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Current Angiogenesis, **2015,** *4,* **000-000**

Vascular Endothelial Growth Factor: A New Paradigm for Targeting Various Diseases

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Abstract: Vascular endothelial growth factor is a signaling protein, which is responsible for the angiogenesis process. Variation in its expression leads to various disorders like cancer, diabetes, psoriasis and neuronal imbalance (depression) etc. The abundance of VEGF (VEGF-A, B, C) concentration is present in the kidney, heart, lung, ovary, thyroid gland, neurons, embryonic tissue etc. The regulation of VEGF expression is controlled by the hypoxia condition, hormonal regulation, inflammatory mediator cytokines and growth hormone. The VEGF binds to the VEGFR1, and VEGFR2 tyrosine kinase receptors causing conformational changes resulting in the endothelial cell proliferation, increased vascular permeability, and formation of new blood vessel. The high level of VEGF- A activity found in the synovial fluid leads to rheumatoid arthritis, whereas in the retinal cell it results in diabetic retinopathy. The tumor growth factor induced VEGF A expression in keratin cell lead to psoriasis. The higher level of VEGF activity increased neovascularization which is beneficial in cerebral ischemia, as well as in the growth of the neurons. VEGF is also considered to be an important factor in tumor invasion and metastasis. Various growth factors stimulate or participated in tumor angiogenesis. Therefore, the Anti-VEGF therapy can be a potential option for treatment of psoriasis, rheumatoid arthritis, diabetic retinopathy, and cancer. The (VEGF) gene expression modulation will lead to the new therapeutic possibilities in the future.

Keywords: Angiogenesis, diabetes mellitus, psoriasis, rheumatoid arthritis, vascular endothelial growth factor.

1. INTRODUCTION

Vascular endothelial growth factor (VEGF) is a protein synthesized by cells that have an important role in the process of angiogenesis and vasculogenesis [1]. VEGF assures the supply of oxygen within the vessel. It is the part of the process that restores the oxygen supply to the tissues when blood circulation is inadequate [2]. Vascular Permeability Factor (VPF) or vasculotropin also increases capillary vascular permeability in the process of vasculogenesis. Angiogenesis is the physiological process which involves new blood vessel formation from pre-existing vessels. Angiogenesis is an important process in growth and development, as well as in wound healing mechanism. Angiogenesis provides a balance between proangiogenic and antiangiogenic factors which is called as angiogenic balance which controls blood vessel growth by stimulation and inhibition of signals. The new blood vessel formation takes place during healing of wound, regeneration of tissue and in the reproductive organs (ovary, uterus, and placenta). Neovascularization is also important in many pathological conditions such as rheumatoid arthritis, diabetic retinopathy, psoriasis, cancer and neuronal disease [3]. VEGF's functions are to create new blood vessels during the development of the embryo, after injury and blockage of vessels. During human embryogenesis, cell division, cellular differentiation and blood vessel formation take place by the differentiation of angioblasts, which is called as vasculogenesis. Vasculogenesis is the process of new blood vessel formation which oc-

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2211-5528/15 $58.00+.00

curs by differentiation, proliferation and migration of endothelial cells under the influence of VEGF and PlGF (Placental growth factor) [3, 4].

2. THE LOCATIONS AND STRUCTURES OF VASCULAR ENDOTHELIAL GROWTH FACTOR

The VEGF is made up of seven isoforms VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, VEGF-F, and PIGF. All isoforms are generated as a result of alternative splicing from a single VEGF gene. The isoforms have eight invariant cysteine residues as a core region. Cysteine residues are involved in disulfide bond formation which enables them to bind to cell surface heparan-sulfate proteoglycans. All of these differ in their molecular weight and in biological properties.

VEGF-A: -It is a 34 to 42 kDa, dimeric, disulfide glycoprotein capable of binding to heparin binding. In normal tissues, VEGF-A is found in the lungs, heart, kidney and adrenal gland in the higher levels. VEGF-A is also found to be present in liver, spleen, and gastric mucosa in small quantity [1]. VEGF-A consist of several amino acids.

VEGF-B: It is abundantly expressed in cardiac tissue, skeletal tissue, and pancreas. VEGF-B167 and VEGF-B186 are isoforms of VEGF-B. The C-terminal domain of VEGF-B167 is hydrophilic in nature and structurally similar to the domain of VEGF-A isoforms. It is able to interact with a co-receptor neuropilin-1 and C-terminal domain of VEGF-B186 is hydrophobic, which requires limited proteolysis to bind to neuropilin-1.

VEGF-C: - VEGF-C consists of seven different isoforms. The VEGF homology domain of VEGF-C is encoded by cysteine-rich motifs. It is present in cardiac tissue, placenta, ovary, intestinal tract and thyroid gland.

VEGF-D: - VEGF-D is found in lung tissue, cardiomyocytes, skeletal muscle and intestine and is found abundantly in the developing lung. VEGF-D is synthesized as a preproprotein and the fully processed growth factor is a noncovalent dimer, which requires activation by proteolytic processing in both the N- and C-terminus.

VEGF-E: -VEGF-E is a virus-encoded, not having a basic domain and has only 19 to 25% identity with VEGF and is involved in the process of pathological angiogenesis. Its cDNA structure has exon in the viral genome. It has a potent endothelial cell growth stimulator activity. Its vascular permeability is similar to VEGF-A.

3. VASCULAR ENDOTHELIAL GROWTH FACTOR RECEPTORS

Three VEGF tyrosine kinase receptors have been identified:

The VEGFR-1 also called as fms-like tyrosine kinase (Flt-1), VEGFR-2 also referred as a fetal liver kinase (Flk-1) and VEGFR-3 (Flt-4) [5]. Each receptor has seven extracellular domains which resemble immunoglobulin-l, a single transmembrane region, and a tyrosine kinase sequence [2, 6] (Table **1**).

VEGFR-2 appears to play an important role in VEGF-induced mitogenesis that regulates blood and lymphatic vessel development and vascular permeability [7, 8]. Receptor activation during the process of angiogenesis leads to the production of platelet activating factor (PAF) having crucial roles in the induction of angiogenesis. PAF stimulates the process of mitosis, migration, and vascularization.

VEGFR-1 has the highest affinity for VEGF-A, and is incapable to produce mitogenesis in endothelial cells when activated by VEGF. It also has weaker kinase activity [9]. VEGFR-1 negatively affects vascularization and modifies endothelial cell division and differentiation during pathological conditions. Differentiated endothelial cells as well as embryos having a deficiency of the VEGFR-1 show increased endothelial cell mitotic index and augmented vascularization, which suggests that VEGFR-1 signaling is involved in the regulation of cell-cycle progression of endothelial cells [11].

VEGFR-1 is also important in cell migration. The interaction between VEGF-A and VEGFR-1 induces a chemotactic response in polymorphonuclear cells. The gene for VEGFR is only expressed by Leukocytes (monocytes and polymorphonuclear cells) [12]. VEGFR-1 also bind VEGF-B, having poor mitogenic property for endothelial cells [13]. VEGF-B increased the expression and activity of plasminogen activator inhibitor-1 (PAI-1) in endothelial cells. The expression of PAI-1 protects the extracellular matrix from extensive

Table 1. The VEGF receptor family.

Receptor	Ligand	Importance
VEGFR-1(flt-1)	VEGF-A110 VEGF-A121 VEGF-A165 VEGF-B	Proteases Growth factors
VEGFR-2 (KDR flk-1)	VEGF-A110 VEGF-A121 VEGF-A145 VEGF-A165 VEGF-C VEGF-D	EC Proliferation EC Migration EC Survival
VEGFR-3 (flt-4)	VEGF-C VEGF-D	LEC Proliferation LEC Migration LEC Survival
Neurophilin-1 Neurophilin-2	VEGF-A165	Enhanced VEGFR-2 Signalling

LEC, Lens epithelial cell; VEGF, Vascular endothelial growth factor; *VEGFR,* Vascular endothelial growth factor receptors.

proteolysis cleavage [13]. VEGFR-2 signaling pathway triggers endothelial cell proliferation [1].

Proteolysis differentiates VEGFR-3 from the other two VEGFRs in their C terminal and in their signaling properties [6, 14]. VEGF-C and VEGF-D bind only with VEGFR-3 because the receptor is generally present in endothelial cells of lymphatic. Activation of VEGFR-3 stimulates proliferation, differentiation and migration of these cells [14].

The VEGFR-1, 2 and 3 receptors have neuropilins-1 and 2 (NPR-1, NPR-2). VEGFR protein phosphorylation produces an enhancement of VEGF signaling. Neuropilins are essential for regulation of angiogenesis. They are present in endothelial cells of blood vessels and play an important role in the regulation and development [2, 15, 16].

4. SIGNAL TRANSDUCTION MECHANISM

VEGF intracellular signaling cascades include dimerization of ligand and receptor (Fig. **1**). VEGF interacts with the receptor through the process of phosphorylation. Although, both VEGFR-1 and VEGFR-2 receptors are required for angiogenesis, VEGFR-2 signaling plays an important role in the central nervous system [5, 17, 18]. Phosphorylation of tyrosine molecules produced by VEGFR activation activates phospholipase C. Activated phospholipase produces activation of protein kinase C (PKC) by diacylglycerol (DAG) generation and leads to the release of intracellular calcium ion. Then, the number of signal transduction molecules is activated or modified in response to protein kinase C activation like activation of extracellular signal-regulated kinase 1/2 (ERK1/2) by Ras and Raf-1 proteins which have an important role in endothelial cell proliferation. Protein kinase C activation also produces activation of mitogen-activated protein kinase (MAPK) which produces endothelial cell migration and an increase in vascular permeability [5, 8, 13]. All these effects are indirectly dependent on NO [15]. Endothelial cell survival is also influenced by phosphoinositide 3-kinase (PI 3-kinase) and its downstream substrate, the serine/threonine kinase Akt. The Akt kinase activation, nuclear factor kappa B (NFkB) and down-regulation of apoptosis gene, which produce up-regulation of the Bcl-2 gene, play a role in the survival of cells [8, 15, 16].

5. REGULATION OF GENE EXPRESSION

Several mechanisms play a role in the VEGF gene expression mechanism. Oxygen deficiency is

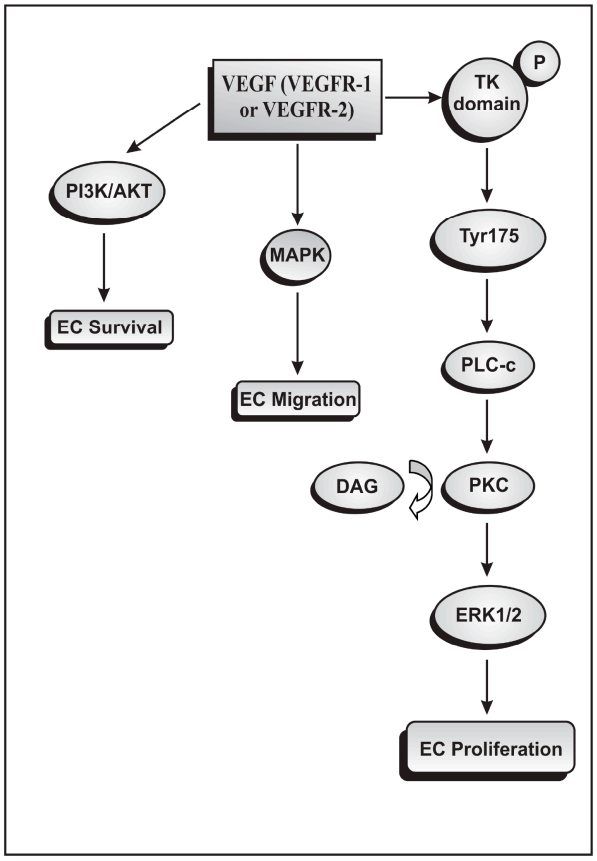

Fig. (1). VEGFR signal transduction mechanism. VEGF, Vascular endothelial growth factor; TK, Tyrosine Kinase; PLC, Phospholipase C; PKC, Protein Kinase C; ERK1/2, Extracellular signal-regulated kinase-1/2; EC, Endothelial cell; DAG, dialkyl glycerol; MAPK, mitogen-activated protein kinase; PI3K, Phosphatidylinositol 3-kinase.

an important regulatory factor involved in angiogenesis. It induces synthesis of certain transcription factor like hypoxia-inducible factor-1 (HIF-1), which produces upregulation of VEGF gene [5, 19]. Oxidative stress induced by hypoglycemia and low pH also increases VEGF gene expression [20].

5.1. Hypoxia

Under normal physiological conditions, cells are nourished with oxygen to perform various metabolic functions. Oxygen is transported by circulating red blood cells and its production is controlled by erythropoietin (EPO). Cells present in the liver and kidneys can sense a change in oxygen concentration which leads to increase in EPO gene transcription. VEGF-A plays an important role in angiogenesis by increasing the supply of oxygen [21-23]. VEGF-A expression can be induced hypoxic condition. While, VEGF-B and VEGF-C expressions are not affected by hypoxia and it is unclear whether VEGF-D and VEGF-E expression is induced by hypoxia or any other factors. The HIF-1 binds to VEGF-A gene and EPO gene. Both VEGFR-1 and VEGFR-2 are upregulated in hypoxic conditions [24, 25].

5.2. Growth Factors and Cytokines

Tumor necrosis factor-alpha (TNF-α) is a cell signaling protein involved in the process of inflammation, which shows various biological activities including angiogenesis. The release of angiogenic factors like bFGF, PAF, VEGF-A, and VEGFC is stimulated by TNF-α. TNF-α also increases the transcription of the VEGFR-2 and NPR-1 gene, which leads to stimulation of wound healing and proliferation and migration of endothelial cells [26, 27]. Various growth factors, such as tissue growth factor-β (TGF-), epidermal growth factor (EGF), keratinocyte growth factor and platelet derived growth factor (PDGF) play important roles in VEGF-A and VEGF-C mRNA expression but do not affect VEGF-B mRNA levels [25]. VEGF-A expression is stimulated by cytokines such as IL-1α, IL-1β, and IL-6 [27].

5.3. Hormonal Regulation

Studies indicate that human breast cancer cells express two isoforms of estrogen receptor, estrogen receptors α and β, which cause activation by binding to an estrogen response element and mediate breast cancer-promoting effects of estrogens. Estrogens stimulate VEGF-A gene expression and have been found to produce estrogen like action [28-30]. Studies have reported that progesterone up-regulates VEGF-A expression and governs uterine angiogenesis and vascular remodeling during pregnancy [29]. However, VEGF-B, VEGF-C, and VEGF-D are not significantly affected by hormones [30].

6. ROLE OF VASCULAR ENDOTHELIAL GROWTH FACTOR IN NONMALIGNANT DISEASE

6.1. Rheumatoid Arthritis

Rheumatoid arthritis (RA) is characterized by chronic autoimmune inflammatory disease where the proliferation of synovial cells, angiogenesis and pannus formation takes places. Multiple cell types contribute to the chronic autoimmune and inflammatory responses of RA, and comprise a pathogenesis of RA [31]. Angiogenesis preserves the inflammatory state by transferring inflammatory cells, nutrient material, and oxygen at the sites of synovitis [32, 33]. Angiogenesis is controlled by many inducers and inhibitors, proangiogenic factors, including acidic and basic fibroblast growth factors (BFGF), TGF-*β*, angiopoietin, and placenta growth factor in addition to VEGF [32, 34].

Roles of VEGF in the Pathogenesis of RA

Recently, several reports have shown that VEGF plays important roles in the pathogenesis of RA [35]. VEGF in synovial fluids is increased in RA and VEGF levels correlate well with RA disease activity. [32, 36, 37]. VEGF genes are highly expressed in the patients with RA, and secretion of VEGF increases under hypoxic conditions as well as in the presence of IL-1, IL-6, IL-17, IL-18, prostaglandin, TGF-*β* [32, 34, 38-40]. Furthermore, VEGF knockout mice showed an increase in angiogenesis synovium in animal models of antigen-induced arthritis [41]. These findings strongly suggest that angiogenesis and inflammation are interdependent processes [37, 42].

Expression and Function of VEGF Receptors in RA

VEGF exerts its biological effects by binding to its receptor subtypes which have tyrosine kinase activity [15, 35, 43]. VEGFR-2 is primarily responsible for endothelial cell proliferation, whereas VEGFR-1 is present in leukocytes [15, 35, 43]. Many studies have demonstrated that NP-1 functions as a non-tyrosine kinase co-receptor for VEGF in endothelial cells and regulates the process of angiogenesis [44-46] (Fig. **2**).

Furthermore, it was found that NP-1 arbitrates the antiapoptotic activity of VEGF and is highly expressed in infiltrating leukocytes in RA [47]. NP-1 could hamper synoviocyte apoptosis by binding to VEGF and thus, function as a survival factor. The up-regulation of NP-1 is responsible for synoviocyte survival, which was found to be associated with down-regulation of Bcl-2 up regulation of Bax. VEGF also stimulates the production of chemokines, which are responsible for chronic inflammation in joints [48, 49]. Therefore, we can conclude that VEGF would regulate the progress of inflammation and angiogenesis in patients with RA.

6.2. Diabetic Retinopathy

Diabetes mellitus is classified under endocrine disorder characterized by hyperglycemia associated with various complications such as retinopathy, nephropathy, neuropathy, cardiomyopathy and diabetic foot. Diabetic retinopathy is a major cause of visual loss associated with neovascularization and increased vascular permeability. Increased levels of VEGF have been reported in the vitreous humor and in fibrovascular tissues from eyes with both progressive and non-progressive retinopathy [50]. VEGF enhances the vascular permeability as well as producing microaneurysm formation and capillary occlusion in the eye [51, 52]. VEGF expression can be increased many times and express high-affinity VEGF receptors and stimulate endothelial cell proliferation, migration, and survival, as well as angiogenesis and microvascular permeability. VEGF-1 and 2 receptors have been reported to be the main contributing factors in patients with both progressive and non-progressive diabetic retinopathy [53]. Anti-VEGF antibodies inhibit endothelial cell growth, with a significant inhibition of angiogenesis in patients with diabetic

retinopathy. Studies suggest that neutralization of physiologic levels of VEGF is a key endothelial survival factor. Decreases in levels of angiogenic factors lead to reduction in retinal ischemia and produce suppression of neovascularization. [54]. Several VEGF inhibitors have been investigated to be effective in ischemic retinopathy [53]. It is also described that VEGF receptor inhibitors produce inhibition of neovascularization in the retina [55].

6.3. Psoriatic Skin Disease

Psoriasis is a chronic inflammatory skin disease with thick, white, silvery, red, erythematous patches of skin. It is also characterized by hyperplastic epidermis. Neovascularization is required to encounter the increased nutritional demand of the epidermal skin. Neovascularization has been found to be increased due to overexpression of VEGF and VEGFR-1 and VEGFR-2 in keratinocytes and fibroblasts [56]. It has been reported that synthesis and secretion of VEGF increased from keratinocytes and are stimulated by TGF-α and EGF in patients with psoriasis [57]. Antiangiogenic treatment using either VEGF antagonists or VEGF receptor antagonist may be a novel selective therapeutic strategy for the treatment of psoriasis [56].

7. ROLE OF VASCULAR ENDOTHELIAL GROWTH FACTOR IN MALIGNANT DISEASE

VEGF receptors are highly expressed in the majority of tumors, especially in solid tumors and interaction of receptors with VEGF plays an important role in the process of tumor vascularization, proliferation, and invasiveness [58-64]. VEGF tumors need blood perfusion for the supply of oxygen and nutrients as well as for removal of waste naturally produced within the body [65]. VEGF acts as a key mediator in angiogenesis in cancer. VEGF is a key factor of angiogenesis in early events of cancer. The tumor blood vessels are more reliant on VEGF for growth than those of normal vascular [66, 67]. VEGF also produces synthesis of other pro-angiogenic factors such as BFGF, EGF, granulocyte colony-stimulating factor (GCSF), interleukins, which participate in the process of angiogenesis [65, 68]. Furthermore, VEGF helps tumor in the process of maturation by increasing vascular permeability which causes a release of plasma proteins and modulation of the extracellular matrix. Thus, VEGF participates in the process of migration and proliferation of various cell types [69].

Neovascularization in tumors is necessary for tumor growth, invasiveness and metastasis and VEGF is an essential factor in facilitating advanced tumor growth and metastatic spread by stimulation of hematopoietic stem cells [70-75]. VEGF contributes to all types of malignancies including lymphoma, acute lymphoblastic leukemia, Burkitt's lymphoma, acute lymphocytic leukemia, histiocytic lymphoma, and promyelocytic leukemia [75]. VEGF signaling pathways can be potential therapeutic targets in the majority of malignancies.

During tumorigenesis, neoplastic lesions undergo angiogenic switch (conversion of phenotype from avascular to vascular). This results in an increase in tumor volume and metastasis (Fig. **3**). Neovascularization provides oxygen and nutrients to the tumor [76-78]. Angiogenesis is controlled by various regulators, which have a positive or negative effect [79, 80]. The p53 tumor suppressor gene, which is responsible for apoptosis, also has an inhibitory effect on angiogenesis [81-84]. It has been reported that hypoxia produces overexpression of both p53 and HIF-1α. Both of them alone and in association initiate apoptosis [85-88]. The p53 enhances expression of thrombospondin which has an inhibitory action on angiogenesis. The loss of p53 expression enhances the expression of VEGF-A in tumor cells. It has been reported that in tumor cells, VEGF-A was found to be expressed by Bcl-2 gene in endothelial cells. Thus, overexpression of antiapoptotic gene Bcl-2 is responsible for inhibition of apoptosis and Bcl-2 also produces potentiation of angiogenesis [92, 93]. Therefore, the balance between activators and inhibitors is required for neovascularization and it can be counteracted by the angiogenesis inhibitors.

8. ROLE OF VASCULAR ENDOTHELIAL GROWTH FACTOR IN CENTRAL NERVOUS SYSTEM

Studies have been carried out and it has been observed that VEGF-induced angiogenesis plays an important role in neuronal regeneration and development as well as in cerebral ischemic injury. VEGF has been reported to have both neurotrophic

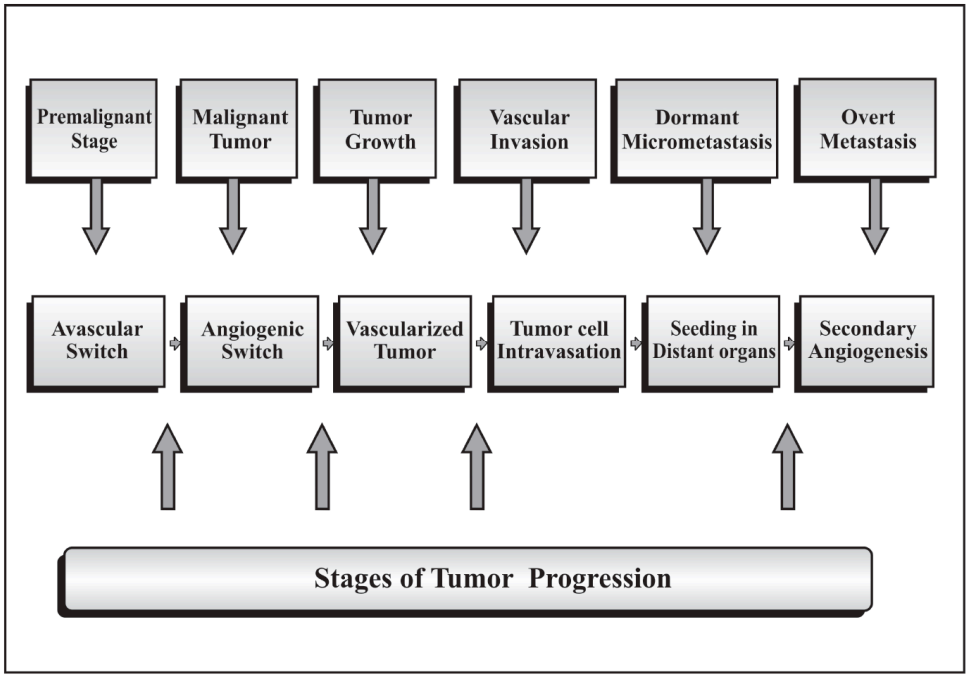

Fig. (3). Role of VEGF in cancer development, growth, and metastasis. Clinical stages and development, growth, and metastasis in cancer.

and neuroprotective potential [16, 94]. The most recent studies have shown an increase in VEGF expression by antidepressant drugs. It was found that VEGF produced its effect by acting on both vascular endothelium as well as on neuronal cells. Many studies have found that VEGF can be a potential therapeutic agent, in depression associated with reduced blood flow to the brain [95]. In the nervous system, VEGFR-2 plays important role in the process of proliferation, survival and migration of neuronal cells (Fig. **4**).

8.1. Intracellular VEGF Signal Transduction in Nerve Cells

It has been previously reported that in central nervous system, VEGF protects nerve cells from apoptosis and also promotes survival of nerve

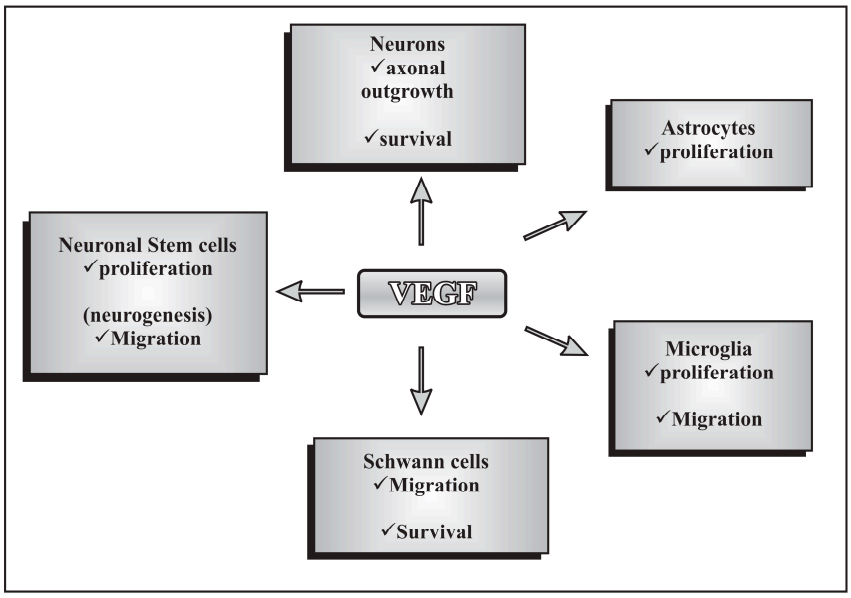

Fig. (4). Role of VEGF on cells in the central and peripheral nervous system. VEGF stimulates the growth and protect motor and sensory neurons. VEGF stimulates proliferation and migration of Schwann cells, neuronal stem cells, astrocytes and microglia. It also stimulate axonal outgrowth and survival.

cells. Regulation mechanisms by which VEGF controls neuronal survival are different in different cells. In neurons and Schwann cells, VEGF acts via activation of PLC pathways while in astrocytes and microglia cells, VEGF acts via activation of the PI3K pathway [16].

8.2. Involvement of VEGF in the Nervous System Development

Recent studies have demonstrated that the mechanism which regulates cell differentiation and development of the nervous system is similar to the circulatory system. VEGF controls neuronal growth as well as vascular development during processes of neurogenesis and angiogenesis [96-98]. Survival of neuronal cells in the brain is effective by both autocrine and paracrine action of VEGF, while angiogenesis is manifested only by paracrine action. Activation of VEGF receptors in a neuron initiates a cascade of an event comprising of PI3, Akt, and tyrosine kinases ERK and STAT3 which play an important part in signal transduction mechanism [99]. Recently, it has been reported that neural tube, from which new vessels develop, undergoes vascularization by the formation of the peripheral vascular plexus (PNVP). It has been reported that inhibitors of VEGF inhibit the vascular plexus formation. VEGF is produced in neuronal precursors participating in vessel formation and VEGF expression was found to be increased in the brain during cerebellar development [97].

8.3. VEGF as a Neurogenesis Stimulating Factor

VEGF regulates vascular growth and also influences the growth of brain cells. VEGF stimulates neurogenesis and regulated by several factors. Differentiation of neuronal stem cells leads to the formation of nerve or glial cells [100, 101]. Neurogenesis is stimulated by environmental factors and is inhibited by aging [95, 102]. It has been reported that VEGF produced by the brain cells stimulates proliferation of neuronal precursors [99, 103]. Many studies have shown the role of brain-derived neurotrophic factor (BDNF) in the survival of nerve cells and synaptic plasticity [95]. Erythropoietin also participates in angiogenesis and neurogenesis process. VEGF-induced proliferation of stem cells in the brain is also enhanced by the presence of GCSF [99, 101]. VEGF produces proliferation and survival of Schwann cells in the peripheral nervous system in a hypoxic condition [104-106].

8.4. VEGF in Synaptic Plasticity

In the central nervous system, VEGF plays an important role in long-term changes in synaptic efficacy. VEGF works as a signal modulator in neurons, by producing modulation of Ca2+/calmodulin complex, camp and subsequently modulation in mammalian Target of Rapamycin kinase (mTOR) pathway. All this collectively produces an enhancement of protein synthesis [107-109].

8.5. VEGF as a Neuronal and Glial Protective Factor

VEGF also has neuroprotective activity and action of VEGF is mediated by Akt and ERK signaling pathways. It protects the cells of the nervous system from a variety of factors. The levels of VEGF and its receptors and phosphorylation of molecules of Akt and ERK signaling pathway were found to be increased in a hypoxic condition. VEGF produces a proliferation of neuronal cell by inhibition of apoptosis by inhibiting caspase-3 pathway [110-112].

9. ANTI-VEGF AS A POTENTIAL TREATMENT STRATEGY

Over the past few years, anti-VEGF therapy has become a standard treatment for neovascular diseases like RA, diabetic retinopathy, psoriasis, cancer and certain CNS disorders. The reports have shown that *in vivo* administration of anti-vascular endothelial growth factor receptor I antibody suppressed arthritis in collagen-induced arthritis mouse model, suggesting that anti-VEGF antibody treatment may serve as a new therapeutic strategy for RA [113]. Several evidences from the scientific literature have shown the use of anti-VEGF agents to be beneficial in the treatment of diabetic retinopathy, especially in cases with neovascular glaucoma, persistent vitreous hemorrhage, and before vitrectomy [114]. Recent evidence indicates that the anti-VEGF antibody treatment produced an overall improvement of the psoriatic lesions in the disease model of mice, leading to a reduction in the number of blood vessels, inflammatory cells within the dermis and a significant decrease in the size of dermal blood, lymphatic vessels [115].

Anti-VEGF therapy is being actively investigated as a treatment of cancer, either as alternatives or adjuncts to conventional chemo or radiation therapy. The therapy includes the use of neutralizing monoclonal antibodies against VEGF or its receptor, tyrosine kinase inhibitors of VEGF receptors, soluble VEGF receptors, which act as decoy receptors for VEGF, and ribozymes which target VEGF mRNA. Recently it was found that clinical trials led to the approval of bevacizumab, an anti-VEGF monoclonal antibody, for metastatic colorectal carcinoma in combination with other chemotherapeutic agents [116].

CONCLUSION

From the above discussion, we can conclude that there has been an ever-growing interest in VEGF and its role in several diseases. VEGF has been found to play a major role in angiogenesis and vasculogenesis as it has been found to be a central regulator in both of these processes. Diseases like rheumatoid arthritis, diabetic retinopathy, psoriasis and cancer, are characterized by abnormal angiogenesis and in many cases, these are accompanied by the aberrant production of VEGF. The understanding of these processes is essential for the development of methods essential for the modulation of VEGF-induced angiogenesis. It has been seen that VEGF promotes angiogenesis by different mechanisms. It has also been realized that in many of these diseases, modulation of VEGF function may contribute to the successful therapeutic treatment of the same. It can thus be a major area of research relating to different diseases and angiogenesis and involvement of VEGF in the same. It is also reasonable to assume the mechanism by which the activity of different angiogenic and anti-angiogenic factors is coordinated. Thus, these would help in better understanding of VEGF and angiogenesis correlation and how it can be targeted in different diseases for its treatment.

CONFLICT OF INTEREST

Authors declare that the authors have not had any economic or personal ties on possible conflict of interest.

ACKNOWLEDGEMENT

Declared none.

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Received: ????? ??, 201? Revised: ????? ??, 201? Accepted: ?????? ??, 201?