Editorial

Low and High-Oncogenic Risk Human Papillomaviruses: Every Rule Has its Exception

ABSTRACT
Papillomavirus are causative agents of epithelial hyperproliferation, also known as warts, in a wide range of vertebrates. Some types of human papillomaviruses (HPV) cause cervical cancer in women, cancer of the penis in men, and anal and oropharyngeal cancers in both genders. Molecular methods have shown approximately 150 types of HPV in humans, and large-scale epidemiological studies have aided in identifying the oncogenic risk of most of these HPV. In clinical practice, HPV are classified as high- or low-risk oncogenic HPV. Low-risk oncogenic HPV cause genital warts (condylomata) and low-grade dysplasia, whereas high-risk oncogenic HPV cause high-grade lesions (cervical intraepithelial neoplasia 2+), which are precursors to cervical cancer. Further, both low and high-risk HPV types are frequently present in asymptomatic forms. There are rare descriptions of high-risk oncogenic HPV causing benign lesions, and low-risk oncogenic HPV causing malignant lesions. From a virological point of view, the role of the host and viral intratypic variability in the development of atypical lesions is not clear. We believe that molecular analysis of HPV isolated from atypical lesions may assist in elucidating the biochemical and cellular mechanisms responsible for the uncontrolled proliferation of keratinocytes in genital dysplasia and neoplasia.
Keywords: human papillomavirus, HPV, genital warts, carcinomas, dysplasia, STD

Human papillomavirus (HPV) infection may be completely asymptomatic or may induce benign proliferative disorders, such as skin warts, laryngeal papilloma, and condylomas, in addition to malignant neoplasia. Molecular evidence suggests that HPV infection is the cause of several cancers affecting the vagina, vulva, anus, and penis, in addition to carcinomas of the oral mucosa, oropharynx, and larynx[1,2]; moreover, it contributes to the occurrence of virtually 100% of cervical cancers[3,4]. About 40 different HPV types are known to be capable of infecting the anogenital region, and they have been classified into low-oncogenic risk types (HPV 6, 11, 40, 42, 43, 44, and 55) and high-oncogenic risk types (HPV 16, 18, 31, 33 , 35, 39, 45, 51, 52, 56, 58, and 59). HPV 26, 53, 66, 67, 68, 70, 73, and 82 are recognized as potential high-risk genotypes[5]. This subdivision is mainly based on the findings of large case–control epidemiological studies[6]. The papillomavirus taxonomic classification, which is based on partial data obtained from their L1 sequences, also reflects the abovementioned division. However, differences have been observed between the phylogeny established using sequence data and the one established using phenotypic/clinical similarity data[7]. Low-risk HPV are grouped into α1, α8, and α10 strains, whereas high-risk HPV belong to the α5, α6, α7, and α9 strains[8].

HPV 16 and 18 infections account for 70% of cervical cancers, and these are the two most common HPV types present in all geographic regions, when considering both asymptomatic infections[9,10] or cervical cancers[11,12]. HPV 6 and 11 are low-risk HPV types that account for more than 90% of cases of condylomata[13,14]. However, studies have shown the presence of low-risk HPV in high-grade lesions[11,15-17] and high-risk HPV in benign lesions[13,14]. Although condylomata acuminata is always associated with low-risk HPV infections, Brown *et al*. showed the presence of high-risk HPV in condylomata acuminata samples obtained from both HIV-positive and -negative patients[18]. The multinational study HPV in men (HIM) showed 6 cases where only high-oncogenic HPV were isolated from warty lesions, with HPV 16 being the most frequently isolated virus[14]. Similar results were obtained by Chan *et al*. [13] who studied condylomata in men and identified five cases, in which only high-risk HPV were detected with HPV 16 again being the most commonly identified virus.

Conversely, low-risk HPV were isolated from high grade lesions[19], but always concomitant with high-risk HPV. In such cases, it is extremely difficult to assign causality to a specific HPV genotype, because the molecular methods used for HPV genotyping generally do not preserve tissue architecture. Thus, it is difficult to identify whether the HPV types found in high grade lesions are effectively involved in the carcinogenic process or if only one specific genotype is involved in tumor formation and the other type/s causes asymptomatic genital infection. Further, there have been very rare reports of cases of cervical cancer, in which only low-risk HPV was isolated, such as HPV 6 and 11[11,15-17]. A study in cervical cancer patients in Kenya[15] showed two non-HIV infected women from whom only HPV 11 and 40, also a low-risk type, could be isolated. Further, a retrospective study by De Sanjosé *et al*.[11], in which 10,575 cervical cancer samples from 1949 to 2009 from five continents were analyzed, showed 16 HPV-positive cases with only low-risk HPV. Recently, our group reported[17] a case of cervical metastatic cancer associated with HPV 11 in 1 HIV-infected patient, and this type of HPV was identified both in samples from the primary cervix tumor and cervical lymph node metastasis.

In the carcinogenic process mediated by HPV, viral proteins E6 and E7 play a central role. Initial observations showed that the E7 protein could bind underphosphorylated forms of tumor-suppressor retinoblastoma protein (pRb), thus, inactivating it, whereas the E6 protein binds to tumor-suppressor protein 53 (p53), thereby accelerating its proteolytic degradation. However, the affinity of these viral proteins for the products of tumor-suppressor genes varied according to the oncogenic potential of the HPV[20,21]. The ability of the E6 protein to degrade p53 seemed to be present only in the species 5, 6, 7, 9, and 11 of the *Alpha-papillomavirus* genus and may be linked to the absence of a basic amino acid in position 31 of the E6 protein. HPV that do not degrade p53, such as HPV 6 and 11, have lysine or arginine in position 31[22]. In the single case of HPV 11-associated cervical metastatic cancer re-

cently shown by our group[17], we performed sequencing of the E6 gene to evaluate whether the malignant transformation could be caused by mutations in the gene and in turn resulted in a gain of function similar to that in high-risk oncogenic HPV. However, the E6 gene sequence showed high similarities to the reference HPV 11 sequences, and we found no mutation that may be associated with gain of function.

Besides the differences in ability to inactivate the products of tumor-suppressor genes, the persistence of lesions and their tendency to progress may differ according to the virus variant, even within the same high-risk HPV type. The Asian-American (AA) and African (Af) HPV 16 variants showed a threefold higher risk for development of cervical cancer than the European (E) variant. The non-E HPV 18 variants are more frequently identified in cancer tissues and high-grade lesions[23-25]. HPV 33 (C7732G) and HPV 58 (C632T and G760A) variants were associated with a higher risk for cervical cancer[26,27] than that observed for infectios with "prototypes" of the same HPV 33 and 58.

Some studies focusing on the upstream regulatory region (URR) of papillomaviruses (PV), that contains transcription factor binding sites (TFBS), showed that some TFBS are common to all PV and some are type-specific[28,29]. Thus, it was concluded that alterations in replicative behavior and oncogenic capacity of different variants of the same PV type may be attributed to mutations in the URR[30,31]. The analysis of the E5 open reading frame (ORFE5) of mucosotropic HPV enabled classifying these HPV into four phylogenetically distinct families, on the basis of their capacity to induce benign and malignant proliferative disorders[32].

In conclusion, the data mentioned above indicate that HPV variants determined from different genomic regions (here we have mentioned URR, E5, and E6) present distinct transforming abilities. It is known that clinical manifestation of an infectious disease is the result of the interaction between agent and host, and certainly the atypical symptoms discussed here can be the result of not only HPV isolates with abnormal biological activity but also of host-dependent features, of which the most obvious is the immune state, since atypical traits are more common in immunosuppressed patients. It is possible that the connection between immunodeficiency and behavior of HPV-induced lesions occurs through intra and intercellular mechanisms controlling the expression of viral oncogenes. Deficiency in certain cell types, such as macrophages and other antigen-presenting cells in the infected mucosa, and low production of anti-proliferative cytokines, such as tumor necrosis factor (TNF)-α and transforming growth factor (TGF)-β, could allow cell transformation by viral oncoproteins with weak transforming activity, such as E6 and E7 proteins from HPV 6 and 11[33].

However, even in these patients, high-risk oncogenic HPV are commonly associated with high-grade lesions, and there is no convincing explanation as to why high-risk HPV would cause hyperproliferative warts (condylomata) in immunosuppressed patients. Whole-genome sequencing of HPV that cause well-characterized atypical infections (low-risk HPV in high-grade lesions and high--risk HPV in benign lesions), and their comparison with the same HPV types isolated from "conventional" lesions may aid in explaining this rare and puzzling clinical manifestations.

Conflict of interest

There is no conflict of interests to declare.

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