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Quarterly Medical Review

Origin and immunoescape of uterine cervical cancer

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Summary

Human papillomavirus associated uterine cervical cancer is an important public health problem since it is classified as the fourth most common cancer in women worldwide with more than 500,000 recorded cases. This review is focused on where and why HPV infection induces cervical cancers and how this virus avoids the host immune response. Immunological therapeutic approaches are also addressed.

Even if the global mortality has diminished in the last years, this cancer still kills more than 200,000 patients every year, accounting for more than 7% of all female cancer deaths, mostly in developing countries [1,2]. Oncogenic human papillomaviruses (HPVs) are the primary etiologic agents of cervical cancer, which occurs usually in the transformation zone (TZ) of the cervix [3]. These HPVs belong to the *Alphapapillomavirus* genus of the Papillomaviridae [4]. Viral HPV genome is detected in almost all cases of cervical cancer with HPV types 16 and 18 causing 70% of them [5]. Persistent infections with one or more of the 15 oncogenic HPVs lead to the development of well-defined preneoplastic lesions or squamous intraepithelial lesions (SILs). Although HPV infections are frequent, most infected patients will clear the virus naturally within two years and more than 80% of the low grade intraepithelial lesions can regress spontaneously. Unfortunately HPV has developed several immunoescape mechanisms allowing persistent infection to progress into cervical neoplasia [6].

Mucosal oncogenic HPVs

To date, 174 HPV types are characterized based on the isolation of complete genomes [7,8] They are organized into five major HPV genera – Alpha-, Beta-, Gamma-, Mu-, and Nu-papillomavirus.

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The *Alphapapillomavirus* genus contains all HPVs for which sufficient evidence qualifies them as oncogenic for humans [9]. They are also classified as cutaneous or mucosal according to which tissues are infected [7]. This review is focused on mucosal oncogenic HPV, which are the causative agents of uterine cervical cancers and are also etiologically associated with other anogenital tumors and head and neck carcinomas [10].

In 2009, an International Agency for Research on Cancer (IARC) Working Group classified 12 oncogenic mucosal HPV types (HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59) also named high-risk HPV. Twelve additional types (HPV 26, 30, 34, 53, 66, 67, 68, 69, 70, 73, 82, 85 and 97) were classified as probably carcinogenic [11]. Other mucosal HPV types in the *Alphapapillomavirus* genus (e.g. HPV6 and 11) are responsible for genital warts and benign infections and are referred as low-risk HPVs [4].

The most prevalent HPV type in the uterine cervix (normal exocervix and every grade of cervical lesions including cancer) is HPV16 [7]. In fact, HPV16 is detected in 52 to 58% of cervical cancers in the world and the second most prevalent HPV type in cancer is HPV18 (ranging from 13 to 22%) [12]. A HPV persistent infection is necessary for the development of cancer, but other cofactors are associated with the malignant transformation of cells infected by HPV such as immunosuppression [13], tobacco smoking [14] or sex hormones [15].

Origin of HPV-induced uterine cervical lesions

Cellular origin of cervix cancer

Histologically, two types of epithelia are present in normal cervix. The endocervical canal is protected by a monolayer of glandular epithelium, which produces mucus, a barrier against pathogens, whereas the exterior of the cervix is covered, like the vagina, by a squamous epithelium. After puberty, a physiological process of squamous metaplasia leads to replacement of a portion of the endocervical epithelium by squamous epithelium. This region of metaplasia is named the transformation zone or TZ. Most of the uterine cervical cancers are squamous cell carcinoma (SCC). In a minority of cases, cervical adenocarcinoma (AC), which develops from the mucus-producing gland cells of the endocervix, is observed.

Determination of the target cell of HPV infection leading to cervical SCC and AC is still not well defined. Since there are two subtypes of cervical cancer, SCC and AC, it was proposed that SCC appears from squamous epithelium whereas AC derives from glandular epithelium [16]. However, some evidences, like the fact that some SCC started in the endocervix, suggested that SCC develops as a result of proliferation of the reserve or basal cells located into the endocervical canal [17]. Those findings have led to advances in the diagnosis of cervix cancer, particularly for intracervical curettage and Pap smears test [18]. Study of Burghardt and Ostor revealed that almost all cervical preneoplastic lesions arise from the TZ, thereby defining more precisely the anatomical origin of cervical cancer [3]. Later, based on keratin expression shared by several carcinomas, it was proposed that this expression pattern reflects a common progenitor cell that could be the endocervical reserve cell since these cells express the same panel of keratins [19]. On the other hand, patients can present cervical multifocal lesions with different grade of severities. Genetic alteration analysis of these lesions highlighted allele-specific losses suggesting that distant lesions are in fact related and probably share a common precursor cell [20]. With the discovery of the role of oncogenic HPV in cervical cancer and the paradigm that HPVs infect basal keratinocytes trough epithelium disruption [21], the following question emerged: why SCC are more frequent than vaginal cancers. Recently, a small cell population located at the squamocolumnar junction (*figure 1*) was identified and potentially represents the first cells that are infected by HPV giving rise to intraepithelial lesions and cervix cancer (*figure 2*) [22]. These cells display particular cuboidal morphology and form a single layer of epithelial cells joining the endocervical glandular epithelium to the TZ. Interestingly, squamocolumnar junction-specific biomarkers (cytokeratin7, AGR2, CD63, MMP7 and GDA) are expressed in almost all high-grade cervical intraepithelial lesions, SCC and AC, suggesting a common cellular origin for all uterine cervical cancers [22] and a particular susceptibility of these cells to oncogenic potential of HPV proteins.

Early proteins E5, E6 and E7 exhibit a variety of oncogenic properties

HPV consists of a double-stranded circular DNA genome coding for early and late genes. Early oncoproteins E5, E6 and E7, are responsible for the occurrence of cervical intraepithelial lesions, whereas E1 and E2 early proteins are implicated in the initiation and regulation of the virus cycle, including repression of E6 and E7 proteins [23]. Late genes encode for the two structural proteins, L1 and L2, forming the viral capsid. HPV virions infect basal epithelial cells of the cervix and need the epithelium differentiation process to produce their late proteins in the upper layer of the epithelium. Then, if infection persists, the viral genome can integrate into the host genome inducing overexpression of oncoproteins, by deletion of E1 and E2, and cancerous transformation of infected cells (reviewed in [24]).

As already mentioned, one of the classifications of HPVs resides in their capacity to induce or not neoplasia [25]. Although E6 and E7 from low-risk HPVs interact with their respective targets, they induce lower degradation of these compared to E6 and E7 from high-risk HPVs [26,27]. The major transforming activity of oncogenic HPVs resides in the E6 and E7 genes whereas E5 displays weaker transforming properties.