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REVIEW ARTICLE

Human Papillomavirus Biology: Review

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Abstract

Sexually transmitted infections (STIs) are more dynamic than any other diseases in both developing and developed countries. Human Papillomaviruses (HPVs) are icosahedral, small, non-enveloped particle measuring ~55 nm in diameter. They are ~8000 base-pair (bp), double stranded circular DNA molecule which wrapped into a protein shell by two molecules namely, L1 and L2. The HPV genome has the coding capacity for two late proteins (L1 and L2) and for six early proteins (E1, E2, E4–E7) which are necessary for the replication of the viral DNA and for the assembly of newly produced virus particles within the infected cells. More than 100 HPV types have been characterized molecularly and about 40 types are able to infect the epithelial lining of the anogenital tract and other mucosal areas of the human body. Human papillomavirus (HPV) is a necessary cause of cervical, anogenital, upper aerodigestive tract and skin cancers. Other cofactors are necessary for progression from cervical HPV infection to cancer. HPVs are highly specific for hosts where they exploit the host cellular machinery for their own purposes by perfectly adapting to their natural host tissue, the differentiating epithelial cell of skin or mucosa. Thus it appears that the biology of Human papillomavirus is still being explored. Therefore this review is an attempt to gather information about biology of HPV which may provide new insight to combat HPV related diseases.
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INTRODUCTION

Sexually transmitted infections (STIs) are more dynamic than any other diseases in both developing and developed countries. Their epidemiological profile varies from country to country and from one region to another region within a country, depending upon ethnographic, demographic, socio-economic and health factors (Sharma and Khandpur, 2004). These days, in India, the bacterial STIs like chancroid and gonorrhea are declining on other hand, viral STIs like HPV and herpes genitalia are increasing (Thapa and Kaimal, 2007). In the early 1980s, Dr. Harald zur Hausen established the link between genital human papillomavirus (HPV) infections and cervical cancer. After that a number of molecular and epidemiological studies demonstrated a strong co-relation between HPV infection and cervical cancer. Cervical cancer is the second most common cancer among women worldwide with an estimated 5,29,409 new cases and 2,74,883 deaths in 2008. About 86% of the cases occur in developing countries and may constitute up to 25% of all female cancers**.** According to WHO: Human Papillomavirus and Related Cancers Summary Report (2010), in India, cervical cancer takes the lives of 8 women in India every hour. India recorded 1,32,000 new cases out of these 74,000 cases lost their lives. Though HPV vaccines are available in the market, they have their own limitations (Sangar and Ghongane, 2013; Sangar and Ghongane, 2013). Therefore this review is an attempt to gather information about biology of HPV which may provide new insight to combat HPV related diseases.

HUMAN PAPILLOMAVIRUS (HPV)

Today, HPVs are viruses of Papovaviridae family but in the mid- 1950s to 1960s, Papillomaviruses and polyomaviruses became amenable to observation by electron microscopy and basic nucleic acid analyses. At that time these two groups were found to be the only viruses that had 1) double-stranded circular DNA genome and 2) non-enveloped particles consisting of icosahedral capsids. As a consequence, they were considered closely related and were placed in the broader family Papovaviridae (Shah and Howley, 1992). All polyomaviruses have genome sizes around 5kb while papillomaviruses has genome size of ~8kb. Polyomaviruses have 2 transcriptional site which reads towards one another while Papillomaviruses transcription occurs only in 1 direction. Most importantly Papillomaviruses and polyomaviruses do not share any substantial amount of nucleotide or amino acid sequences similarity. For these reasons, they are now officially recognized by the International Committee on the Taxonomy of Viruses (ICTV) as two separate families - Papillomaviridae and Polyomaviridae (Doorbar, 2005; Bernard et al., 1994a; de Villiers et al., 2004).

Structure

Human Papillomaviruses (HPVs) are icosahedral small non-enveloped ~55 nm in diameter. They are ~8000 base-pair (bp), double stranded circular DNA molecule which wrapped into a protein shell and this shell is composed by two molecules namely, L1 and L2 (Finch and Klug, 1965; Pfister, 1987). The minor structural proteins, L2, have a molecular mass of about 75 kDa and are less-well conserved among papillomaviruses (Pfister and Fuchs, 1987; Komly et al., 1986). HPV genome contains approximately 8-9 ORFs that are all transcribed from a single DNA strand. The ORF can be divided into three functional parts: the early region (E), the late region (L) and the upstream regulatory region (URR). The viral E proteins are transcribed from the early promoter on other hand the L proteins are transcribed principally from the late promoter (Hoenil and Jae, 2005; IARC, 2007; IARC, 2012). Both sets of genes are separated by an upstream regulatory region (URR) which is about 1000 bp. This URR does not code for proteins but contains cis-elements required for regulation of gene expression, replication of the genome, and its packaging into virus particles (Hoenil and Jae, 2005; Muñoz et al., 2006).

HPV types

More than 100 HPV types have been characterized molecularly and about 40 types are able to infect the epithelial lining of the anogenital tract and other mucosal areas of the human body (Muñoz et al., 2006). Depending upon their degree of association with human malignancy, HPVs can be further subdivided into high risk (HR) and low risk (LR) types (IARC, 2012). Low risk HPV (LR-HPV) subtypes are mainly found in genital warts whereas high risk HPV (HR-HPV) subtypes are frequently associated with invasive cervical cancer. Intermediate risk HPV types are found in the presence of preinvasive lesions. High risk HPV types have been reported in 90–99% of invasive cervical cancers (Soliman et al., 2004).

LIFE CYCLE OF HPV

Papillomaviruses are strictly species-specific and do not infect hosts other than their natural one (Shadan and Villarreal, 1993; Muñoz et al., 2006). Papillomaviruses exploit the host cellular machinery for their own purposes by perfectly adapting to their natural host tissue, the differentiating epithelial cell of skin or mucosa.

Binding, entry and uncoating

Although several potential cell surface receptors have been reported, it is unclear which of them is of physiological importance. According to Evander et al., (1997), ά6β4 acts as promising candidate for human papillomavirus (HPV) infection (Evander et al., 1997). The mechanism for virus entry into the basal cells is not entirely understood. Most of the studies proved that different types of HPVs entered cells in distinct pathways including clathrin-mediated endocytosis, caveolar endocytosis and clathrin- and caveolae-independent endocytosis (Letian and Tianyu, 2010). HPV infection needs to access the cells which are present in the basal layers of stratified epithelium and for that some HPV types require microtraumas to occur in stratified epithelium. Such breaks may not be readily apparent and these conditions occur where the skin is exposed to water or is abraded. To maintain the HPV infection, the virus has to infect an epithelial stem cell (Doorbar, 2005; IARC, 2012; Muñoz et al., 2006; Stubenrauch and Laimins, 1999).

Establishment and Maintenance of the non-productive infectious state

Following HPV infection and uncoating, the HPV replication cycle within the epithelium can be divided into two parts nonproductive and productive. Initially, basal cell comprises the proliferating cellular component of stratified epithelium where the viral genome is established when a low copy number, nuclear plasmid and early genes are expressed at low levels. The HPV viral genome is replicated to a copy number of about 100 and maintained for varying periods of time. The ability of HPVs to establish their genome in basal cells relies upon the E1, E2, E6 and in some cases E7. The viral proteins E1 and E2 are essential for this basal DNA replication (Hoenil and Jae, 2005; IARC, 2012). This is consequently referred to as the 'non-productive' stage of infection. This requires that the viral genome be maintained over multiple cell divisions; how this is achieved is still unclear (Muñoz et al., 2006; Doorbar, 2005).

Productive stage

For the production of infectious virions, human papillomaviruses amplify their viral genomes to ~1000 copy numbers per cell and package them into infectious particles (Hoenil and Jae, 2005; Thomas and Shah, 2004). In HPV-positive human keratinocytes and cervical epithelial cells, after producing sufficient number of HPV progenies in the basal cells, basal cells are pushed to the suprabasal compartment where they fail to withdraw from the cell cycle and continue to support DNA synthesis (Doorbar, 2005; IARC, 2007). For high risk HPV types such as HPV16, this occurs in the mid or upper epithelial layers following an increase in activity of the late promoter. It is proved that E7 up-regulation leads to increased expression of E1, E2, E4 and E5 proteins which are involved in viral DNA replication without directly affecting expression of the E6 and E7 proteins. Amplification of viral genomes begins in a subset of cells in the proliferative compartment and requires expression of all viral early gene products including E4 and E5 whose roles in replication are not yet fully understood (Doorbar, 2005; Malik, 2005).

Virus synthesis

The amplified HPV genome encodes two structural proteins L1 and L2. L2 is a minor coat protein and is produced in a subset of the cells that express E4. The major capsid protein (L1) is expressed after L2 allowing the assembly of infectious particles in the upper layers of the epithelium (Doorbar, 2005; Ozbun and Meyers, 1998b). The critical molecules involved in the process of virus replication are the viral proteins E6 and E7 (Doorbar, 2005).

Virus release

For HPV particles release into the environment, the HPV virus has to escape from the infected skin cell and survive extra-cellularly prior to re-infection. Papillomaviruses are non-lytic and are not released until the infected cells reach the epithelial surface. Extra-cellular survival of the Papillomaviruses may be enhanced if they are shed from the epithelial surface within a cornified squame. This may compromise the immune detection of the virus and thus limit the presentation of viral epitopes to the immune system in the lower epithelial layers (Doorbar, 2005; Muñoz et al., 2006).

Viral transmission

According to epidemiologic studies vaginal and anal sexual intercourse is the primary route for anogenital HPV infection. However, penetrative sexual intercourse is not a requirement for HPV transmission (Wright, 2009). There is a strong relationship between the number of both lifetime and recent sexual partners and the prevalence of HPV in women (Shukla et al., 2009).

Animal models

Till date no in vitro system of Human papillomavirus (HPV) infection is readily available and no animal model of HPV infection exists. The current preclinical models of natural infection include rabbit, dog and bovine models. There is no natural papillomavirus infection model for small laboratory rodents available (Kanodia et al., 2012).

HUMAN PAPILLOMAVIRUS DISEASES

Sexually active individuals acquire at least one genotype of HPV infection at some time during their lifetime (Muñoz et al., 2006). Human papillomavirus (HPV) can cause cervical, anogenital, upper aerodigestive tract and skin cancers. The evidence for the carcinogenicity of HPV is also reported in the nose and nasal sinuses, lung,

colon and rectum, breast, ovary, prostate and urinary bladder and urethra cancers (Shukla et al., 2009). According to reported epidemiological studies, cancers of the anogenital tracts (vulva, vagina, penile and anal cancers) are rare. However, due to men sex with men (MSM), incidence of anus cancer increases with an increase of >160% in men and 78% in women in the USA (Daling et al., 2009). The upper aerodigestive tract cancer includes cancers of oral cavity, oropharynx, tonsil, oesophagus and larynx. These aerodigestive tract cancers strongly associate with smoking and drinking habits as compared with subject who do not exposed to smoking or drinking. Most cancers of the vagina and anus are likewise caused by HPV, as are a fraction of cancers of the vulva, penis, and oropharynx (IARC, 2012). The HPV-16 and 18 types cause about 70% of cancers of the cervix, vagina, and anus and about 30-40% of cancers of the vulva, penis and oropharynx. Other types of HPV can also cause certain cancers of the head and neck (http://www.phac-aspc.gc.ca/std-mts/hpv-vph/fact-faits-eng.php; Zur Hausen, 1999).

CERVICAL CANCER: ROLE OF CO-FACTORS

Although HPV is a necessary cause of cervical cancer but it is not a sufficient cause. Other cofactors are necessary for progression from cervical HPV infection to cancer.

Sexual intercourse, Pregnancy and delivery routes

Several cross-sectional studies provided strong evidence that earlier sexual intercourse (includes both vaginal and anal intercourse) is the primary route of genital HPV infection and this probably occurs due to cervical immaturity, inadequate production of protective cervical mucus and increased cervical ectopy. The women who initiate sexual activity before age 16 have about a twofold or greater risk compared with women becoming sexually active after the age of 20 years (Kahn et al., 2002). In 1842, an Italian physician, Rigoni-Stern analyzed death certificates of women in Verona during the period 1760-1839 and noted a high frequency of cervical cancer in married women, widows and prostitutes but have rare occurrence in virgins and nuns. Then he concluded that the development of cervical cancer should be related to sexual contacts. The possible mechanism has been proposed. According to this hypothesis, the serum concentrations of oestrogen and progesterone increase as pregnancy progresses and it reaches to peaks during the third trimester. These increases in serum concentration of hormone may be associated with the development of an atypical transformation zone and squamous metaplasia at the endo/ecto-cervical junction (Malik, 2005). According to Schiff et al (2000), in a clinic-based, case-control study on women who had underwent more than 3 vaginal deliveries; it was observed that their risk increases fivefold for cervical intraepithelial neoplasia CINII/III. Women with more than 1 miscarriage are at an increased risk for (CIN I) (Schiff et al., 2000). Muñoz et al., (2003) reported in International agency for research on cancer (IARC) multicentric case-control study that nulliparous women were at lower risk of squamous-cell carcinoma of the cervix than parous ones. Along with these findings, some interesting new findings emerged regarding vaginal delivery. Women who reported caesarean deliveries showed a somewhat reduced risk compared with those who had vaginal ones, after allowance for number of full-term pregnancies (Muñoz et al., 2002).

The number of full-term pregnancies is associated with an increased risk of invasive cervical carcinoma after adjustment for the number of sexual partners and age at first intercourse. According to the International Collaboration of Epidemiological Studies of Cervical Cancer (ICESCC), the relative risk (RR) for invasive cervical cancer increases with number of full-term pregnancies and with decreasing age at first full-term pregnancy. However, the effects of these two variables were found to be independent (International Collaboration of Epidemiological studies of Cervical cancer, 2006).

Tobacco smoking

Winkelstein first put forward the hypothesis that tobacco smoking has been associated with cervical cancer (Moodley et al., 2003). Later this hypothesis has been supported by subsequent epidemiological studies. Although it has been found to be difficult to rule out residual confounders, these cofounders are chiefly arising from sexual habits known to be related to both smoking and cervical cancer (Hoenil and Jae, 2005; Winkelstein, 1977). Various mechanisms have been proposed to explain the association between smoking and cervical cancer. Tobacco smoking (either active or passive) and chewing is able to induce its carcinogenic effect in pancreatic, kidney and bladder cancer (Layde, 1989; Rajkumar et al., 2003). Major classes of carcinogens present in tobacco and tobacco smoke are converted into DNA reactive metabolites by cytochrome P450 (CYP)-related enzymes. The mechanism by which polycyclic aromatic hydrocarbons (PAHs) such as benzo(α)pyrene (BαP) interact

with DNA activate oncogenes and initiate the carcinogenic process involves the formation of bay-region diolepoxides as the major ultimate carcinogens. BαP is converted into phenolic metabolites and BαP-7,8-diol by a CYP- mediated process. Secondary metabolism mainly involves epoxide hydrolase and other CYP isoforms which leads to the formation of the highly reactive (+)-anti-BPDE ((+/-)-r-7,t-8-dihydroxy-t-9,10-oxy-7,8,9,10-tetrahydrobenzo[a]pyrene). Smoking increases risk of cervical cancer by affecting the ability of host to mount an effective local immune response against viral infections in the cervix and smokers show reductions in the number of Langerhans cells (Hoenil and Jae, 2005).

Szarewski et al, (1998) found the traces of nicotine derivatives like nicotinine and tobacco specific nitrosamines in cervix. In addition to that DNA adducts are detected in exfoliated cervical cells (Szarewski and Cuzick, 1998; Plummer et al., 2003). International Agency for Research on Cancer conducted series of case-control studies of invasive cervical carcinoma (ICC) and carcinoma in situ (CIS) between 1985 and 1997 where all studies used a similar protocol and questionnaires and included an accurate evaluation of HPV DNA in cytological smears or biopsy specimens. This study shows that current smokers have an excess risk of cervical cancer as compared to ex-smokers. However no clear pattern of smoking association with invasive cervical carcinoma (ICC) and carcinoma in situ (CIS) was detected (Rajkumar et al., 2003).

According to the International Collaboration of Epidemiological Studies of Cervical Cancer (ICESCC), after adjusting for potential confounders, current smokers were found to have a significantly increased risk of SCC (squamous cell carcinoma) of the cervix compared to never smokers. The risk was lower for past smokers but there was no trend in the risk estimates with time since had been stopped smoking. In current smokers, the risk increased with the number of cigarettes smoked per day but not with duration of smoking (International Collaboration of Epidemiological studies of Cervical cancer, 2006).

Contraceptive Methods

Prolonged use of steroid contraceptive hormones has been identified as a cofactor of HPV-related cervical carcinogenesis in many, but not all, epidemiological studies. Till now very few articles are published which can explain the mechanisms by which Oral contraceptives (OCs) increases the risks of acquiring or progressing HPV infection to cervical cancer (Hoenil and Jae, 2005). Two possible mechanisms have been proposed. According to first hypothesis, the increased uptake of OCs would increase the likelihood of transformation zone exposure to HPV and other potential carcinogens. The second hypothesis concerning the stimulation of cell proliferation and HPV transcription by estrogens and progesterone is gaining support because OC binds to specific DNA sequences within transcriptional regulatory regions on HPV DNA to either increase or suppress the transcriptions of various genes which occurs due to presence of estrogen (de Villiers et al., 2004; Moodley et al., 2003). Kruger-Kjaer et al (1998) reported a pattern of decreasing risks of Atypical Squamous cells of Unknown Significance (ASCUS), Low-grade Squamous Intraepithelial Lesion (LSIL) and High grade squamous intraepithelial lesion (HSIL) with years with OC use among HPV DNA positive women. IARC's pooled analysis of eight case control studies reported that the odds ratio (OR) of cervical cancer resulting from the use of oral contraceptives was 2.82 (95% CI 1.46-5.42) for 5-9 years and 4.03 (2.09-8.02) for use for 10 years or longer (Kruger-Kjaer et al., 1998). Almost a decade ago, a paper has been published in International Journal of Epidemiology on the contraceptive and reproductive risk factors for CIN in American Indian women. This study is clinic - based case-control study. According to this study, oral contraceptives use greater than 5 yrs was negatively associated with CIN I but no association was found for oral contraceptive use with CIN II/III. Current, past and ever use of Intra uterine device (IUD) was moderate risk factor for CIN II/III while use of depot-medroxyprogesterone was risk factor for CIN (Schiff et al., 2000). On other hand Peter et al., (1986) in a case-control study of risk factors for cervical cancer among Los Angeles area Hispanic women found no association between IUD use and cervical cancer (Peter et al., 1986).

In another study, Smith et al., (2003) conducted a systematic review on cervical cancer and the use of hormonal contraceptives. The risk of invasive cervical cancer increases with increasing duration of oral contraceptive use as compared to never users. However limited available data suggest that this risk decreases after use of oral contraceptives has ceased but the risk is still significantly elevated for use that ceased more than about 8 years ago (Smith et al., 2003).

Sexually Transmitted agents

In many epidemiological studies the specific role of other infectious agents in the pathogenesis of cervical cancer has been studied. Till now, the most studied sexually transmitted infectious agents for which some evidence has been shown in relation to cervical cancer are Herpes Simplex Virus (HSV-2), Chlamydia trachomatis (CT) and Human Immunodeficiency virus (HIV).

Herpes simplex virus (HSV).

Several in vitro and in vivo HSV-2 studies found to be carcinogenic and possible mechanisms for the role of HSV-2 in cervical cancer have been suggested. According to the Zur Hausen article on "Human genital cancer: Synergism between two virus infections or synergism between a virus infection and initiating events?. He postulated that HSV-2 and HPV may act synergistically to initiate mutations and carcinogenesis in HPV-infected cervical cells" published in Lancet journal in 1982 they postulated that HSV-2 and HPV may act synergistically to initiate mutations and carcinogenesis in HPV-infected cervical cells (Zur Hausen, 1982). However, due to a lack of consistency in detecting HSV-2 DNA in cervical cells, it has been postulated by Galloway et al, (1983) that a "hit-and-run" mechanism may play a role in the initiation of cervical cancer (Galloway and McDougall, 1983). In 2002, Smith JS et al., conducted study on HSV-2 as a human papillomavirus cofactor in the etiology of invasive cervical cancer. According to them, HSV-2 seropositivity increases risk of both squamous cervical cancer and adenocarcinoma among HPV-positive women (Smith et al., 2002). Smith et al., (2003) in collaboration with International Agency for Research on Cancer (IARC) conducted multi-centric Cervical Cancer case -control study to support the role of HSV-2 as a cofactor of HPV infection in cervical cancer. In this study, HSV-2 seropositivity found to be significantly higher among women with invasive squamous cell carcinoma (44.4%) and adeno- or adenosquamous carcinoma (43.8%) than in control women (25.6%). This association was observed after adjusting for potential confounders (Smith et al., 2004).

Chlamydia trachomatis (CT).

Chlamydia infection is similar to HPV and this infection may cause chronic cervical infection. The intracellular localization of Chlamydia along with associated chronic inflammation, reactive oxygen release and epithelial damage could potentially promote neoplastic transformation (Malik, 2005). In 2004, Smith JS et al., analyzed pooled IARC data regarding Chlamydia trachomatis and invasive cervical cancer from seven countries. HPV DNA positive cases with squamous ICC were 1.8 times more likely to have Chlamydia infection than HPV DNA positive controls (Smith et al., 2004).

Human Immunodeficiency virus (HIV).

Individuals with Human Immunodeficiency virus (HIV) infection or organ transplantation are at increased risk of HPV-associated anogenital cancers compared with age matched healthy individuals. HIV-positive women are at an increased risk of cervical Squamous Intraepithelial Lesions (SIL) when compared with their HIV-negative counterparts. This association appears to be stronger for women with a low CD4 T-lymphocyte count. Women infected with both HIV and HPV are at a higher risk of SILs than women infected with either of the two viruses separately. HIV-infected men and women show higher incidence rates of anal HPV infection, Anal Intraepithelial neoplasia (AIN) and anal cancer (Palefsky and Holly, 2003).

Thus it appears that the biology of Human papillomavirus is still being explored. The pathogenesis of the disease is complex and multifactorial. The incubation period is still uncertain. Development of appropriate animal models and tissue culture technology may help to understand its intricacies and better approach to combat HPV related diseases.

CONFLICT OF INTEREST

Conflict of interest declared none.

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