Editorial

Interaction of HPV with vaginal ecosystem in vaginal and cervical carcinogenesis

In 1951, Henrietta Lacks died at the Johns Hopkins Hospital (Baltimore, USA) due to cervical cancer, and then a more comprehensive study on this tumor was born and put immortal cells to the scientific world: the cells of Henrietta Lacks, HeLa cells[1].

Only in the 1970s and 1980s the various studies on virology and epidemiology associated with clinical evidence concluded that infection by one or more high-risk human papillomavirus (HPV) type is the leading cause of anogenital cancer[2]. In the end of the 20th and beginning of 21st century, epidemiological studies reported the concept of high-risk HPV repeatedly and its establishment as a main risk factor for cervical cancer. HPV 16 and 18 are responsible for 70% of all cervical cancer cases, and probably other squamous cell carcinomas[3].

The discrepancy between the high frequency of HPV infections among young women, including the oncogenic types, and cervical cancer clearly shows that the infection itself is not all it takes to the development of a neoplasm, even in cases of persistent infection.

HPV has a characteristic tropism — in cutaneotropic or mucosotropic forms —, in its different preferred locations of the human body. The most common clinical presentations of viral infection are condylomas and cervical cancer.

Viruses, especially HPVs, are essentially intracellular parasites with a genetic and structural complexity that requires a complex response by the host. They bind to cells through specific receptors, which shows their tropism (epitheliotropic viruses). Likewise, they require a specific biochemical and metabolic structure of the host cell in order to replicate. They get into defensive stratagems, to avoid being recognized by the host cell, through toll like receptors (TLR) and attempt to break the immune system. Immune response to HPVs is quite different than that to other viruses, once it is accompanied by low levels of antibodies in the blood (acquired immunity). By adopting the mimetic behavior of the host cellular immunity, it will cause cytopathic effects in some specific tissues[4].

HPV infection is exclusively intraepithelial, with its replication depending on the viral cycle, on the cell differentiation, as well as persistence to epithelial cells level. Once they reach the basal layer of keratinocytes, they can remain in the episomal form, or latency, or take advantage of this differentiation to perform viral integration (linear form) or replication.

HPV replication needs the cell differentiation so that its proteins can be expressed. On the other hand, immune response is far, so there is no recognition by Langerhans cells or antigen-presenting cells (APC). This virus has no cytolytic activity, so its infection is not accompanied by inflammation (neutrophils, monocytes, macrophages, *natural killer-cells* – NK, dendritic cells and APC, B and T lymphocytes, cytokines, acute phase proteins, complement proteins, and lysozymes), but it performs viral replication, a phenomena that can explain the decrease or block in effective immune response of the innate and acquired immunities[4]. These infections may become chronic and lesions can persist and establish for months or years.

Many studies based on the agent characteristics suggest that, in women presenting pathological cytology, the determination of viral load and the detection of overexpression of E6/E7 *RNAm* may be important indicators of prognosis, which may avoid overtreatment and lead to a more customized assistance.

So cervical carcinogenesis is influenced by — besides the agent characteristic (genotype, variants, viral load per cell unit, presence of multiple genotypes, expression and integration to the host's genoma) — environmental factors (such as alcohol consumption, smoking habit) and by the host's features (vaginal microbiome, immune tolerance) that can determine the risk of malignancy.

Therefore, beyond the aforementioned agent's characteristics (HPV), we must emphasize the importance of external factors, such as smoking and alcoholic habits, long-term use of sex steroids (oral contraceptives and hormone replacement therapy), gynecological infections (Herpes simplex virus – HSV, Cytomegalovirus – CMV, *Chlamydia trachomatis* and other sexual transmitted viruses), and some other unspecific inflammations that may lead to changes in the immune system and to an unbalance in vaginal microbiome. Some recently published studies have suggested the possibility of association between cervical cancer and changes in the vaginal ecosystem through the modification of microbiome[5,6]. Thus, all these agent and host characteristics may contribute with cervical immunosuppression and favor carcinogenesis. This information may help in primary and secondary prevention in order to identify risk groups.

As to the host, we give importance to genetic and immunologic factors, as well as nutritional features and sexual behavior (number of sexual partners and their characteristics, age of sex initiation), and to some endogenous factors that could cause genotoxicity, mutagenicity, irreversible cell transformation and proliferation.

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The female genitalia is widely affected when it comes to HPV, namely the cervix. This led scientists to perform exhaustive research on the physiology of lesions in this spot. The cervix is part of a reproductive organ (uterus) that plays an important role during fecundation and gestation, being subjected to hormonal influences (endogenous and exogenous), traumatic, infectious factors by the host that facilitates HPV infection.

Currently, the changes in sexual behavior of the population (especially in developed countries) have increased the incidence of HPV infection in other regions of the body, including oro-pharyngeal and anal tissues, among others. As a consequence, there was a diversification in scientific studies and publications on HPV.

Markers of cervical carcinogenesis prognosis are based on the natural history of HPV lesions (agent and host). Therefore, biomarkers of all biological levels (genotype and phenotype) may help understand the complex mechanism of carcinogenesis; especially the interaction between different cofactors and acquired (environmental) and genetic (individual) susceptibility. Consequently, these mechanisms may contribute with the clarification of cervical cancer etiology and pathogenesis in the different phases of a woman's life.

Advances in molecular biology techniques (research on types of viruses, virus load, overexpression of RNAm, specific biomarkers p16 and Ki-67) and their application in clinical trials, namely epidemiological studies, allowed the characterization and estimative of HPV infection in different populations, specific localizations, after migrations, and the etiology between infection and certain types of genotypes.

To sum up, we suggest a customized clinical/therapeutic management to avoid unnecessary treatments, based on the patient's past medical history (age of sex initiation, number of sexual partners, anovulatory cycles, parity, nutrition, alcohol and smoking habits, genetics, immunity etc.), on gynecologic infections, on the assessment of the vaginal ecosystem (pH, lactobacillus), on cytopathologic diagnosis (atypical pavimentous cells of undetermined significance; low grade squamous intraepithelial lesions – LSIL; high grade squamous intraepithelial lesions – HSIL, Atypical glandular cells – AGC; Cervical Intraepithelial Neoplasia I – CINI; and Cervical Intraepithelial Neoplasia I and II – CINII/III), on molecular diagnosis (HPV, viral load, HSV, CMV, *Chlamydia trachomatis, Mycoplasma*, *Ureaplasma*, *Neisseria gonorrhoeae*) and on the Immunohistochemical study (p16 e Ki-67) of dysplasia components[7-9].

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