Chapter 9

Serological Biomarkers for the Prediction and Detection of Human Papillomavirus Associated Cancers

Lourdes Gutierrez-Xicotencatl,
Azucena Salazar-Piña, Lilia Chihu-Amparan and
Adolfo Pedroza-Saavedra

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Abstract

High-risk human papillomavirus (HPV) types are not only associated to uterine cervical cancer, but also to a fraction of cancers of the vulva, vagina, penis, anus, head and neck. An HPV infection generates a protective humoral immune response against the capsid proteins L1 and L2; however, an immune response against other HPV early proteins is also generated. This latter is not a protective response, but those antibodies can be useful as biomarkers of the status of the infection and/or the stage of the cancer lesion. Until now, there are no conclusive results regarding the use of anti-HPV antibodies as biomarkers in diagnosis. In this review, we hereby summarized the actual panorama of the humoral immune response against different HPV early proteins during the development of the disease as possible biomarkers for the prediction and detection of HPV-associated cancers.

Keywords: serological biomarkers, human papillomavirus, humoral immune response, HPV-associated cancers, cancer diagnostic

1. Introduction

Prevention of cervical cancer (CC) and other related human papillomavirus (HPV) diseases constitutes a public health priority worldwide [1]. Primary prevention has been achieved through the introduction of the prophylactic HPV vaccines, but the target groups are only adolescent girls and young women (up to 25 years old) [2]. Secondary prevention has been

implemented through screening methods to prevent precancerous lesions from progressing to cancer [3]. The CC prevention programs in the world are based on cervical cytology and colposcopy to detect precancerous lesions, which have helped to reduce significantly the incidence of this illness in countries with well-organized programs and good coverage of the target population, but this is not the case in developing countries [4, 5]. The main problems are the lack of qualified personnel, the poor quality of the screening tests, lack of follow-up colposcopy and treatment, and over-saturation of the health system facilities, estimating that less than 20% of the CC cases are detected opportunely in these countries [6]. The HPV has been the target for the new molecular diagnostic technologies to detect high-risk (HR)-HPV DNA in cervical cells, but these tests have not been sufficient to discriminate women with precancerous lesions in progression to cancer, from those that eliminate the infection and the lesion. Thus, the increasing incidence of HPV-related cancers worldwide, the inefficacy of the cancer prevention programs in developing countries, and the lack of efficient HPV diagnostic tests, make this a priority health problem worldwide [7].

For this reason, it is important to develop new screening methods, which should achieve high sensitivity, specificity, and should be inexpensive for developing countries. These new diagnostic methods could be used in triage with the cytology or HPV-screening tests to detect opportunely women at risk to develop CC. In addition, it would be important to develop new technologies and to identify new biomarkers that allow the early detection of other HPV-related cancers. In this sense, antibodies against HPV antigens have become the new biomarkers that can be used to detect persistent HPV infection that in combination with other molecular tests could be useful for early detection of HPV-associated cancers.

2. Differential expression of human papillomavirus proteins during the viral cycle

The HPV is a non-enveloped icosahedral virus of approximately 50 nm in diameter that contains a double-stranded circular DNA genome of around 8 Kb, which is divided into three regions: the long control region (LCR) that regulates the viral DNA transcription and replication; the early region (*E1*, *E2*, *E4*, *E5*, *E6*, and *E7* genes) that controls the transcription and replication of the viral genome as well as to control the carcinogenesis; the late region (*L1* and *L2* genes) that contains the genes that expresses the viral capsid proteins [8, 9]. Differential expression of HPV proteins during the viral cycle is important for virus replication and evasion of the host immune response. In new infected cells, the HPV replication starts with the expression of low levels of HPV E6 and E7 viral oncoproteins that generates cellular proliferation and genome instability [10, 11]. First, the major viral oncoprotein E7 binds to the retinoblastoma tumor suppressor protein (pRb), which allows the cell to continue into the cell cycle [12]. Simultaneously, the E6 oncoprotein is expressed, and binds to the cellular ubiquitin ligase E6AP, which in turn results in degradation of the p53 protein, a transcription factor for cell cycle arrest, and in extreme situations, for induction of apoptosis [12]. As the infected basal cells migrate to the upper layers and differentiate, viral DNA replication is favored by the binding of E1 and E2 proteins to the LCR to regulate viral proteins expression [13, 14].

Once the viral DNA replication ends, the E2 protein represses the expression of the E6 and E7 oncogenes to allow the continuation of the viral cycle [15]. In the middle of this process, the E5 oncoprotein is expressed to maintain for a longer time the S-phase of the cell cycle and to delay the differentiation process to allow the complete expression of the viral proteins and the viral DNA replication [16, 17]. In the upper layers, E4 protein interacts with the cytoskeleton collapsing the cytokeratin filaments and enhancing the liberation of viral particles [18, 19], and it is also involved in the viral DNA replication [20]. Finally, the two viral capsid proteins L1 and L2 are expressed in terminally differentiated cells, once the replication of the viral genome has been completed, and ending with the release of the viral particles [21–23].

On the other hand, during a HPV persistent infection, there is a gradual loss of regulation of the E6 and E7 expression genes, which allows the development of early cervical lesions (CIN 1–3; cervical intraepithelial neoplasia grade 1–3) [24]. However, more than 70% of the CIN lesions are eliminated by the immune system. Progression to CC occurs due to an over-expression of E6/E7 oncoproteins, as a result of integration of the viral genome, which leads to the loss of the regulator *E2* gene [15]. This is an important event in the carcinogenesis of CC, as the over-expression of E6 and E7 oncoproteins generates cellular immortalization [25], stop cellular differentiation that generates dysplasia, the cells became anergic for TNF-α (tumor necrosis factor) and TGF-β (transforming growth factor) [25, 26], and chromosomal rearrangements could occur, as has been observed with the *c-myc* gene [27].

During a normal viral cycle, all the early HPV proteins carry out their functions inside the cells, and the viral antigens are poorly exposed to the immune system of the host. However, persistence of HPV infection allows the production of antibodies. Although the antibodies generated against the early HPV proteins are not of neutralizing type, these are suitable for their study as possible biomarkers, which recently is under investigation.

3. Cancers associated with HPV infection

Among all human cancers, 15% are caused by viral infections. HPV infection is recognized as one of the major causes of infection-related cancers in both men and women. Generally, HPV has been associated with more than 90% of anal and cervical cancers, about 70% of vaginal and vulvar cancers, 70% of oropharyngeal cancers, and more than 60% of penile cancers [28].

The HPV is the most common sexually transmitted virus and the HR-HPV types 16 and 18 are more prevalent in CC (approximately 70%) [28]. This type of cancer has been a major public health problem among adult women in developing countries. The last worldwide report for CC identified more than 440,000 incident cases and over 230,000 deaths due to this disease [1]. HR-HPV infection is necessary but not sufficient to cause this cancer, which develops over a long period of time through precursor lesions at the squamocolumnar junction cells near the transformation zone [29]. These cells shown to be multipotent residual embryonic cells have also been identified at the anorectal junction similar to the cervix [29]. Although, the cellular origin and the HPV-DNA prevalence are similar in the anus and in the cervix, the incidence ratio of cervical/anal cancer is quite different (17:1) [30]. The majority of low-grade squamous

intraepithelial lesions (LSIL) do not progress to high-grade lesions (HSILs) or carcinoma, which suggests that the HPV infection alone is not sufficient to generate cancer, as other cofactors such as immune deficiency, host genetic factors, among others are involved [30].

In anal cancer (AC), the HPV infection is detected in 80–90% of the cases, and HPV16 is the predominant type (80%) [31, 32] with a frequency higher than in other anatomical sites [32, 33]. This high frequency of HPV16 may reflect a differential tropism of this type that leads to malignant transformation in the anal mucosa. The prevalence of HPV in AC differs by geographic region, with the highest prevalence in North America and Europe and the lowest in Africa [31]. From the gastrointestinal tract malignancies, the prevalence of AC is around 2–3%, with 27,000 new cases reported worldwide in 2008 [31].

Vulvar cancer (VC) is originated from a precursor in intraepithelial lesions named vulvar intraepithelial neoplasia (VIN) and this type of cancer accounts for >90% of the malignant tumors in the vulva [34]. Recently, there is increasing evidence that suggests two different etiopathogenic pathways for the development of VC, one that is associated to HR-HPV and the second that is HPV independent. The prevalence of HPV-DNA in VIN lesions varied from 52 to 100%, but it is over 90% in VC [32, 34]. Over the last decade, the incidence of HPV-associated VC has increased mainly in young women, probably because of high-risk sexual behavior and a better recognition of these lesions due to HPV-DNA detection [32, 35].

On the other hand, penile cancer (PC) has been considered a relatively rare malignancy in the western world, although recent reports indicate an increase in incidence rates in developing countries (from 0.8 to 1.4/100,000) [36]. The etiology of PC is multifactorial with multiple established risk factors including infection with HPV. Epidemiological studies found that 48% of evaluated PC samples were positive for HPV-DNA and the type 16 or 18 was implicated in approximately 31% of these tumors, with HPV16 being the predominant type [37, 38]. In men, HPV infection can result in a spectrum of genitourinary manifestations that can cause genital warts, penile intraepithelial neoplasia (PIN), and PC. However, most HPV infections are asymptomatic, and up to 70% are cleared within 1 year [38].

The final group of the HPV-associated cancers is the one related to the head and neck cancer (HNC) that is the fifth most common cancer in the world [1]. Every year, there are more than 640,000 cases of this cancer reported and it causes over 350,000 deaths [1]. Squamous cell carcinoma is the most frequent type of neoplasia lesions affecting the head and neck area [39]. The laryngeal cancer (LC) is the most common among head and neck neoplasia and it accounts for about 60% of all cancers in the head and neck area [39]. LC may result from late complications of squamous cell papilloma (SCP), although most of those malignant changes develop without papillomas. Generally, squamous laryngeal cancer development begins with dysplastic changes within the epithelium of mucosa membrane lining the organ, this is followed by an intraepithelial neoplasia and finally the development of the pre-invasive cancer (carcinoma in situ) [39, 40]. However, HPV involvement in LC etiology has not yet been fully evaluated [41].

Within this group of cancers, oropharyngeal carcinomas (OPC) are the most dependent on HPV. The incidence of HPV-positive OPC has been markedly increasing in North America and Europe, with a higher rate in men than in women in North America [30], and HPV16 has been detected in the majority of these cancer cases [40]. Until now, little is known about the transmission and immunogenicity of HR-HPVs within the oropharynx. There is a strong

association with having performed oral sex and the number of lifetime partners [42], suggesting that initial infection of HPV in the oropharynx is related to high-risk sexual activity. HPV nucleic acid examination in rinse and gargle samples showed a prevalence of 4.7% of HR-HPV infection in the general population among the ages 45–65 years old. However, it is still unclear the implications of the viral infection in the development of OPC [42].

Moreover, esophageal cancer (EC) is the leading cause of cancer mortality worldwide, with approximately 500,000 incident cases and more than 400,000 deaths each year [1]. There are two types of EC; the most common is the squamous cell carcinoma (ESCC), which is highly prevalent in Eastern countries and in developing countries. The second type is the adenocarcinoma (EAC), which is associated with Barrett's esophagus, and its incidence has raised by 5–10% each year, in developed (Western) countries [43].

4. Immune response to the HPV infection

Mucosal HPV infections frequently arise in the anogenital tract and in the head and neck region, and these sites of infection have high threshold of immune tolerance [44].

The infection and replication of HPV is restricted to differentiating epithelial cells, where there is a limiting presentation of viral antigens to the host immune system. As a result, there is a low but detectable humoral immune response in most infected individuals [45]. HR-HPV types 16 and 18 mainly induce persistent infections without frequent serious complications for the host; they are also highly successful in releasing viral particles transmissible to others [46]. This virus takes the host to a point of balance where the infection does not represent a serious drawback, and viral replication is not limited by the host immune response [46], because the virus does not have a blood-borne phase or viremia. The HPV infection does not induce necrosis, cytolysis, or inflammation, and as a result, there is little or no release of pro-inflammatory cytokines in the local environment [47]. The HPV viral cycle occurs in cells that are destined for death by anoikis (detachment), and because of this, there are no danger signals to alert the immune system to generate an efficient response to eliminate the infection [48].

It is well documented that more than 80% of the genital lesions caused by HPV infections are cleared as a result of a successful cell-mediated immune response, during which cells of the innate immune system such as keratinocytes, dendritic cells (DCs), Langerhans cells (LgCs), macrophages, natural killer (NK), and NKT cells, may play an important role in clearing the infection by promoting a pro-inflammatory process [49]. In the female genital track, the natural host of the HPV infection, there are keratinocytes that could act as immune sentinels, as it has been shown in skin [50]. These cells express Toll-like receptors (TLRs, belonging to the pathogen recognition receptors (PRR) family) on the cell surface (TLR-1, -2, -4, -5 and -6) and in the endosomes (TLR-3 and -9). Specifically, TLR-9 is activated by unmethylated double-stranded CpG-rich DNA [51], allowing the secretion of interferons (IFNs) to activate the NK cells [52], which in turn kill the HPV-infected cells [53]. However, if the HPV infection becomes persistent, there is a downregulation of the innate immune response, which facilitates the virus to escape from the immune system. This mechanism could be through the downregulation of the IFN response by the oncoproteins E6 and E7 that interfere with different molecules involved in the signal transduction pathways of these cytokines [54].

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