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Review Article

The effect of vascular endothelial growth factor in the progression of bladder cancer and diabetic retinopathy

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Abstract: Bladder cancer and diabetic retinopathy is a major public health and economical burden worldwide. Despite its high prevalence, the molecular mechanisms that induce or develop bladder carcinomas and diabetic retinopathy progression are poorly understood but it might be due to the disturbance in balance between angiogenic factors such as VEGF and antiangiogenic factors such as pigment epithelium derived growth factor. VEGF is one of the important survival factors for endothelial cells in the process of normal physiological and abnormal angiogenesis and induce the expression of antiapoptotic proteins in the endothelial cells. It is also the major initiator of angiogenesis in cancer and diabetic retinopathy, where it is up-regulated by oncogenic expression and different type of growth factors. The alteration in VEGF and VEGF receptors gene and overexpression, determines a diseases phenotype and ultimately the patient's clinical outcome. However, expressional and molecular studies were made on VEGF to understand the exact mechanism of action in the genesis and progression of bladder carcinoma and diabetic retinopathy , but still how VEGF mechanism involve in such type of disease progression are not well defined. Some other factors also play a significant role in the process of activation of VEGF pathways. Therefore, further detailed analysis via molecular and therapeutic is needed to know the exact mechanisms of VEGF in the angiogenesis pathway. The detection of these types of diseases at an early stage, predict how it will behave and act in response to treatment through regulation of VEGF pathways. The present review aimed to summarize the mechanism of alteration of VEGF gene pathways, which play a vital role in the development and progression of bladder cancer and diabetic retinopathy.

Keywords: Vascular endothelial growth factor (VEGF), bladder cancer, diabetic retinopathy, progression

Introduction

Bladder cancer and diabetic retinopathy is a major public health and economical burden worldwide [1, 2]. Despite its high prevalence, the molecular mechanisms that induce or develop bladder carcinomas and diabetic retinopathy progression are poorly understood.

The development and progression of bladder cancer and other are thought to result from the accumulation of multiple genetic alterations including activation of oncogenes [3, 4], inactivation of tumor suppressor genes [5], alteration in angiogenic factors [6, 7]. The accumulation of genetic alterations in the genes determines a tumor's phenotype and ultimately the patient's clinical outcome. Earlier investigators showed that several types of proangiogeneic motif plays vital role in the genesis of several types of tumours including bladder tumours [8-11]. Angiogenesis is important factors in this process of development of diabetic retinopathy and diabetic retinopathy with step wise processes [12-16]. It is a normal and vital process in growth and development, as well as in wound healing. It is important and crucial in the transformation of tuomr from a dormant state to a malignant conditions. It as an independent prognostic tumor marker in several types of tumors and VEGF is major player in this process [17]. VEGF is crucial survival factor for Endodethelial Cells in the process of physiological and tumor angiogenesis and induce the expression of antiapoptotic proteins in the ECs [18]. VEGF is the key mediator of angiogenesis

Table 1. Chromosomal location, protein sizes, tissue specification, affinity with receptors of the VEGF

Gene	Chromosomal Location	Receptor	Tissue specification	Protein size (Kd)	Function
VEGFA	6p23.1	VEGFR1, VEGFR2	Lung, kidney, heart, and adrenal gland.	34-45	vascular permeability
VEGFB	11q3	VEGFR2	Myocardium, skeletal muscle, and pancreas.	21-30	Maintenance of vascular permeability
VEGFC	4q34	VEGFR3	kidney, lung, pancreas, prostate, brain, liver or thymus	20-21	lymphangiogenesis
VEGFD	Xp22.31	VEGFR3	Lung, heart, skeletal muscle, colon, and small intestine	20-21	lymphangiogenesis

in cancer, where it is up-regulated by oncogenic expression and a variety of growth factors. The study of new methods like immunohistochemistry and other recent techniques for therapeutic implications are the main areas of biomedical research that will give benefit from the ongoing research.

The present study aimed to study the mechanism and alteration of VEGF gene pathways that play a vital role in the development, progression of bladder cancer and diabetic retinopathy.

Genetic and protein structure of VEGF

VEGF is family with four members: VEGF-A, VEGF-B, VEGF-C, VEGF-D. All member of VEGF performs important and specific functions in normal physiologic and pathological conditions.

VEGF-A

VEGF-A (VEGF) is a potent growth factor for blood vessel endothelial cells, showing pleiotropic responses that facilitate cell migration, proliferation, tube formation, and survival. The chromosomal location of VEGF-A is 6p23.1 (**Table 1**). It is the first member of VEGF family, is a disulfide-bonded glycoprotein with a molecular mass of 34–45 Kd [19]. The alternative splicing of VEGF mRNA gives important isoforms such as: VEGF121, VEGF165, VEGF189, and VEGF206 [20]. Each type of isoform come from the alternative splicing of mRNA. All isoform performs special and unique functions in VEGF-A. The main function of VEGF-A protein is vascular permeability, inducing angiogenesis, vasculogenesis and endothelial cell growth in normal and pathological conditions Each exon of VEGF-A plays important role in recognition and binding with receptors [21]. It is present mainly in the lung, kidney, heart, and adrenal gland.

VEGF-B

The chromosomal location of VEGF-B is 11q3.3 (**Table 1**). The VEGF-B is second member of the VEFG family with total seven exon. VEGF-B_{167} and VEGF-B_{186} isoform are generated by alternative splicing of exon [22]. These two known isoforms of VEGF-B spanning about 4 kb of DNA.The C-terminal domain of VEGF-B_{167} and VEGF-B_{186} are hydrophilic and hydrophobic in nature. It is mainly expressed in the cardiac and skeletal muscle [23].

VEGF-C

The chromosomal location of VEGF-C is 4q34.3 (**Table 1**). The VEGF-C gene contains seven exons. It has multiple isoforms with varying numbers of amino acids: VEGF-C62, VEGF-C129 and VEGF-C184. VEGF-C62 play a major role in phosphorylation of kinase and thereby promote cell adhesion in proximal tubular epithelial cells [24, 25]. The VEGF-C is mainly expressed in breast cancer, prostatic cancer, gastric cancer, colon cancer, and lung cancer [26-30].

VEGF-D

The VEGF-D is located on chromosome Xp22.31 (**Table 1**). The human cDNA encodes a protein of 354 amino acids. VEGF-D is initially synthesized as an immature protein with N- and C-terminal propeptides [31]. This type of N- and C-terminal propeptides is not present in other VEGF family members. VEGF-D undergoes in process for the maturation through proteolytically cleavage [32, 33], then performs functions.

It is expressed in different organ of the body such as lung, heart, skeletal muscle, colon, and small intestine [34-36].

VEGF receptors

The VEGF family members show their biological action through binding to receptors. There are three important receptors of the VEGF family like: VEGFR-1, VEGFR-2, and VEGFR-3. The total 30 exons are involved in coding of receptor and they perform different and important functions. Exon 1 and exons 2-15 encodes the secretary region and the extracellular region respectively. The exon 16 mainly encodes the transmembrane- spanning polypeptide and exons 17-30 encode the tyrosine kinase. All different types of VEGF binds with different receptors and exert their response at cellular level [37, 38]. VEGFR-1 and VEGFR-2 is main player in angiogenesis [39] whereas VEGFR-3 contributes in hematopoiesis and lymphogenesis [40].

VEGFR-1

The basic and important components of VEGFR-1 (fms-like tyrosine kinase, Flt-1) are seven extracellular immunoglobulin (Ig) domains, a single transmembrane region and an intracellular tyrosine kinase (TK) domain [41]. Each components of receptors perform important and special functions. VEGFR-1 (Flt-1) is mainly expressed on haematopoietic stem cells, monocytes and macrophages [42-44]. The function of VEGFR-1 is not fully understood, but it might be involved in signalling of VEGFR-2 and in angiogenesis [45].

VEGFR-2

VEGFR-2 is a glycoprotein with molecular weight 200-kDa. It consists of three important components an extracellular region composed of seven immunoglobulin (Ig)- like domains, a short transmembrane domain, and an intracellular region containing a tyrosine kinase domain, split by a 70 amino acid insert. This type of receptors is mainly expressed in hematopoietic and retinal cells [46-51]. The VEGFR-2 plays a vital role in the regulation of endothelial cell migration, proliferation and differentiation [52]. VEGFR-2 protein is translated without significant glycosylation in the cell whereas multiple steps of glycosylations involve in the conversion of immature to mature protein, then it is expressed on the cell surface and exerts functions.

VEGFR-3

VEGFR-3 is the third member of the receptor family with molecular weight 195 kDa. This receptor shows high affinity for the VEGF-C and VEGF-D. After the proteolytic cleavage it converts into a 120 kDa and a 75 kDa form during biosynthesis. The resulting polypeptide chains remain linked via a disulfide bond [53-55]. After alternative splicing, VEGFR3 generates two types of isomers that differ in their C-termini [56]. VEGFR-3 is mainly found in endothelia during development whereas in the adult it becomes restricted to lymphatic ECs [57, 58]. Upon binding with ligand, this receptor activate a multiple signal molecules including phosphatdylinositol 3 kinase(PI3K)/AKT/MAPK pathways.

Molecular mechanism of VEGF action

The most important member of VEGF is VEGF-A. VEGF-A binds to VEGFR-1 (Flt-1) and VEGFR-2 (KDR/Flk-1). VEGFR-2 appears to mediate almost all of the known cellular responses to VEGF [59]. VEGF-C and VEGF-D, but not VEGF-A, are ligands for a third receptor (VEGFR-3), which mediates lymphangiogenesis. VEGF receptor plays an important role in binding with VEGF and performs cellular response. The VEGF receptors are made up of three important domain: seven extracellular immunoglobulin (Ig) domains, a single transmembrane region and an intracellular tyrosine kinase (TK) domain. All members of the VEGF family stimulate cellular responses by binding to tyrosine kinase receptors on the cell surface, causing them to dimerize and become activated through trans-phosphorylation. When phophorylation occur in receptor, the receptor activate a multiple signal molecules including phosphatdylinositol 3 kinase (PI3K), Akt and MAPK. PI3K/Akt signaling pathway is important in mediating cell survival, proliferation, migration, and angiogenesis. PI3K catalyzes the production of the lipid secondary messenger phosphatidylinositol-3,4,5-triphosphate including the serine/threonine kinase Akt [60, 61]. The PI3K contains p85 regulatory sites; VEGFR1 binds to the p85 regulatory subunit of PI3K on Tyr1213 and 1333 show a significant role in controlling cell migration, differentiation, and angiogenesis

[62, 63]. VEGF receptor 2 has binding site with tyrosines 799 and 1173 for the p85 subunit of PI3K, by this way phophorylate the p85 subunit and activated PI3K is responsible for endothelial cell proliferation with VEGFR3 [64].

Akt is activated by phosphatidylinositol 3 phosphates, the products of phosphatidylinositol 3 phosphates kinase (PI3K) [65]. Generally, dysregulated Akt activity occurs in many type of tumors through inactivation of tumour suppressor gene PTEN, which negatively regulates phosphatidylinositol 3 phosphate levels [66-68]. PTEN is a multifunctional phosphatase whose major substrate is phosphatidylinositol-3,4,5-trisphosphate (PIP3) [69]. PTEN with lipid phosphatase activity, which is involve in dephosphorylation of PIP3. By this way PTEN negatively regulates the phosphoinositide-3-kinase (PI3K)–PKB/Akt pathway and thus exerts tumor suppression.

VEGF is the key player in tumour angiogenesis

Angiogenesis is complex process, this process start with the activation of endothelial cells, then proteoltic enzymes involves in the degradation of the basement membranes. After degradation, the periendothelial cell act as stabilizing factor in the newly formed capillary network [70-73].

VEGF is the important angiogenic factors that play important role in the development and progression of tumour [74-76]. The tumour development occurs by two important step: tumor prevascular or avascular phase and the vascular phase [77, 78]. During prevascular phase the tumour remains in a specific/localized area whereas in the vascular phase, invasion and metastasis is a critical step. Tumour angiogenesis factors play a vital role in transformation of avascular to vascular stage via switch remains turned on. After the switched on, the new capillaries continue to grow, extending the blood supply throughout tumour and with process grows rapidly [79]. The important and driving factors play vital step in this process is VEGF with the best characterized angiogenic factor and also is responsible for secretion of proteases, migration and proliferation [80-82]. VEGF acts via endothelial-specific receptor tyrosine kinases. After binding of receptor and autophosphorylation, several signal transduction molecules are activated (VEGF Receptor-Associated Protein), PI3K (Phosphatidylinositol 3-Kinase), Akt. PI3K/Akt signaling pathway play vital role in development and progression of tumour through the overexpression of angiogenic factors and the inhibition/suppression of antiangiogenic motif.

The factors that alter the functions of VEGF

Activators of VEGF

The angiogenic factors play a vital role in the normal angiogenesis and tumour angiogenesis. The development and progression of tumour from latent phase to the invasive and metastatic phase is a complex process. VEGF, vascular endothelial growth factor is the key player in this process. There are several factors which influence or alters the functions of VEGF including cigarette smoking, stress, hypoxia, reactive oxygen species and environmental factors.

Cigarette smoking is the principal factor in the genesis and progression of cancer. The main constitute of cigarette smoke is nicotine and PAHs contribute to carcinogenesis through multiple process like initiation, promotion, and progression. The route or mechanism by which nicotine may contribute to tumor progression is angiogenesis a process necessary for tumor growth and metastasis [83]. These factors stimulate endothelial cells in the existing vasculature to proliferate and migrate through the tissue to form new channels, enhance angiogenesis and metastasis.

Hypoxia and HIF-1: Hypoxia stimulates angiogenesis through the up-regulation of vascular endothelial growth factor and other angiogenic cytokines.The factor involve in this phenomenon is HIF-1 that promote vascular endothelial growth factor (VEGF) transcription and initiating its expression [84, 85]. Such endothelial cells ultimately help to form new blood vessels, supplying the given area with oxygenated blood.

The another factors also influences the activity of angiogenesis are reactive oxygen species (ROS) including superoxide ($O_2^{\bullet -}$) and hydrogen peroxide (H_2O_2), play vital role in angiogenesis and mutagenesis. VEGF stimulates Reactive oxygen species production via activation of gp91phox (Nox2)-based NADPH oxidase, and ROS are involved in VEGFR2-mediated signaling linked to EC migration and proliferation [86, 87].

Suppressor of VEGF

Angiogenesis is an important and complex step in the tumour progression and it is controlled by two factors like stimulators and inhibitors. VEGF is the important angiogenic factors that play important role in the development and progression of tumour [88-90]. Recognition and regulation of the VEGF pathway in several type of diseases has emerged as VEGF-targeted approaches. The control of angiogenesis pathways is a promising strategy for treatment of many type diseases including cancer and diabetic retinopathy. Therapeutic angiogenesis is an exciting step in the regulation of several type of diseases progression. Several factors involve in this process and play a vital role in the suppression of angiogenesis via inhibition of VEGF/angiogenesis pathway.

The promising anti-VEGF approach is the use of antisense oligodeoxynucleotides (AS-ODN). Suppression of angiogenicity and tumorgenicity by AS-ODN was reported in various type of cancer [91, 92]. AS-ODN reduce gene expression by efficient annealing of complementary sequences to the target mRNA.

The another important blockers of VEGF pathways in the supression of tumour growth the use of monoclonal antibodies ie. bevacizumab that antagonize the formation of new blood vessels, is act as blockers of VEGF receptor in endothelial cells, thereby shutting off the tumour blood supply [93]. The treatment with bevacizumab is beneficial in the regulation of angiogenesis pathways but that can cause serious side effects, such as hypertension, bleeding and gastrointestinal perforation [94].

The recent treatment of diabetic neuropathy relies on the control of glycemic, oxidative stress, and neural and vascular risk factors [95, 96], but this does not fully prevent its occurrence or progression. In addition, the current approaches for treatment of diabetic retinopathy rely on laser photocoagulation, which can damage nervous tissue, and worsen visual abilities. The emerging strategies aiming at the treatment and prevention of diabetic retinopathy by mitigating excessive angiogenic responses and retinal vasopermeability have opened a new window for research.

Our Holy Prophet Mohammed (PBUH) used certain herbs and recommended various medicinal plants for cure of several diseases. Various medicinal herbs have been used and considered excellent candidates for oral therapy in the ancient time as medicine as they are effective, affordable and easy to access worldwide. In search for new therapeutic alternatives, and most importantly for modern medicine have an unlimited source of therapeutic compounds with anti-mutagenic and anti-carcinogenic antidiabetic properties and rich in anti-VEGF agents [97-101].

VEGF in diabetic retinopathy (DR) and bladder cancer

Vascular endothelial growth factor (VEGF) is best known as an endothelial and permeability factor and plays a role in both normal (e.g. embryonic development) [102] and pathological angiogenesis (e.g. in tumour growth, inflammation, wound healing and various ocular diseases) [103-105]. VEGF is known to stimulate endothelial cells [106] and many non-vascular cells, such as Tenon fibroblasts [107].

Diabetic retinopathy (DR) is one of the known -characterized complication of diabetes, with vascular structural and functional changes in the retina [108]. Vascular changes cause the altered adhesion of leukocytes to the vessel wall and blockage of the retinal capillaries causes localized hypoxia. Angiogenesis and increased vascular permeability is the key players in vision loss in diabetic retinopathy. The mechanisms by which diabetes mellitus induces the vascular retinopathy are complex and not fully understood but it might be disturbance in balance between angiogenic factors such as VEGF and antiangiogenic factors such as pigment epithelium derived growth factor (PEDF) [109]. The overproduction of VEGF is associated with altered or changed angiogenesis and increases the permeability of retinal capillary that causes in retinal dysfunction [110-112].

There are many factors like hypoxia, oxidative stress and activation of Akt/PI3K pathways and altered the production of VEGF in diabetic retinpathy.

Diabetic retinopathy causes changes in retina like capillary occlusion, blocking blood flow and generating capillary-free areas [113]. The hypoxic conditions in this process induce upregulation of angiogenic factor production, such as VEGF and intercellular adhesion molecules [114, 115] with vascular dilatations, tortuous blood vessels, microaneurysms, and endothelial cell proliferation.

Vascular endothelial growth factor with another name vascular permeability factor which has a significant role in retinal leakage and neovascularisation [116]. Ocular levels of VEGF correlate with new vessel formation in patients with diabetes. VEGF binds with receptors and triggers phosphoinositol hydrolysis and release of DAG, which in turn leads to activation of PKC-α, β, and δ [117]. The exact mechanism of Preotein kinase C involvement in the diabetic retinopathy is not understood fully. Hyperglycemia is a major risk factor for the development and progression of diabetic microvascular complications and also induce activation of PKC pathways in retinal cells [118-120]. Members of the protein kinase C (PKC) family of serine-threonine kinases are activated by many growth factors, including VEGF. Activation of PKC involve in the directly increase of permeability of macromolecules [121-124], across the endothelial or epithelial barriers by phosphorylating cytoskeletal proteins [125, 126], Earlier investigator reported that PKC shows a important role in activation and expressions of various growth factors and this ultematly affect capillary permeability by PKC activation [127-130].

The Akt/PI3K pathways also play vital role in the development and progression of Diabitic retinopathy via actvation of VEGF pathways. The extracellular growth factors increase the angiogenesis process through activation of oncogenes including PI3K, and inactivation of mutations of tumor suppressor genes [131]. PI3K/Akt signaling pathway is important in mediating cell survival, proliferation, migration, and angiogenesis. PI3K catalyzes the production of the lipid secondary messenger phosphatidylinositol-3,4,5-triphosphate including the serine/threonine kinase Akt.

The PTEN Tumor suppressor gene has a significant importance in the regulation through activity of phosphatase on both lipids and proteins; it antagonizes PI3K pathway by transforming PIP3 into PIP2 [132] and dephosphorylates proteins such as SHC or FAK [132-134]. The roles of PTEN in the neural retina remain poorly understood. PTEN deficiency leads to elevated phosphorylation of Akt, especially in the developing inner plexiform layer, where high levels of PTEN are normally expressed.

Bladder carcinomas is the most common type of carcinoma with second highest cause of cancer related mortality in developed countries [1, 2]. Despite its high prevalence, the exact molecular mechanisms of bladder carcinomas development and progression are not well understood. Tumoriogenesis and tumor progression of bladder cancer are thought to result from the accumulation of multiple genetic alterations. The accumulation of genetic alterations in the genes determines a tumor's phenotype and ultimately the patient's clinical outcome. Earlier investigator showed that several types of proangiogeneic motifs plays vital role in normal and diseases cases.

Angiogenesis is a complex process, which plays an important role in the development of new blood vessels from the endothelium of a preexisting vasculature. It is a normal and vital process in growth and development, as well as in wound healing and in granulation tissue. However, it is also a fundamental step in the transition of tumours from a dormant state to a malignant one.

It also contributes to other pathological conditions, including tumour growth, diabetes, rheumatoid arthritis and other inflammatory processes [135]. However, the exact mechanisms responsible for angiogenesis in bladder carcinoma patients are not well defined.

In malignant condition, the angiogenesis pathways is upregulated by oncogenic expression and variety of growth factos [136]. Urinary bladder cancer is heterogeneous and unpredictable type lesions. There is a need for a better treatment and regulations of this type tumours adapting the therapeutic load to tumor aggressiveness. Among various molecular abnormalities associated with tumor progression and development [137-139], study of VEGF gene in the genesis of urinary bladder carcinoma is appears a critical event/findings.

Earlier investigator reported that high expression of VEGF was found in tumor cell whereas the expression was very low or not in the normal transitional epithelium of bladder. Another immunohistochemical study reported that the expression of VEGF and VEGFR2 was observed in 58% and 50% of urothelial tumor cells respectively. Earlier investigators showed that VEGF expression is reported to be more prevalent in advanced and progressing bladder carcinoma [136], it might be due to the reason that the smoking exposure impairs VEGF-induced endothelial cell migration and tube formation [140]. VEGF and the VEGFR showed a vital role in the in development and progression of bladder cancer [141-143] and may represent a potential therapeutic target. VEGF and the VEGFR expression and the exact function of VEGF/VEGFR receptor signaling in bladder cancer development remain unclear. A few investigations showed that VEGF receptor as a ligand-regulated transcription factor plays a vital role in the development and progression of bladder cancer. Earlier investigator showed that there is association between grade/stage and VEGF expression in bladder cancer [144]. An immunohistochemical study also showed that negative expression of VEGF in the human urinary bladder [7].

However, expressional and molecular studies were made on VEGF to understand the exact mechanism of action in the genesis and progression of bladder carcinoma and diabetic retinopathy , but still how VEGF mechanism involve in such type of disease progression are not well defined. Some other factors also plays a significant role in this process of activation of VEGF. Therefore, further detailed analysis via molecular and therapeutic study is needed to know the exact mechanisms or mutations in this angiogenesis/related pathways.

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