

## A Short Review of the Role of Genetic in Oral and Squamous Cell Carcinoma

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### Abstract

This review aimed to analyze the role of genetic in oral cancer. Head and Neck cancer is multifactorial disease in which a wide factors play a role in its apparition and progress. More than 90% of malignant neoplasms are oral squamous cell carcinoma developed on the mucous epithelium and the sixth most common cancer in the world. The environment, such as smokeless tobacco, alcohol, betel quid chewing are most common factors are involved in the etiology of the oral cancer. Several genes and pathways associated with oral squamous cell carcinoma are significant in terms of early detection and prognosis. Molecular biomarkers are being discovered in oral cancer diagnostic. It could be used as screening for detection and improve therapeutic strategies of oral pre-cancer and oral squamous cell carcinoma.

**Keywords:** Oral Cancer; Biomarkers; Molecular Pathways

### Abbreviations

OSCC: Oral Squamous Cell Carcinoma; HPV: Human Papillomavirus; MAPK: Mitogen-Activated Protein Kinase; ERK: Extracellular Signal-Regulated Protein Kinase; PI3K: Phosphoinositide 3-Kinase; JAK: Janus Kinase; STAT3: Signal Transducer and Activator of Transcription 3; PLC $\gamma$ : Phospholipase C- $\gamma$ ; PKC: Protein Kinase C; FDA: Food and Drug Administration; TCGA: The Cancer Genome Atlas; CPTAC: Clinical Proteomic Tumor Analysis Consortium

### Introduction

Malignant neoplasms are one of the most important and feared causes of morbidity and mortality around the world [1]. The oral cavity represents the most frequent location of primary malignant tumors in the head and neck region [2]. More than 90% of malignant neoplasms are oral squamous cell carcinoma (OSCC) developed on the mucous epithelium and the sixth most common cancer in the world [3-6]. Incidence worldwide is of 0.7 million new cases per year, and a low 5-year survival rate for both localized and advanced disease (69 and 34%, respectively) [7]. It represents 2.5% of all new cancer cases and 1.9% of all cancer deaths annually [3]. The rest is adenocarcinoma of the minor salivary glands [3]. Head and Neck cancer affects with more than two-thirds of oral cancer cases in males than females [3,4].

Oral cancer is a multifactorial disease in which a wide factors play a role in its apparition and progress. While that incidence and mortality in oral cancer relatively low in certain countries, in many

other European countries a dramatic increase has been reported [1]. The survival for OSCC is stagnant at 50% at 5 years [8].

In the Easter world, especially in South Asian, the most prevalence of oral cancer is due to smokeless tobacco, alcohol, betel quid chewing, in the other side, in the western world, other factors are age, site of disease, etiology and molecular biology [3,9,10]. High risk human papillomavirus human infection (HPV-16 and HPV-18) has been identified as a significant risk factor for oropharyngeal cancer in developed countries and shows better prognosis than HPV negative oral cancer [9,11,12].

### Molecular pathways

So, environmental, genetic and epigenetic factors are involved in the etiology of the oral cancer [3,9,10]. Two important observation were revealed: (a) tumors with the same origin vary considerably with respect to their genomic variation and (b) similar patterns of genomic variations are shown by tumors with different origins [3].

The multistep progression of OSCC involves an accumulation of both genetic and epigenetic alterations in oncogenes or tumor suppressor genes, leading to cell cycle dysregulation, inhibition of growth suppressors, and resistance to apoptosis, such as the Ras-MAPK-ERK (Ras-mitogen-activated protein kinase-extracellular signal-regulated protein kinase), the PI3K/Akt/mTOR (phosphoinositide 3-kinase/Akt/mechanistic target of rapamycin), the

JAK/STAT3 (Janus kinase/signal transducer and activator of transcription 3) and the PLC $\gamma$ /PKC (phospholipase C- $\gamma$ /protein kinase C) [9,10].

The tumor suppressor gene *p53* is commonly mutated in oral cancer, its alteration makes it functionally inactive in oral tumors and involved in the progression of OSCC [10,13]. Another one tumor suppressor gene is *NOTCH1*, it is reported to be mutated in 54% for OSCC and 60% for paraneoplastic lesions in Chinese patients [10]. *NOTCH1* mutations are proposed to development in OSCC [10,14,15]. For other side, *MDM2* is a proto-oncogene amplified in 25% - 40% of all human cancers [10]. The mutation of tumor suppressor gene *p53* has been characterized for pre-cancerized fields in OSCC [9]. The co-expression of *p53/MDM2* proteins is suggested to be an indicator of aggressive tumor behavior in OSCC. The overexpression proto-oncogene *Akt1* promotes cell proliferation, survival, and metastasis of cancer cells and progression of oral cancer [10]. The activated PKB/AKT pathway initiates various cellular functions and induces tumor growth and results in poor prognosis [10,13]. Another via affected is EGFR, its overexpression is associated with aggressive phenotype and poor prognosis in oral cancer [10,16].

Furthermore, TC21 belongs to the Ras family, which is involved in various cell functions, interaction with Erk2, 14-3-3  $\sigma$  and PI3-K suggest that TC21 is a signaling pathway for oral cancer. Besides, increased expression of TC21 was observed in the early stages of OSCC (T1 + T2) than in the advanced stages (T3 + T4). It is suggested poor prognosis of OSCC [9,17,18].

Enzyme cyclooxygenase-2 (COX-2) is the target molecule of NF- $\kappa$ B, and it synthesizes prostaglandins from arachidonic acid. Overexpression of COX-2 induces cancer progression by increasing vascularity and cellular proliferation and the evasion of apoptosis processes. This indicates that an increase in NF- $\kappa$ B may result in reduced patient survival [10,17].

Mutations of *CDKN2A*, *CCND1*, *PIK3CA*, *PTEN* and *HRAS* can also cause cell cycle dysregulation and immortalization and are associated with OSCC initiation and progression [9].

The Wnt/ $\beta$ -catenin signaling pathway is often mutated, it plays a very important role in the carcinogenesis, and there is a significant correlation between metastatic grading and lymph node metastasis. Wnt/ $\beta$ -catenin pathway can be a potential target for anticancer therapy [17].

Bmi1<sup>+</sup> cells can be visualized in the basal cell layer of normal lingual epithelium, regulating tissue maintenance and regeneration. Recent studies revealed that Bmi1<sup>+</sup> subpopulation in OSCC was a subset of slow-cycling tumor propagating cells and mediated invasive growth and regional metastasis of OSCC [9,19].

### Clinical characteristics

The primary tumors originating from the surface of the oral mucosa of the oral cavity are variable [2]. The most common presentations are that of an ulcerated lesion in the oral cavity, patients may also present with mobile teeth, bleeding, pain or numbness in the mouth or face or a will fitting dental prosthesis. White lesions of the oral cavity can represent a variety of diagnoses, including frictional keratosis, oral lichen planus and viral lesions such as warts [20]. Most Oral squamous cell carcinoma tumors develop from pre-malignant lesion such as leukoplakia, erythroplakia and proliferative verrucous leukoplakia [9,21]. Malignant transformation rate is extremely high, with an estimated yearly of 9.3%. For this reason, partial or total surgical removal (when feasible), repeated biopsies, and strict follow-up measures seem the most reasonable management of this subset of patient, its treatment may be subdivided into conservative or surgical depending on the severity of symptoms, but it should take into account the non-negligible risk of progression to cancer [21].

### OMICS technologies and treatment strategies

Omics technologies have grown over the last two decades and they are now highly intertwined with other biological functional analysis. Omics can be presented as follows: a) genomics analyses the whole sequences of coding and non-coding portions of the genome and targeted sequences (such as exome or clinical exome sequences). Genomics allows the identification of possibly relevant variants, such as single nucleotide polymorphisms (SNPs), copy number variation (CNV), mutations and translocations; b) transcriptomics involves all the RNA transcripts (with a particular attention in the last decade to mRNA, and more recently to long non-coding RNA [lncRNA]), monitor their differences in expression and infer the impacts of their alteration; c) epigenomics essentially studies DNA methylation variations and the functional consequences of the spatial behavior of the DNA; d) other cellular molecules have been analyzed by high-throughput methodologies and entered in the omics sciences, such as Proteomics, Metabolomics, Lipidomics [7,8]. Omics technologies now have extended their role to molecular diagnostics and biomarker discovery [9].

The oral squamous cell carcinoma treatment varies based on the stage at time of diagnosis. Patients with localized disease typically receive surgery and/or radiotherapy, leading to a high probability of long-term survival but with considerable morbidity. With metastatic OSCC, chemotherapy and radiotherapy are the mainstays of treatment. Recently, targeted therapeutics have been introduced into treatment regimens or ongoing clinical trials to improve survival rate and reduce toxicity, such as cetuximab (monoclonal epidermal growth factor receptor [EGFR] antibody), bevacizumab (monoclonal vascular endothelial growth factor [VEGF] antibody) and mechanistic target of rapamycin (mTOR) inhibitors. With the advancement of immunotherapy, monoclonal antibodies that target programmed cell death protein-1 (PD-1), a receptor of the immune escape pathway, such as nivolumab and pembrolizumab, have been approved by the Food and Drug Administration (FDA) for recurrent and/or metastatic head and neck SCC [9,22].

Many treatments were studied, such as, eliminating Bmi1<sup>+</sup> OSCC cells significantly reduced the occurrence of metastasis, indicating the potential therapeutic value of Bmi1<sup>+</sup> inhibitors in OSCC treatment [9,19]. Ogi, *et al.* [23] described that nivolumab treatment results in a good response in patients with CD8 T cell infiltration and PD-L1 expression in addition to genetic alteration and pseudo-progression in oral cancer. Recently, several PD-1 inhibitors have shown benefit in recurrent or metastatic head and neck, with a subset of patients achieving durable responses [24]. Also, pembrolizumab and nivolumab, PD-1 inhibitors, have generated enthusiasm in recurrent/metastatic OSCC [11].

Although several chemotherapeutic agents have shown to have activity in metastatic or recurrent head and neck cancer, prognosis is overall poor [24]. Furthermore, a multidisciplinary therapeutic approach is recommended for all patients with head and neck cancer.

## Discussion

Oral squamous cell carcinoma is a complex disease exhibiting tumor heterogeneity and tumor plasticity [9]. It is the predominant mucosal cancer of the head and neck region.

Analysis of existing “omics” datasets on head and neck cancers can help in the identification of signaling modules linked to tumor progression, therapy, and prognosis [25].

Several groups around the world including “The Cancer Genome Atlas” (TCGA) and “The Clinical Proteomic Tumor Analysis

Consortium” (CPTAC) have carried out genomics, transcriptomic and proteomic analysis of various cancers and made these datasets publicly available to the scientific community. However, in the case of oral cancers, studies involving mining of existing omics datasets are limited [25]. From this review it is also concluded that these genetic variations can be used for diagnostic, prognostic and screening purposes.

In the future, the development of more refined pathology tools, based on genetic profile/molecular markers, would help in improving the management of every single Potentially malignant disorders of the oral cavity [21].

## Conclusion

Therefore, studies aimed at personalized diagnosis based on specific biomarkers will determine new therapeutic strategies for the benefit of the patient with oral squamous cell carcinoma.

In this review, we show the importance of genetics for diagnosis, prognosis and therapeutic decision in patients with oral cancer. Similarly, in the very near future, based medicine will require re-viewing and performing protocols for the management of head and neck cancer.

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