How Does Human Papillomavirus Contribute to Head and Neck Cancer Development?

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Human papillomavirus (HPV) is the major etiologic factor in the development of cervical cancer (1) and has been the target for detection and prevention of the disease (2,3). Results of recent molecular and epidemiologic studies suggest that HPV may also be an etiologic factor in a subset of head and neck squamous-cell carcinomas (HNSCCs), particularly those that develop at oropharyngeal sites (4–6).

In this issue of the Journal, Braakhuis et al. (7) report the striking finding that HNSCCs with active HPV type 16 DNA (i.e., HPV16 DNA that expressed the viral E6 and E7 genes) had substantially lower rates of loss of heterozygosity (LOH) at chromosomal regions 3p, 9p, and 17p than tumors that contained inactive HPV DNA (i.e., HPV DNA that did not express E6 and E7). This finding did not extend to LOH at chromosomes 13q, 18q, 8p, and 6q (7). Not surprisingly, Braakhuis et al. (7) also observed a negative association between active HPV DNA and mutations in TP53, the gene encoding the p53 tumor suppressor, as has been reported by other groups (5,8).

Because the chromosomal regions analyzed in the Braakhuis et al. study contain tumor suppressor genes and are commonly deleted in HNSCC, it is believed that LOH at these regions plays a role in head and neck tumorigenesis. The striking finding, therefore, suggests that HPV16 may play a role similar to those of the tumor suppressor genes located at the three chromosomal regions.

In cervical cancer, the retention of HPV16 DNA and continued expression of viral E6 and E7 genes are required to maintain the malignant phenotype of the tumor cells (9). The finding by Braakhuis et al.—that only HNSCCs that expressed the HPV16 E6 and E7 genes showed distinct patterns of LOH but not the tumors that carried inactive HPV16 DNA (7)—supports the notion that active HPV16 is required in a subset of HNSCC to maintain the malignant phenotype. The lack of TP53 gene mutations in any of the tumors with active HPV16 in this study, and the observation that tumors with inactive HPV16 DNA had a similar TP53 mutation frequency as tumors that lacked HPV DNA, further underscore the importance of continued activation of HPV16 in maintaining a malignant phenotype.

It is interesting that deletions at 3p and 9p, two of the three chromosomal regions that lacked LOH in tumors with active HPV16 E6 and E7, are among the earliest abnormalities detectable in head and neck tumorigenesis (10,11). It is possible that a lack of LOH at these regions reflects the absence of exposure to etiologic factors that cause DNA damage and genomic instability. The fact that many HNSCC patients whose tumors have active HPV DNA do not smoke or drink alcohol (5) supports this notion. Alternatively, HPV infection could occur before the deletion events. In this case, if HPV contributes to tumorigenesis through pathways that are similar to those resulting from the loss of tumor suppressor genes located at 3p and 9p, deletion of these chromosomal regions would no longer be required for tumorigenesis. The 9p region analyzed by Braakhuis et al. (7) harbors
the gene encoding p16, a tumor suppressor that controls the activity of the pRB tumor suppressor (12) and is commonly inactivated during head and neck tumorigenesis (13,14). Because binding of the HPV16 E7 protein to pRB inactivates pRB (15), it may bypass the need to inactivate p16 in the tumorigenic process. The recent finding that all HNSCCs with integrated HPV16 DNA overexpressed p16 (16) supports this hypothesis. However, the sample sizes in these studies (7,16) were small; additional studies are needed to test the hypothesis.

The fragile histidine triad (FHIT) gene is a tumor suppressor gene located at chromosome region 3p14, where an HPV DNA integration site has been reported (17). Inactivation of FHIT is common in HNSCC and often occurs through LOH and/or aberrant transcription (18). Although no association has been reported between inactivation of FHIT and HPV infection, Sagawa et al. have reported that, among HPV DNA–positive cervical tumors, those with abnormal FHIT expression have statistically significantly lower levels of E6 and E7 gene expression than those with normal FHIT expression (19). These data raise the possibility that integration of HPV DNA into the FHIT locus may contribute to rearrangement of this chromosomal region, resulting in abnormal splicing patterns and repression of the viral genes. If this is the case, it may partially explain the high frequency of LOH at 3p among the HPV16 DNA–positive, E6/E7–negative tumors reported by Braakhuis et al (7).

LOH at the TP53 locus (i.e., chromosome region 17p) and mutation of TP53 are the common mechanisms by which this tumor suppressor gene is inactivated in head and neck tumorigenesis. Other less common mechanisms could also play a role in the inactivation of TP53. For example, it has been shown that HPV16 E6 binds to E6–associated protein (E6AP), a protein ligase of the ubiquitin pathway of proteolysis, and the E6–E6AP complexes can then target p53 for rapid degradation by proteasome (20). Therefore, it is unlikely that malignant transformation of cells with a constitutively active E6 gene would require inactivation of the TP53 gene, either through deletion or mutation. The observation by Braakhuis et al. that other chromosomal regions (e.g., 13q) have a similar LOH frequency in HPV16–active and HPV16–inactive tumors suggests that other alterations in addition to HPV16 activity might be required for the development of HNSCC. However, the frequencies of LOH at 3p, 9p, and 17p appeared to be similar to those at 6q, 8p, 13q, and 18q in the E6/E7–positive tumors in the report by Braakhuis et al. (7). Because the LOH frequencies in the latter group of chromosomal regions were also low in the E6/E7–negative tumors, it is possible that cells with constitutively expressed E6 and E7 viral proteins may bypass most of the genetic events necessary for malignant transformation in the development of this subset HNSCC.

At this point, it is accepted that infection with high-risk HPV types has an etiologic role in the development of a subset of HNSCCs. HPV DNA–positive tumors, particularly those with active E6 and E7 proteins, appear to have distinct biologic features, and such tumors have better clinical outcomes than HPV DNA–negative tumors (21–23). Understanding how the viral proteins interact with cellular proteins and/or DNA in host cells may allow us to design strategies to block malignant transformation. The promising results from a trial of an HPV vaccine to prevent cervical cancer (24) raises hope that such a strategy can also be used to reduce the incidence of HNSCC.

**References**

