The role of human papillomavirus-16 in the pathogenesis of oral squamous cell carcinoma

Recently, several papers showed that HPV may be involved in the pathogenesis of a subgroup of oral and cervical squamous cell carcinoma (SCC), leading to distinct molecular characteristics compared with HPV-negative ones. Several factors are involved in oral carcinogenesis, such as age, gender, ethnicity, lifestyle, genetic background, status of health and exposure to one or more oncogenic factors (tobacco smoking and alcohol consumption). However, 15-20% of head and neck cancers have no known tobacco or alcohol exposure. Thus, other agents, such as viruses are being investigated. In particular, with regard to viral involvement, it is still highly controversial whether HPV, widely reported as one of the prominent mechanism behind the development of cervical SCC, can also be considered an aetiological or a malignant risk factor in oral carcinogenesis. HPV16, the most common HPV type detected in biopsies from woman with cervical SCC (55%), is also the most common type detected in biopsies from head and neck SCC (85-95%). Aside from HPV16, other oncogenic HPV types commonly detected in invasive cervical cancer biopsies (e.g. HPV18, 31, 33, 35, 45, 56, 58 and 59) are rarely or never detected in head and neck SCC biopsies.

The majority of HPV-related cancers contain HPV DNA integrated into the host cell genome and express only two viral genes, E6 and E7, both of which encode oncoproteins. The E6 protein of the high-risk HPVs (e.g. HPV16) binds wild-type p53 and induces its degradation via an ubiquitin-mediated process. The loss of functional p53 impairs apoptosis and induces genetic instability. Moreover, E6 inactivates telomerase, an enzyme that maintain telomeric DNA stability. The high-risk E7 may play a role in the HPV life cycle by disrupting pRB family member-mediated transcriptional repression of certain genes involved in cell cycling. Therefore, pRb down-regulation by HPV E7 results in p16 up-regulation. Loss of cell cycle and apoptosis control, therefore, constitutes an early and central event in HPV-mediated carcinogenesis and the integration of HPV DNA into the host genome is believed to be the key event.

Oral cancer occurs as the final stage of the multistage process of carcinogenesis. Apoptosis is genetically regulated. It develops due to the balance between antiapoptotic and proapoptotic genes and their products-proteins. To determine the importance of HPV16 infection in the pathogenesis and progression of oral SCC, we investigated
The immunohistochemical expression of proapoptotic (p53) and antiapoptotic proteins (survivin) in oral SCC tissue.

This study is based on samples retrospectively and prospectively collected from patients with surgically removed oral squamous cell carcinomas, localized on the lower lip, tongue or floor of the mouth. The patients were being followed up in a three years period, some of them even longer. Immunohistochemistry was performed on formalin fixed and paraffin embedded tissue samples. Immunohistochemical identification of p53 and survivin oncoproteins was performed using the streptavidin-biotin-peroxidase technique according to standard LSAB + procedure (DAKO, Denmark). Standard PCR method was performed for HPV16 genomes detection.

The incidence of HPV16 infection in oral SCC in our population is 23.3%. The time interval without disease recurrence is significantly shorter in HPV16 positive female patients compared to HPV16 positive men. There is dominated HPV16 independent mechanism of oral oncogenesis. Also, it has been detected HPV16-associated mechanism of oral oncogenesis, but in less percentage of cases.