MINI-REVIEW

Diagnostic and Therapeutic Implications of the Vascular Endothelial Growth Factor Family in Cancer

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Abstract

Cancer progression is attained by uncontrolled cell division and metastasis. Increase in tumor size triggers different vascular channel formation to address cell nutritional demands. These channels are responsible for transferring of nutrients and gaseous to the cancer cells. Cancer vascularization is regulated by numerous factors including vascular endothelial growth factors (VEGFs). These factors play an important role during embryonic development. Members included in this group are VEGFA, VEGFB, VEGFC, PIGF and VEGFD which markedly influence cellular growth and apoptosis. Being freely diffusible these proteins act in both autocrine and paracrine fashions. In this review, genetic characterization these molecules and their putative role in cancer staging has been elaborated. Prognostic significance of these molecules along with different stages of cancer has also been summarized. Brief outline of ongoing efforts to target hot spot target sites against these VEGFs and their cognate limitations for therapeutic implications are also highlighted.

Keywords: Metastasis - VEGF family - angiogenesis - prognosis - carcinogenesis

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Introduction

Members included in this family include VEGFA, VEGFB, VEGFC, and VEGFD along with three core receptors named as VEGFR1, VEGFR2 and VEGFR3. These molecules exist in glycosylated homodimer forms and expressed on endothelial cells. These proteins are responsible for increased vascular permeability, angiogenesis, endothelial cells growth and promotion of cell migration. Interestingly, heterodimerization of these molecules receptor also stimulate vascularization (Nilsson et al., 2010). Association of these molecules with cancer are mentioned below

VEGFA: Vascular endothelial growth factor (VEGFA), also termed as vascular permeability factor (VPF) is localized on chromosome 6p12. It encodes a protein of 412 amino acids from 8 exons. Alternatively spliced transcript variants, encoding either freely secreted or cell-associated isoforms, have also been identified (Meiron et al., 2001).

VEGFB: Based on it expression in different tissues, two isoforms (VEGF-B 167 and VEGF-B 186) have been identified. VEGF-B167 isoform accounts for more than 80% of the total VEGF-B transcripts in many tissues including cardiac, skeletal muscles and neural tissues when compared with VEGF-B186 (Li et al., 2001).

VEGFC: Based on chromatography approach, localization of VEGFC on 4q34.3 region has been reported. It encodes protein of 419 amino acids from 7 exons. Increase expression has also been reported in both bronchial epithelial and smooth muscle cells.

VEGFD: Vascular endothelial growth factor D, also termed c-fos-induced growth factor (FIGF) located on Xp22.31. Abundant expression of VEGFD in fetal lung and skin tissue while lowest in skeletal muscle, colon and pancreas are detected.

VEGFE: A wide range of molecules like GM-CSF, G-CSF, IL-1b, IL-15, TNF-α, IL-6, IL-3, LT-1 significantly regulates VEGFE expression. Interestingly, increase pro-angiogenic potential of VEGFE as compared to VEGFA induced complications (odema and inflammation) make an ideal choice for their use in different therapeutics (Shibuya, 2009).

VEGFR1: also termed as FMS-like tyrosine kinase (FLT) is localized on 13q12. It encoding region contain 15 exons with a protein size of 150.6 kDa. It encompasses1,338-amino acids. It is expressed in placenta, liver, muscle, and kidney.

VEGFR2: It belongs to tyrosine kinase family and also named as FLK with localized region identified at 4q12. It comprises of 30 exons encoding a protein of 1356 amino acids. A splice variant of VEGFR2 has been observed in RT-PCR analysis of human umbilical vein endothelial cells. In frame retention of intron 13 containing an in-frame termination codon have been reported. This truncated protein retains a unique 16 amino acids out of 679 amino acids content at C-terminal sequence (Albuquerque et al., 2009).

VEGFR3: It is also termed as FMS like tyrosine kinase 4 (FLT4) which has been identified on 5q34-35 encompassing 30 exons. Two isoforms of this molecule

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has been categorized with amino acid variation of 1363 and 1298 respectively. Its association in lymphatic metastasis has quite recently been explored in head and neck cancer (Wang et al., 2012).

Involvement of VEGFs in Different Cancer Types

Effect of VEGFA in cancer

Expressional dysregulation of VEGFA has been observed in different cancers. Interestingly, up-regulation of VEGFA is also associated with lethal hepatic syndrome (Chen et al., 2014), gastric (Liu et al., 2011), lungs (Jin et al., 2011; Zhang et al., 2014), ovarian (Khemapech et al., 2012) pancreatic (Tang et al., 2006) head and neck (Srivastava et al., 2014), thyroid papillary carcinoma (Klein et al., 2001), myeloid tumors (Stockman et al., 2008; Kim et al., 2009), breast cancer (Schneider et al., 2010; Zhang et al., 2013), medulloblastoma (Pereira et al., 2010), osteosarcoma (Zhu et al., 2010), bladder (Chen et al., 2012; Pignot et al., 2009), colorectal cancer (Sheffer et al., 2009) myeloma (Vlajnic et al., 2010) and glioblastoma (Hose et al., 2009). Although no significant association of VEGF with hormone receptors (ER, PR and HER status) has been established, yet a strong prognostic correlation in relation to mammary, prostate, hepatic, head and neck tumors had been established (Ryden et al., 2005; Yu et al., 2010; Wang et al., 2012; Xu et al., 2013; Srivastava et al., 2014). Hence a consistent finding of VEGFA over expression in majority of cancer strongly suggests it prognostic significance when analyzed with other markers.

Effect of VEGFB in cancer

Association of VEGFB in relation to diabetes, cardiovascular complications, Parkinson disease and obesity are very well established in the literature (Falk et al., 2009). However, effect of VEGFB on different cancer progression is still an area that requires further investigations. Fauconnet (2009) observed a significant association of VEGFA with bladder cancer while no salient association VEGFB was observed. VEGFB expressional dysregulation has been reported in hepatic cellular carcinoma, breast cancer nodal metastasis and invasiveness (Mylona et al., 2007; Kanda et al., 2008). Evaluation of VEGFB as a prognostic marker requires further validation on large cohort samples.

Effect of VEGFC in cancer

Increased expression of VEGFC in bladder (Suzuki et al., 2005), gastric (Kabashima et al., 2001) pancreatic (Sipos et al., 2004), colon (Furudoi et al., 2002), prostate (Qi et al., 2014) and cervical (Fujimoto et al., 2004; Mitsuhashi et al., 2005) had also been observed. A direct correlation of VEGFC with COX2 has also been established in earlier published reports (Byeon et al., 2004; Su et al., 2004; Kyzas et al., 2005). Earlier in 2004, Lee (2004) a strong impact of COX2 in cervical cancer angiogenesis had been established. Hence, VEGF-C is suggested as downstream effectors of COX2 in relation to cancer proliferation as observed *in vivo* assays and breast cancer cells invasion. A

Effect of VEGFD in Cancer

Metastasis promotion in relation to lymphatic vessels involvement has been correlated with VEGFD expression. It triggers lymphatic nodules formation ultimately leading to angiogenesis and tumor growth. VEGF-D over expression at both protein and mRNA level have been observed in colorectal, prostate, breast and endometrial cancer (Yokoyama et al., 2003; Coen et al., 2005; Van Iterson et al., 2007; Zhang et al., 2010). Over expression of VEGFC and VEGFD also led to neoformation of lymphatic vessels in gastric tumor cell lines (Yonemura et al., 2005). In another study, although no association of VEGFC with clinical or histopathological parameters of bladder cancer patients has been observed, but a significant correlation of VEGFD had been established. Interestingly, a full length of VEGFD molecule is unable to induce angiogenesis while proteolytic cleaving fragments of VEGFD fragment is mainly thought to be responsible for metastasis progression and angiogenesis (McColl et al., 2007).

Effect of VEGFR1 in cancer

Inverse correlation of VGEFR1 and sFLT-1 was observed on clinical onset of preeclampsia when compared with serum levels of other woman belonging to same age group retaining a normal gestation (Levine et al., 2004). Similarly, both VEGFA and VEGFR1 increased expression had also been associated with choroidal neovascularization resulting in age related macular degeneration. In a quite recent report, genetic variation of VEGFA and VEGFR1 was also found to be increase risk towards breast and lung cancer susceptibility (Beeghly-Fadiel et al., 2011; Cao et al., 2013).

Effect of VEGFR2 in cancer

Increased VEGFR2 expression has been observed in induced hypoxia among breast cancer and retinal neovascularization (Li et al., 2014). Similarly, frequent aberrations on the genomic portion of VEFR2 have also been observed in hemangiomas (Walter et al., 2002). A novel approach regarding TIMP3 inducing blockade of VGEF mediated inhibition also led to fundus dystrophy (Qi et al., 2003).

Effect of VEGFR3 in cancer

VEGFR3 mutations were extensively been observed in patients of a relative less common tumor lymphedema type IA (Ghalamkarpour et al., 2006). Its over expression has strongly been correlated with lymphatic metastasis among head and neck cancer patients.

Further studies regarding role of these receptors in regulating cancer progression and metastasis are required. Molecular cross talks of the receptors not only with VEGFs but also with other proteins increase their functional diversity in tumor vasculature. The main focus of the current therapeutic regimes is to impair tumor persistent growth and pervasiveness into the surrounding environment. VEGF based therapeutic approaches cover a range of different molecules which may be able to impede molecular signaling at different levels of the VEGF pathway.

Table 1. Clinical Correlation of VEGF Molecules with Different Types of Cancer

Molecules	Types of Cancer	Expressional Regulation
VEGFA	Gastric, Lungs, Ovarian, Pancreatic, Head and Neck, Breast, Bladder, Colorectal cancer, Thyroid papillary carcinoma, Myeloid tumors, Medulloblastoma, Osteosarcoma, Myeloma and Glioblastoma	Increase expression with poor disease over all survival and tumor progression
VEGFB	Lung cancer progression, Hepatic cellular carcinoma, Breast cancer nodal metastasis and invasiveness	Expression yet to be ascertained in large cohorts
VEGFC	Squamous cell carcinoma of the cervix, Bladder Gastric, Pancreatic Colon and Prostate Cancer	Increase expression with poor outcome
VEGFD	Colorectal, Prostate, Breast, Endometrial, Gastric and Bladder Cancer	Increased expression of protein and mRNA as well
VEGFR1	Breast cancer susceptibility	Genetic variations are attributed
VEGFR2	Retinal neovascularization	Increased expression profiling
VEGFR3	Hemangioma	Decreased expression due to mutation

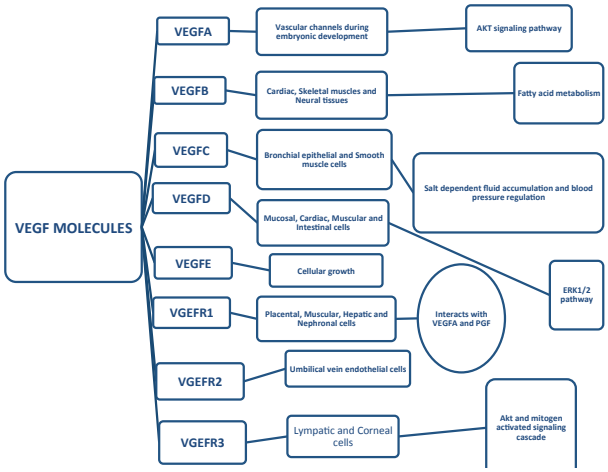

Figure 1. VEGF Members and their Expression in Endothelial Cells

Therapeutic Implications of VEGF Inhibitors

Over expression of COX-2 resulted in increased angiogenic stimulation and tumor proliferation. Celecoxib (drug selective for COX-2 inhibition) expression plays a pivotal role in suppression of angiogenesis. Its potential benefits in hepatocellular carcinoma (HCC) patients have been observed. Marked reduction in seroangiogenic factors (VEGFs) had been observed after a combinatorial administration of bevacizumab along with 5-fluorouraci (5FU) and cyclophosphamide (endoxan) (Bassiouny et al., 2010).

Targeting VEGF Molecule (Avastin)

A monoclonal antibody Bevacizumab (Avastin®; Genentech, Inc., South San Francisco, CA) specifically target VEGFA expression. Earlier, it showed showed increase colon cancer patients survival over conventional chemotherapeutics medicines (Los et al., 2007). This compound is found responsible for regression of tumor vasculature, inhibition of new vessels formation and even blockade of progenitor cells from bone marrow (Wood et al., 2000; Willett et al., 2004). FDA recommends this drug against colon, kidney, brain, and lung cancers cases however it was not suggested for breast cancer affected patients as more complications are introduced in this regard (FDA recommendations 2010). One possible reason of reduced efficiency in late breast cancer affected patients is because of wide molecular cross talks responsible for angiogenic induction. Hence alternative substitute for angiogenic suppression are required.

Targeting VEGF Receptors (Semaxanib SU 5416, SU 6668)

Tyrosine kinase inhibitors have been used to target VEGFR by introducing autophosphorylation. Semaxanib (SU5416) drug was found very effective against Kaposi's sarcoma and advanced stage malignancies (Mendel et al., 2000). However, it side effects leading to suppression of lymphocyte germination and immune response stop their further usage (Grailer and Steeber, 2013). Another drug of choice namely su6668 from Sugen pharmaceuticals designed competitively against VEGFR is also withdrawn due to quite similar findings (Lee et al., 2001). FLJ10540 blockage mediated by VEGFR2 or PI3K inhibitors results in halt of VEGF and Akt pathway expression of lung cancer cells invasion and migration (Liu et al., 2010). Vatalanib (PTK787/ZK 222584) is a small molecule tyrosine kinase inhibitor against VEGFR-1 to -3. TK787/ZK 222584 might have more clinical potential in AML when combined with a chemotherapeutic drug such as amsacrine. In future, it will be interesting to study whether the complications and the long-term effects of chemotherapy can be reduced by lowering the dosages of amsacrine, and by replacing it with other drugs with lower toxicity profiles, such as PTK787/ZK 222584 (Weidenaar et al., 2008), TGFβRII significantly inhibits tumor progression and also resulted in loss of VEGFA expression. TGFβRII also inhibit ascites formation and improve ascites drainage (Liao et al., 2011). Similarly AEE788 also showed a wide spectrum efficiency by inhibiting expression of epidermal growth factors receptors as well as VEGFRs in medulloblastoma established cell lines (Meco et al., 2010). Serious AEs, most commonly grade 3/4 liver function test elevations, were responsible for treatment discontinuation in 17% of patients. AEE788 concentrations were reduced by EIACD. The best overall response was stable disease (17%) (Reardon et al., 2012).

Conclusion and Future Prospectives

VEGF molecules increase vascular permeability, cell growth, cell migration, and inhibit apoptosis. Role of VEGF-A is of clear prognostic importance and is targeted by monoclonal antibody based product Bevacizumab. Better insights of pathways underlying the involvement of other VEGFs mediated regulation is an important avenue to explore. Many drugs are being tested clinically in this regard and future studies targeting both VEGFs and VEGFRs in order to develop therapeutics will proof efficient in reducing the complications of chemotherapy in various types of cancers.

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