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# Pathogenesis of Human Papillomavirus – Immunological Responses to HPV Infection

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## Abstract

Papillomavirus is an oncogenic virus which infects mucosal and cutaneous epithelia where it induces benign hyperproliferative lesions. Few studies have been conducted on the causative factors associated with the development of cancer. Infections by high-risk human papillomaviruses (HPVs) have been implicated as causative agents in a variety of cancers such as anogenital, and head and neck cancers. HPVs appear to have evolved mechanisms resulting in escape from host immune surveillance and delay of resolution of infection. The HPV E5 oncoprotein is one of the possible effectors that allows the virus to escape from host immune system through the downregulation of surface classical major histocompatibility complex class I (MHC I) and not the nonclassical MHC I. Lack of classical MHC I in infected cells expressing E5 would allow evasion of cytotoxic T lymphocytes (CTLs) killing and thus establishment and persistence of viral infection.

In this chapter we discuss the process of immunomodulation by HPV and review our recent discoveries on the association of HPV with cancers and its implication in medicine.

**Keywords:** cancer, HR-HPV, E5, MHC I, CTL

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## 1. Introduction

The global cancer burden is markedly increasing and is thus a leading cause of death, second only to cardiovascular disease [1–3]. Based on the most recent available data collected by the international agency for cancer, an estimated 14.1 million new cancer cases and 8.2 million cancer-related deaths occurred in 2012, compared with 12.7 million and 7.6 million, respectively, in 2008 [4].

The human body is dependent on regulated cell division and elimination which forms homeostasis within the body. Certain genes play vital roles in regulating the cell cycle. These genes are grouped into three categories, tumour suppressor genes (TSGs), proto-oncogenes and DNA repair genes. Any alteration in these groups of genes downregulates the cell control mechanisms and ultimately causes cancer cell development and malignant transformation [5]. Genetic changes in the progression of cancer typically affect two different types of genes, oncogenes (e.g., *Ras*) and TSGs (e.g., P53 and pRB). Both of the oncogenes and TSGs encode many kinds of proteins that play a key role in cancer induction. These genes control cell growth and proliferation, and mutations in these genes can contribute to the development of cancer.

Despite of the evolving medical significance of cancers, few studies have been conducted to identify the possible risk factors that implicated in the initiation of cancer. However, there are well-established risk factors that have been identified for its association with the development of cancer such as clinical, genetic and epidemiological factors. In addition, biological agents have been implicated in various cancers including viruses, bacteria and parasites.

Viruses have been the most studied in their relation to tumour formation. They are thought to be associated with 15–20% of all human cancers worldwide of which about 80% are cancers of the cervix and liver [6, 7]. Viruses have evolved multiple strategies to transform host cell. One common route is to alter the expression of cellular genes by integration of the viral genome into the cellular DNA. Viruses also help cause malignancy by introducing an oncogene into a cell to disrupt the regulation of cell division [8–10].

Infectious agents have been implicated, either as direct carcinogens or as promoters. Viral infections, in particular, human papillomaviruses (HPVs) are recognised as carcinogenic agents in humans and are responsible for a significant share of the global cancer burden [7, 11, 12].

HPVs are small double-stranded DNA oncogenic viruses of approximately 8 kbp. HPVs are ubiquitous in the human population, and occasionally infection leads to cervical cancer. Although the body is working to get the infection under control, HPVs infect and disturb cutaneous and mucosal epithelial cells of the anogenital tract, hands or feet which can lead to a variety of diseases with a range of severities depending on the types of HPV infection.

To date, over 100 different types of HPV have been identified, and about one-third of these infect epithelial cells in the genital tract. The type HPV family is divided into two categories: low-risk HPVs and high-risk HPVs (HR-HPVs). The low-risk HPV types such as HPV 6 and HPV 11 commonly cause benign genital warts (condylomas). These lesions can regress even without treatment [13], due to cell-mediated immune responses [14]. While the high-risk types of HPV which include HPV 16, 18, 31, 35 and 45 are associated with the development of anogenital cancers and found in up to 99% of all cervical carcinomas [15, 16]. These HR-HPV types cause benign genital epithelial hyperproliferative lesions, such as low-grade pre-malignant cervical intraepithelial neoplasia (CIN I). In most pre-malignant cases, lesions can regress even without treatment. However, in a limited number of cases, the lesions persist or progress to invasive cancer due to the lack or ineffective immunological responses.

It has been reported that the low-grade CIN I would progress to high-grade lesion (CIN III) and eventually invasive cervical cancer [17]. Consequently, the associations of the HPV infection in the development of cancer are an area of ongoing interest.

## 2. The host immune evasion by HPV

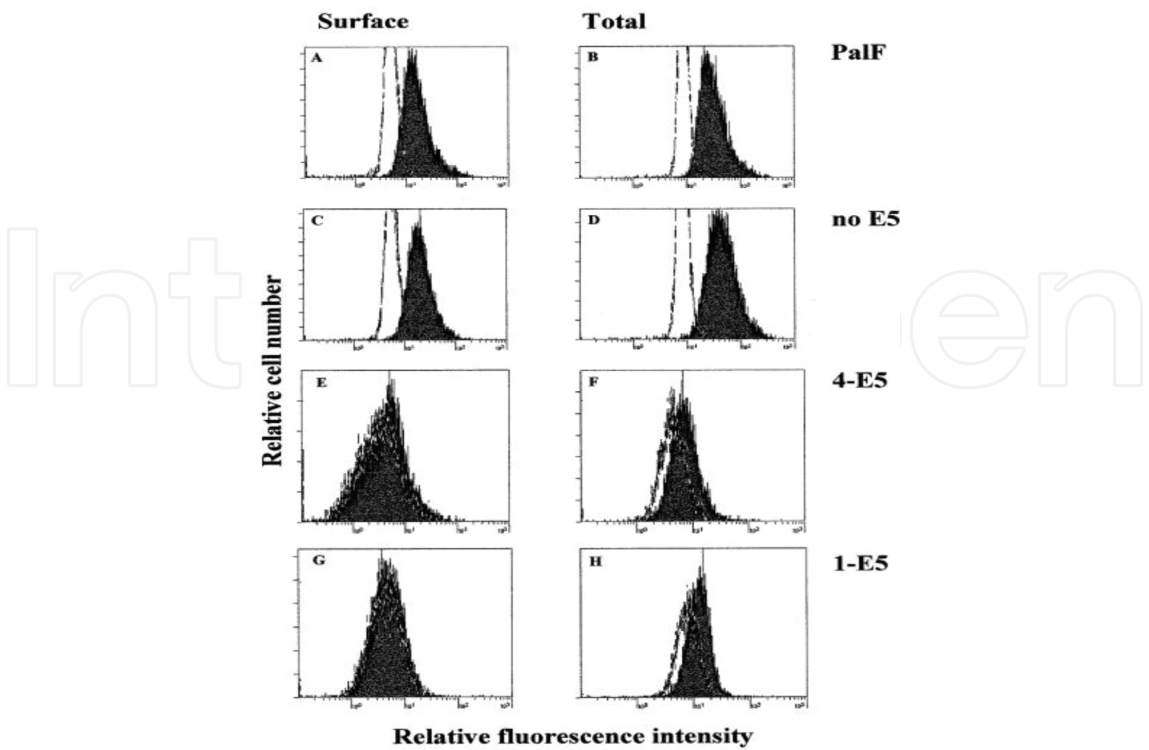
The papillomaviruses are small double-stranded DNA viruses which belong to the papillomaviridae family [6]. HPVs infect cutaneous or mucosal epithelial cells initiating benign or cancerous lesions that depend on the HPV types. The lifecycle, oncogenic characteristics and molecular-based evidence of HR-HPVs are suggestive of a causal role for cancer. HPV infections are normally cleared by the immune system; however, the persistence of HPV could trigger a progression to malignant lesion in the presence of other risk factors. For instance, it is well documented that the persistent infection of the cervix with HR-HPV types 16 and 18 is an initiating event of the cervical cancer [18, 19]. Therefore, the establishment, persistence of HR-HPV infection and evasion of the host immune system are necessary for premalignant lesions to initiate and progress towards squamous carcinoma [20–22].

The host immune response mechanism plays a significant role in controlling and limiting HPV infection. The suppression of HPV-induced lesion depends on the host inflammatory reaction and penetration of lymphocytes to the infected tissue [14]. Thus, the prevalence of HPV-induced lesions is higher in immunosuppressed individuals such as transplant recipients or human immunodeficiency virus (HIV)-infected patients [23, 24].

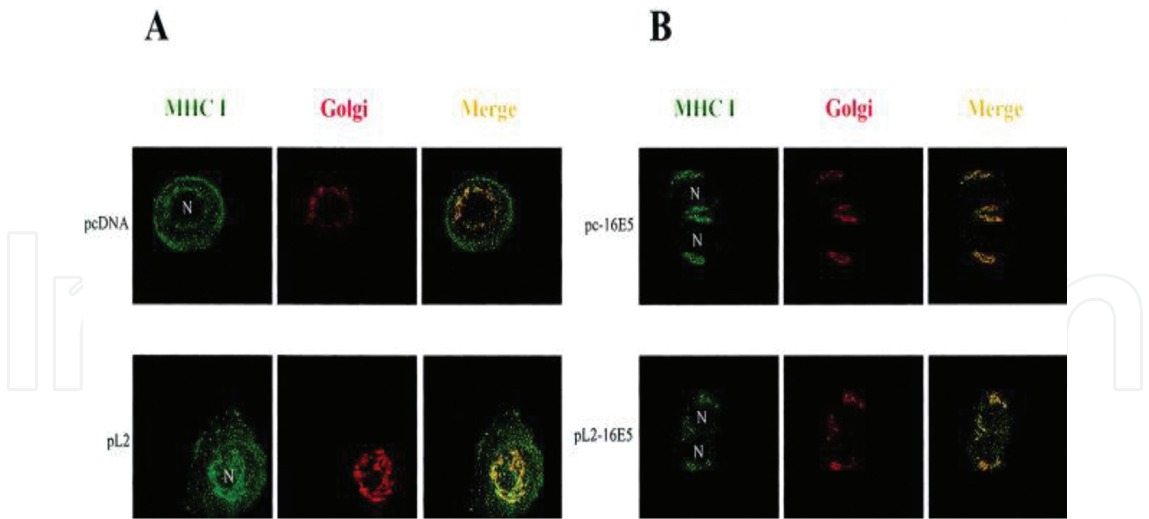
Lack of HPV clearance and persistence of viral infection for many months are necessary before the onset of an immune response. The reasons of this fact are still unknown. And perhaps one of the most important ongoing questions in the field of papillomavirus research is the latency of the host immune response in eliminating the virus in immunocompetent hosts as well as immunosuppressed hosts.

The nonlytic feature of HPV is one of the explanations for evading the recognition of HPV infection. HPV does not lyse the infected cell or cause viremia, and this will reduce the exposure of viral antigen to cell-mediated immunity and consequent lack of inflammation. HPV life cycle characterised by the physical evasion from the immune cells' recognition through HPV restoration and protection within infected cells' nuclei [25, 26]. Additionally, HPV has the ability to downregulate major histocompatibility complex class I (MHC I) and disrupt the interferon (IFN) pathway. HPV facilitates this mechanism using early oncoproteins, E5, E6 and E7, which have the ability to interfere and actively participate to the downregulation of host immune system. The role of E6 and E7 is to inhibit the production of IFN in natural killer (NK) cells or the expression of transporter associated with antigen processing (TAP) [27, 28].

E5 oncoprotein downregulates surface MHC class I by retaining it in the Golgi apparatus (**Figures 1 and 2**) [20, 29]. Downregulation of MHC class I has been observed with E5 from different PVs, including HPV-85 and HPV-16 (**Figure 3**), indicating that key functions of E5 are conserved between the PV species and HPV types [21].

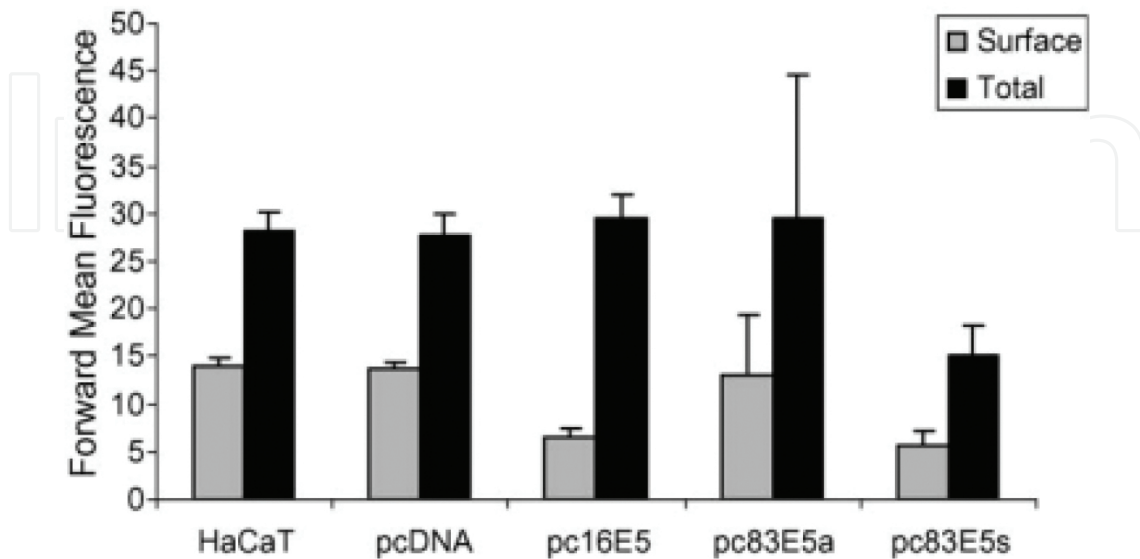


**Figure 1.** The expression of MHC I in control and transformed PalF cells using Define FACS as “Fluorescence-activated cell sorting” (A and B), control cells (C and D), 4-E5 transfected cells (E and F) and 1-E5 transfected cells (G and H) were incubated with anti MHC 1 antibody. Surface MHC I (A, C, E and G) and total MHC I (B, D, F and H) [29].



**Figure 2. Visualisation of the GA and MHC I.** HaCaT cells carrying empty vectors or cells expressing HPV-16 E5 were costained with anti-HLA class I antibody (mAb W6/32) and anti-golgi GM130 antibody (mAb 4A3) and analysed using Leica TCS SP2 fluorescence confocal microscopy. Representative cells are shown. (A) Control HaCaT cells carrying either pcDNA or pL2 empty vector. (B) HeCaT cells expressing HPV-16 E5 in either pcDNA (pc-16E5) or pL2 (pL2-16E5). N = nucleus [20].

## Down-regulation of MHC- I by HPV-83 E5



**Figure 3.** Total and surface expression of MHC-I using FACS analysis in normal HaCaT cells transfected with pcDNA (empty vectors), pcHPV16E5, HPV83-E5a (antisense orientation) and HPV83-E5s (sense orientation) [21].

E5 is the smallest HPV oncogenic protein that is located in the membranes of the endoplasmic reticulum (ER) and Golgi apparatus of the transformed cells. This hydrophobic protein is a structure of 83 amino acids in HR-HPV type 16, is expressed before the onset of viral replication. E5 contribute to cell transformation through interaction with several cellular proteins, including the epidermal growth factor receptor (EGF-R), the human receptor for colony stimulating factors (CSF-1). E5 may also reduce the processing and presentation of viral antigen through the interaction with 16 kDa subunit of the vacuolar H<sup>+</sup>-ATPase acidification of endosome [30].

The human MHC class I molecules are known as human leukocyte antigen (HLA) system, which have a critical function in the recognition of virally infected cells. The proteasomes and other cytoplasmic proteases are playing a role in viral protein degradation into short chain peptides of 8–10 amino acids long. HLA molecules and intracellular viral antigenic peptides complex are transported through the Golgi apparatus to the cell surface of infected cells where it is presented and recognised by the cytotoxic CD8<sup>+</sup> T cells. The activated cytotoxic T lymphocytes (CTLs) are able to destroy the infected cell through the mechanism of apoptosis that mediated either by granulate exocytosis (perforin and granzymes) or by Fas-Fas ligand interaction [26].

High frequency of virus-specific CTLs is a characteristic of persistent viral infection such as cytomegalovirus (CMV) and Epstein-Barr virus (EBV), however low frequency of HPV-specific CTL has been detected in CIN III and cervical cancer patients [31, 32].



CD4<sup>+</sup> T helper lymphocytes (Ths) are able to identify foreign antigens that presented on MHC class II molecules (antigen-MHC II complex). MHC class II molecules are mostly expressed on professional antigen presenting cells (APCs) such as dendritic cells, macrophages and B cells, but they can also be expressed on the epithelial cells (target for HPV) by IFN treatment.

T helper cells are capable of secreting cytokines that allow the proliferation and maintenance of cytotoxic lymphocytes. Additionally, they play a role in activation of B cells for antibody production, as well as dendritic cells for antigen presentation. Th cells potentially have an important role in cell-mediated immunity against HPV infection. The reactivity of HPV-restricted Th cells was found in patients with a persistent papillomavirus infection [33, 34].

While E6 and E7 are presented throughout the course of the HPV infection, their functions are necessary for the maintenance of a transformed status. Expression of E5 takes place in the early stage of papillomavirus infection and in the deep layers of the infected epithelium. Ashrafi et al. [29] were the first to report that E5 protein of HPV downregulates the classical HLA (A and B) but not the nonclassical HLA-E. This potentially allows the cell to escape CTL and also NK cells' killing [20].

The downregulation of MHC class I by E5 oncoprotein allows the infected cell to evade cell-mediated immune response and this potentially enables other HPV oncoproteins in the establishment and persistence of virus infection. Interestingly, it has been reported that the oncogenic E5 also inhibits the Fas receptor [35] and HLA II [36]. This strongly indicates that E5 might have additional major role in negatively regulating the immune response.

The downregulation of MHC I is an imperative mechanism to evade CTL-mediated immune clearance, however, the lack of surface MHC I will activate NK cells to attack and destroy the infected cells. Human NK cells express surface receptors (NKR) that interact with HLA class I molecules, including killer cell immunoglobulin-like receptors (KIRs) that mainly recognise classical HLA-C and also C type lectin receptors which identify nonclassical HLA-E molecule. In the absence of classical HLA-C and non-classical HLA-E, NK-mediated cell lysis would be inhibited due to the recognition of MHC class I molecules by their inhibitory receptors. Consequently, certain viruses, including HIV and CMV, have the ability to escape both CTL and NK cells' killing. HIV-negative proteins (Nef) and CMV US3/UL40 proteins have evolved to selectively downregulate HLA (A and B), the main presenters of peptides to CTLs, but not HLA-C or nonclassical HLA-E [37, 38].

### 3. HR-HPVs and cancers

HR-HPV types are considered as the most important aetiological factors for many types of cancers such as cervical cancer. The risk of cervical cancer has increased in parallel with the incidence of certain genotypes of HR-HPV. Therefore, the presence of these genotypes indicates a significant risk factor for the initiation and progression of almost 90% of cervical cancer cases [18].

Despite the medical significance of HR-HPV infection, there is still a lack of information on the incidence of cancers that are caused by different HR-HPV genotypes in different popula-

tions. An investigation on the incidence and distribution of HR-HPV genotypes in cervical cancer patients confirmed the presence of additional high-risk types (HPV-45 and HPV-39) other than common types (HPV-16 and HPV-18) [19].

Being a sexually contagious virus, HPV virus has the ability to spread through sexual and skin-to-skin contact. HR-HPVs have also been found to be the causative agents for almost up to half of vaginal, penile, anal and oral cancers. These findings suggest that HR-HPV virions might be spread from the original infected site to other organs and lead to cancer development in various organs [18].

To date, studies on the role of HPV in breast carcinogenesis have generated considerable controversies and it is still not clear whether HPV infection is implicated in breast cancer pathogenesis [39]. HPV infection is a sexually transmissible disease, and most breast cancers originate from mammary duct epithelia. Therefore, the relationship between HPV and breast cancer is imperative for many reasons. The exposure of the mammary ducts to the external environment increases the risk of HPV infection. Our unpublished data have shown the presence of HR-HPV types of viral DNA other than 16 and 18 in freshly collected human breast cancer tissue and this provides a solid basis to advance research in a crucial health problem affecting women.

These initial findings support the association of HPV and breast cancer and highlight possible causative agents of breast cancer. Therefore, further research is required to investigate whether HR-HPV infection plays a role in the pathogenesis of breast cancer. The information gained will pave the way to better awareness of breast cancer risk factors other than those recognised to date.

## 4. Conclusions

Identification of HPV pathogenesis offers means of therapeutic intervention targeted against HPV oncoproteins (E5, E6 and E7) which will facilitate early lesion eradication. This will also provide results central to our understanding of HPV pathogenesis and help elucidate early events in HPV infection that may determine persistence and disease development.

Moreover, our findings on the presence of high-risk HPV-39 and HPV-45 types in cervical cancer other than types 16 and 18 [19] and the presence of different types of HR-HPV in breast cancer will postulate a need for further assessment of the influence of current prophylactic vaccination programs that is protective against the two most common oncogenic papillomaviruses, HPV-16 and HPV-18, but not against other high-risk mucosal HPVs detected in our studies.

Viral carcinogenesis and cancer prevention are rapidly developing sectors of this field, and the future translation of this chapter lead to a faster resolution of HPV infection, and with obvious advantages for all HPV-affected patients, and in particular for individuals affected by early HPV-related cancer diseases.



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