Proangiogenic factors in Cancer: A briefing.

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Abstract

Angiogenesis plays a key role in the progression of cancer. The rapid proliferation of tumor cells is mainly due to disruption of cellular homeostasis, resulting in up regulation of angiogenic factors. Initiation of cancer is from a single cell or a small group of cells often called field cancerization. Within a period of time after the clone of cells emerges to adapt to the primary site further promotion of tumor cells occurs and the cells undergo various modifications. Tumor cells attain stability and some of the external as well as internal, tumor cells itself result in neovascularization and angiogenesis.

Keywords: *Angiogenesis, Tumor cells, Neovascularization*.

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Introduction

Tumor cells attain genetic and epigenetic changes that alter DNA sequence. Continuous proliferation of tumor cells occurs leading to progression of the tumor. At this stage, the tumors most importantly release chemokines and cytokines which regulate angiogenesis, required for the nutrition and oxygen supply to the tumor cells. Angiogenesis to the tumor cells gives access to the metastasis of the tumor leading to the spread of the tumor in the body. Metastasis is either through blood vessels or by lymphatic stream [1]. Many angiogenic factors are known till date and the common and important one is vascular endothelial growth factor. Other common proangiogenic factors are basic fibroblast growth factor, angiogenin, hepatocyte growth factor, transforming growth factor, tumor necrosis factor, platelet derived growth factor. Neovascularization results in a more stable tumor microenvironment and leads to rapid progression of cancer [2].

Vascular endothelial growth factor

It is the primary proangiogenic factor involved in formation of new blood vessels. These factors are expressed in nearly fifty percent of cancer cases. It's derived from platelets during injury and wound healing. It is also produced by tumor cells and other cells like macrophages and keratinocytes. Vascular endothelial growth factors are expressed in pluripotential hematopoietic stem cells suggesting they principally cause hematopoiesis [3]. Hence it plays an important role in neovascularization in cancer cells. High levels of expression of VEGF in tumor cells are known to have poor prognosis, in many cancers. The specific receptor for VEGF is a tyrosine kinase receptor and it can also regulate angiogenesis in autocrine and paracrine signalling mechanisms. Hypoxic conditions stimulate the production of VEGF. VEGF is of the following types namely VEGF A, VEGF B, VEGF C, VEGF D, Placental Growth Factor (PGF). VEGF A is the most common type associated with vascularization. There are different forms of VEGF A which act accordingly in various mechanisms. Recently VEGF is known to alter the immune response of the host cells towards the tumor cells. Its association with viral oncogenesis is also proven. The levels of VEGF are increased in cancers of viral origin, like kaposi's sarcoma, cervical cancer and head and neck cancers. As VEGF's role in providing a stable tumor microenvironment is identified, research has been done to use anti - VEGF therapy in some cancers. Bevacizumab is the first FDA approved drug, inhibitor of VEGF and is used along with chemotherapy in treatment of metastatic carcinoma [4].

Fibroblast growth factor

Fibroblast Growth Factors (FGF) are the signalling proteins with diverse applications. Their role in angiogenesis is important as they add structural integrity to the blood vessels and have the capability to develop new blood vessels from already existing vasculature. They enhance the activity of VEGF and promote formation of blood vessels. FGF'S stabilize the formed blood vessels and help in differentiation and maturation of the endothelial cells. FGF's act at early stages of development of embryo and during organogenesis. Abnormal synthesis of FGF's is also known to mediate tumor origination, like kaposi sarcoma, breast cancer. Hence anti-FGF therapy along with chemotherapy at early stages can inhibit growth of the tumor in such cases.

Angiogenin

Angiogenin is involved in some of the cancers, like prostate cancer, colon cancer, squamous cell carcinoma of lung, melanoma and hepatocellular carcinoma. It is known that increased angiogenin causes metastasis. Angiogenin is involved with aggressive tumors which undergo prompt metastasis. Expression of angiogenin in serum is indicated to be associated with poor prognosis and requires leading investigations and treatment. Neomycin is known to inhibit angiogenesis caused by angiogenin. Most aggressive tumors or the tumors which are insidious in onset and take a rapid growth rate are identified by increased levels of angiogenin and treated accordingly [5].

Hepatocyte growth factor

Hepatocyte growth factor was initially identified in the rat liver where it was primarily involved with regeneration of cells. They cause structural organization and differentiation of blood vessels including branching and tubular morphology. It is interesting to note that hepatocyte growth factor is down regulated in hypoxic conditions which are in contrast with other angiogenic factors (10). It inhibits other anti angiogenic factors. It also inhibits apoptosis of cells which has an implication in cancer progression by dividing cells rapidly.

Transforming growth factor

The importance of transforming growth factor lies in stimulation of angiogenic factors and indirectly causing angiogenesis. It has a lesser contribution to tumor development. It has both pro and anti angiogenic potential. It can stimulate secretion of thrombospondin which inhibits formation of blood vessels. Therapeutic potential of transforming growth factor in cancer treatment is still in research and needs further studies to be conducted.

Tumor necrosis factor: It is a major cytokine involved in mediating inflammation. Chronic inflammatory carcinogenesis may be caused by tumor necrosis factor according to some studies. It is produced by macrophages as a result of hypersensitivity reactions. Type four hypersensitivity reaction, called delayed type hypersensitivity is promoted by tumor necrosis factor. Tumor necrosis factor has a limited role in angiogenesis. Along with secondary mediators, tumor necrosis factor acts as an angiogenic factor. Very subtle therapeutic role has been known by inhibiting TNF in cancer treatment.

Conclusion

Oncogenesis requires a tumor microenvironment containing all the favourable factors necessary for the stabilization of the tumor. Disrupting the microenvironment has a better and faster therapeutic potential along with incorporation of cell cycle inhibitors and regulators, in the treatment of cancer. Angiogenesis is the principle access of the tumor for gaining nutrition, oxygen and also a medium for metastasis. Inhibition of some of the proangiogenic factors is known to improve prognosis of patients. Studies have to be conducted on tumor specific angiogenic factors, based on site and type of cancer.

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