Human Immunodeficiency Virus and Human papillomavirus in Immunopathology of Cervical Cancer

Mahima Lall[1], Sourav Sen[2], Rajiv Mohan Gupta[3]

ABSTRACT

The field of cancer immunobiology has been fast expanding. The realms of cervical cancer and immunodeficiency interacting at the molecular level has been actively investigated. The role of the Human papillomavirus and developement of cervical cancer admist a background of immunodeficiency is reviewed for the novelty of the interaction between the HPV induced oncogenesis and the host cellular responses in HIV positive women.The review aims to revisit the subject and generate interest and research on HPV induced oncogenesis with an ultimate aim to prevent cervical cancer. Greater understanding of the molecular pathways that underlie progression of high-grade IN to invasive cancer would be of great importance in the identification of the genetic markers that are able to identify the women who have a high risk of progression to cancer, and therefore in need of aggressive monitoring and therapy to prevent the development of cervical cancer.

Keywords: HPV, HIV, Cervical Cancer, Oncogenesis

INTRODUCTION

The Human papillomavirus (HPV) is a double stranded, small, non-enveloped DNA virus which belongs to the family *Papillomaviridae*. It has a genome of 7.9 kilo base (kb). More than 200 genotypes are known, of which 40 are mucosal subtypes including 15 high risk HPV (HRHPV) types.[1]

In 2012, the International Agency for Research on Cancer (IARC) grouped HPV into following categories: group 1 includes types which are carcinogenic to humans, group 2A has types that may probably be carcinogenic to humans and group 2B which possibly may be carcinogenic to humans. The HPV types included in IARC group 1 are HRHPV and are the following HPV16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58 and 59. HPV 68 is grouped into 2A as present day evidence is sufficient only to categorize it as probably carcinogenic. Group 1 and 2A account for almost ninety-six percent of the cancer of cervix. Few other alpha papilloma viruses, are rarely associated with cervical cancer and are placed in group 2B of probable carcinogens.[2] Papillomaviruses (PVs) are known to have species specificity, thus HPV refers to papillomaviruses infecting humans.[3]

Genome

HPV is 55 nm diameter in size. The upstream regulatory region is the long control region (LCR) also noncoding region or upstream regulatory region, it covers about 10% of the genome. It contains origin of replication, multiple transcription binding sites, early and late open reading frames (ORFs). Early region comprises of 6 ORFs- E1, E2, E4, E5, E6, E7 and accounts for 50% of the genome. E1 is the most conserved, hexameric, ATP-dependent DNA helicase encoded by PVs. It enables the viral episome's replication and amplification within the nucleus of the infected cell. Replication of viral DNA begins by E1 assembling into a double hexamer, unwinding DNA at the replication fork. E4 proteins are expressed before L2 and L1 and may indicate active viral infection especially in cases of infection by HRHPV and may is a potential biomarker of disease severity. The E5 proteins which have transforming ability have a role to play in the productive life cycle of the virus. They are thought to modulate the activity of cellular proteins. DNA replication and regulation of transcription is a function of the E1 and E2 genes. The E4 protein is essential for viral assembly and virion release from the infected cells which is seen to occur during productive infection. The function of E5, E6 and E7 genes is to modify cellular environmental conditions thus completing viral replication. Expression of E5 gene is associated with oncogenic potential, in HRHPV types, these proteins interact with cellular targets, leading to over expression of the epidermal growth factor receptors (EGFR) and proto-oncogenes, evasion of immune detection and thus inhibiting apoptosis. The late region occupying 40% genome encodes late genes L1 and L2 that encode for major and minor viral capsid proteins used in formation of new viruses.[4]

Pathophysiology

Tissue tropism

HPV is epitheliotropic in nature.[5,6] It replicates and assembles within the nucleus of the basal cells of stratified squamous epithelium which are the target cells of HPV.

Life-cycle HPV

They invade mucosa of the anogenital tract and oral cavity. The life cycle initiates in the basal and parabasal cells[7] with infection at the site of trauma through micro abrasions of

[1]Associate Professor, Deparment of Armed Forces Medical College, Pune, Maharashtra, [2]Professor and Head Deparment of Microbiology, Armed Forces Medical College, Pune, Maharashtra, [3]Professor and Dean, Armed Forces Medical College, Pune, India

Corresponding author: Dr Mahima Lall, MD (Microbiology), Associate Professor, Armed Forces Medical College, Pune, Maharashtra, India

How to cite this article: Mahima Lall, Sourav Sen, Rajiv Mohan Gupta. Human immunodeficiency virus and human papillomavirus in immunopathology of cervical cancer. International Journal of Contemporary Medical Research 2019;6(11):K15-K17.

DOI: http://dx.doi.org/10.21276/ijcmr.2019.6.11.41

the epithelium. Initial viral replication occurs independently, often not involving the host cell. Thus, maintaining the virus in these undifferentiated cells in low copy numbers. Once the viral genome gets established in basal cells, the early genes (E1, E2, E6 and E7) are expressed. After cell division, there is migration of basal cells to the upper suprabasal layer and finally they undergo terminal cellular differentiation. In HPV infected cells, however, the cells of the suprabasal layers continue to proliferate instead of undergoing terminal differentiation. This may potentially be due to the high expression of E6 and E7genes resulting in reactivation of cellular DNA synthesis, inhibition of the apoptotic pathways and a delayed differentiation of the HPV infected keratinocytes. The amplification of the virus and assembly of progeny virus increases the number of viral copies per infected cell to at least 1000. E4 is responsible for DNA amplification and L1 gene expression. L2 is required for encapsidation of viral DNA and for infectivity of the virions.

Epidemiology

Papillomaviruses and Cancers: Global Scenario

HPV is now a recognized causal factor for infection related cancers especially cervical, anogenital and head and neck oropharyngeal cancers.[8,9] Current estimates are 528,000 new cases of cervical cancer occurring worldwide with 266,000 deaths attributable to cervical cancer.[10,11,12]

Papillomaviruses and Cancers: Indian Scenario

Studies from our country have highlighted the prevalence in a select subset of patients. Authors have studied trends of oropharyngeal cancer in population from north India. The prospects and prejudices of the vaccines in India have been reviewed.

Immunopathology

How HPV is able to evade the immune surveillance

HPV has the ability to produce chronic persistent infections. The virus is able to reproduce inside the host cells without causing them any harm. It avoids host defences by inhibiting viral recognition. Due to the absence of cytolysis and necrosis there is no inflammatory response at the site of infection. Since viremia does not occur, the virus is not exposed to the immune cells and antibody response is negligible. In addition, Langerhans cells do not get activated during infection of basal cells. HPV inhibits the production of interferons (IFN-a and IFN-b) which have an antiviral effect. HRHPV down regulate expression of the IFN-a inducible gene. E6 and E7 interfere with interferon signalling pathways.[13]

Immune response

The immunological response to HPV infection is cell mediated, hence conditions impairing the cell mediated immune response such as renal transplantation and HIV predispose to HPV infection. The local Immunity plays an important role along with the cervical microbiota.[14] HIV positive women having high plasma viral loads have diminished Langerhans cells in cervical intraepithelial lesions (CIN) lesions. Also, immune cell numbers of CD4+ T-cells, macrophages, neutrophils, natural killer cells and expression of IFN-γ are significantly lower compared to CIN lesions in HIV-negative women. Regulatory cytokines get down-regulated in this subset of women. Thus, indicating that both anti and pro-inflammatory response suppression occurs in HIV seropositive women with high-grade CIN lesions. HIV infection may cause variation in cytokine levels, thus modulating HPV infection at the tissue level. Increased monokines—including IL-1, IL-6 and TNF modulate HPV transcription.

Oncogenic properties of HRHPV

The HRHPV oncogenesis can be attributed to E6 and E7 proteins.[15] These proteins disrupt DNA repair and the control of the cell cycle by interacting with the tumour suppressor genes p53 and retinoblastoma (RB), respectively. E6 and E7 induce genomic instability and imbalance of the chromosomal copy numbers in cervical and anal cancers. Studies have shown that HPV DNA gets integrated into the host.[16] Copy-number abnormalities (CNAs) alter host gene expression either causing over expression of an oncogene or tumour suppressor gene loss.

HIV HPV interaction

The mucosa of the cervix is part of the innate immunity of the genital tract, a monolayer in comparison to the vaginal stratified squamous epithelium. It is relatively rich in potential HIV target cells. Especially the transformation zone, which has a high concentration of macrophages and CD4+ cells. E7 protein decreases the expression of E-Cadherin, an epithelial adhesion molecule, hence increasing the permeability of the epithelium to HIV.

Most HPV infections, however are transient and tend to get spontaneously cleared by the host immune system.[17] The progression, outcome and final clearance depends on the HPV type, location, nature of infection and interplay between the cellular tissue immunity. In susceptible and immunocompromised individuals, it is the persistent infections that lead to high grade cervical intraepithelial neoplasia. HIV positive individuals have a higher prevalence of anal, oral and cervical HPV infection as compared with those negative for HIV. HIV, HPV may interact at the sub molecular level via HIV-1 *tat* protein, causing activation of the HPV LCR, thus in turn leading to an increased expression of HPV E6 and E7 oncogenes.

Increase in the grade of cancer results in CNA increase with chromosome 3q being the commonest genetic change. Integration of HPV DNA within the host genome leads to CNAs. Epigenetic changes such as hypermethylation have been seen to be occurring with increased frequency in cancers of higher grades, in turn down-regulating tumour suppressor genes. Data put together does suggest the important role of immune suppression perhaps in the early stages of HPV infection. Development of cancer may result due to accumulation of HPV associated genetic instability in addition to other host factors. HIV may not play a direct role in the causation of HPV- related cancers, but HIV induced immunosuppression may lead to the infection persisting giving time for genetic changes to accumulate ultimately

progressing to cancer.

Clinical Implications

Cervicovaginal human papillomavirus infection in HIV positive women

The Women's interagency HIV study (WIHS) compared HIV positive women and risk matched HIV negative women. It showed HIV positive women having a higher prevalence of genital HPV infection than the control group. However, spectrum of HPV genotypes was found to be similar between both study groups. A met analysis published the significant genotypes reported from various parts of the world.[18] Thus, highlighting the importance of knowing the prevalent HPV genotypes in a particular region.[19,20]

CONCLUSIONS

This review aimed at re-examining the immunopathology of HPV infections with special reference to HIV infected immunocompromised host. The epitheliotropic nature of this virus was understood by elucidating the HPV genome, the various genes and their role during each step of the virus life cycle. The modifications in the cell cycle due to the virus induced modifications. The aim being to keep interest alive for research to advance in the field of a HPV induced cancers which would facilitate better prevention strategies in future.

REFERENCES

1. Bosch FX, Lorincz A, Munoz N, Meijer C, Shah KV. The causal relation between human papillomavirus and cervical cancer. J Clin Pathol 2002;55:244–65.
2. International Agency for Research on Cancer, Biological agents. IARC monogr eval carcinog risks hum 2012;100B:1-475.
3. Munoz N, Bosch FX, de Sanjose S, Herrero R, Castellsague X, Shah KV et al Epidemiologic classification of human papillomavirus types associated with cervical cancer. N Engl J Med 2003;348:518–27.
4. zur Hausen H. Papillomaviruses and cancer: from basic studies to clinical application. Nat Rev Cancer 2002;2:342–50.
5. Egawa N, Egawa K, Griffin H, Doorbar J. Human Papillomaviruses; epithelial tropisms, and the development of neoplasia. Viruses 2015;7:3863–90.
6. Doorbar J. Model systems of human papillomavirus-associated disease. J Pathol 2016;238:166–79.
7. Pett M, Coleman N. Integration of high-risk human papillomavirus: a key event in cervical carcinogenesis? J Pathol 2007;212:356–67.
8. Maxwell JH, Grandis JR, Ferris RL. HPV-associated head and neck cancer: unique features of epidemiology and clinical management. Annu Rev Med 2016;67:91-101.
9. Mehanna H, Beech T, Nicholson T, El-Hariry I, McConkey C, Paleri V et al. Prevalence of human papillomavirus in oropharyngeal and nonoropharyngeal head and neck cancer–systematic review and meta-analysis of trends by time and region. Head Neck 2013;35:747–55.
10. Forman D, de Martel C, Lacey CJ, Soerjomataram I, Lortet-Tieulent J, Bruni L et al. Global burden of human papillomavirus and related diseases. Vaccine 2012;30 Suppl 5:F12–23.
11. De Martel C, Plummer M, Vignat J, Franceschi S. Worldwide burden of cancer attributable to HPV by site, country and HPV type. Intl J Cancer 2017;141:664– 70.
12. Wakeham K, Kavanagh K. The burden of HPV-associated anogenital cancers. Curr Oncol Rep 2014;16:402.
13. Verma M, Erwin S, Abedi V, Hontecillas R, Hoops S, Leber A, et al. Modeling the mechanisms by which HIV-associated immunosuppression influences HPV persistence at the oral mucosa. Poli G, editor. PloS One 2017;12:e0168133.
14. Reimers LL, Mehta SD, Massad LS, Burk RD, Xie X, Ravel J, et al. The Cervicovaginal microbiota and its associations with human papillomavirus detection in HIV-infected and HIV-uninfected women. J Infect Dis 2016;214:1361–9.
15. Gray E, Pett MR, Ward D, Winder DM, Stanley MA, Roberts I, et al. In vitro progression of human papillomavirus 16 episome- associated cervical neoplasia displays fundamental similarities to integrant-associated carcinogenesis. Cancer Res 2010;70:4081–91.
16. Arias-Pulido H, Peyton CL, Joste NE, Vargas H, Wheeler CM. Human papillomavirus type 16 integration in cervical carcinoma in situ and in invasive cervical cancer. J Clin Microbiol 2006;44:1755–62.
17. Travassos AG, Netto E, Xavier-Souza E, Nóbrega I, Adami K, Timbó M, et al. Predictors of HPV incidence and clearance in a cohort of Brazilian HIV-infected women. PloS One 2017;12:e0185423.
18. Clifford GM, Tully S, Franceschi S. Carcinogenicity of Human Papillomavirus (HPV) Types in HIV-Positive Women: A meta-analysis from HPV infection to cervical cancer. Clin Infect Dis 2017;64:1228–35.
19. Choi YJ, Park JS. Clinical significance of human papillomavirus genotyping. J Gynecol Oncol 2016;27:e21.
20. Palefsky JM. Human papillomavirus-associated anal and cervical cancers in HIV-infected individuals: incidence and prevention in the antiretroviral therapy era. Curr Opin HIV AIDS 2017;12:26–30.

Source of Support: Nil; **Conflict of Interest:** None

Submitted: 25-10-2019; **Accepted:** 06-11-2019; **Published:** 30-11-2019