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Review Article

A Gynecological Oncovirus: HPV and Cervical Cancer

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Abstract

Cervical cancer is the second most common cause of death among women after breast cancer, and may constitute up to 25% of all female cancers. Molecular and epidemiologic studies have solidified the association between high-risk strains of Human Papillomavirus (HPV) and cervical squamous cell carcinoma. Thus, HPV is considered the first gynecological oncovirus that received the attention of scientists over the past 3 decades to study its carcinogenic features, which I attempted to simplify in this short article. The development of an effective cancer vaccine has further added another shield of protection, after cervical screening program, against cervical carcinoma.

Keywords: *Human Papillomavirus; Cervical Carcinoma; Oncovirus; Vaccine; ASCUS; Gynecology*

Abbreviations

HPV: Human Papilloma Virus; ASCUS: Atypical Squamous Cells of Undetermined Significance; LSIL: Low Grade Squamous Intraepithelial Lesion; HSIL: High Grade Squamous Intraepithelial Lesion; DNA: Deoxyribonucleic Acid; HSPG: Heparin Sulfate Proteoglycans; VLP: Virus-Like Particles; pRB: Retinoblastoma Gene; p53: Tumor Suppressor Gene

Viral oncogenesis

There are viruses that are associated with the development of many human carcinomas. The mechanism of tumorigenesis depends on the virus genome and its capsid, collectively called virion. The possibility that a virus can cause cancer dated back to animal experimentation in the first decade of the 20th century, when infected chicken with avian virus led to the development of leukemia and in other cases sarcoma in chicken. Mammalian similar discoveries were found in the fourth decade. Following the creation of the U.S. Special Virus Cancer Program in 1964 looking for human oncoviruses, the first discovery was in the 1970's. It was hepatitis B virus as a causative agent in hepatocellular carcinomas followed by the human papillomaviruses (HPV) in the 1980's as the causative agent for cervical cancers worldwide. The latter was first demonstrated by a German virologist (Harold zur Hausen, who won the Nobel Prize in Physiology or Medicine 2008). This association was considered stronger than that between smoking and lung cancer.

Since then, the science of human viral oncogenesis expanded and branched over the years to identify nearly thirty more oncoviruses related to various human cancers as well as novel inventions of vaccines for prevention, and virotherapy for the treatment of such malignancies.

The human papilloma virus

This is a relatively small, circular nonenveloped virus, 55 nm in diameter that resemble a golf ball when viewed by electron microscopy. The HPV genome consists of a single molecule of double-stranded, circular DNA containing approximately7,900 bp associated with histones. The genome is functionally divided into three regions: 50% is a noncoding region, 10% is involved in viral replication and oncogenesis (E1-E7 genes), and 40% encodes the L1 and L2 structural proteins for the viral capsid [1].

Out of more than 200 types of HPV, only 13 types (HPV16, HPV18, HPV31, HPV33, HPV35, HPV39, HPV45, HPV51, HPV52, HPV56, HPV58, HPV59, and HPV 68) are considered carcinogenic to humans and allied to 96% of all cervical cancers in women [2]. Most of those cases (70%) are related to HPV 16 and 18; while HPV serotypes 18 and 45 are linked to the more aggressive, age dependent, cervical adenocarcinomas which are mostly seen in women younger than 40 years [3]. On the other hand, HPV 6 and 11 are low-risk types of HPV and are linked to approximately 90 percent of genital warts. It has been noticed that, HPV DNA in benign lesions is located extrachromosomally in the nucleus, while it is generally integrated into the host genome in high-grade intraepithelial neoplasia and cancers.

The prevalence of high-risk HPV infection among females undergoing cervical screening ranges between 30 - 40% in the 20's age group to < 10% in those above the age of 40 [4].

HPV and cervical carcinogenesis

Cervical cancer is considered one of the best examples of how malignant transformation is triggered by a virus infecting human tissue. The most vulnerable site to HPV infection is the squamocolumnar junction of the cervix where HPV is recognized to affect both the squamous and the columnar components leading to cervical dysplasia and premalignant squamous intraepithelial lesion (SIL), which typically develop into cervical cancer due to an ongoing infection with high-risk HPV. It has been shown that the high-grade SIL were tenfold higher when persistent infections were documented in the same person. Persistence is defined as the identification of the same high-risk HPV types at 2 visits 4 - 6 months apart [5].

Cervical squamous epithelial cells infected by HPV undergo koilocytosis. Koilocytes are recognized histologically by their dark, large, and asymmetrical nuclei that are surrounded by an area of transparent space, called the perinuclear halo. SILs can be detected cytologically as atypical squamous cells of undetermined significance (ASCUS) that carries a 10 - 20% possibility of HPV infection, or definite low-grade (LSIL) or high-grade (HSIL) lesions. Progression to HSIL is characterized by multiplying smaller cells running up towards the epithelial surface with partial loss of differentiation [1,6].

It is assumed that the HPV replication cycle begins with entry of the virus into the cells of the basement membrane of the epithelium through mild abrasion or microtrauma of the epidermis. HPV virions usually enter basal cells upon the binding of its major capsid L1 protein to heparin sulfate proteoglycans (HSPGs) and cleavage of its minor capsid L2 by the extracellular Furin. Inside the infected basal keratinocyte, HPV DNA is integrated into the host DNA and replication starts at a minimum rate using host DNA to synthesize its DNA on an average once per cycle. However, as cells move up towards higher differentiation viral DNA amplifies to high copy number along with capsid protein synthesis causing genomic instability. The normal function of the tumor suppressor proteins p53, a gene located on the short arm of human chromosome 17 (17p13.1) that is sometimes called Guardian of the Genome, is controlling G1 arrest of cell cycle, apoptosis, and DNA repair. These activities become nullified when it is bound by HPV E6 protein. Furthermore, the HPV E7 gene product binds cell cyclins and retinoblastoma gene, pRB, the other cellular proteins that regulate cell growth, which allows the transcription of genes whose products are required for the cell to enter the S phase of the cell cycle for replication. As a result, once the virion is inside the keratinocytes, inactivation of both p53 and pRB leads to increasing replication of its DNA, increase cellular DNA mutations, and inability to repair damaged DNA with lack of apoptosis that result in immortalization. There will also be delayed differentiation of the epical surface

epithelium imposed by the late effect of E1 and E2 viral proteins. Finally, the expression of the viral E4 disintegrates those cells to undergo the usual surface sloughing and the release of HPV virions with maximum spread; hence completing its life cycle (Figure 1).

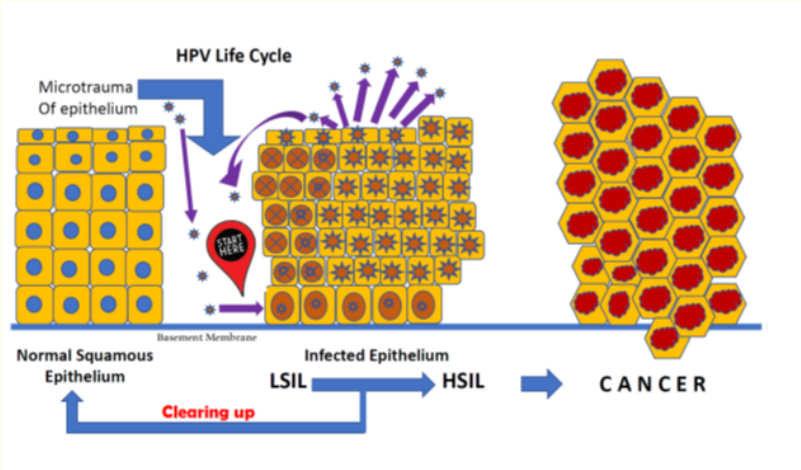

Figure 1: *HPV life cycle and progression to cancer.*

At this stage the HPV dysplastic lesion can be diagnosed as LSIL or HSIL and treated accordingly, or may even spontaneously regress to normal epithelium. However, if the viral E5 gene product is released in this late gene expression, the mitogen-activated protein kinase is induced leading to continuous proliferation and more genomic mutations with loss of cellular differentiation. This is the stage of full transformation of the host epithelial cells to cancer cells [7]. While most of LSIL tend to regress than to progress, progression to cancer generally takes place over a period of 10 to 20 years. Some lesions become cancerous more rapidly, sometimes within a year or two [8]. A summary of the characteristic features of HPV pathogenesis is outlined in table 1.

1. It starts at basal cells and remain within the epithelium.
2. It produces no inflammation.
3. It creates an immune deception to maintain its persistence.
4. It does not lead to cell death.
5. It generates a gradual histopathological progression of the disease.
6. Viruses shed locally and no viremia.

Table 1*: Characteristic features of HPV infection.*

HPV and pregnancy

Pregnancy is a state of immunosuppression. Moreover, the hormonal milieu in pregnancy stimulates the glucocorticoids and their response elements in the non-coding area of the virus which intensifies the transcription of HPV genes. Accordingly, it appears that

pregnancy increases the chance of contracting genital HPV infections. Brianti., *et al*. showed that 52.5% of mothers tested positive for HPV DNA in the third trimester of pregnancy, while only 17.5% in postpartum visits [9]. Transplacental cord blood and amniotic fluid infestation with HPV infections has been documented. HPV DNA was found in 75% of amniotic fluids obtained from mothers who tested positive for cervical HPV DNA [10]. Vertical transmission from mother to fetus has been speculated by the finding of HPV DNA in newborn oral mucosa, the significance of which remains debatable at this stage. Pregnancy outcome of mothers who tested positive for HPV has been associated with increased spontaneous miscarriage rate (up to 30%) and premature delivery. Vaccination wise, the World Health Organization and the vaccine manufacturers recommend avoiding HPV vaccination during pregnancy. However, in case of accidental vaccination of pregnant women there are no interventions and no mandatory pregnancy testing before vaccination recommended so far [11].

HPV vaccines

HPV vaccine is a non-infectious recombinant vaccine contains purified virus-like particles (VLPs) of the major capsid (L1) protein of HPV and enhanced by an adjuvant which is responsible for triggering an immune response higher than a natural infection. There are 3 HPV vaccines classified according to the VLP types included: 16 and 18 (Bivalent), 6, 11, 16 and 18 (Quadrivalent), or 6, 11, 16, 18, 31, 33, 45, 52, and 58 (9-Valent). The latter is the most recent one which includes seven oncogenic types that are known for causing high grade precursors of cervical cancer. All HPV vaccines have been found to have high efficacy (close to 100%) among persons without evidence of prior infection with HPV vaccine types. Nevertheless, prior infection with one HPV vaccine type did not diminish vaccine efficacy against the other HPV vaccine types. These types of VLPs generate strong reactions from the immune system and produce antibody titers that are much greater than those prompted by natural infection [12].

The best preventive measures

Healthy sexual lifestyle and scheduled cervical smear screening combined by HPV vaccination is the ideal method of cervical cancer prevention. Moreover, vaccination of men against HPV is considered a secondary way to protect against HPV-induced cervical cancer. Since HPV 16 and 18 are connected to 70% of anal cancers and premalignant lesions of the penis, the HPV vaccine can limit the occurrence of these conditions in heterosexuals who participate in anal intercourse. It was shown that 35.9% of women and 42.3% of men 18 - 44 years of age have anal intercourse with people of the opposite sex [13].

Conclusion

HPV, the only Gynecological oncovirus identified so far, is able to complete its life cycle within the squamous epithelium of the cervix without directly causing cell death and without systemic viraemia or apparent inflammation to avoid alerting the local immune responses and maintain its existence for long time. HPV oncogenesis comprises a distinct correlation between its induced intracellular molecular effect and a gradual recognizable cytological and histopathological finding on the cervix, ranging from ASCUS to HSIL, which gives time to diagnose and treat before reaching the stage of cancer. The World Health Organization has put a strategic goal to eliminate cervical cancer through effective screening, vaccination, and treatment.

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