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Review

Oral squamous cell carcinoma: Key clinical questions, biomarker discovery, and the role of proteomics

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ABSTRACT

Background: The molecular and cellular mechanisms underlying the pathogenesis of oral squamous cell carcinoma (OSCC) are relatively poorly understood and remain a subject of significant importance. However, it is well established that OSCC is associated with a variety of risk factors and notably, the high incidence rates of OSCC found in developing countries are attributable to exposure to different forms of smokeless tobacco. Despite this, the way these factors contribute to the disease pathogenesis and, in particular, the transformation from oral premalignant lesions (OPLs) to primary tumor remains unknown. Recent developments in 'omics' technologies hold promise for deciphering these mechanisms through the discovery of key molecular and cellular regulatory pathways which are involved in disease progression.

Objective: The aim of this critical review is to outline, through the current etiological, epidemiological, and molecular understanding of OSCC highlighting the role of key signaling pathways in the disease, and discuss the opportunities offered by recent proteomics strategies to identify potential biomarkers and novel mechanisms for OSCC.

Results and conclusions: The recent consolidation of methods for LC-MS/MS based protein expression analysis mass spectrometry and targeted protein measurement should support the discovery of new drug targets and diagnostic methods. We suggest that such studies will be most effective if they are focused on addressing the key clinical issues in the progression and treatment of this prevalent disease.

Contents

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1. Introduction

Oral squamous cell carcinoma (OSCC) is one of the most widely occurring cancers throughout the world (Petersen, 2009). Developing countries have high incidence rates and it is expected that these will keep increasing in the coming years (De Camargo Cancela et al., 2010; Tanaka & Tanaka, 2011). For instance in India, OSCC accounts for 35% of all diagnosed cancer cases in men each year (Shah & Gil, 2009). OSCC is a multi-factorial disease affected by various genetic alterations and environmental factors, and for this reason it seems that conventional diagnostic methods such as histopathology alone will not be able to support the diagnosis of the disease at an early stage (Fukuda, Kusama, & Sakashita, 2012; Ralhan, 2007). In terms of treatment, surgery remains the best option for OSCC patients but it is not effective on late-stage metastatic tumors. Although chemotherapy and radiotherapy are applied in combination with surgery for treating late-stage tumors, five year survival rates are disappointingly low with a high possibility of recurrence (Ralhan, 2007; Nagler, 2009).

OSCC is a major subtype of head and neck squamous cell carcinoma (HNSCC) which displays many pathological differences to cancers found at other sites in the head and neck region. OSCC has been studied separately from other subtypes of HNSCC and this is because of the risk factors which are specific to oral cavity (Bertolus, Goudot, Gessain, & Berthet, 2012; Johnson, Jayasekara, & Amarasinghe, 2011). Notably, Weinberger et al. analyzed molecular differences in protein expression between tumors that arise from different sites of head and neck region. They used automated quantitative analysis (AQUA) and two-dimensional differential gel electrophoresis (2D-DIGE) and found considerable molecular diversity between different SCCs within the head and neck region (Weinberger et al., 2009). This evidence supports the idea that OSCC is distinct from cancers found at other sites of the head and neck region.

OSCC is a malignancy of the squamous epithelium of the oral cavity includes tumors found in the tongue, lip, gingival, palate, floor of mouth and buccal mucosa (Estilo et al., 2009). It is the advanced form of precancerous lesions which develop in the form of benign or malignant tumors. Precancerous lesions can be in the form of leukoplakia (white lesions), erythroplakia (red lesions), erythroleukoplakia (combination of white and red lesions), or oral submucous fibrosis (deposition of collagen on fibromuscular connective tissue) and all of these potentially give rise to primary tumor in the oral cavity (Boy, 2012; Feller & Lemmer, 2012; Mahomed, 2012; Scully & Bagan, 2009; Van der Waal, 2009). The biological understanding of these lesions is of key importance for the overall diagnosis and treatment of the disease.

It is generally accepted that the pathogenesis of OSCC is a 'Darwinian process' that involves a series of mutations resulting in the selected growth of mutated cells which replace the normal cells in a specific region (Feller, Wood, Khammissa, & Lemmer, 2010a). In the case of OSCC, this process is supposed to comprise a series of gradual alterations (changes in the mucosal layers) that presumably occur in the entire epithelial surface of the oral cavity and are followed by invasion of tumor cells (Fukuda et al., 2012).

As is the case for many solid tumors, early detection and therapeutic intervention offers the best opportunity to improve the current low survival rates in OSCC. Furthermore, a key to the development of more effective treatment lies in a better understanding of the mechanisms involved in the progression of the disease. While a number of studies have been undertaken to examine genetic alterations, the role of tumor suppressor genes, and potential molecular mechanisms associated with progression of tumor, it is evident that further insights and understanding is much needed (Da Silva et al., 2011; Fukuda et al., 2012).

Here, we briefly review the global burden of OSCC and incidence rates between different geographical regions, as well as describe risk factors including Human papillomavirus (HPV). We have sought to highlight the key clinical questions which remain unanswered and propose studies that may provide better understanding of OSCC pathogenesis. In particular, we highlight the potential of advanced proteomic approaches including label-free LC-MS/MS and targeted protein measurements by multiple reaction monitoring (MRM) (Figs. 1 and 2).

2. Global burden of OSCC

Cancer is the third leading cause of death worldwide with more than 10 million new cases and 6 million deaths every year (Petersen, 2009; Thun, DeLancey, Center, Jemal, & Ward, 2010). Oral squamous cell carcinoma is the eighth most common cancer in males worldwide whereas in females it is relatively rare and not ranked among the top ten cancers (Petersen, 2009; Ferlay et al., 2010; Jemal et al., 2011). While the incidence and mortality rates vary widely among different populations, OSCC is generally found to be more common in developing countries (Petersen, 2009; De Camargo Cancela, de Souza, & Curado, 2012).

The higher incidence and low survival rates have been reported from India (De Camargo Cancela et al., 2010; ncrpindia), Taiwan (Lee, Ho, & Chou, 2010; Liu et al., 2010), Pakistan (De Camargo Cancela et al., 2010; Bhurgri, 2005), and Hungary (Nemes et al., 2008). The recent data available in GLOBOCAN 2008 report shows that a total of 263,900 new cases and 128,000 OSCC deaths occurred across the world in 2008 (Jemal et al., 2011). These figures give a clear indication that oral cancer remains a huge global burden and the rising rates are a cause of concern.

3. Risk factors associated with oral cancer and the role of human papillomavirus (HPV)

A number of elements have been reported as potential risk factors for initiating the process of carcinogenesis in the oral cavity (Da Silva et al., 2011). Tobacco alone is well recognized as the major cause for a number of cancer types including those of the oral cavity. Overall 43% of all cancers are supposed to be caused by tobacco and its carcinogenic effect is well established (Petersen, 2009). While there is much debate and disparity on the carcinogenic effects of alcohol, a general trend of alcohol users to be more susceptible to develop OSCC than non-consumers has been observed (Zygogianni et al., 2011). Alcohol increases the risk of developing malignancy in the oral cavity to a higher extent when used in the combination with tobacco (Johnson et al., 2011). Alcoholic beverages not only contain ethanol, glucose and water but also have considerable amount of *N*-nitrosodiethylamine and polycyclic aromatic hydrocarbons. It has been reported that the excessive alcohol consumption is significantly associated with increased mucosa permeability to toxins, and reduction in epithelial thickness. Acetaldehyde, the first metabolite of ethanol, is a well established mutagenic and carcinogenic substance (Ogden & Wight, 1998; Figuero Ruiz et al., 2004; Reidy, McHugh, & Stassen, 2011a; Reidy, McHugh, & Stassen, 2011b). The adverse effects of tobacco and alcohol in oral cancer are observed in developed