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Review

Genomic diversity of human papillomaviruses (HPV) and clinical implications: An overview in adulthood and childhood

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ABSTRACT

During the last years, several researchers have highlighted the importance of characterizing more than one genomic region in order to detect recombination and classify variants of human papillomaviruses (HPVs) properly. HPVs variants differ in their biological, molecular and chemical properties. Therefore, this genomic diversity can present differences in the natural history and pathogenicity of HPVs. Different 'high-risk' HPVs variants of the genotypes HPV 16 and 18 can confer varied risks of viral persistence in the human cervix and influence HPVs progression to cervical cancer. Moreover, different 'low-risk' HPVs variants of the genotypes HPV 6 and 11 can play a unique role in the development of anogenital and cutaneous warts, recurrent respiratory papillomatosis (RRP) and ophthalmic pterygium. In future, the precise impact of genomic HPVs diversity to the clinical course of HPVs-associated diseases as well as to the efficacy of the current HPVs vaccines remains to be elucidated.

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1. Introduction

Human papillomaviruses (HPVs) are small non-enveloped double-stranded DNA viruses that belong to the *Papillomaviridae* family. At the beginning of the 1980s, the first HPVs were isolated and cloned using molecular techniques and this initiated a rapid expansion of molecular and epidemiological studies, which, just one decade later, impressively supported HPVs as the principal causative factor for cervical cancer (zur Hausen, 2002). This link had initially been suspected by Professor Harold zur Hausen, who was convinced by the early 1970s that HPVs infections are associated with cervical cancer. Almost 40 years later, Professor Harold zur Hausen received the Nobel Prize in Physiology and Medicine for 2008 and his observation provided the background for attempts to develop human vaccines against 'high-risk' HPVs, including genotypes HPV 16 and 18, using virus-like particles (VLPs). Since 2007, specific vaccination programs have been

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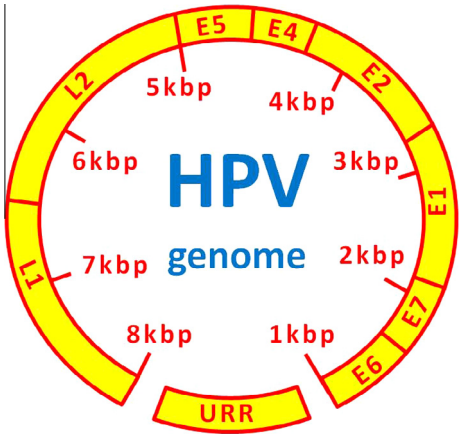

Fig. 1. HPV DNA genome: a schematic presentation.

implemented into clinical practice, while research on the next generation of multivalent VLPs-based vaccines against a wider array of HPVs continues.

HPVs are epitheliotropic and infect the cutaneous or mucosal epithelial cells, exclusively. After entering the host cells of the epithelial basal layer, replication of the virus occurs in the nuclei of the infected cells and the production of mature virions occurs in the suprabasal epithelial cell layers (Bonnez, 2002). HPVs infection is highly transmissible with a variable incubation period and can cause a diverse range of epithelial lesions. It can culminate in latent infection, which is insufficient to support transmissibility; in subclinical infection, which is active, but without clinical signs; or in clinical infection leading to benign epithelial lesions or malignant neoplasms. The majority of latent, subclinical and clinical manifestations of HPVs infection are capable of undergoing spontaneous resolution.

The oncogenic role of HPVs has been well-established by the regular presence of HPVs DNA in cervical cancer biopsy specimens as well as by the precise identification of the transforming properties of the E6 and E7 viral proteins that interact with the growth-regulating host-cellular proteins (Burd, 2003). In addition to cervical cancer, a major proportion of anal, perianal, vulvar and penile cancers appear to be primarily linked to HPVs. Moreover, extended research during the last decade has also led to the identification of HPVs in other non-genital cancers, such as breast and lung cancer (Mammas et al., 2011).

All HPVs have the same general organization of their genome, as shown in Fig. 1. Their genome consists of a single molecule of double-stranded, circular DNA containing approximately 7900 bp, which is functionally divided into three regions (Baker et al., 1991; Sapp et al., 1995). The first is a non-coding upstream regulatory region (URR) of 400–1000 bp. This region contains the p97 core promoter along with enhancer and silencer sequences that regulate DNA replication by controlling the transcription of the open reading frames (ORFs) (Apt et al., 1996). The second is the early (E) region that carries early ORFs encoding for the non-structural regulatory proteins E1, E2, E4, E5, E6 and E7, which are involved in viral replication, transcription, transformation, adaptation and oncogenesis. The third is a late (L) region, encoding the major capsid protein L1 and the minor capsid protein L2, which are structural proteins forming the icosahedral viral capsid comprising 72 capsomers (Baker et al., 1991; Sapp et al., 1995). The URR encompassing the origin of replication, the E6/E7 gene promoter, enhancers and silencers, is located between the early (E) and the late (L) regions (Longworth and Laimins, 2004).

2. Genomic diversity of HPVs

Different genotypes of HPVs are defined by a genomic sequence dissimilarity of more than 10% in their nucleotide sequences in the E6, E7 and L1 ORFs (Van Ranst et al., 1993; de Villiers, 2013; Bernard et al., 2013). Isolates within the same genotype differing by 0–2% in their sequences compared with the reference sequence are referred to as HPVs variants and those differing by 2–10% are referred to as subtypes. The URR region of HPVs contains the highest degree of genomic diversity (Apt et al., 1996). HPV 16 and 18 genomic sequences create evolutionary trees with the bifurcation driven by variants with a high prevalence in cohorts from different regions of the world (Ho et al., 1993; Ong et al., 1993). This evolutionary diversity is reflected in the phylogeny of these strains and is reminiscent of the migration patterns of *Homo sapiens*. Thus, it has been suggested that HPVs variant lineages may have co-diversified with human populations as they exponentially expanded across the planet.

During the last two decades, research on the genomic diversity of the genotypes HPV 16 and 18 was initially inferred from the URR and E6 sequences and has been recently expanded to include the complete genomes (Chen et al., 2005,2009; Arias-Pulido et al., 2005a,b). Genomic diversity of the HPV 16 genotype has been largely studied and to date different genomic variants have been described (Icenogle et al., 1991; Yamada et al., 1997; Kurvinen et al., 2000), including the Asian (As), Asian-American (AA), African 1 (Af-1), African 2 (Af-2) and the European (E), as well as a recent variant of North American 1 (NA1). These variants have been identified based on nucleotide changes in the E6, L1 ORFs and the URR and have been found in different biological environments and geographical locations (Icenogle et al., 1991). Among the ethnic groups of Africans, Asians and Caucasians, the European variants are usually found in all regions except Africa. The Asian variants are a subclass of the European lineage and are commonly detected in South-East Asians (Yamada et al., 1997).

HPV 18 genomic variants are grouped into three main branches: the Asian-American (AA), the European (E) and the African (Af) (Arias-Pulido et al., 2005a,b). These three branches have been equally distributed among controls and cases and stratified by Hispanic and non-Hispanic ethnicities. Among invasive cervical cancer cases, no significant differences in the three HPV variant branches have been observed among ethnic groups or when stratified by histopathology. The African (Af) branch has shown the greatest nucleotide variability when compared to the HPV 18 reference sequence and has been more closely related to the genotype HPV 45 than either the Asian-American (AA) or European (E) branches. These variants have been identified based on nucleotide changes in the E6, L1 ORFs and the URR.

Detailed sequence analysis of genotypes HPV 6 and 11 of the E7, E1, E2, E4, L2 ORFs and the URR has revealed the existence of several genomic variants (Burk et al., 2011; Kocjan et al., 2011). Phylogenetic analysis of complete genomes derived from published HPV 6 variants has suggested the presence of two deeply separate branches for HPV 6, with the reference genome HPV 6b forming lineage A and reference genomes HPV 6a and 6vc forming lineage B (Burk et al., 2011). Within the HPV 6 lineage B, there are three sublineages with HPV 6vc belonging to sublineage B1 and HPV 6a belonging to sublineage B3. It has been found that HPV 11 variants are more highly conserved, thereby not meeting the criteria for classification into more than one lineage (Burk et al., 2011). The nomenclature proposed for the HPV 11 lineage is based on two branches: sublineage A1, which includes variants clustering with the HPV 11 reference genome and sublineage A2, which includes all other variants.