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Review Article

Diagnostic Applications of VEGF in the Head and Neck Pathologies - An Overview

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Abstract

Vascular endothelial growth factor (VEGF) plays an important role in promoting angiogenesis and is overexpressed in several malignancies. Angiogenesis plays a crucial role in tumor growth, progress and metastasis. In human tumors such as breast, non-small cell lung, colorectal and prostate cancer, VEGF frequently is overexpressed and higher levels of VEGF have shown to be related with adverse prognosis and decreased survival rates. Past few years have seen lot of research associated to the use of angiogenesis inhibitors as anticancer agents. The Vascular endothelial growth factor (VEGF) and its receptors are key regulators of the process of angiogenesis, which makes them attractive therapeutic targets. Given the role of VEGF and its receptors in various diseases, VEGF could serve as an important diagnostic tool in monitoring the disease progression and survival rates. This review is an attempt to explore the various diagnostic applications of VEGF in head and neck region.

Keywords: *Vascular Endothelial Growth Factor (VEGF); Head and Neck Pathologies; Angiogenesis; Fibroblast Growth Factors (FGFs)*

Introduction

Angiogenesis is the process of new blood vessel formation from pre-existing vascular networks by capillary sprouting. During this process, mature endothelial cells divide and are incorporated into new capillaries [1].

Primarily, angiogenic growth factors such as vascular endothelial growth factors (VEGFs) and fibroblast growth factors (FGFs) induce the secretion of endothelial proteinases and plasminogen activators that cause the breakdown of the vessel basement membrane, allowing the cells to intrude the adjoining matrix. Subsequently, the endothelial cells migrate, multiply and ultimately differentiate to give rise to a new, lumen-comprising vessel. Thereafter, the endothelial cells establish a new basement membrane and release additional factors such as platelet-derived growth factor (PDGF), which draws the supporting pericytes to interact externally with the endothelial cells in order to stabilize the newly formed vessels [2].

Angiogenic sprouting is coordinated by a gentle balance between several pro- and anti-angiogenic factors, such as VEGFs, FGFs, angiopoietins (Ang1-4), PDGF, transforming growth factor beta (TGFβ), tumor necrosis factor alpha (TNFα), integrins, adhesion molecules and matrix degrading enzymes [3]. Among the inducers of angiogenesis, the VEGFs, FGFs, and angiopoietins probably stand out to be the most essential angiogenic molecules [4]. This narrative review focuses on the role of vascular endothelial growth as a diagnostic marker.

Vascular endothelial growth factor (VEGF)

Vascular endothelial growth factors (VEGFs) are a family of polypeptides secreted in the body with a highly conserved receptor-binding structure [5]. The human VEGF family consists of five members: VEGF (or VEGF-A), VEGF-B, VEGF-C, VEGF-D and placental growth factor (PlGF) [6,7]. Their major function in vertebrates is to stimulate blood-vessel formation in endothelial cells coordinated through a family of cognate receptor tyrosine kinases.

Embryogenesis and development involve two fundamental processes namely vasculogenesis and angiogenesis. Vasculogenesis is the differentiation of endothelial cell progenitors and their assembly into the primary capillary plexus whereas angiogenesis is the sprouting of new capillaries from pre-existing vessels [8]. Vascular endothelial growth factor (VEGF) signaling is required for the full execution of vasculogenesis and angiogenesis [1].

Functions of VEGF in health and disease: VEGFs and their cognate receptors studied so far are able to regulate angiogenesis, and several have key biological roles in the formation of vascular structures either during development or in the adulthood. Angiogenesis in adulthood plays an important role in tissue growth and repair, during pregnancy and is a key underlying process in the pathogenesis of neoplasia and many other diseases [5].

VEGF also called as VEGF-A, or vascular permeability factor was discovered in 1983 [9] and has emerged as the single most important regulator of blood vessel formation in health and disease. In addition to its major role in angiogenesis, *in vitro* and *in vivo* studies have proven the role of VEGF-A also as neuro-trophic and neuro-protective activities [10,11].

VEGF-A driven angiogenesis also contributes in the pathogenesis of diverse human diseases, including various cancers, eye disorders and rheumatoid arthritis [12].

Vascular endothelial cells are ordinarily quiescent in adult humans and divide less than once per decade. During the process of carcinogenesis, when tumors reach a size of about 0.2 - 2.0 mm in diameter, they become hypoxic and limited in size in the absence of angiogenesis. There is interplay of pro-angiogenic and anti-angiogenic factors modulating the carcinogenesis.

There are about 30 endogenous pro-angiogenic factors and about 30 endogenous anti-angiogenic factors. In order to increase in size, tumors undergo an angiogenic switch, allowing the action of pro-angiogenic factors, resulting in angiogenesis and tumor progression [1].

The VEGF family plays an integral role in angiogenesis, lymphangiogenesis and vasculogenesis which are crucial for the growth of neoplastic cells.

Mechanism of action of VEGF

Each of five forms of human VEGF family contain a signal sequence that is cleaved during biosynthesis. In addition, multiple isoforms of VEGF, VEGF-B, and PlGF are generated by alternative splicing of their corresponding pre-mRNAs generates multiple isoforms of VEGF, VEGF-B, and PlGF. There are three receptor protein-tyrosine kinases for the VEGF family of ligands (VEGFR1, VEGFR2, and VEGFR3) and two non-enzymatic receptors (neuropilin-1 and -2). Additionally, several of the VEGF family ligands bind to heparan sulfate proteoglycans that are found on the plasma membrane and in the extracellular matrix [1]. In human tumors (for example, breast, non-small cell lung, colorectal and prostate cancer), VEGF frequently is overexpressed and higher levels of VEGF have shown to be related with adverse prognosis and decreased survival rates [13]. This supports the fact that VEGF can serve as important diagnostic tool in predicting the prognosis of the disease progression as it has major role in angiogenesis, lymphangiogenesis and vasculogenesis.

It is also established that, VEGF is the most important regulatory factor in tumor angiogenesis, which in turn enhances the process of tumor growth, by activating host vascular endothelial cells and promoting malignant proliferation by increasing local availability of oxygen and nutrients for tumor metastasis [14].

This function paved way for harnessing its role as a prognostic indicator especially in neoplastic conditions [15].

Among the various head and neck pathologies, odontogenic cysts, periodontal diseases, oral potentially malignant disorders, oral squamous cell carcinoma and salivary gland carcinomas have consistently shown increased VEGF expression. This emphasizes the importance of clinical research aiding in understanding the role of VEGF as one of the crucial prognostic markers for diagnosis and assessment of prognosis in head and neck pathologies.

Various sources of VEGF

VEGF can be isolated from various sources like blood, tissue and from saliva. VEGF may be located in the plasma, or in the blood-borne cells and formed elements, in particular, platelets and leukocytes. It is mostly concentrated in the platelets, although a significant portion is localized in leukocytes during cancer development [16]. In neoplastic tissues the quantity of VEGF in the tumors is 7 - 70 times higher than the quantity in serum. This indicates that tumor tissue is a significant source and reservoir for VEGF in neoplasia. In addition to the biofluid Saliva is also considered to be a known source of VEGF. Salivary VEGF plays an important role in regulating physiologic and pathologic angiogenic and other vascular responses in salivary and mucosal tissues. The presence of VEGF in saliva may contribute to the remarkable healing capacity of the oral mucosa as well as other regions of the digestive tract [17]. The presence of considerable quantities of VEGF in normal human saliva suggests an important role for this cytokine in the maintenance of mucous membrane homeostasis. Rapid induction of neo-angiogenesis by salivary VEGF helps accelerate the wound healing within the oral cavity. Additionally, salivary VEGF may permeabilize intraglandular capillaries and thus participate in the regulation of saliva production itself [18]. It is hypothesized that the salivary VEGF content of these patients may yield as much prognostic information about the primary tumor as the serum VEGF [19]. In addition to these various sources, genetic modifications controlling VEGF may serve as useful adjunctive aid as an indirect indicator for the role of VEGF in many conditions. Amongst these is assessment of Single nucleotide polymorphism (SNP). Single nucleotide polymorphisms (SNPs) in VEGF may alter VEGF protein concentrations, influence the process of angiogenesis and may relate to inter-individual variation in the risk and progression of selected tumors, and their resistance to treatments. It is well known that single nucleotide polymorphisms (SNPs) in VEGF can affect the expression of this gene.

The VEGF gene is located on chromosome 6 at location 6p21 [20]. Numerous SNPs in the promoter, 5'-, and 3'- untranslated regions (UTR), are present in VEGF. Previous studies showed that -2578C/A (rs699947), -1156G/A (rs1570360), +1612G/A (rs10434), +936C/T (rs3025039) and -634G/C (rs2010963) are five common SNPs in the VEGF, and they are reported to have a role in VEGF protein synthesis (influence of vascular endothelial growth factor single nucleotide polymorphisms on non-small cell lung cancer tumor angiogenesis [23].

Role of VEGF in head and neck diseases

VEGF in oral cancer (OSCC)

Angiogenesis is proven to be a crucial step in tumor growth, progression, and metastasis. Among the various, angiogenic factors VEGF is thought to be most potent angiogenic factor for the induction of angiogenesis in tumor growth [25,26] and is also thought to be a selective mitogen for vascular endothelial cells.

Wang., *et al*. [27] in their study suggested, that VEGF overexpression plays a significant role in the primary transformation of tumors at earlier stages, but the interplay of genetic factors influences progression and metastasis at a later stage have suggested it.

Note only was the tissue expression of VEGF was increased in OSCC, but also the serum levels of VEGF have a significant role. Shang., *et al*. in their study noted, that OSCC was associated with significantly elevated serum VEGF concentration and that higher level of serum VEGF also correlated with lymph node metastasis and clinical stage of OSCC. This established that serum levels of VEGF in OSCC had the potential to be used as a prognostic marker [28].

Ku., *et al*. in their study assessed whether VEGF gene polymorphism could be a genetic marker in OSCC. It was inferred that, the most frequently seen polymorphism was located at the 460th nucleotide upstream of the VEGF gene. The odds ratio per copy of the ''T/C'' ratio was 9.62, implying that for a group with a higher T/C ratio has higher risk of developing oral cancer. The results concluded that BstUI polymorphism of the VEGF gene is a suitable genetic marker of oral cancer [20].

In addition, VEGF-C expression was established to be associated with lymph node metastasis, recurrence in OSCC [29].

Few other researches have established the role of VEGF as a tumor marker in OSCC [30].

VEGF's role in oral potentially malignant disorders (OPMDs)

In 2005, the WHO instead proposed to use the term "oral potentially malignant disorders" (OPMDs), which is defined as "the risk of malignancy being present in a lesion or condition either at the time of initial diagnosis or at a future date.

The most common OPMD lesions are oral leukoplakia, OSMF, erythroplakia and verrucous carcinoma. Some miscellaneous inherited/acquired diseases such as xeroderma pigmentosum, dyskeratosis congenita, Fanconi's anemia, chronic iron deficiency anemia and immunodeficiency are the other potentially malignant disorders for oral carcinoma [31].

As per recent literature, the values of the malignant potential of oral leukoplakia (OL), oral lichen planus (OLP) and oral submucous fibrosis (OSF) are 3.5% (range, 0.13 - 34.0%) [32], 1.1% [33] and 7% - 13% [34], respectively.

Prevention and early detection of OPMDs have the potential of not only decreasing the incidence, but also in improving the survival of those who develop oral cancer in later stage. The identification of preneoplastic lesions of the upper aerodigestive tract, through clinical, morphological and more recently, molecular means, helps in the early detection and treatment of head-and-neck squamous cell carcinoma [31].

Oral leukoplakia (OL)

The first report on the angiogenic potential of VEGF in pre-malignant lesions was proven by Folkman., *et al* [35]. This report also demonstrated the induction of angiogenesis during the transition from hyperplasia to neoplasia.

Few other studies [36] have, assessed the role of angiogenesis in the process of malignant transformation of clinical diagnosed oral leukoplakia (OL). It was evident that angiogenesis increases during the transition from OL through dysplasia to OL-Oral Squamous Cell Carcinoma (OSCC). Similarly reports from study by Gandolfo., *et al*. reported that leukoplakia exhibited an increase in VEGF expression and has a role in sub-epithelial vascularization, also the expression was significantly greater in leukoplakia with dysplastic changes than in leukoplakia without dysplasia [37].

In particular, OL-OSCCs of the tongue, VEGF-A expression may be used for estimation of malignant progression of Oral leukoplakia [36].

These studies have proven that VEGF can be used as a potential marker in diagnosis of malignant transformation of oral leukoplakia.

Oral submucous fibrosis (OSMF)

Oral submucous fibrosis (OSMF) is a complex, debilitating, and precancerous condition. Formerly confined to the Indian subcontinent, it is now often seen in the Asian populations of the United Kingdom, USA, and other developed countries and is understandably a serious problem for global health. The condition is thought to be multifactorial in origin with a high incidence in people who chew areca-nut [38] and a significant percentage of patients show malignant transformation (7 - 13%) [34]. This high malignant transformation rate necessitates identification of biomarkers to be employed for early detection of malignant change. This will influence the prognosis in addition to adding better quality of life to patients.

Molecular biology studies have confirmed that VEGF expression is regulated by certain single nucleotide polymorphisms (SNPs), which have tissue- and age-specific expression patterns [39].

In an attempt to establish the relationship of influence in VEGF gene polymorphism and OSMF, Rai DV., *et al*. in their study confirmed that there is a strong association of polymorphism VEGF -460C/T gene in patients with OSMF. The fact that polymorphism was noted in later stages supports the role VEGF as a biomarker for malignant transformation and also in the progress of OSMF stages [40].

Reduced E-cadherin expression and increased VEGF expression [41] is known to be involved in tissue growth and transformation of oral potentially malignant disorders (OPMDs) to malignancy. VEGF expression increased as the disease progressed from normal to increasing grades of oral epithelial dysplasia to malignancy. E-Cadherin and VEGF could be used as combination markers to predict the potential risk for malignant transformation in OEDs.

Oral lichen planus

The role of angiogenesis in the pathogenesis of chronic inflammatory diseases is of substantial interest. A positive feedback loop, in which an inflammatory state promotes angiogenesis and the angiogenesis in turn facilitates chronic inflammation, has been found in some inflammatory diseases [42].

Oral lichen planus (OLP) is a chronic inflammatory disease with an autoimmune inflammatory pathogenesis. Many researches [42-44] have established that there is association expression of VEGF in OLP indicating neo-angiogenesis in oral lichen planus.

VEGF in periodontal diseases

Angiogenesis represents an early and continuous process in periodontal lesions, being present in all developmental stages of the disease, this ensues as a result of interaction between the gingival epithelium and stromal compartment [45].

VEGF was proven to be relevant to angiogenic processes in healthy as well as diseased periodontal tissue and that the periodontal status influences the salivary level of VEGF [46,47].

VEGF in odontogenic cysts

VEGF has proven to have an important role in odontogenic pathologies like odontogenic keratocyst (OKC) and dentigerous cyst (DC). It has been observed that there was higher expression of VEGF in OKC, influencing clinical outcome of OKC and its recurrence [48]. VEGF is also known to influence these conditions regardless of inflammation [49].

It was also evident that higher positivity of VEGF in OKC could be attributed to its aggressive biological behavior [50].

Increased VEGF expression in various head and neck pathologies				
Various Pathologies	**Study details**	**Authors and year of study**	**Source**	**Inference of the study**
Odontogenic cysts				
Odontogenic keratocyst (OKC) and Dentigerous cyst (DC)	Tissue sections of 46 samples of OKC and DC were stained through IHC using Vascular Endothelial Growth Factor (VEGF) antibody. VEGF expression was evaluated in epithelial cells, fibroblasts and endothelial cells.	Sadri., *et al*. (2016) [47]	Tissue sections (IHC).	Higher expression of vascular endothelial growth factor in OKC than DC, and also angiogenesis may have great impression on clinical outcome of OKC.
Odontogenic keratocyst Dentigerous cyst (DC) Radicular cyst (RC)	Forty-two cases of OK, 26 cases of dentigerous cyst (DC), and 15 cases of residual cyst (RC) were retrospectively examined by immunohistochemistry for VEGF, Ki67/Mib-1 and anti-caspase-3.	Mitrou., *et al*. (2009) [48]	Tissue sections of OKC, DC and RC were used (IHC).	The VEGF was expressed in the epithelium of OK, DC, and RC with a variable intensity, and in OK VEGF expression was related to Ki67. It is suggested that VEGF expression by the odontogenic epithelium is not induced solely by inflammation.
Potentially malignant disorders				
Oral leukoplakia	A total of 131 histological preparations [oral leukoplakia/hyperkeratosis without dysplasia (OL; *n* = 49), oral leukoplakia/hyperkeratosis with mild dysplasia (OL-SIN1; *n* = 33), with moderate dysplasia (OL-SIN2; *n* = 13) and leukoplakia-derived oral squamous cell carcinoma (OL-OSCC; *n* = 36)] were evaluated for microvessel density (MVD), vessel diameter as well as for vascular endothelial growth factor (VEGF-A) expression.	Daniel., *et al*. (2017) [35]	Histological sections of leukoplakia	Angiogenesis increases during the transition from OL through dysplasia to OL-OSCC. In particular, OL-OSCCs of the tongue, VEGF-A expression may be used for estimation of malignant progression of OL
	96 biopsies of (1) leukoplakia with and without dysplasia, (2) nontumoral borders adjacent to squamous cell carcinomas with and without dysplasia, and (3) normal oral mucosa were taken. Number, size, and localization of vessels labeled immunohistochemically for the antigen CD34 were assessed	Gandolfo., *et al*. (2011) [36]	Biopsy specimens of leukoplakia	Demonstration of expression of epithelial VEGF and sub-basal vascularization could be an additional aid for evaluation of the severity of potentially malignant lesions in oral mucosa routine biopsies.

Oral submucous fibrosis	Thirty patients with Oral submucous fibrosis and 20 controls free from habits and any form of lesions were included in the study. The polymorphism of VEGF gene was detected by polymerase chain reaction-based restriction analysis.	DV Rai., *et al*. (2016) [39]	Peripheral blood samples (PCR based restriction analysis)	VEGF 460C/T has the potential to be used as a prognostic marker in predicting the malignant transformation of OSMF.
	Ten cases each of Normal Oral mucosa (NOM), Mild Oral Epithelial Dysplasia (OED), Moderate OED, Severe OED, Oral Submucous Fibrosis, (OSMF) and Oral Squamous Cell Carcinoma (OSCC) were stained and evaluated for the expression of Ecadherin and VEGF. Quick score (QS) for expression intensity in all epithelial layers was calculated for both markers	Sharadha P., *et al*. (2018) [40]	Tissue samples (IHC)	E-Cadherin and VEGF could be used as combination markers to predict the potential risk for malignant transformation in OEDs.
Oral lichen planus	Thirty OLP patients and thirty healthy subjects were enrolled in a study. The immunohistochemical analysis of the VEGF and vascular-endothelial adhesion molecules was carried out by means of primary antibodies and anti-CD34, anti-VEGF, anti-CD106 antigen (VCAM-1) and anti-CD54 antigen (ICAM-1)	Scardina G A., *et al*. (2009) [42]	Biopsy samples of oral lichen planus (IHC)	Results of the study showed that significant neoangiogenesis occurs in oral lichen planus.
	In this case-control study, 4-µm sections were prepared from selected OLP (erosive type) blocks and normal mucosa samples for immunohistochemistry (IHC) staining with VEGF marker. VEGF expression was quantitatively assessed via counting the positive-stained cells.	Farhadi S., *et al*. (2018) [43]	Tissue sections (IHC)	The study concluded that VEGF expression in erosive OLP samples was significantly higher than that in normal mucosa
	Microvessel density (MVD) and VEGF level in 30 OLP subjects and 7 matched controls were detected by immunohistochemistry and ELISA.	Tao., *et al*. (2007) [41]	Tissue sections (IHC and ELISA)	The results indicate that angiogenesis and VEGF expression are closely correlated to the different clinical forms of OLP lesions, which may give new insights into the mechanisms and treatment strategy of OLP.
Salivary gland tumours				

Malignant salivary gland carcinomas Adenoid cystic carcinoma	An immunohistochemical study was conducted on the expression of VEGF protein in 66 salivary gland carcinomas and the relation between VEGF and clinicopathological parameters were explored.	Lequerica Fernández., *et al*. (2007) [50]	Tissue sections (IHC)	VEGF expression correlated with progression of salivary gland carcinomas, neck node metastasis, worse survival and poor local control of the disease.
	To detect the expression of nerve growth factor (NGF) and vascular endothelial growth factor (VEGF) in salivary adenoid cystic carcinoma (SACC) tissues, as well as to determine the correlation between growth factor expression and prognosis in SACC. Medical records of 63 patients surgically treated for SACC between January 1988 and October 2005 were reviewed.	Hao., *et al*. (2010) [51]	Tumor tissue sections (IHC)	The study concluded that NGF and VEGF are expressed increasingly in the tissues of SACC cases with invasion and metastasis. NGF expression and VEGF expression are independent prognosis factors for survival.
*IHC: Immuno Histochemical Method *ELISA: Enzyme-Linked Immunosorbent Assay				

Conclusion

Angiogenesis in adulthood plays an important role in tissue growth and repair, during pregnancy, and is a key underlying process in the pathogenesis of neoplasia and many other diseases. Vascular endothelial growth factor (VEGF) plays an important role in promoting angiogenesis and is overexpressed in several malignancies. Vascular endothelial growth factor (VEGF) signaling is required for the full execution of vasculo-genesis and angiogenesis. In this review, we have attempted to explore the diagnostic uses of VEGF in various head and neck pathologies.

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