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SPECIAL ARTICLE

Molecular aspects in HPV-dependent laryngeal and oropharyngeal carcinoma

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Summary

Human papillomavirus (HPV)-mediated cervical carcinogenesis represents a well analyzed model of viral implication in epithelial malignant transformation. Mechanisms of high risk (HR) HPV-related infection seem to demonstrate a similar action regarding its implication in head and neck (HN) carcinomas, predominantly in squamous cell carcinoma (SCC) histological type. The prevalence of HR HPV subtypes - mainly HPV16 - is characterized by a broad geographic heterogeneity. Furthermore, HPV-associated HNSCCs demonstrate differences regarding sexual, molecular, epidemiological, and prognostic features compared to alcohol and tobacco dependent ones. Based on these differences, HPV-derived HNSCC appear to be a specific well-defined entity mostly affecting young to middle-aged - male mainly - non-smokers. This is a strong reason of detecting an increased HR-HPV DNA levels -due to viral transmission - in oropharyngeal and laryngeal anatomic regions. Additionally, different response rates to chemoradiation and targeted therapeutic regimens are another significant field for handling these SCC malignancies in the corresponding patients. In the current special article we explored the role of HPV-related carcinogenesis in oropharyngeal and laryngeal SCC focused on the latest molecular aspects.

Key words: *carcinoma, human papillomavirus, larynx, oropharynx*

Introduction

Head and neck squamous cell carcinoma (HNSCC) is the sixth most common malignancy worldwide (600.000 cases/year), and is responsible for ~ 350,000 deaths each year. Unquestionably, alcohol consumption and smoking are recognized and already established risk factors for the development of HNSCC [1]. Additionally, persistent infections with oncogenic HR HPV have emerged as another significant etiologic factor for HNSCC [2,3]. It is reported that prognosis of patients with HNSCC is strongly age and stage-related. Moreover, 5-year survival rates higher than 55% for young patients (15-45 years) and higher than 35% for older patients (>75 years of age) are reported. It has to be highlighted that despite recent advances in HNSCC therapeutic management, for advanced-stage disease the mortality rate is still very high and HNSCC remains a major health problem [4]. Thus, solid scientific data support that therapeutic management for HNSCC requires a multidisciplinary approach. According to the American Joint Committee on

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Cancer (AJCC) for locally advanced disease a multimodal treatment including surgery, chemotherapy and radiotherapy is recommended, while for early-stage disease surgery or radiotherapy are considered more appropriate [5].

Based on innovative molecular methods, understanding of the HNSCC genetic landscape and especially regarding the mechanism of carcinogenesis has been substantially improved [6]. Furthermore, significant development of various novel therapeutic tools that are now available, as well as the scientific focus on intra-patient and intra-tumor heterogeneity could open a new roadmap in HNSCC management. In this way, cetuximab (an anti-EGFR monoclonal antibody) was the first targeted agent to be approved by FDA for the treatment of HNSCC [7]. It has also to be highlighted that according to National Comprehensive Cancer Network (NCCN) guidelines, cetuximab and platinum and 5-fluorouracil are currently the number one treatment option for recurrent/metastatic or non-resectable non-nasopharyngeal HNSCC [8]. Interestingly, HPV-associated HNSCCs demonstrate differences regarding sexual, molecular, epidemiological, and prognostic features compared to alcohol and tobacco dependent ones. In the current short molecular review, we explored the role of HPV-related carcinogenesis in oropharyngeal and laryngeal SCC focused on the latest molecular aspects.

Genetic nature of HPV

HPV-mediated cervical carcinogenesis represents a well analyzed model of viral implication in epithelial malignant transformation. HPVs are described as icosahedral non-enveloped particles. Their capsid consists of ~72 capsomers, is 55 nm in diameter and contains a circular double DNA molecule of approximately 8 kb. Moreover, their genome is organized in 8 reading frames and a non-coding region [9]. The proteins involved in DNA replication and transcription are encoded by the six early open reading frames. The non-coding region contains regulatory sequences that respond to steroid receptor hormones. Up to date > than 100 different types of HPV have been described in the literature infecting human epithelial cells of skin and mucosa [10]. HPV types evolve very slowly, and have diverged since the origin of humans by only about 2%. These divergent isolates are called 'variants'. HPV infections are associated with a wide spectrum of epithelial lesions including benign hyperplasia that rarely leads to cancer. However, an important group of HPVs - the HR HPVs - are associated with lesions that progress to malignant tumors. The prevalence of HPV infection in the general population varies in accordance with multiple factors. Two peaks of HPV infection are commonly described at 26-30 and 46-50 years. The diagnosis of HPV infection is largely based on molecular methods, which are mainly PCR-based. General or consensus PCR primers have been developed, which detect a broad spectrum of HPV genotypes in a single PCR. Several techniques have been used to detect the presence of HPV in tissues. Notably, it has to be highlighted that HPV 16 is the most common HR HPV virus and its contribution to neoplastic progression is through the viral oncoproteins E6 and E7 [11-13].

HPV in laryngeal and oropharyngeal carcinoma

Several attempts have been made by the scientific community and the literature offers some studies assessing the potential role of HPV in the laryngeal and oropharyngeal carcinogenesis setting. Thus, a recent research study based on laryngeal SCCs and laryngeal nodules combined analyses reported that HPV - especially HR HPV 16/18 subtypes - were detected in significant percentages of them (~33%). The main conclusion of this study was that HPV infection is not likely to influence survival rates as an independent prognostic factor in patients with laryngeal SCC and that further studies are necessary so that safe conclusions to be reached about its potential prognostic role in those patients [14]. Furthermore, another research group reported that a similar HPV DNA type 16 positivity was detected in their analyzed specimens [15]. Additionally, aberrant expression of p16INK4a, pRb, cyclin D1 and p53 was assessed by immunohistochemistry. Another molecular study identified a significant prevalence of HPV infection and its association with laryngeal SCC. According to their results, 20 HPV genotypes (HR HPV: HPV-16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, and 68 low risk (LR) HPVs: HPV-6, -11, -40, -42, -44, -61, and -73) were reported among those patients. The researchers reported that the overall HPV prevalence in laryngeal cancer tissues was 28.0% (95% confidence interval [CI], 23.5%–32.9%). In addition, a total of 27% laryngeal cancer patients were infected with HR HPV types only. Moreover, it was reported that HPV 16 was the most frequently observed type [16]. The meta-analysis performed on 12 eligible case-control trials suggests a robust association between HPV infection and laryngeal SCC, with a summary odds ratio

(OR) of 5.39 (95% CI, 3.25-8.94). The authors have concluded that HPV infection, especially infection from HR type HPV 16, was significantly associated with the risk of laryngeal SCC carcinogenesis. However, a review published recently reported that the association between HPV infection and laryngeal carcinogenesis is highly unclear, and different anatomic sites or different populations might present different HPV genotypes [17]. HPV 16 was the most frequently observed type in laryngeal cancer specimens and showed a robust association with the laryngeal carcinogenesis. Another original research study based on HPV DNA amplification by the short PCR fragment (SPF 10) primer set using PCR/DNA method was reported [18]. The authors concluded that no statistically significant association was observed between the presence of HPV and the epidemiological and clinicopathological characteristics and tumor recurrence. Moreover, no statistically significant association was observed between the HPV presence and overall survival (OS) and disease free survival (DFS). The presence of HPV infection in 28% of the patients suggests a potential role in the pathogenesis of laryngeal SCC, but this rate is not considered statistically strong. The authors of this study support that the SPF10 PCR/DEIA method is the most accurate way for HPV detection in patients with laryngeal SCC, but the results of the study although revealed a potential association rate of HPV with laryngeal cancer are not considered statistically strong.

A similar molecular study performed in primary laryngeal SCC and HPV was assessed using real-time quantitative PCR [19]. It was reported that HPV 16 was identified in 27% of SCCs combined by an important statistical association towards higher HPV prevalence in Caucasian Americans versus African Americans and also with gender. High prevalence of HPV in males was observed. No significant association between HPV and tumor stage was observed. The presence of genotype-specific HPV DNA was evaluated using the Linear Array HPV Genotyping Test and the INNO-LiPA HPV Genotyping Assay in invasive laryngeal SCC cases was assessed in another recent original study [20]. The authors reported that HPV DNA was detected in 20% of invasive laryngeal cancers. Thirteen different genotypes were identified in this study. Notably, they found that HPV 16 and HPV 33 were the most commonly identified types. HPV was detected in 33% (9/27) of women compared with 18% (22/121) of men. The authors reported also that female patients were more likely to have HPV-positive laryngeal tumors compared to males. HPV 16 and 18 constituted half of HPV-positive cases in men while among women only 1 was HPV 16 positive and none were positive for HPV 18. Another important finding of this study was that overall 5-year survival did not present variations in correlation with HPV landscape. They also concluded that HPV may be involved in the development of a small proportion of laryngeal carcinogenesis and its role may be predominant in women compared to men. However, this small subset of association of HPV and development of laryngeal cancer does not permit to draw statistically strong conclusions. Concerning the oropharyngeal SCC, current evidence suggests that HPV type 16 has a crucial aetiological role in a significant proportion of those cases. These tumors are located mainly near the lymphoid tissues of Waldeyer's ring, such as the tonsils and base of the tongue. A multivariate analysis implemented by a research group in analyzing oropharyngeal SCC, identified that T1-3 stage and also the combination of HPV DNA positivity and p16 (INK4a) overexpression led to a significantly better recurrence-free survival. They also suggested that this combination is a more accurate marker for active HPV infection in HNSCC than HPV DNA status or general p16 (INK4a)-positive status alone [21].

In conclusion, several original studies with different detection methods and systematic reviews have been conducted to date in order to explore the association of human HPV infection with laryngeal and oropharyngeal carcinogenesis. However, current findings are heterogeneous and controversial regarding biological behavior and prognosis in these malignancies. Extensive HPV gene analysis based on novel molecular techniques (i.e. complementary DNAs- c-DNAs, Linear Array HPV Genotyping) should enlighten specific genetic events during the progression of carcinogenesis in the corresponding patients. Furthermore, development of novel prophylactic vaccines against HPV should be a significant step in preventing persistent infections in laryngeal and oropharyngeal epithelia as it happens in cervical ones, avoiding precancerous lesions in vaccinated individuals by anti-HPV 16/18 predominantly [22].

Conflict of interests

The authors declare no conflict of interests.

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