REVIEW ARTICLE

A Review on the Role of Vascular Endothelial Growth Factor Receptors in Human Papilloma Virus-related Oral Squamous Cell Carcinoma

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ABSTRACT

Oral squamous cell carcinoma (OSCC) is a neoplasm at the epithelial lining of the oral cavity that is prevalent worldwide. Smoking tobacco and consumption of alcohol are the main risk factors for OSCC. However, human papillomavirus (HPV) could also be an aetiological factor for OSCC. Transmission through urogenital contact increases the risk of developing OSCC, especially in developed countries. HPV-related cancer displays different pathogenesis and clinical outcomes. HPV through its oncogene E6 and E7 play a critical role in carcinogenesis by disrupting the DNA repair mechanism and cell cycle. Increased expression of VEGF ligand in HPV-related cancer has been reported in numerous studies. In OSCC, VEGFRs, i.e., VEGFR-1, VEGFR-2, and VEGFR-3, are overexpressed, with a higher expression on VEGFR-2. In HPV-infected OSCC, HPV is associated with VEGF expression. However, VEGFRs show no such association. This review highlights the possible role of angiogenesis in the progression of HPV-related OSCC. Also, it discusses how VEGF/VEGFR regulated the angiogenic activity caused by the HPV infection. Data on VEGF/VEGFR associated with HPV status is limited, and their role in OSCC progression remains unclear. Elucidating the mechanism of angiogenesis in HPV-associated OSCC may help develop strategies for OSCC-targeted therapy.

Keywords
HPV, OSCC, VEGFR

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INTRODUCTION

Oral squamous cell carcinoma (OSCC), which emerged from the epithelial lining of the oral fissure, is a locally aggressive tumour with an increased rate of metastasis and risk for recurrence.[1] The number of new cases increases globally, especially in South-central Asia.[2] While smoking and betel quid chewing are highly associated with OSCC risk factors among the Asian population[3], numerous studies reported a connection between human papillomavirus (HPV) infection and OSCC.[4] HPVs are divisible into low- and high-risk genotypes based on their likelihood of developing OSCC with two common high-risk oncological factors, i.e., HPV-16 and HPV-18.[5] Comparatively, the HPV-positive OSCC subgroup showed a higher five-year survival rate, indicating that HPV-positive OSCC possessed a better prognosis than HPV-negative OSCC.[6] Examples of well-characterised viral oncogene HPV-16/18 proteins required for OSCC progression are E6 and E7.[7]

Activating HPV E6 and E7 increases the autocrine of HPV-infected cells. These cells stimulate the proangiogenic vascular endothelial growth factor (VEGF).[8] Also, VEGF receptor (VEGFR)-1, VEGFR-2, and VEGFR-3 are consistently expressed in OSCC, with a predominant overexpression of VEGFR-2.[9] However, the mechanism by which HPV E6 and E7 proteins mediate VEGF/VEGFR signalling in OSCC development remains unclear. Thus, this review highlights the importance of angiogenesis in the progression of HPV-related OSCC. Additionally, this review discusses the role of VEGF/

VEGFR in controlling the angiogenic activity in the development of HPV-related OSCC.

Incidences of OSCC and its risk Factors

In 2020, the International Agency for Research on Cancer reported an increase in the worldwide burden of OSCC, with considerably more prevalence in developing countries than in developed ones.[10] In 2018, the global estimation showed that Asia accounted for 64.2% of the 354,864 new cases of lip and oral cavity cancer.[11] In 2020, the number of new cases of OSCC in Southeast Asia is about 18,381 cases with 11,297 cases involving men and 7,084 cases for women.[12] In general, OSCC was prevalent throughout Asia and the Pacific Islands. Papua New Guinea had the highest prevalence.[13] In India and Sri Lanka, it is the top cause of cancer mortality among males.[14] OSCC patients now have a 60% five-year survival rate in developed countries, such as the United States of America, due to advancements in diagnostic and treatment approaches.[15] Unfortunately, the survival rate in developing nations was lower, i.e., between 48.4 and 55.9%[16,17], suggesting that further improvements are necessary to enhance the clinical result for OSCC.

OSCC has been related to several established risk factors. HPV infection which is transmitted via sexual interactions is a significant risk factor for OSCC.[18] HPV infection transmits through urogenital contact which reflects towards sexual behaviour of the community. An increased number of sexual partners have been associated with a high prevalence of HPV infection.[18] Higher cases were reported in developing countries due to differences in socio-economic status and lifestyle.[12] This could be seen in the attributable fraction of HPV-related head and neck cancer worldwide such as 60% in the Republic of Korea, 51% in North America, 50% in Eastern Europe, 46% in Japan, 42% in North-Western Europe, 41% in Australia/ New Zealand, 24% in South Europe, 23% in China, 22% in India, and 13% in elsewhere.[12] Even though, HPV-related carcinoma is more prevalent in western countries, recent studies show that there is an increase of HPV-related OSCC in Southeast Asia such as in Thailand and Indonesia.[19,20] This is due to socioeconomic growth in these countries in the past decade.

Although there are over 200 distinct HPV strains, HPV-16 and HPV-18 are carcinogenic and are frequently associated with OSCC.[21] In Malaysia, there were 1,975 reported cases of OSCC from 2012 to 2016[22] with over 60% of them were diagnosed at advanced stages which are the third and fourth stages. Such a late diagnosis was primarily associated with a lack of awareness, late presentation of the symptoms, and delayed referral by medical professionals.[23] Recent study shows a significant correlation between HPV and OSCC, suggesting that HPV16 was the most prevalent genotype among Malaysian patients with OSCC.[24] In the state of Kelantan, Malaysia, 41 tissue specimens from OSCC patients in Hospital Universiti Sains Malaysia from 2005-2015 shows 10% of HPV-16 positivity.[25] Compared to tobacco-related OSCC, HPV-linked OSCC showed a better prognosis and responsiveness to chemo-radiation treatment.[26] Thus, an early diagnosis and greater awareness of HPV-related OSCC subtypes may reduce patients' mortality.

HPV and OSCC

Of all reported cases of OSCC, 24.2% was due to high-risk HPV subtypes worldwide, and HPV-16 and 18 accounted for 84.9% of cases in developed countries.[27,28] Numerous molecular techniques, including polymerase chain reaction, p16 immunohistochemistry, and *in situ* hybridization, were used to detect HPV in patients. In general, HPV-16 and 18 were the most frequent subtypes.[29]

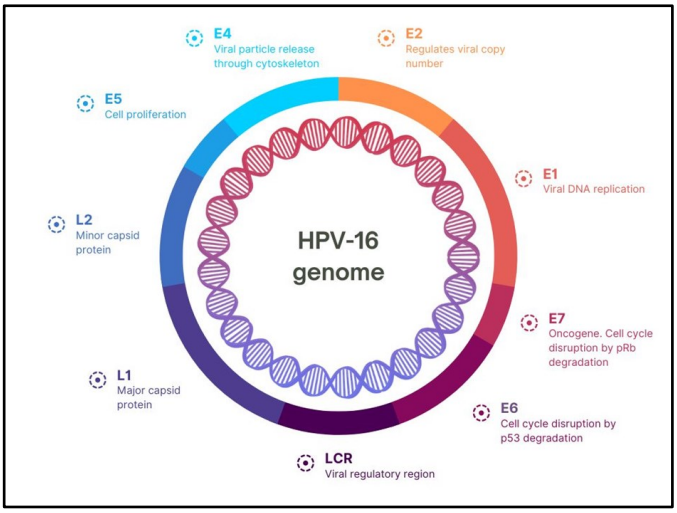

Figure 1. HPV-16 genome structure and its function.

HPV is a double-stranded DNA virus relegated to the family Papillomaviridae. Its genome contains 8,000 base pairs of DNAs and is divided into three distinct regions; the early region (E), late region (L), and long-control region (LCR) (Figure 1). The E region comprises seven genes, designated E1 to E7.[30] The L region contains the structural proteins, comprising L1 major viral capsid and L2 minor viral capsid. Both L1 and L2 encode the structural proteins for forming viral capsids in the final stage of the replication. In comparison, LCR contains DNA sequences that serve as promoters and enhancers, regulating viral replication and transcription.[31] Among these HPV genomic structures, E6 and E7 are linked to malignancy formation[32]; their roles in carcinogenesis are elaborated below.

HPV and carcinogenesis

The E6 and E7 proteins are about 100 and 150 amino acids in length. They are crucial in carcinogenesis through the evasion of cell death, deregulation of the cell cycle, modulation of the immune system, mediate cell invasion characteristics, and cause genomic instability of the host genome.[33] Since the E6 and E7 proteins of high- and low-risk HPV function differently, their biological behaviours vary. In the most common cell alteration of HPV-induced cancer, the E6 and E7 proteins of high-risk HPVs degrade the tumour suppressor pathways of p53 and pRb (retinoblastoma) proteins, respectively. By contrast, these proteins show a weaker binding ability in low-risk HPVs types, with no degradation of p53 or pRb.[34]

As a tumour-suppressor gene, p53 functions as a nuclear transcription factor, transactivating many target genes in the induction of cell cycle arrest and, or apoptosis.[35] When DNA damage occurs, p53 expression increases, activating the downstream target p21 and signalling the cell to enter cell cycle arrest. Thus, p53 could effectively stop cell growth or induce apoptosis. In HPV infection, E6 degrades the p53 gene, leading to tumour development.[36] A complex, composed of E6 and an E6-associated protein (E6AP), degrades the p53 gene. This E6AP functions as an E3 ubiquitin ligase, ubiquitinating and directing p53 to the proteasome for degradation (Figure 2), thereby inhibiting apoptosis.[21]

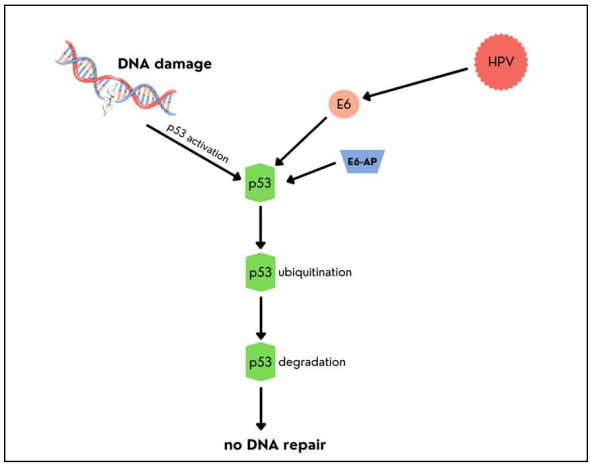

Figure 2. Role of E6 in p53 degradation preventing DNA repair. When DNA damage occurs, p53 will initiate the DNA repair process. However, combination of E6 and E6-associated protein induces p53 ubiquitination.

The retinoblastoma (Rb) protein is active in the hypophosphorylated state. It inhibits the S-phase entry by binding to E2F transcription factors. The phosphorylated retinoblastoma (pRb) is phosphorylated by cyclin D1/cyclin-dependent kinase 4 (CDK4) and cyclin E/CDK2 complexes. These complexes dissociate pRb from E2F and the subsequent progression to the S-phase. The E7 protein of high-risk HPV binds to pRb, preventing it from interacting with E2F.[37] As a result, the checkpoint control at the G1/S transition is lost. Cells continue to traverse the cell cycle uncontrollably.

HPV and OSCC development

OSCC is persistently associated with high-risk HPV infections.[31] HPV-positive and HPV-negative OSCC differ in tumour differentiation, p53 pathway involvement, response to chemotherapy, and prognosis. Moderately differentiated OSCC is usually seen in HPV-negative OSCC while HPV-positive OSCC shows poorly differentiated tumour.[38] In general, HPV-positive OSCC shows no mutation of p53, while HPV-negative OSCC exhibits genetic alteration of p53.[37] For responses to chemotherapy and prognosis, HPV-positive OSCC shows a better prognosis than HPV-negative OSCC.[39] Zooming into investigating these differences may allow researchers to gain insight into potential new molecular targets and pathway involvements for treating them.

ANGIOGENESIS IN CANCER

Angiogenesis is a natural physiological process required for embryonic development, wound healing, and creating vessels to increase organ perfusion. It is a complex process regulated on a local and systemic level by endogenous chemical signals, including the coordinated activity of endothelium and smooth muscle cells. New blood vessels are generated upon the disruption of a blood artery by extending the current vascular tree via endothelial cell sprouting. This process is divisible into several stages, which are as follows: production of proteases, migration of endothelial cells, development of vascular tubes, anastomosis of newly created tubes, synthesis of a new basement membrane, and integration of pericytes and smooth muscle cells.[40] However, pathogenic conditions that increase angiogenesis may exist.[41]

Numerous factors may induce angiogenesis. They include VEGF, angiogenin, tumour necrosis factor-α, transforming growth factor (TGF)-α, TGF-β, basic fibroblast growth factor, platelet-derived endothelial growth factor, placental growth factor, granulocyte colony-stimulating factor, and interleukin-8.[40] Angiogenesis is a hallmark of cancer development. Tumour growth and metastasis require the delivery of nutrients to the tumour microenvironment.[42] Without sufficient numbers of new blood vessels, known as an angiogenic switch, the tumour's growth may be constrained.[43]

The tumour microenvironment regulates itself through activating tyrosine kinase receptors, such as VEGFR, platelet-derived growth receptors, fibroblast growth factor receptor, and epidermal growth factor receptor.[40] The interaction between VEGF and VEGFR is critical for pro-angiogenic activities, including mitogenic activity on endothelial cells, increased vascular permeability, and cell migration.[44] Thus, cancer treatment may benefit from targeting angiogenesis and its regulatory signals.

Additionally, hypoxia is crucial in regulating VEGF expression in both healthy and malignant cells. The hypoxia-induced response of VEGF is primarily regulated by the transcription factor hypoxia-inducible factor-1 (HIF-1)[45], which comprises two subunits: HIF-1α and HIF-1β. Only HIF-1α is activated in response to low oxygen tension. Under normoxia, oxygen-dependent prolyl hydroxylases hydroxylate two prolyl residues (i.e., Pro402 and Pro562) of the HIF-1α subunit.[46] The hydroxylated protein is targeted for degradation by interacting with the von Hippel-Lindau (VHL) proteasome pathway. Prolyl hydroxylation is inhibited during hypoxia, preventing VHL-mediated degradation and causing the accumulation of HIF-1α within the cell. Consequently, HIF-1 target genes, including VEGF, are activated.[47]

VEGF/VEGFR and HPV-related OSCC

Angiogenesis is mediated through VEGF signalling that plays a critical role in tumour growth and invasion. In OSCC, the expression of VEGF upregulates according to tumour differentiation as poorly differentiated tumour shows higher VEGF expression.[48,49] With regard to HPV status, HPV-16 E6 and E7 oncoprotein had shown to induce higher VEGF expression through PI3K/Akt signalling pathway in non-small cell lung cancer.[50] VEGF levels were also increased in HPV-positive cervical cancer tissues.[51] However, the study of immunohistochemical expression of VEGF with regard to HPV status in oral and oropharyngeal cell carcinoma shows no significant difference in VEGF expression to HPV status.[52] Further analysis of VEGF expression with regard to HPV status needed to be performed using more robust detection method such as ELISA on OSCC samples to validate the VEGF expression in HPV-related OSCC.

On the other hand, VEGFR-1, VEGFR-2, and VEGFR-3 are overexpressed in OSCC cells in 88% of the clinically examined human specimens[53], suggesting that VEGFRs are crucial targets for OSCC treatment. In particular, VEGFR2 is biologically the most crucial receptor for VEGF in angiogenesis.[54] A study on selective small molecule inhibitors on VEGFR-1 expression in HPV positive and negative of oropharyngeal, laryngeal and cervical squamous cell carcinoma shows that VEGFR-1 expression increases in HPV positive cells following treatment with nilotinib, dasatinib, erlotinib and

gefitinib.[55] Recent study on VEGFR-2 expression in HPV -positive and negative OSCC reveals significant different in VEGFR-2 expression between blood vessels of tumour regions and tumour-free region in HPV-positive group.[56] However, the expression VEGFR-2 is said to be higher in HPV-negative tumour cells as compared to HPV-positive.[56] Further data is required to evaluate the VEGFRs level with regard to HPV status in OSCC as various findings were reported despite of having the same genomic interaction involved in HPV-related cancer.

CONCLUSION

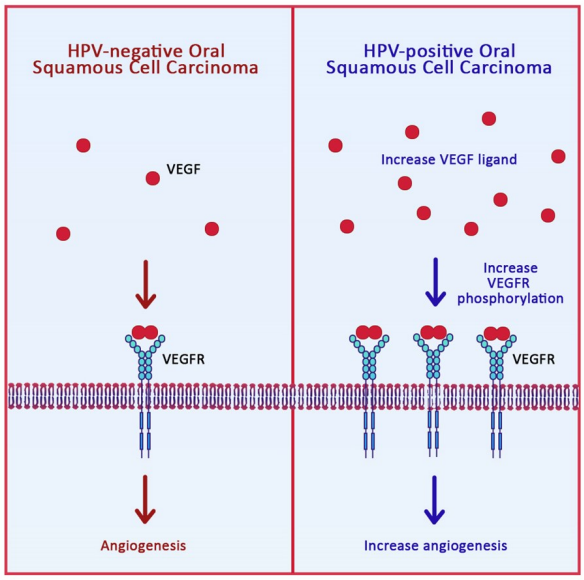

Figure 3. The possible mechanism on how HPV increase the angiogenesis process in tumour through VEGF/VEGFR pathway.

Overall, all three VEGFRs, i.e., VEGFR-1, VEGFR-2, and VEGFR-3, were consistently expressed in tumour cells, with VEGFR-2 overexpression predominating. In OSCC, overexpression of VEGF could be associated with HPV infection (Figure 3). However, such an association was not known for VEGFRs. Similarly, the mechanism by which E6 and E7 oncoproteins of HPV mediate VEGF/VEGFR signalling in OSCC development is unclear. Based on the association of HPV infection with VEGF expression and VEGF/VEGFR signalling mechanism, VEGFRs might overexpress in HPV-infected OSCC (Figure 3). This overexpression was probably due to the stimulation of the viral oncogenes, E6 and E7. These genes increased the autocrine mechanism of HPV-infected cells, exciting the proangiogenic factor VEGF. Data on VEGF/VEGFR associated with HPV status are limited, and their role in OSCC progression remains unestablished. Elucidating the angiogenesis mechanism in HPV-associated OSCC may aid in developing strategies for OSCC-specific treatment.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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