [2]. Carcinogens are a broad

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category that includes both natural and manmade products [3]. Surprisingly, all chemical carcinogens are electrophiles that combine with electron-rich atoms like RNA, DNA and protein [4]. Lung and prostate cancers can be improved by metals such as arsenic and arsenic compounds, chromium, nickel, cadmium, and beryllium [5]. Physical carcinogens, such as X-rays and UV rays, can cause the development of pyrimidine dimers and apurinic web sites in DNA, as well as the generation of free radicals, which cause DNA damage and somatic mutations [6]. In animals, a large variety of DNA and RNA viruses have been found to be carcinogenic, but only a few viruses have been linked to human cancer [7]. Metastasis is the most life-threatening feature of the oncogenic process [8]. 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 [Fig. 1] [9].

2. MATRIX METALLOPROTEINASES

MMPs (matrix metalloproteinases) are a group of zinc metallo endopeptidases that have a role in the turnover of extracellular matrix components [10]. These enzymes are involved in various disorders such as arthritis, cancer, periodontitis, glomerulonephritis, encephalomyelitis, atherosclerosis, and tissue ulceration, as well as normal embryogenesis and tissue remodelling [11]. The main physiologic inhibitors of MMPs are tissue inhibitors of metalloproteinases (TIMPs) [12]. TIMPS are secreted proteins that form complexes with human MMPs and regulate their activity [13]. MMPs and TIMPs form a sophisticated organic device that tightly controls extracellular matrix breakdown [14]. MMPs and TIMPs play a large role in tumour invasion and metastasis, not only through their direct role in degrading extracellular matrix, but also through interactions with other biological structures involved in tumour invasion, such as cell adhesion molecules, cytoskeletal proteins, and boom elements [15].

3. TIMP-1 AND 2

TIMP-l mRNA expression is up-regulated in a variety of human cancers and is associated with a worse clinical outcome in a few cases, such as colorectal carcinoma, non-small cell lung carcinoma, and breast carcinoma [16]. TIMP-1 has been shown to have proneoplastic and antineoplastic effects at various stages in the progression of primary and metastatic tumours in experimental mice models [17]. TIMP-2 is a multifunctional angiogenesis, tumour growth, and tumour invasion inhibitor [18]. These methods entail not only the manipulation of tumour cells, but also the manipulation of intricate tumor-host relationships [19]. Because the host response to the tumour microenvironment can help or hinder tumour invasion and dissemination, regulating those host reaction aspects has been a major focus of new anticancer research [20]. TIMP-2 can impede MMPs' activities, but it can also rely on MMP-independent pathways to control tumor-host interactions [21]. TIMP-2 plays an immediate role in modulating the activation of tyrosine kinase-type growth issue receptors [22].

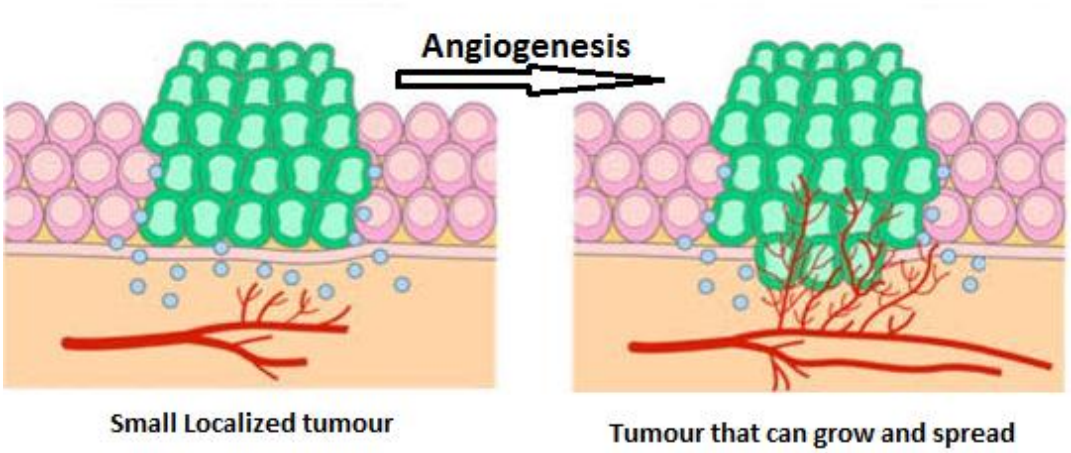

Fig. 1. Tumors induce blood vessel growth in promoting angiogenesis, Image courtesy of the National Cancer Institute, Cancer Information and Support Network

4. ANGIOGENESIS

Angiogenesis, or the generation of new capillaries, is a fundamental event in a variety of harmful pathologic processes, such as tumour growth, metastasis, arthritis, and so on, as well as physiologic processes like as organ growth and development, wound healing, and reproduction [23]. Blood vessels are the embryo's first organ and the body's largest network, but they're also the most dangerous [24]. The development of new blood vessels contributes to severe neoplastic, ischemic, inflammatory, infectious, and immunological illnesses when it is dysregulated [25]. Molecular insights into these procedures are being developed at an unexpectedly fast rate, resulting in new treatment possibilities that are currently being investigated [26].

5. TUMOR GROWTH AND METASTASIS

Angiogenesis is required for invasive tumour growth and metastasis, and it is a critical component of cancer management [27]. Tumors must perform an angiogenic flip by disrupting the local stability of proangiogenic and antiangiogenic factors in order to broaden in length and reach metastatic potential [28]. Increased levels of proangiogenic proteins, such as vascular endothelial growth factor (VEGF) and simple fibroblast boom factor (bFGF), are typically found in neovascularized tumours [29]. Many factors can trigger the production of proangiogenic proteins, including hypoxia, oncogene activation, and tumour suppressor gene inactivation [30]. Antiangiogenic components are downregulated in some cancers, resulting in angiogenic transfer [31]. The stability of proangiogenic and antiangiogenic signals favours vasculature in most mature tissues [32]. However, in some cases, proangiogenic activities win out, resulting in tumour vascularization and metastatic spread [33]. In the creation of antiangiogenic agents, two general strategies have been used: inhibition of proangiogenic problem and therapy with endogenous angiogenesis inhibitors [34].

6. VASCULAR ENDOTHELIAL GROWTH ELEMENT

Cancer and stromal cells, the extracellular matrix (ECM), and the vasculature are the three primary compartments in solid tumours [35]. The volumes of these components differ depending on the tumor's foundation and length, as well as the organ in which the main tumour originates [36]. Tumors require vasculature to gain access to oxygen and other nutrients, allowing them to grow and spread [37]. One of the most potent angiogenic agents produced by tumour cells has been identified as VEGF (vascular endothelial growth factor) [38]. It binds to endothelial cell surface receptors and activates a variety of mobile activities, including angiogenesis [39] Fig. 2 [40].

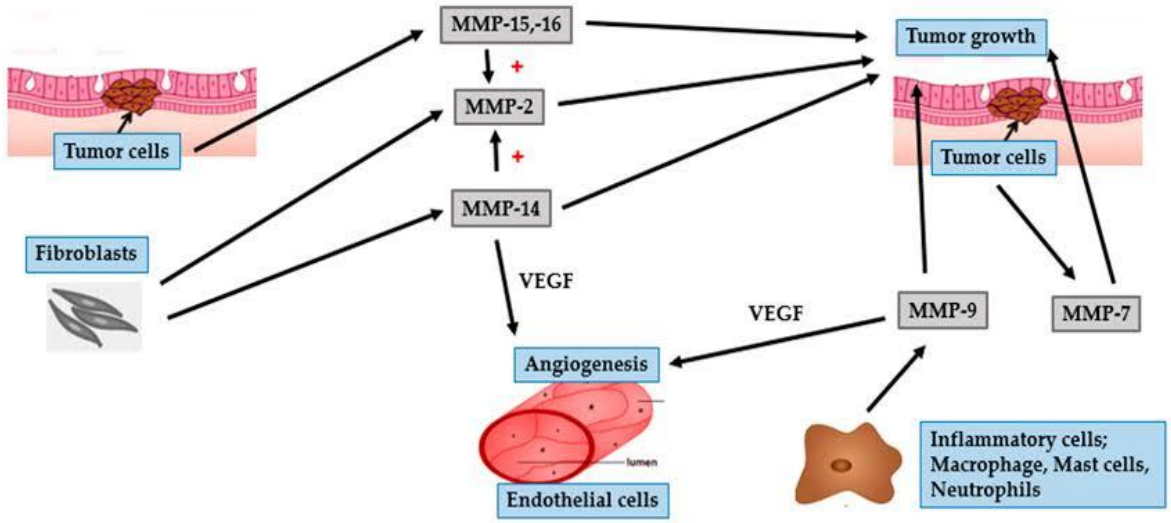

Fig. 2. Role of MMPs in tumor growth and progression to angiogenesis [41]

7. ROLE OF HYPOXIA

After a certain distance, simple oxygen transport to metabolising tissues becomes insufficient [42]. To fulfil the demands of the expanding quantity of cells, the increased rate of cell division in cancer involves metabolic pathways. [43]. Many cancers create a dangerously hypoxic milieu and release angiogenesis-stimulating factors such platelet-derived growth factor (PDGF) and VEGF [44]. VEGF expression is increased in tumour zones around necrotic foci, suggesting a mechanism through which a hypoxic microenvironment can promote tumour angiogenesis [45]. The hypoxia-inducible aspect (HIF) gene family, which codes for heterodimeric fundamental helix-loop-helix proteins made up of and D subunits, is activated. HIF-1s: is synthesised in the cytoplasm of cells but rapidly destroyed under normoxia; nevertheless, after a decrease in oxygen anxiety, the intracellular concentration of HIF-l increases immediately [46]. HIF-1 is a transcription factor that mediates hypoxia-induced reactions [Fig. 3], including apoptosis and the expression of the VEGF gene [47]. As a result, the availability of oxygen is a critical regulator of tumour angiogenesis [48].

8. T-LYMPHOCYTES

In the host, CTLs provide efficient anticancer immunity. CTLs can also perform a surveillance function by identifying and eliminating potentially malignant cells that express peptides derived from mutant mobile or oncogenic viral proteins that are displayed in conjunction with class I MHC molecules [49]. The role of NK cells and macrophages NK cells can be triggered by direct tumour identification or by cytokines released by tumor-specific T lymphocytes [50]. The ability of NK cells to recognise tumour cells is not limited by MCH [51]. Fc receptors on NK cells can connect to antibody-covered tumour cells in some situations, resulting in antibody dependent mobile cytotoxicity (ADCC) [52]. Activated macrophages play a key role in immune responses to malignancies by releasing lysosomal enzymes or reactive oxygen metabolites [53]. Macrophages also have Fc receptors, which allows them to mediate ADCC [54]. TNF-a is produced by activated macrophages and has anticancer properties [55]. Immune Surveillance and the Role of Immune Devices in Tumor Improvement Host allows for both humoral and cellular immune responses to tumour antigens, and has been shown to be effective in tumour immune elimination [56]. CTLs (cytotoxic T lymphocytes) with tumor-specific characteristics have been found in a variety of malignancies [57]. Natural killer cells, macrophages, and tumor-specific antibodies are all important effectors [58]. CTLs (cytotoxic T lymphocytes) produce potent anti-tumor immunity in the host [59]. CTLs can also undertake surveillance by detecting and destroying potentially cancerous cells that include peptides derived from mutant cell or oncogenic viral proteins that are expressed in combination with class I MHC molecules [60].

9. ROLE OF NK CELLS AND MACROPHAGES

NK cells can be triggered either by tumour direct popularity or by cytokines generated by tumor-specific T-lymphocytes [61]. MCH isn't required for NK cells to recognise tumour cells [62]. Fc receptors on NK cells can attach to antibody-coated tumour cells in some cases, resulting in antibody-based cellular cytotoxicity [63]. Activated macrophages may also play a role in immunological responses to malignancies by releasing lysosomal enzymes, reactive oxygen metabolites, or generating TNF-a, according to numerous observations [64]. Macrophages have Fc receptors that allow them to mediate ADCC [65]. TNF-a is produced by activated macrophages and has anticancer properties [66].

10. ADCC

Antibody Dependent Cell Cytotoxicity (ADCC) is a technique in which tumour cells that have been coated with IgG antibodies are selectively destroyed by killer cells, a type of lymphomonocytic cytotoxicity [67]. Several distinct leukocyte populations, including neutrophils, eosinophils, mononuclear phagocytes, and natural killer cells (NK cells), are capable of lysing target cells [68]. FcyRIII, also known as CD16, is a low affinity Fcy receptor on the leukocyte that recognises certain antibodies [69]. The antibody molecule sends out a specific popularity signal, whilst the nonspecific effector cells are directed to the target cells to deliver the cytotoxic impact [70].

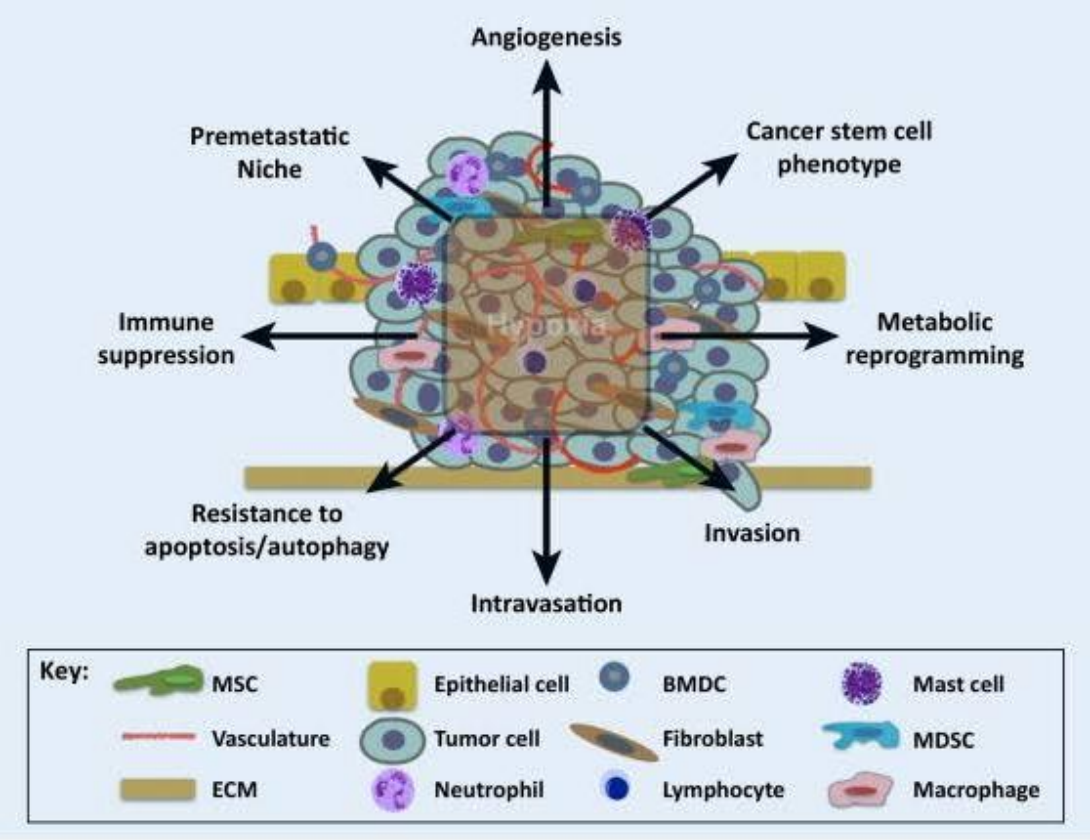

Fig. 3. Role of hypoxia in cancer, Image adopted from Trends in Cancer; Rankin EB *et.al,* 2016 [48]

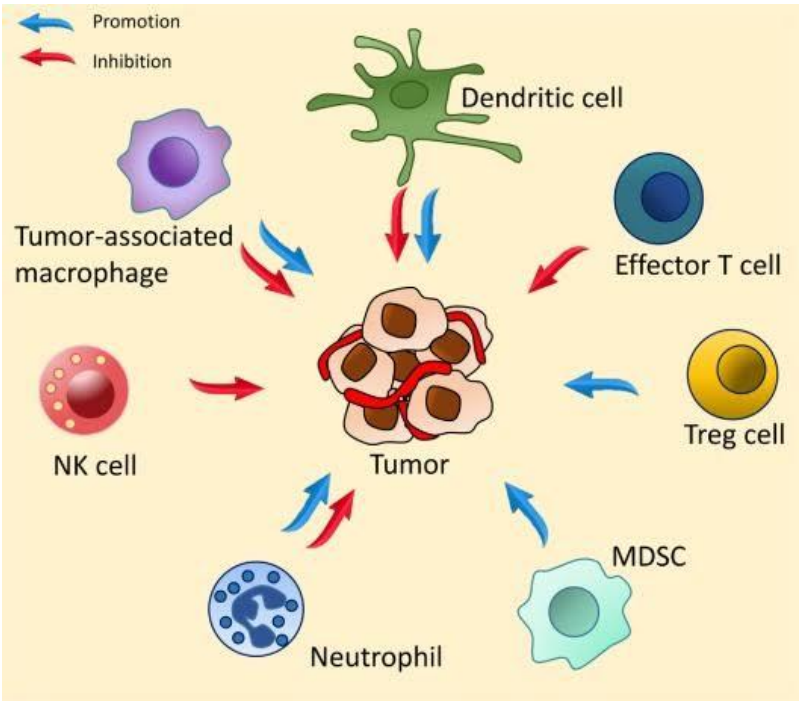

Fig. 4. Role of immune cells in promotion and inhibition of cancer, Image adopted from Le QV et.al., 2019 [71]

11. TUMOR ESCAPE MECHANISM

Although immunosurveillance may limit the outgrowth of some malignancies [Fig. 4], it is clear that the immunological gadget rarely saves the incidence of human fatal cancers [71]. It could be because a tumor's rapid development and dissemination overwhelms the immune system's effector mechanisms [72]. The host's inability to expand an efficient immune response has also been demonstrated in numerous classes [73]. The way a tumour spreads can be caused by a variety of causes, as listed below [74]. A) Tumor cells can have their Class I MHC expression reduced, which is essential for CTL identification [75]. B) Tumor products (e.g., TGF-P) may decrease antitumor immune responses [76, 77]. C) Loss of tumour antigen expression [78]. D) Antigens on the surface of tumours can be masked from the immune system [79].

12. CYTOKINES

Small secreted proteins called cytokines mediate and control immunity, infection, and hematopoiesis [80]. They are tiny structural proteins that range in molecular weight from 8 to 40 KD [81]. They work by attaching to specific membrane receptors, which then sign the cells via second messengers, such as tyrosine kinases, to control its behaviour (gene expression) [82]. Growing or decreasing the expression of membrane proteins (together with cytokine receptors), proliferation, and release of effector molecules are all responses to cytokines [83]. Endogenous immunostimulatory proteins are known as cytokines [84]. Cytokines are important players in tumour metastasis [85]. Some cytokines may also reduce tumour growth by interfering with host tumour dating, for example, by reducing tumour angiogenesis and modulating the larger cellular matrix [86].

13. CONCLUSION

Apoptosis, rather than necrosis, is the most common mode of physiological cellular death. Abnormalities in this approach have been linked to a range of diseases as a cause or contributing factor. Inhibition of apoptosis can accelerate neoplastic transformation, especially when combined with a disrupted cellular cycle, and may affect tumour cells' response to anti-cancer therapy. Caspase regulators, including activators and inhibitors of mobile loss of life proteases, have also been discovered. In multicellular organisms, it is a key procedure for maintaining tissue homeostasis. 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.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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