Role of Genes Tp16, Tp53 and Rb on Genetics Oral and Oropharyngeal Cancer: A Review

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Abstract
With the advancement of molecular biology and knowledge about genetic aspects in recent decades the study of the processes that determine the emergence, evolution and prognosis of tumors in different tissues and body regions, has become increasingly necessary and crucial for the approach of better treatment, care or relief that improve the quality of life of cancer patients. Damage in TP16, TP53 and RB genes are related to various tumors squamous cell, and studies have shown their relationship with head and neck carcinomas. Risk factors such as smoking, alcohol consumption and the presence of human papilloma virus in the affected tissue influence the pathophysiology of these tumors, especially over action in these genes or on their products. This brief study meant to address issues of concern that has been studied about the genetics of cancer of the oral cavity and oropharynx, considered the most prevalent and incident of head and neck carcinomas group.

INTRODUCTION
The squamous cell carcinomas (SCC) represent the vast majority of carcinomas affecting the head and neck region, representing 90% to 95% of neoplasms. Squamous cell carcinoma of the head and neck (SCCHN) begin from aggression caused by chemical, physical or biological agents that lead to the formation of differentiated cells that can develop into a tumor [1]. Changes in gene of the cell lead to the formation of an abnormal process, which culminates in cell proliferation, which, if not diagnosed and treated in time, trigger the formation of a tumor process with unfavorable prognosis for the patient [2].

Evolution depends on causal factors beyond the affected site. Alone, factors such as smoking, alcohol consumption and the presence of high-risk HPV[1] can trigger the process of carcinogenesis, however, with a lower speed and form of aggression than when these factors are associated [3].

This study aims to address genetic aspects related to the carcinogenic process in squamous cells of the oral cavity and oropharynx, from a review of the literature on this approach, focusing on genes TP16 and TP53 associated with cancer process this type of tissue.

Overview of the oral cavity and oropharynx carcinomas
The latest estimates of the International Agency for Research on Cancer (IARC) report that in the world, the oral cavity tumors accounted for about 264,000 new cases and 128,000 deaths in 2008. The incidence is higher in men than in women, with an approximate estimate of 2.3: 1.

In the United States, according to Surveillance Epidemiology and End Results (SEER), 2014, there were an estimated 42,440 new cases of oral cavity and oropharynx carcinomas, with 8,590 deaths. The average age of patients diagnosed with carcinoma of the oral cavity and oropharynx is 62 years, with the highest incidences are between 55 and 64, corresponding to 29.5% of all cases. The incidence rate was estimated at 11 cases per 100,000 inhabitants.

In the European Union, the latest data show an incidence of 73,014 cases with 28,171 deaths for oral cavity and oropharyngeal carcinomas, with a rate of 12 new cases per 100,000 inhabitants, according to data from EuCAN, 2012. Hungary is at the top of list with a rate of 24 new cases per 100,000 inhabitants. The largest number of cases was Germany with 15,891 new cases and 5,016 deaths in 2012, and an incidence rate of 14 new cases per 100,000 inhabitants.

The smoking, alcohol consumption and HPV infection are the most important risk factors for oral cavity and oropharyngeal carcinomas [4,5]. Smoking and drinking together represent the main risk factors associated with a large part of the oral cavity and oropharyngeal carcinomas. Carcinomas associated with...
smoking and alcohol consumption include the most aggressive cancers and poor prognosis [6]. These substances, alone offer carcinogenesis risk in the oral cavity and oropharynx, however, when associated with other factors such as lack of oral hygiene, genetic factors and HPV infection, the risk becomes considerably higher [7,8].

Smoking and alcohol consumption, associated with polymorphisms in genes GST (glutathione S-transferase) which metabolize components of the cigarette, increase the risk of SCCHN, and smoking results in increased to 3.5 times the susceptibility to cancer compared an individual nonsmoker [9].

Tumors of the oral cavity and oropharynx induced by tobacco occur from genotoxic effects of tobacco components, such as nitrosamines and polycyclic hydrocarbons. The alcohol metabolite, acetaldehyde, also interferes with the synthesis and DNA repair. Alcohol greatly increases the tobacco carcinogenic potential; it acts as a solvent for the constituents of this substance [10].

With increasing anti smoking campaigns and against the abuse of alcohol worldwide, the number of cases of oral cancer associated with HPV was highlighted [11]. The prevalence of HPV was reported in several studies that assess the frequency of this virus in the oral cavity and oropharynx carcinoma. [3,8,12,13], unprotected oral sex practice, and of the practice of unprotected sex contribute to the spread of the virus and the changing nature of its location, since HPV is most common in the genital area. These factors are exacerbated with the increasing number of partners [14]. HPV infection, especially by types 16 and 18 direct the evolution of the tumor and the prognosis for a different frame [15,16].

Genetics of oral cavity carcinomas

Tumor cells have genetic alterations that determine the evolution, aggressiveness and prognosis of a cancer. However, the ways and different mechanisms that trigger this process are still unclear [17]. Tumors can arise from changes in tumor suppressor genes, activation of oncogenes, change in expression of multiple genes or chromosomal changes such as deletions, amplifications or translocations [2].

Whether for single nucleotide polymorphisms or multiple chromosomal deletions, a single modified cell, which acquires immortality and proliferation properties, is able to initiate the formation of a tumor tissue [2,18]. Genetic polymorphisms of GSTs, multigenic families of detoxification enzymes, increase the risk of impairment for carcinomas in metabolizing capacity of toxic compounds, such as in tobacco, and these polymorphisms, ranging from individual to individual, give some greater susceptibility the cancer [9].

Among the different genetic mechanisms, stand out in SCCHN, particularly in carcinomas of the oral cavity and oropharynx, significant changes in the properties of the products of the TP16 tumor suppressor gene, TP53 and Rb [19].

The TP16 gene product [p16], mapped to 9p21, cyclin D1 is an association of inhibitor with cyclin dependent kinase CDK4 and CDK6. This association, in turn, causes the phosphorylation of retinoblastoma protein (pRb) protein associated E2F transcription factor. This allows the release of E2F, which promotes the passage from G1 to S phase, continuing the process of cell division (Figure 1). The expression of p16 is regulated by phosphorylation of pRb and the availability of the E2F (Figure 2) [12,20]. P16, therefore, plays a key role in cell cycle and its low expression or inactivation contributes strongly to a cell proliferation process, since it results in increased availability of the E2F transcription factor. The low expression of this protein in SCCHN, pointing to a worse prognosis [16].

The product TP53 (p53), mapped to 17p13 acts in genomic stability and the control of cell proliferation. Since faults occur in the DNA during the transcription process, and that these failures are not corrected, there is induction of apoptosis. Changes to TP53 are described in many tumors, such as cervical carcinomas, especially for the degradation of p53 induced by E6 viral protein, present in cells infected by the human papilloma virus or by mutations in the TP53 gene caused by chemical agents, such as present in tobacco [17,19,21].

Figure 1 Representative scheme of p16 action on cell proliferation in normal conditions (A) and when no change in expression of this protein (B).

Figure 2 Regulation of the expression of p16. (A) pRb and E2F associated, low expression of p16. (B) phosphorylated pRb and free E2F, increased expression of p16.
The retinoblastoma protein (pRb) encoded by the RB gene, mapped to 13q14, operates in association with the E2F transcription factor and is directly related to the transition from G1 to S phase, the cell division process. Phosphorylation of pRb releases the transcription factor E2F which in turn acts promoting cell division [22]. Besides the influence of the decrease in the expression of p16, the presence of the viral oncoprotein E7 HPV induces degradation of pRb to E2F linked via proteasomes also favoring cell proliferation [12,23]. In this case, the degradation of pRb stimulated by E7 induces the production of p16. The increase in p16 expression was observed in situations where there is presence of high-risk human papillomavirus, such as HPV 16 and 18 [23]. The degradation of pRb induced by E7 results in increase in p16 expression [24].

Other changes in protein expression correlated with tumor behavior, include the case of Ki-67 protein, a protein expressed by the gene mapped to 1q025 and has to be increased in situations where there is increased cell proliferation [5]. Increase in Ki-67 expression has been associated with the prognosis of the oral cavity and oropharynx carcinomas [25].

CONCLUSION
Changes in products interfering gene TP16, TP53 and RB have been associated relevant in the onset, progress and prognosis of tumors oral and oropharyngeal cavity. As the TP53 is a gene that works in genomic stability and control of cell proliferation, the failures that occur it is of utmost importance for cancer biology knowledge, as well as regulation and phosphorylation of TP16 promotes fundamental role in the cell cycle, in phase passes and HPV also is another important factor that can trigger changes in these cycles The p16 protein is an important prognostic marker because its low expression has been commonly associated with the presence of more aggressive tumors. Mutagenic and carcinogenic factors, as alcohol consumption and smoking have capacity of potentiate the effects.

REFERENCES
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