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VEGF in Renal Cell Carcinoma – A Mini Review

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ABSTRACT

Angiogenesis is a very important process in the progression of the tumor growth. Vascular endothelial growth factor (VEGF) is a key factor in angiogenesis. The main function is vascular permeability, angiogenesis and endothelial cell growth. An inactivated or impaired tumor suppressor gene Von Hippel Lindau (VHL) causes accumulation of hypoxia inducible factor (HIF-1A) and leads to increased production of VEGF. The more the expression of VEGF, the worse is the survival and recurrence in many malignancies like Renal Cell Carcinoma. VEGF-targeted therapy plays a major role in various carcinomas involving VEGF pathway for their cancerous growth.

Key Words: Angiogenesis, VEGF, Carcinoma

INTRODUCTION

Cancer is rapidly becoming a major cause of death both in developed and developing nations(1). Kidney cancers are high in western population and low in eastern countries. But recent studies have found the increasing incidence of renal tumors in Asian countries(2) Among the various adult tumors, 3% of the tumors occur in the kidney of which common is the renal cell carcinoma about 90%. The incidence rate is about 2,00,000/year worldwide(2). The estimated incidence of RCC in India among males is about 2/100,000 population and among females is about 1/100,000 population (3). Etiology includes both internal factors like genetic involvement (mutations), poor immune status and external environmental factors like food habits, pollution, industrialization etc(4).

Renal cell carcinoma (RCC) is a heterogeneous type of tumor showing variation in histological features, clinical multiplicity and unpredictable behavior. RCC having high mortality-incidence ratio constitutes 2-3% of adult malignancies(5) It is common in men than women, often in the elderly age group. Surgical treatment is effective only in tumors localized to the kidney (5,6).

Initial treatment is radical or partial nephrectomy, which is a most successful intervention. When the cancer is limited to the renal parenchyma, the 5 year survival rate is about 60-70%. Renal cell carcinoma being resistant to radiation and chemotherapy, responds targeted therapy in some cases(6). This helps to shrink the tumor to half of its size. Malignant tumors grow due to abnormal cell signaling, proliferation, apoptosis inhibition, and supporting angiogenesis (7,8). Molecular targeting plays a potential role in treatment as it helps in designing new anti angiogenic remedies. It is therefore of therapeutic significance to define the VEGF expression(9).

Activation of an oncogene or inactivation of a tumor suppressor gene is essential to bring about a genetic alteration in RCC. The tumor suppressor gene VHL inactivation leads to accumulation of hypoxia inducible factor (10). This induces the mRNA transcription of growth factor and produces anti-apoptotic signaling which leads to angiogenesis.

Angiogenesis:

Angiogenesis is the process of new capillary formation. They are the outgrowths of endothelial cells from the already existing vessels. The early event in tumorigenesis is the onset of angiogenesis (11). This facilitates tumor growth and

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metastasis. Folkman and coworkers demonstrated that the tumors can grow up to 1.75mm when the required nutrition is available. But growth beyond this size requires additional new blood vessels. Angiogenesis is brought about by hypoxia or increased angiogenic stimulators(12). It is essential for the modification of tumor from dormant state to malignant state.

Tumor development occurs by two important steps such as tumor avascular phase and tumor vascular phase. During the avascular phase, the tumor remains localized whereas in vascular phase, metastasis begins (12,13). Then new capillaries begin to grow, extending their supply throughout the tumor and it grows rapidly. The important step in this process is the vascular endothelial growth factor(VEGF). It helps in secretion of proteases, migration and proliferation. It is an independent prognostic tumor marker. Cancers expressing VEGF grow and metastatise at a faster rate(14).

Vascular Endothelial Growth Factor:

It is a disulfide bonded dimeric glycoprotein. Its molecular mass is 34-46 kDa. Its main role is stimulating vascular permeability and proliferation of the endothelial cell. During the Embryonic stage VEGF helps in endothelial cell differentiation, migration and maturation of the nephron. In the adult stage VEGF plays an important role in vascular permeability, regulation of glomerular permeability, maintaining basement membrane composition, podocyte survival and mediates endothelium dependant vasodilatation (14).

VEGF is the key mediator of angiogenesis in cancer. The main function is vascular permeability, angiogenesis and endothelial cell growth. The four members in the VEGF family are VEGF-A VEGF-B VEGF-C VEGF-D. All members of the family perform important functions both in normal and tumor conditions (15).

VEGF-A:

The prototype member of this family is VEGF-A. Its main function is angiogenesis. VEGF-A is a potential factor in the growth of endothelial cells. VEGF-A is located on the chromosome 6p23.1. Using the reverse transcription polymerase chain reaction, various isoforms of VEGF identified are VEGF 121, VEGF 165 VEGF 189 and VEGF 206. VEGF-A plays an important role in binding with the receptors. It is mainly present in lungs, kidneys and heart. Molecular mass is 34-45 kDa(14,15).

VEGF-B:

VEGF-B is located on the chromosome 11q3.3. It is the second member in VEGF family. Its isoforms are VEGF B167 and VEGF B 186. Its main function is embryogenic angiogenesis. It is expressed in cardiac and skeletal muscles. Molecular mass is 21-30 kDa(14,15).

VEGF-C:

VEGF-C is located on the chromosome 4q34.3. It has multiple isoforms like VEGF C62, VEGF C129 and VEGF C184. VEGF C62 plays major role in kinase phosphorylation and cell adhesion in epithelial cells of the proximal tubule. It mainly takes part in lymphangiogenesis. It is expressed in breast cancer, gastric and colon cancer. VEGF B and C are less expressed in RCC. Molecular mass is 20-21kDa(14,15).

VEGF -D:

VEGF-D is located on chromosome Xp22.31. VEGF-D is synthesized as an immature protein. It has N and C terminal propeptides which are absent in other VEGF family members. It is expressed in lung, heart, muscle and colon. Molecular mass is 20-21kDa(14,15).

VEGF receptors:

The VEGF family members act by binding with receptors. There are three important receptors. They are VEGFR-1, VEGFR-2 and VEGFR-3. 30 exons are involved in coding of these receptors. Exon 1 encodes the secretory region and exon 2-15 encode the extracellular region. The exon 16 encodes the Transmembrane- spanning polypeptide and exons 17-30 encode the tyrosine kinase. All different types of VEGF bind with different receptors and exert their response at cellular level. VEGFR 1 and VEGFR 2 play major role in angiogenesis whereas VEGFR3 helps in lymphogenesis. VEGF A binds with VEGFR1 and 2, and is highly expressed in RCC. VEGFR 3 binds with VEGF C and D. It is mainly found in the lymphatic endothelial cells (15,16).

VEGF and the Kidney:

VEGF is expressed in the glomerular podocytes and tubular epithelial cells present in the proximal, distal and collecting ducts. VEGF receptors are localized in the mesangium, glomerular and peritubular capillaries. By double label immune histochemistry, VEGF receptor proteins were identified in the endothelial cells of preglomerular, glomerular and post glomerular vessels in the adult (17).

An inactivated or impaired tumor suppressor gene (VHL) causes accumulation of hypoxia inducible factor (HIF-1A) and leads to production of VEGF(18). The more the expression of VEGF the worse is the survival and recurrence in many malignancies like RCC. VHL gene inactivation in most of clear cell RCC tumors (approximately 60%) leading to VEGF overexpression promotes tumor angiogenesis, development and growth.

Molecular mechanism of VEGF action:

VEGF A is the important member of the family. It binds to VEGFR 1 and VEGFR2. VEGFR2 appears to mediate almost all of the cellular responses to VEGF. The three important

domains of the receptor are: seven extracellular immunoglobulin Ig domains, a single transmembrane region and an intracellular tyrosine kinase (TK) domain. The VEGF family members initiate cellular responses by binding to these tyrosine kinase receptors present on the cell surface. Then they become activated through transphosphorylation(19).

The phosphorylation occurring in the receptor activates phosphoinositol 3 kinase (PI3K)/Akt and mitogen activated protein kinase(MAPK). PI3K/Akt signaling pathway mediates angiogenesis(19). The production of the secondary messenger phosphatidylinositol-3, 4, 5-triphosphate and the serine/threonine kinase(Akt) is catalyzed by PI3K. VEGFR1 binds to the p85 regulatory subunit of PI3K on Tyr1213 and 1333. This helps in controlling angiogenesis. Similarly VEGFR2 binds to p85 subunit of PI3K on Tyr799 and 1173. Akt is activated by the products of phosphatidylinositol 3 phosphates kinase. Dysregulated Akt activity occurs in many tumors by tumor suppressor gene inactivation (19,20).

Factors that alter functions of VEGF:

VEGF is the important angiogenic factor. The VEGF pathway recognition and regulation is the important step in targeted approaches. The control of angiogenesis is a promising factor in the treatment of cancer.

Activators of VEGF:

Cigarette smoking: Smoking increases the RCC risk through chronic tissue hypoxia and increased DNA damage due to sensitivity to tobacco carcinogens. Tobacco smoking is an important source of cadmium (nephrotoxic agent) exposure. An individual inhales 10% of cadmium through smoking(21). Cigarette smoking is the principal factor in cancer progression. Nicotine is the major chemical component responsible for addiction in tobacco products. All tobacco products contain carcinogenic substances like polycyclic hydrocarbons (PAH) and tobacco specific nitrosoamines(TSNA), which play a vital role in development of cancer. It causes carcinogenesis through initiation, promotion and progression. These factors stimulate endothelial cells to proliferate, migrate and enhance angiogenesis and metastasis (22).

Hypoxia: The up-regulation of VEGF expression is stimulated by hypoxia. Thereby new blood vessels form and supply the deoxygenated area with the needed nutrition. **Obesity:** It is hypothesized to induce oxidative stress and chronic tissue hypoxia (23). **Hypertension:** It is hypothesized to include formation of reactive oxygen species and chronic renal hypoxia, thereby leading to HIF upregulation(24). **Reactive oxygen species:** VEGF stimulates Reactive oxygen species(ROS) production. VEGFR2-mediated signaling involves ROS followed by endothelial cell proliferation. Other factors include stress and environmental factors(25).

RNA and protein microarray studies show the high expression of VEGF in all RCCs. This over expression increases the vascularity leading to tumor growth and poor survival. Blocking this factor results in regression of the tumor. VEGF also suppress antitumor immune responses by inhibiting dendritic cell activation. This supports the fact that VEGF blockade can enhance the immune response against the tumor. Based on this property, VEGF targeted therapy has become a promising treatment for RCC (26).

Suppressor of VEGF:

Several factors suppress the angiogenesis by inhibiting the VEGF pathway. The most promising anti-VEGF approach is antisense oligodeoxynucleotides (AS-ODN) (27). Suppression by AS-ODN was reported in many cancers.

Anti-angiogenesis or angiogenesis inhibitor therapy:

Many anti-angiogenesis agents were developed to target cell proliferation, growth and induce regression of the existing vessels. They were all developed to target the various malignant tumors and non-neoplastic conditions which benefit from anti VEGF therapy, suggesting the influence of VEGF as a pathophysiologic mechanism in the disease processes (27). Metastatic renal cell carcinoma is resistant to radio and chemotherapy. Immune mechanisms are found to be useful in regulating tumor growth. Interleukin-2 and IFN-alpha are the immunotherapeutic agents used.

The two main targeted therapies are the monoclonal antibody eg: bevacizumab (Avastin), and small-molecule tyrosine kinase inhibitor eg: sorafenib (BAY 43-9006). Mechanism of action of bevacizumab is found to be through the following processes such as microvasculature regression, angiogenic normalization and inhibition of new vessel formation (28). The continued use of bevacizumab can prevent the new vessel formation and thereby improving the duration of response, and delaying disease progression(29). The treatment with bevacizumab is beneficial but cause side effects like hypertension, gastrointestinal perforation etc.

Targeting VEGF as a Therapeutic Strategy:

The rationale for targeting VEGF is because of its action in tumor vascularisation. VEGF circulating in the blood acts on the endothelial cells. It need not penetrate tumor tissue to inhibit tumor vasculature through VEGF. Angiogenesis has limited importance in normal physiology like wound healing and female reproduction. Therefore inhibition of VEGF would not be expected to cause any side effects that can occur with other cancer treatments, particularly chemotherapy(29,30). It acts on endothelial cells, which are stable, dormant and have a long lifespan. This stability means the cells are less likely to mutate to a treatment-resistant phenotype making them a potential target for long-term therapy (30).

Anti VEGF agents are currently used for malignant tumors like renal cell carcinoma, Rheumatoid arthritis and other inflammatory conditions and other non-neoplastic conditions.

CONCLUSION

VEGF is found to play a major role in angiogenesis and maintenance of immature vessels. This coordination is lost in tumor tissues stimulated by VEGF, leading to prolific growth of disordered vessels. VEGF increases the permeability of blood vessels, resulting in poorly perfused tumors, followed by hypoxia stimulating further VEGF production. These effects make it difficult for chemotherapy to access to tumor tissue. Inhibition of VEGF results in normalization of permeability, improving ease of access for treatments such as chemotherapy. Hence the role of VEGF in tumor progression and whose inhibition leading to regularization is understood.

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Conflicts of interest: nil

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