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Mechanism and Therapeutic Potential of Vascular Endothelial Growth Factors (VGEF)

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Abstract

Angiogenesis hold great relevance in cancer development and growth. Control of angiogenesis facilitates restriction of cancer tumor development. Angiogenesis is a valid target for treatment of tumor and restriction of tumor growth. The growth and development of the tumors depend on formation and the physiology of micro vessels.

Keywords: Angiogenesis; Anti-VGEF Therapy; VGEF Therapies

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Introduction

The growth of the tumors requires nutrients and the exclusion of the waste that takes place thought micro vessels. The new generation anti-tumor medications depends on inhibition of the micro vasculature of the tumors by restricting the endothelial growth factor A also called as VGEF-A splice isoforms that engage in micro vessel differentiation and growth. The balance with the VGEF isoforms is controlled by the mRNA splicing that modulates the angiogenesis [1]. So there are two groups of VGEF one is pro-angiogenesis and anti-angiogenesis families. One of the newly evolving strategies is to reprogram the synthetic capacity of the malignant cells to produce factors that inhibit the cancer growth. The anti-VGEF therapeutic strategies have successfully demonstrated antitumor efficacy under different types of malignancies and they were even more effective when combined with conventional cytotoxic therapies [2]. However, the mechanisms of action of anti-VGEF therapies have not been fully evaluated under different types of malignancies. Anti-VGEF therapy has definitely enhanced the clinical outcomes of anticancer therapies and has ever since provided new dimension to the treatment of malignancies. Generally, the monoclonal antibodies such as bevacizumab are used to target VGEF thus inhibiting tumor growth. The physiological markers that predict the anti-VGEF agents have not yet been developed and consequently the efficacy of the treatment could not be quantified to categorize the patients [3].

It can be observed that anti-VGEF therapy with bevacizumab has increased the overall survival of the patients affected with colorectal, breast, lung cancer and those with glioblastoma multiforme when it is administered in combination with cytotoxic agents. However, the method has not yet gained the status of active adjuvant therapy. In fact the anti-VGEF therapy was found to have tuned the tumor vasculature to deliver the drugs and oxygen and making them susceptible to chemotherapeutic agents and radioactive agent sensitivity. VGEF mediates several alterations in the tumor vasculature including the endothelial cell proliferation, migration, invasion, survival rate [4], chemotaxis of bone marrow derived progenitor cells, vascular permeability and vasodilation. Currently, there are several approaches that are available for inhibiting the action of VGEF and the signaling associated with VGEF action. Such approaches include the neutralization of the ligand or the receptor by using antibodies and blocking the VGEF receptor activation and signaling using the tyrosine kinase inhibitors [5].

As a single agent the VGEF targeted therapy was effective in case of renal cell carcinoma and hepatocellular carcinoma whereas the metastatic colorectal, non-small cell lung and metastatic breast cancer the treatment showed benefit only in combination with chemotherapy. The VGEF targeted therapy affects several cell types within the vicinity of tumor micro environment that includes endothelial cells, haematopoietic progenitor cells, dendritic cells and tumor cells thus affecting the vascular function all together such as the flow and the permeability and addition to blocking the growth of new blood vessels.

In case of advanced malignancies the combined treatments have shown to be of immense benefit. The basic principle of the anti-VGEF treatment is that it starves the tumor of the necessary oxygen and the nutrients by blocking the growth of the new blood vessels. However, the comprehensive mechanism of action is very complex involving multiple factors and a focused

research on these factors will enable efficient management of the malignant tumors [6].

VGEF has different pathophysiological consequences under the condition of malignancy and under the ischemic condition. VGEF disrupts the vascular barrier function by uncoupling the cell to cell junctions and therefore increases the permeability and oedema and may cause injury to the ischemic tissue. In cancer condition such disruption can lead to widespread metastasis. Thus it is important to block the vascular permeability function of VGEF [7].

VGEF regulates vascular, endothelial, haematopoietic and lymphatic endothelial cell functions and a balanced signaling from VGEFR is essential for regulation and this process involved more than one of the VEGFRs. VEGRF1 is essential for haematopoietic cell migration. A soluble splice variant of VEGFR1 lacking the intracellular domain is implicated in preelampsia during pregnancy. The signal transduction of VEGFR1 might regulate the VEGFR2 activity either positively or negatively [8]. VEGFR2 is required for the endothelial cell development and the survival of the blood vessels. Tyrosine phosphorylation sites of VEGFR2 regulate kinase activity and binding of phospholipase C-γ, as well as the adaptor molecules TSAd, Shb and Sck. Blocking of VEGRF2 is under clinical evaluation for treatment of human malignancies. VEGRF3 are required for cardiovascular development and lymphangiogenesis. Heterodimer formations, coreceptors sucha s heparin sulphate proteoglycans and neuropilins and phosphorylations and the resultant signal transduction regulate certain functions in local areas.

Vascular endothelial growth factors receptors functions

VEGRF: regulation of the cardiovascular system.

VEGRF1: recruitment of haematopoietic precursors and migration of monoctes and macrophages

VEGRF2 and VEGRF3: vascular endothelial and lymphendothelial functions

VGEFR signaling is controlled by ligand receptor expression, co-receptors and accessory proteins as well as accessory proteins such as neuropilins, proteoglycans, integrins and inactivating tyrosine phosphates. All these control the rate of cellular uptake, degradation and recycling [9]. Therefore VEGF and their receptors VEGRF and the mutual interactions determine the maintenance and remodeling of vasculature. Recent literature focused on the VEGRF2 signalling and interactive proteins on VEGRF2 endocytosis, trafficking and signaling. There studies are essential for successful therapeutic suppression or stimulation of vascular growth [10].

The development of the vascular system is complex process involving intricate intrinsic and extrinsic environmental patterns. The vascular system is highly sensitive to genetic disruptions and genetic studies have revealed several potential targets including VGEF for therapeutic interventions. VGEF also have several non-vascular functions in the context of endothelial cells in adult organs and stem cell areas and therefore there could be potential side effects of anti-angiogenic therapies.

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