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Review Article

A Short Review of Biologic Aspect of Human Papilloma Virus (HPV) in Head and Neck Region

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ABSTRACT

Human Papillomavirus (HPV) is a small DNA virus of ~55nm in diameter, which infects the squamous epithelium of the skin or mucosa and can lead to pathologies ranging from infections to benign or malignant lesions. Although high-risk HPVs have been detected in malignant and potentially malignant oral lesions, they have also been found in the normal oral mucosa. Understanding the role of HPV in oral carcinogenesis is complicated by different frequencies varied from 0-100% in premalignant and malignant lesions, probably due to differences in sampling or analyzing methods. HPV-positive oropharyngeal squamous cell carcinoma (OPSCC) is genetically distinct from HPV-negative cancer with respect to patterns of loss of heterozygosity, chromosomal abnormalities, and gene-expression profiles. A better understanding of HPV and its associated lesions are essential for the development of HPV targeted strategies.

Key words: Human Papillomavirus, HPV, DNA virus, oropharyngeal squamous cell carcinoma (OPSCC).

INTRODUCTION

Viruses are the smallest obligate intracellular infective agents that contain only one type of nucleic acid either DNA or RNA as their genome. Viral diseases range from minor ailments such as common cold to terrifying diseases such as AIDS or fatal encephalitis. [1] Papova viruses are a highly diverse group of viruses which are small, naked, icosahedral particles having a double-stranded DNA genome. The family Papovaviridae consists of two subfamilies or genuses, the Papilloma viruses (PV) containing human and animal viruses, and Polyoma viruses which contains the simian vacuolating virus. Papilloma viruses have co-evolved with their respective hosts over millions of years and have led to the heterogeneity of HPV family. Currently; more than 200 different HPV types have been identified on the basis of genomic nucleotide sequence homology. [2]

Human Papillomavirus- Evolution

Research on papillomaviruses began more than 100 years ago. One of the earliest work was by McFadyean and Hobday (1896, London) who demonstrated cell-free transmission of canine warts. Reports of HPVs have been driven not by these extensive in apparent infections, but by the severity to which HPV associated disease can progress. A number of cases of malignant conversion of genital warts in the medical literature have resulted in speculation on a possible causal role of HPV infections in cervical cancer. [3] Harald ZurHausen was the first to demonstrate that HPV can cause cervical cancer [4] and proved that HPV 16 and 18 were consistently found in 70 % of cervical

cancer leading to the successful production of HPV vaccine. [4]

In 1951, a Canadian cytologist Ernest Ayre described and demonstrated squamous epithelial cells with a 'perinuclear halo' in smears from the uterine cervix. Ayre proposed that these squamous cells with 'halo' were 'precancer cells and some long-standing infection was responsible for the appearance of these cells. Koss and Durfee, in 1956, named these squamous cells with perinuclear halo, as "KOILOCYTES", from the Greek word 'koilos' meaning 'hollowcell'. [5] In 1968, ultrastructural studies showed presence of viral particles within koilocytes and it was established these are virus infected squamous cells. E5 protein is found to have a role in its formation. [5]

Virus Structure and Genome Organization

Papilloma viruses share a common non enveloped icosahedral structure, despite different disease associations. These are DNA viruses of approximately 8000 base pairs with a diameter of 52–55nm and are enclosed in an outer capsid of viral protein. [4] The viral capsid is composed of 72subunits, which are arranged in symmetrical, icosahedral pattern that gives the individual virionan almost spherical shape on electron microscopy. The capsid contains two structural proteins which are important targets of immune response to infection. [3,6,7]

HPVs have a closed circular, double-stranded DNA genomes with a nucleotide length of about7.9 kb and a molecular weight of about 5.2 x 10 6 Daltons. The PV genomes are functionally divided into two long domains and reveal a well preserved genomic organization. All putative open reading frames (ORF) that code for the viral proteins are transcribed from a single DNA strand. [3,6,7] The second strand which is apparently noncoding, contains only short ORF s which are conserved regardless of localization and composition.

The ORF can be divided in to three functional parts and include an early region that encodes nonstructural viral regulatory proteins (45 %); a late region that encodes 2 structural proteins L1& L2, (about 40 %) and long control region (LCR 15 %) with no coding capacity. [6] Early genes are expressed shortly after infection, and includes regulatory genes E1, E2, E4, and oncogenes E5, E6 & E7. [3] The early viral genes E1 and E2 are well conserved and play an important role in viral genome replication and transcriptional gene regulation. [8] Oncogenes E5, E6 & E7 have roles in driving viral cell cycle entry, immune evasion and virus release, thus promoting unrestrained cell proliferation and progression of cancer. [7] HPV late genes L1 (55 kDa in size; 80% of total viralprotein) and L2 (70 kDa) are activated only during the final stages of the viral cycle. LCR is present between the 5 end of the E region and 3 ends of the L region, with no coding capacity representing about 15 % of the viral genome. This region is also known as the non-coding region or upstream regulatory region which contains promoter elements and various transcription factor binding sites. [3]

Diversity of Papillomavirus

Over 200 different HPV types have been identified and completely sequenced, and are further divided into cutaneous types that infect the skin, and mucosal types that infect the mucosa. The HPVs are classified according to the DNA sequence of the L1 gene with individual one's having a nucleotide sequence that's at least 10% dissimilar from other. [2] The L1 gene is useful for the classification and construction of the phylogenetic trees, as it is reasonably well conserved and can be aligned for all the known PVs. The HPV types that infect the genital mucosa are grouped into the genus alpha-papillomavirus- the largest group, and the HPV types that infect the nongenital skin, are called cutaneous types. (Table 1) [2,3]

Classification can also be made in accordance with their relationship with cancer genesis oroncogenic risk, which may be high risk (HR), intermediate (IR) or low

risk (LR). LR types are associated with benign lesions such as warts, while infections with high-risk types progress to malignant lesions (Table 4). [9]

GENUS	Biological properties (*From de Villiers et al. (2004)*
Alpha-papillomavirus	Mucosal and cutaneous lesions in humans and primates High- and low-risk classification based on molecular biological data: High-risk types (pre- and malignant lesions) immortalize human keratinocytes; Low-risk types (benign lesions) do not.
Beta-papillomavirus	Cutaneous lesions in humans Infections exist in latent form in general population, activated under conditions of immune suppression. Also referred to as EV–HPV types due to close association with disease EV
Gamma-papillomavirus	Cutaneous lesions in humans Histologically distinguishable by intracytoplasmic inclusion bodies specific for type species

Table 1 showing various Papillomavirus genus and its biological properties [2]

ORF	*Function or product*
E1	Initiation of viral DNA replication
E2	Regulation of viral transcription
E4	Expressed late; disrupts cytokeratin and aids in virus release
E5	Interacts with growth factors; oncogenic for bovine papillomas
E6	Transforming protein, targets p53 degradation
E7	Transforming protein; complexes with retinoblastoma protein.
L1	Major structural protein; proposed immunogen for preventive vaccines.
L	Minor capsid protein

Table 2 showing function of HPV protein. [3]

Table 3 showing Identified Functions of HR- HPV Oncoproteins E6 and E7 [4]

Viral oncoprotein	*Investigators*	*Identified function*
E6	*Band et al. 1990*	Cell immortalizaion
	Werness et al.1990	Binding of E6-associated protein results in degradation of specific host cell proteins (p53) Antiapoptotic effect
	White et al. 1994	Chromosome destabilization
	Klingelhutz et al. 1996	Activation of telomerase
E7	*Munger et al. 1993*	Cell immortalizaion
	Arroyo et al 1993	Activation of cyclins E and A
	Dyson et al 1989	Inactivation of retinoblastoma related pocket proteins
	Puthenveettil et al. 96	Induction of apoptosis
	Jones et al. 1997	Inhibition of cyclin dependent kinase inhibitors
	Kessis et al.	Enhancement of foreign DNA integration and mutagenicity

Table 4 showing HPV types based on oncogenic risk

HPV $_{LR}$: 6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81, and 89
HPV $_{1R}$: 26, 53, and 66;
HPV $_{HR}$: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82

Although phylogeny provides insight into disease associations, closely related types can show discrete pathologies. Though HPV 6 & 11 share 85% sequence identity, HPV 11 is the primary cause of laryngeal papilloma while HPV 6 is more commonly associated with anogenital warts. [7] Similarly, HPV 13, which shares 78% sequence identity with HPV 6 & 11 does not cause either anogenital warts or laryngeal papillomae. [7] Epithelial tropisms of individual HPV types are controlled mainly at the level of viral gene expression, with regulatory elements within the long control region as an important determinant. Furthermore, successful infection requires conformational changes in the capsid followed by furin cleavge of minor L2 capsid protein which may also impact the affinity of specific HPV types. [7]

Risk factors for HPV infection

Epidemiological studies have obviously confirmed that in cervical cancer HR mucosa trophic HPV viruses are transmitted by sexual contact. The means by which HPV infection is transmitted to oral cavity and oropharynx are not firmly established. Oro-genital sexual contact, increased number of sex partners, HIV and HIV related immunosuppression, and smoking are the known risk factors for oral HPV infection. [8,12] Reported HPV infections in newborn babies of infected

mothers and children prior to the sexual activity are rare. [8]

HPV infection precedes the development of HPV-positive HNSCC: the presence of HR HPV in the oral mucosa significantly increases the risk of malignancy with a variable rate of predilection. The local microenvironment of the tonsil and base of tongue trap HPV viral particles and provide an optimal setting for infection to occur. [8] HPV-positive OPSCC, report absence of classical risk factors as tobacco and alcohol exposure compared to HPV negative patients. However, Park's study showed that smoking and drinking alcohol help in promoting HPV invasion, as it alters a wide range of immunologic functions in the oral cavity including adaptive and innate immune responses. HIV affected individuals show multiple recurrences of infection, which appears to reflect an increased risk of progression from subclinical to clinical HPV infection. Moreover, studies suggest an elevated risk of HPV-related cancers as explained by the effects of HIV-related immunosuppression; and altered sexual behaviors. [12]

Increased susceptibility to HPV infections are also been reported with a syndrome named WHIM, an acronym designation for a rare autosomal dominant syndrome characterized by warts, hypogammaglobulinemia, infections, and retentions of mature neutrophils in the bone marrow. Multiple, disfiguring, cutaneous warts and susceptibility to HPV related dysplasia or carcinomais been reported in women. Cipriani et al have reported the occurrence of HPV related oral squamous cell carcinoma in two siblings with WHIM syndrome. [13]

Therefore, risk factors associated with precancerous and cancerous changes include early sexual debut, multiple sexual partners, oro-genital sexual contact, associated HPV & HIV infections, immunosuppression, nutritional deficiencies, genetic factors, low socioeconomic status, tobacco and alcohol usage.

What Differentiates High risk from Low-risk HPV?

Infections by LR HPV types, induce benign warts that rarely progress to malignancy whereas, lesions by HR types has the potential for malignant transformation. Both HPV types infect keratinocytes and induce virion production upon differentiation, but varied biologic action of E6 and E7 oncoproteins makes the difference.

HR HPV infection can cause a "silent" or asymptomatic infection in which viral particles remain in the basal layer without development of disease, or can alternatively lead to some productive lesions [14] such as low grade dysplasia C1N1 [cervical intraepithelial neoplasm] in which viral expression is regulated as the infected cells differentiate. [10] In some cases, infection can lead to higher-grade neoplasia such as CIN2 and CIN3, with deregulated viral gene expression and added secondary genetic changes. [11]

E6 and E7 proteins of HR HPV can inactivate tumor suppressors p53 and retinoblastoma protein (pRb), which prompts accumulation of genetic errors in cell cycle regulatory genes (Table 2& 3). [7] Though E6 protein cannot bind to p53 by itself, it can bind to a cellular ubiquitin ligase named E6AP, which make ternary complexes with p53 and becomes ubiquitinated. E6 protein has functions independent of p53 inactivation, for instance, ubiquitin ligase E6AP also cause the activation of telomerase which leads to cell immortalization. In addition, HR HPV E6 can interact with PDZ-domain *(Post-synaptic density 95, Drosophila Discs-large, and Zonula occludens-1*containing proteins through its *C*-terminal motif, leading to their degradation. This ability of E6 is important for cell transformation as PDZ-domain-containing proteins are involved in a variety of cellular functions such as cell signaling and cell adhesion. Most recently, it has been found that E7 promotes *C*-terminal cleavage of pRb by the calcium-activated cysteine

protease calpain, which in turn leads to p-16 up-regulation. [3,6]

LR HPV in keratinocytes maintain viral episomes in their productive life cycle, but have a lower transforming activity and do not induce genomic instability. LR E7 binds to Rb but with a greatly reduced affinity compared to HR E7, and this is due to a single differing amino acid residue. Moreover, LR E6 does not show any efficient interaction with p53, PDZ binding domains and does not induce telomerase activity. [3,6]

Carcinogenic Mechanism of HPV

On the basis of molecular and epidemiologic basis International Agency for Research on Cancer have recognized HR HPV 16 and 18as carcinogenic in humans. [15] HPV owes its oncogenic potential to its ability to insert early genes (E6, E7) into the host cellular genome. [8] Through wounds or abrasion, the Papilloma viruses infect undifferentiated basal epithelial cells as these are the only actively dividing cells in the epithelium. The infectious cycle of these viruses is tailored to the differentiation program of the target cell. E1/E2 proteins are important for initial amplification phase and E6/E7 mediated proliferation allows an expansion of the lesion. [8] TheE6 protein induces degradation of p 53 tumor suppressor protein via ubiquitin-mediated process while E7 oncogenes inactivate retinoblastoma gene involved in cell cycling. This leads to the destruction of tumor suppressor factor function, inhibition of apoptosis and cell cycle regulation which is considered to be the onset of HPV mediated carcinogenesis. As a result of these virus induced changes, HPV related OPSCCs does not need many mutations to undergo the malignant transformation as compared to HPV unrelated OPSCCs. [15,16]

Characteristics of HPV related OSCC

Head and neck cancer is the fifth most common cancer diagnosed worldwide and the eight most common cause of cancer death. Since 1970 the incidence rates of some OPSCCs, particularly those of tongue base and tonsil have risen steadily in the USA and Northern Europe especially in younger patients without recognized risk factors. [17] Even though HPV related OPSCCs are seen in an advanced stage, improved survival and treatment response are distinguished in such cases. [21, 22]

Five-year relative survival rates of HPV positive and negative OPSCC; independent of age, gender have been reported between 70-80% and 25-40 % respectively. [18] HPV-positive cases are genetically distinct from HPV-negative cancers with respect to patterns of loss of heterozygosity, chromosomal abnormalities, gene-expression profile, inverse correlation with biomarkers and higher rates of response to therapy among patients with HPV-positive cancer. The higher survival rate among patients with HPV positive cancer is due to greater local regional control and higher intrinsic sensitivity to radiation. Possible explanations may be inactivation of p53 and pRB along with p16 upregulation by high risk HPV E6 and E7 proteins.

Crucially, the model eliminates the need for mutational inactivation of p53 and pRB; leaving these tumor suppressor genes essentially intact. The presence of intact p53 may, therefore, be one mechanism whereby removal of HPV E6 and E7 expression leads to the restoration of apoptotic pathways rendering the tumor more sensitive to chemoradiation treatment. [18,19] Tobacco and alcohol-related head and neck cancers would have mutations in p53 and pRB, deleting the activity of these pathways. The absence of "field cancerization" may be another factor leading to a better prognosis for HPV+ cancers. [20]

Therefore, potential factors contributing to improved outcomes in patients with HPV positive OPSCC include the presence of wild-type p53, HPV oncogene modulated genomic instability, an absence of field cancerization, viral specific antitumor immunity, and alterations in tumor microenvironment resulting in less tumor hypoxia. [8]

Literature evidence for HPV involvement in OPSCC:

Syranjen et al gave the first report suggestive of viral etiology in oral squamous cell carcinoma in 1983. [9] A couple of years later, Loning et al confirmed presence of HPV DNA in oral premalignant and malignant lesions using in situ hybridization. [22] Syrjanen's observations in 1983, the reported prevalence of HPV DNA in oral cancer tissues has varied from 0-100%. Lack of clarity could be due to non-standardization, different detection techniques, sampling and storage. [4]

Meta-analysis on HPV prevalence in non-controlled studies published between 1982 and 1997showed that HPV was 2-3 times more likely to be detected in oral precancer lesions, and 4.7times in oral carcinomas when compared to normal mucosa. Miller et al., using in situ PCR studied 30 SCCs and presented that HPV is distributed in scattered foci throughout the epithelium, suggesting a non-clonal origin of the tumor. [21] HPV 16 is the most common type found in 87 to 90 % of HPV positive OPSCC and as a co-infection, it was associated with HPV56. [21] Balram et al have reported a high prevalence of HPV-16 and 18 (42% & 47% respectively) in their study on oral cancer from Indian betel quid chewers. [5] Syrjanen et al, in his systemic review to calculate the pooled risk estimate for the association of HPV with OSCC, found a significant association between HPV and OSCC and even for HPV 16. [4]

Methods of investigation of HPV

A technique generally used to detect any papillomavirus infection has its own advantages and disadvantages. They vary greatly in sensitivity and in specificity. None of the tests can be labeled as an ideal method to be used as a diagnostic tool. Various non-molecular techniques for the detection of genital HPV infection includes visual inspection, colposcopy, cytology, and histology - however, they do not detect the factual presence of HPV. Cytology and histology are indirect methods that detect the clinical sequelae of an HPV infection, then to be correlated with the presence of HPV. Several possible molecular techniques which are available at present with its pros and cons are reviewed. [23] (Table 5)

Table 5 shows brief description of methods of investigation of HPV [21]

Methods	Pros & Cons
Immunohistochemistry (p16 IHC)	Commonly performed in clinical laboratories, Highly sensitive. May be elevated in HPV-negative cases
Insitu Hybridization (ISH)	Highly specific and can be performed on paraffin-embedded sample. Low sensitivity for tumors with low numbers of copies of the HPV genome
Polymerization chain reaction (PCR)	Highly specific and fast turnaround time. False-positive results
Reverse transcriptase PCR (RT-PCR)	Sensitive and specific. Better results from fresh or frozen tissue than from paraffin-embedded tissue

Immune responses to HPV-associated lesions

Papillomavirus life cycle and organization in the infected epithelium play a role in its immune responses. The infectious cycle of these viruses is tailored to the differentiation program of the target cell. There is no cytolysis or cytopathic death as a consequence of HPV replication, assembly, or viral particle release because the keratinocyte is a cell destined for death and desquamation. Thus, HPV infection is not accompanied by inflammation, and there is no obvious "danger signal" to alert the immune system.

Effects on the immune system

HR-HPV infection makes the immune system more tolerant to the infection, thus creates a favorable microenvironment for cancer progression. The mechanisms that have been proposed and proved are as follows: Firstly, HR-HPV remains silent for a long time; its duplication and assembly do not cause cytolysis or the cytopathic death of the host cells. [24] Secondly, HR-HPV inhibits interferon (IFN) synthesis through E6 and

E7 oncoproteins interfering with its signaling pathways. [25] Thirdly, HR-HPV infection induces regulatory T cell infiltration and interleukin (IL-10) or transforming growth factor β (TGF-β) production. Fourthly, the infected cells express low levels of MHC class I, resulting in impaired cytotoxic T lymphocyte (CTL) function. Lastly, they could induce an accumulation of ineffective CD4 and CD8 T lymphocytes in lesional sites. [26]

Innate immunity affected by HR-HPV infection.

In the squamous epidermis macrophages, Langerhans cells (LC), keratinocytes, T lymphocytes, dendritic cells (DC), natural killer cells(NK) and B lymphocytes play important roles during an immune response to infection. Typically, once the HR-HPV contacts the mucosal epithelium, the innate immune mechanism mediated by the epithelial barrier twitches to conflict with it. Langerhans cells are immature DCs, and in the transformation zone, their numbers are significantly decreased. The mechanism proposed for this is the direct interaction of E7 with CCAAT/enhancer binding protein β, a transcription factor of chemokine ligand 20 (CCL20) which has a decisive role in the migration of LC precursors into the epidermis, thereby inhibiting the transcription of CCL20 and thus hindering its recruitment. [27]

Toll-like receptors (TLRs) are an important type of pattern recognition receptor located at the endolysosomal compartments. Their function is in sensing the bacteria or virus and triggering the associated innate immune response. HPV18 E6 and E7 down regulate TLR9 expression at the infection site, this is an important strategy for its seepage from immunosurveillance. In contrast to TLR9, theTLR3/5/8 pathways are activated in HRHPV infected keratinocytes. [28] HR-HPV infection compromises NK cell activation which is predominate at the initial stage of the infection and in the low-grade lesions. Levels of NK activating receptors, such as NKp30, NKp45, NKp46,

NKG2D, and NKp80, are significantly decreased in HPV16 cervical cancer. These receptors are closely associated with the low cytotoxic activity of NK cells, facilitating lesion progression and carcinogenesis. [29] The number of M2 macrophages is also significantly increased in many HPV associated lesions that can promote cancer cell proliferation and migration, angiogenesis and the restriction of immune defenses. [30]

Adaptive immunity affected by HR-HPV infection.

HPV infection compromises T cell activation which is the basis for the progression from HR-HPV infection to cancer. Cytotoxic T lymphocyte is the main agent in cancer-specific immunity, and it recognizes antigens with the assistance of MHC class I. HPV16 E5 could suppress CTL through the downregulation of MHC/HLA class I expression. [31] Distorted equilibriums between T helper cells (Th1) and Th2 cell is another property of cellular immunity during HR-HPV infection. Increased Th2 cytokine (IL 10) and reduced Th1 cytokine (IFN γ, IL 12, IL 2 and TNF α) levels have been detected in cervical exudates of HR-HPV+ patients. This indicates that reduced Th1 response and increased Th2response lead to cellular immunity suppression and cancer progression. [32]

HR-HPV E6 expressing cancer cells can inhibit the differentiation of monocytes into fully functional DCs. One of the mechanisms involved in the induction of compromised DC activation in HR-HPV infection is the stimulation of programmed death ligand (PD-L1) pathway by chronic HR-HPV infection in DCs. [33] There is generation and recruitment of Treg (Regulatory TCells) which are inducers of immune tolerance. Firstly, improper activation of the immune response induced by HR-HPV infection provides the possibility of the toleration of T cell generation. Secondly, the weakened innate

immune functions elicited by the infected keratinocytes create an immunosuppressive microenvironment, promoting HPV specific Treg expansion. [34] IL-10 is a Treg producing cytokine whose presence would decrease CD8+ T cell infiltration and increase the amount of intra-tumoral Foxp3+ Treg cells, a critical event for lesion progression. [35] Thus all these factors create an immune tolerant microenvironment for persistent infection and cancer progression.

CONCLUSION

The prevalence of oral HPV infections and HPV related OPSCC are expected to surpass that of invasive cervical cancers by the year 2020, therefore, the need for future HPV vaccination trials in both genders should be highlighted for OPSCC prevention. A better understanding of HPV associated lesions in carcinogenesis is necessary for the development of HPV targeted strategies.

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