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Review

VEGF mediated signaling in oral cancer

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Abstract: Increasingly it is being realized that oral cancer arises from genetic/epigenetic mutations, dysregulations of spatio-temporally controlled signal transduction cascades and loss of apoptosis. Epidemiological studies have provided a stronger association between tobacco use (chewed and smoked) and oral cancer. Nevertheless, alcohol has also gained attention as a significant risk factor, having a multiplicative synergistic cancer promoting effect with tobacco. Vascular Endothelial Growth Factor (VEGF) mediated signaling has gained limelight because of its instrumental role in endothelial cell proliferation, survival, invasion, migration, chemotaxis of bone marrow (BM)-derived progenitor cells, vasodilation and vascular permeability. In this review we provide most recent updates on involvement of VEGF/VEGFR signaling axis in oral cancer. We partition this multi-component review into different sections and summarize latest advancements related to therapies against VEGF/VEGFR signaling axis and how microRNAs tactfully modulate VEGF and VEGFR in oral cancers. Data obtained through preclinical and clinical studies has revealed that therapeutic benefits associated with VEGF-targeted therapy are complicated in different cancers and involve myriad of mechanisms. A better understanding of VEGF/VEGFR mediated signaling in oral cancers and testing of novel therapeutic agents in preclinical models will prove to be helpful in effective translation of safest drugs from benchtop to the bedside.

Key words: VEGF, VEGFR, Signaling, Apoptosis, Therapy.

Introduction

The earliest detectable and morphologically identifiable change associated with oral cancer is the appearance of the 'precancerous' lesions. Leukoplakia and erythroplakia are most common precancerous' lesions. Oral leukoplakia is a whitish lesion in mucosa of oral cavity. It is a commonly occurring precursor lesion of oral squamous cell carcinoma (OSCC) and shows high degree of variability in its prevalence. It is becoming progressively more understandable that epigenetic factors, dysregulations of cell signaling cascades and loss of apoptosis are some of the widely studied mechanisms which underpin oral cancer development and progression.

In 1983, a major breakthrough was made by Senger, Dvorak and their colleagues, when the team studied Vascular Endothelial Growth Factor (VEGF) and elucidated its protein structure in 1990. The research team carefully studied underlying cause of rapid accumulation of ascites fluid and enhanced micro-vascular permeability (1,2). Scientists reported that increased permeability of peritoneal vessels was main cause of formation of tumor ascites. Partial amino acid sequence of a peptide that stimulated mitosis of endothelial cells was reported by Ferrara and Henzel in 1989. In 2006, another high impact research by Roy et al. confirmed that the studied peptide was VEGF, a multifunctional molecule that modulated wide ranging biological activities. VEGF family members (VEGF, VEGF-B, VEGF-C, VEGF-D, VEGF-E and placental growth factor (PlGF)) bind to two specific tyrosine kinase receptors (VEGFR 1 and VEGFR 2) that transduce the signals in different types of the cells (1,2). Several members have also been found to interact with non-tyrosine kinase receptors. Neuropilins (NRP) belong to a family of non-tyrosine kinase receptors. NRP-1 and NRP-2 act as co-receptors for the VEGFRs. VEGFR-2 expression is specifically noted in endothelial cells where it functions to regulate the process of angiogenesis. VEGFR-1 has a wider distribution across a variety of cell types and mediates nonvascular-related functions (1,2). VEGFR1–R3 share structural similarity in 7 extracellular immunoglobulin homology domain repeats, a trans-membrane domain and a split tyrosine kinase domain. Despite structural similarity, the receptors may show highly divergent signaling and biological effects (1,2). Shown in Figure 1 and 2.

Tissue based expression analysis of VEGF/VEGFR in oral cancer

NRP1 and SEMA3E were found to be upregulated

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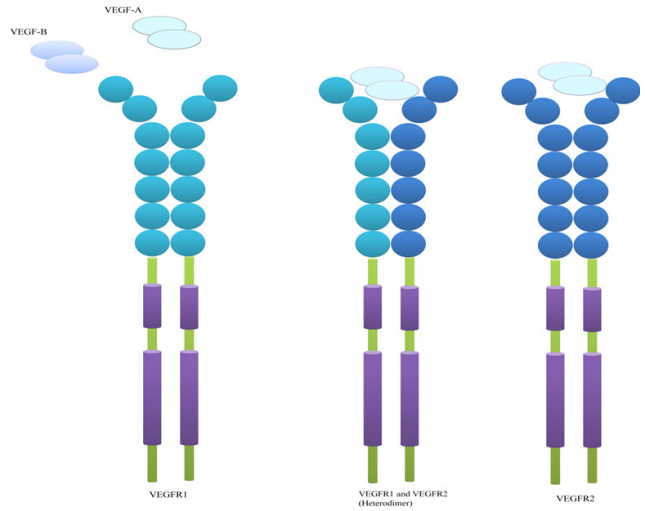

Figure 1. Structure of VEGFR1 and VEGFR2.

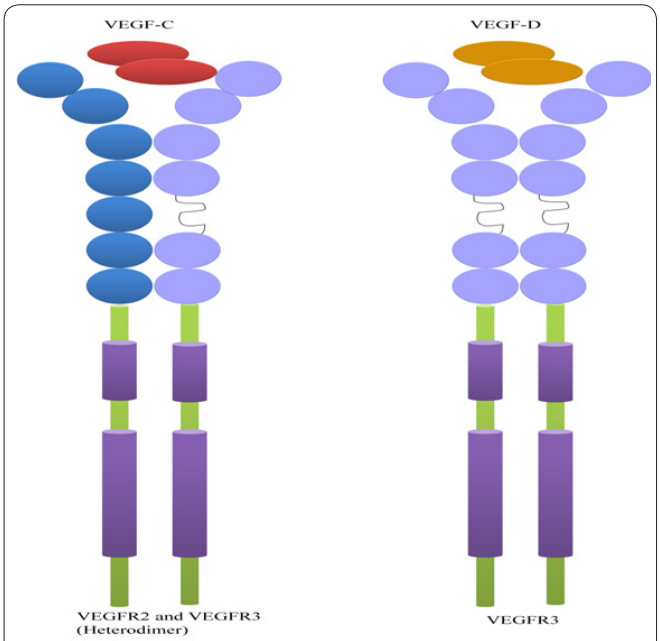

Figure 2. Structure of VEGFR2 and VEGFR3.

in immunohistochemically analyzed cancerous tongue tissue. Univariate logistic regression analysis verified that NRP1 and SEMA3E expression levels were noted to be considerably associated with metastasis of lymph nodes (3).

In a recent study, VEGFR-3 cytoplasmic immuno-expression was recorded in all cases of lower lip squamous cell carcinoma (LLSCC). In non-metastatic tumors, median percentage of VEGFR-3 positive cells was 92.35% and 98.00% in metastatic tumors (4).

In the tumor core, percentage of immunopositive cells for VEGF-C was noted to be 95.95% in young patients and of 55.48% in old patients. In the deep invasive front, percentage of immunopositive cells for VEGF-C was 97.93% in younger patients and 66.09% in older patients (5). Data clearly suggested that aggressive behavior of SCC of the tongue in younger patients was associated with a higher expression of VEGF-C.

Upregulated VEGF-C in the primary tumor was also noted to enhance the chances of micrometastasis and isolated tumor cells (ITCs) in the lymph nodes (6).

Patients with VEGF-D-High or VEGF-A-High tumors had significantly higher Podoplanin-positive Lymphatic Vessel Density (LVD) as compared to the patients with their lower counterparts. In cases with lymph node metastasis, expression score of VEGF-D was markedly higher as compared to those patients which did not have metastasis of lymph nodes (7).

VEGF-C/VEGFR-3 expression may prove to be a predictor of risk assessment of development of regional recurrence in oral tongue squamous cell carcinoma patients (8). There was a significant association of combined VEGF-C/VEGFR-3 expression with depth of invasion, regional recurrence and clinical growth pattern. Lymphatic vessel count was also found to be considerably higher in VEGF-C/VEGFR-3-positive cases (8).

Significantly different expression levels of VEGFR were recorded in OSCC specimens between female and male patients and a weaker correlation was noted between VEGFR1 overexpression and female gender (9). Positive correlation was found between a history of risk factor exposure and VEGFR overexpression (particularly VEGFR2) in OSCC samples. VEGFR1 overexpression was detected in 56%

of samples, VEGFR2 in 42% and VEGFR3 in 60% (9).

Lymph node metastasis, recurrence, lymphatic vessel invasion (LVI), lymphatic vessel density (LVD), VEGF-C, NRP2 and SEMA3F expression levels were found to be considerably associated with 5-year overall survival (10). Survival curves also indicated that prognostically poor patients had higher levels of NRP2 or VEGF-C, or lower SEMA3F (10).

Expression levels of Cyclo-oxygenase-2 (COX-2), VEGF-C and lymphatic vessel density (LVD) in the lymph node metastatic group were significantly higher (11). Expression levels of COX-2 and VEGF-C were found to significantly correlate with each other. COX-2 expression was significantly related to metastasis of lymph nodes and VEGF-C expression (11).

Therapy

Canstatin, a 24-kDa peptide derived from human basement membranes was noted to effectively inhibit tumorigenesis and angiogenesis in mouse models. SCC-VII cells were injected into the anterior buccal mucosa of C3H/HeN mice. Recombinant canstatin significantly inhibited the expression levels of VEGFR-1, VEGFR-2 and VEGF-A in SCC-VII-induced tumors (12).

In a recent study it was shown that gene silencing of p53 concomitantly inhibited expression of VEGF and consequently apoptosis was induced in SSC-4 cells (13).

Administration of bevacizumab 3 days prior to cetuximab (Neoadjuvant group) resulted in considerably improved tumor specific delivery as compared to simultaneously administered antibodies (14).

Celecoxib and cetuximab worked with effective synergy and significantly inhibited expression of VEGF. Both drugs synergistically inhibited tumor growth in female BALB mice xenografted with HSC3 tumor cells (15).

Recently emerging scientific data has started to scratch the surface of co-operation of lncRNAs with adjacently located protein-coding genes and formation of “lncRNA-mRNA pairs” that impact their molecular functions (16). Close relationships are often found

between these lncRNAs and their nearby mRNAs in expression or function. The "lncRNA-mRNA" pair has now come from shadow to limelight and regarded as a versatile regulator of complex gene expression modulating network (16). FOXC1 upstream transcript (FOXCUT), a lncRNA transcribed from the upstream region of FOXC1 promoter was found to play an important role in proliferation and migration of SCC-9 and Tca8113 cells. Knockdown of FOXCUT inhibited the proliferation and migratory ability of SCC-9 and Tca8113 cells. VEGF-A was also notably reduced in FOXCUT and FOXC1 knockdown cells (16).

SAS-LM3 cells are highly metastatic and invade into peri-tumoral lymphatic vessels and disseminate through lymphatic vessels towards the regional lymph nodes. There was a significant increase both in number and size of lymphatic vessels in mice inoculated with SAS-LM3 cells (17). SAS-LM3 cells were noted to secrete lymphangiogenic growth factors VEGF-C. VEGF-C mRNA was remarkably downregulated in COX-2 knockdown SAS-LM3 cells. VEGF-C mRNA was also reduced in cells treated with NS-398 (COX-2-selective inhibitor) (17).

Treatment of OSCC cells with an integrin αvβ3 antibody significantly reduced WISP-1-mediated increase in the expression of VEGFA. c-Src and phosphorylated FAK were considerably higher in WISP-1 treated OSCC cells (18). Downstream signaling proteins FAK and c-Src were blocked in cells pretreated with an integrin αvβ3 antibody or FAKi. These findings suggested that WISP-1 regulated expression of VEGFA in OSCC cells and contributed to angiogenesis through the FAK/c-Src signaling axis (18).

Natural products mediated targeting

Isocudraxanthone K (IK), a phytochemical isolated from methanolic extract of root bark of *Cudrania tricuspidata* was effective against oral cancer. Isocudraxanthone dose dependently downregulated expression level of VEGF in HN4 and HN12 cells (19).

Different natural products are currently being tested as potential anticancer agents against chemically induced hamster buccal pouch carcinogenesis. Carnosic acid, a phenolic diterpene, isolated from *Rosmarinus officinalis* (10mg/kg bodyweight) markedly inhibited occurrence of the tumor and reduced the severities of dysplasia and hyperplasia (20).

Extracts of *Physalis angulata* considerably suppressed migratory and invasive potential of highly metastatic HSC-3 cells. Release of significant VEGF levels was detected in serum-free media at approximately 130 pg/10^5 HSC-3 cells (non-treated). Treatment of cells with extracts (5–15 g/mL for 24 hours) dose-dependently and significantly decreased release of VEGF (21).

Berberine, an isoquinoline alkaloid isolated from Cortex phellodendri and Rhizoma coptidis was also noted to significantly downregulate protein and mRNA levels of VEGF in FaDu cells (22).

Genistein (0.5 mg/kg) was injected into xenografted mice and tumor growth rate and metastasizing ability of cancer cells to invade lung or lymph node was compared. Downregulated VEGF and a significantly lower CD31 immunoreactivity were noted in genistein-treated xenografted mice. Surprisingly, growth rates of tumor and metastatic behavior patterns in the treated and non-treated xenografted mice were similar with no significantly different findings (23). Garcinol, a polyisoprenylated benzophenone has also shown potent anticancer activity. This natural product was isolated from the rind of Garcinia indica. Concentration of VEGF declined from 1002.7 to 703.4 (SCC-9), 339.8 to 245.8 (SCC-4) and 894 to 682.2 pg/ml (SCC-25) upon treatment with garcinol (24).

Geraniol, an acyclic monoterpene alcohol was found to be effective against chemically induced hamster buccal pouch carcinogenesis (25).

In the following section we discuss how miRNAs modulate VEGF/VEGFR signaling axis in oral cancer.

miRNA regulation of VEGF/VEGFR signaling axis in oral cancer

MicroRNAs (miRNAs) are noncoding RNAs of ~22 nucleotides reportedly involved in post-transcriptional regulation of genes by binding to the 3′ untranslated region (UTR) of messenger RNA (mRNAs). miRNAs have a key role in fine-tuning cellular functions such as proliferation, metastasis and apoptosis (26). In this section we summarized how miRNAs modulated VEGF/VEGFR signaling axis.

miR-126 is frequently inhibited in cancer tissues and reconstitution of cancer cells with miR-126 dramatically reduced tumor growth and migration of cancer cells. miR-126 overexpression considerably reduced VEGF secretion in OSCC-15 cells, however VEGF secretion was markedly enhanced in miR-126 silenced cells (27).

VEGF was significantly upregulated in Lin28B overexpressing oral cancer cells. Furthermore, these oral cancer cells showed remarkable migration and invasion potential (28).

Integrin αvβ3/integrin-linked kinase (ILK)/Akt signaling cascade is reportedly involved in cancer development and progression. WNT1-inducible signaling pathway protein 1 (WISP-1), is a cancer promoting molecule and frequently involved in carcinogenesis. WISP-1 promoted VEGF-C expression through integrin αvβ3/ILK signaling pathway in OSCC cells (29). WISP-1-induced VEGF-C expression was significantly downregulated in Akt inhibitor treated cells or Akt siRNA transfected cells. Treatment of oral cancer cells with an integrin αvβ3 monoclonal antibody or KP-392 remarkably reduced WISP-1-induced ILK activity and phosphorylation of Akt (29). miR-300c was noted to quantitatively control VEGF-C mRNA. Detailed mechanistic insights revealed that WISP-1 promoted expression of VEGF-C and lymphangiogenesis by suppression of miR-300 expression (29).

Although overwhelmingly increasing research work highlighted different oncogenic and tumor suppressor miRNAs as major regulators of oral cancer, we still have incomplete knowledge of the miRNAs which target VEGF and VEGFR in oral cancer.

In the upcoming section we discuss most recent advancements in preclinical studies.

Xenografted mice

Fibronectin-1 belonged to a family of high molecular weight glycoproteins present on cell surfaces. V-SAS-LM8 cells are highly metastatic and reportedly had upregulated expression levels of Fibronectin 1 (FN1) and VEGF-C as compared to V-SAS-cells (30). Phosphorylated FAK was also noted in immunocytochemically examined V-SAS-LM8 cells. Data clearly suggested that FN1 transduced the signals intracellularly through FAK and gene silencing of FN1 notably reduced phosphorylated levels of FAK. FN1 silenced V-SAS-LM8 cells were inoculated into the tongue of mice. Lymphangiogenesis was markedly reduced in V-SAS-LM8 (FN1 silenced) tumor/s in immunohistochemically examined tumor/s developed in the tongue of mice (30).

SCC4 cells stably transfected with WISP-1 shRNA were implanted in a mouse model. Data obtained from bioluminescence imaging revealed that control-shRNA transfected SCC4 cells profoundly induced tumor mass formation. However, tumorigenesis was drastically reduced in mice xenografted with WISP-1 knockdown cells (18).

Hypoxia-inducible factor-1 (HIF1), a transcription factor played contributory role in cellular and homeostatic responses to hypoxia. HIF1 is a heterodimerically structured protein composed of HIF1-α subunit complexed with a HIF1-β subunit. Hypoxia Inducing Factor (HIF-1α) siRNA notably inhibited protein expression of HIF-1α and VEGF in siRNA treated CAL-27 cells at 48 hours. Moreover, both tumor growth and tumor weight were markedly reduced in mice treated with HIF-1α siRNA (31).

There was a notable reduction in tumor volume in tumor implanted mice transcutaneously supplied with CO2. Expression level of VEGF was also significantly lower in the CO2-treated mice as compared to control group (32).

Conclusion

Oral cancer is genomically complex and substantial fraction of information has been added into existing pool of knowledge related to versatile regulators of oral cancer development and progression. VEGF mediated signaling is widely studied in oral cancer and tremendous breakthroughs have been made in development of different therapeutics against oral cancer. Natural products have shown efficacy and noted to be exert tumor suppressive effects via inhibition of VEGF and VEGFR both at mRNA and protein level. It will be essential to study effect of different phytochemicals in preclinical models for a better understanding of the mode of action of these chemicals. MicroRNAs (miRNAs) are still insufficiently studied in oral cancer. In-depth analysis of the miRNAs which negatively regulate VEGF and VEGFR will be helpful in the development of miRNA mimics to effectively treat cancer. Similarly, identification of miRNAs which promote VEGF induced signaling will be useful for the development of inhibitors against these miRNAs. Oral cancer is difficult to target and future studies must converge on deeper analysis of positive and negative regulators of VEGF signaling. More importantly different chemicals epigenetically modify various genes involved in VEGF mediated signaling and anti-apoptotic mechanisms. There reconceptualization of genetics, epigenetics and proteomics will improve clinical efficacy of different therapeutic interventions.

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