Original Article

Analysis of octamer-binding transcription factor-4 expression in oral leukoplakia

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Abstract

Background: Oral potentially malignant disorders have a risk for malignant transformation but are difficult to reliably identify and predict which patients are at the risk for malignant transformation. OCT4 has been hypothesized to play a key oncogenic driver in a variety of solid tumors. A deeper understanding of the aberrant molecular pathways which lead to carcinogenesis needs to be identified by the potential markers.

Aims: To assess the OCT4 stemness factor in oral leukoplakia for its potential risk to malignant transformation.

Settings and Design: 20 cases of oral leukoplakia were obtained from archives at Oral Cancer Research & Coordinating center (OCRCC) Malaysia Subjects and Methods: 20 cases of oral leukoplakia were assessed by OCT4 immunohistochemically. Oral squamous cell carcinoma was used as a control.

Result: no expression of OCT 4 was observed in any cases of oral leukoplakia.

Conclusion: The molecular mechanisms of Oct4 regulation and in particular of its switch on and off in tissues depends upon its microenvironment, which makes it challenging in fundamental and applied research fields of regenerative medicine and cancer therapy. It's better that patients should undergo multiple biopsies for the early detection of malignant transformation with close follow-up during the first two to three years, a large amount of work remains to be done with multi-marker panel investigation, as cure rates have remained constant over three decades.

Keywords: Malignant transformation, Oral leucoplakia, Oral dysplasia, OCT-4, Oral potentially malignant disorders, Progression to cancer

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INTRODUCTION

Oral leukoplakia is a clinical term that has been applied to white lesions in the oral cavity since it was first reported in the literature by Ernő Schwimmer in 1877. The global prevalence of oral leukoplakia varies from 0.5% to 3.4%, and its risk of malignant transformation (MT) ranges from 0.13% to 17.5%. The term "premalignant" implies that an individual lesion may inevitably become malignant; therefore, the term "potentially malignant," which suggests that the progression to malignancy is only potential risk more widely accepted. A new terminology,

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"Potentially premalignant oral epithelial lesion," has been proposed, that is, in maintaining the concept that not all lesions will have any potential to progress to malignancy, such as leukoplakia, and the clinician is faced with a mucosal change that is only a potentially premalignant lesion. The majority of squamous cell carcinomas of the oral cavity develop from an existing premalignant lesion such as leukoplakia, erythroplakia or proliferative verrucous leukoplakia. Unfortunately, which dysplastic lesion advances to a frankly oral squamous cell carcinoma (OSCC) nor the rate of such transformation can be predicted with sureness based on the degree of the dysplastic changes observed histologically.[1-7] Octamer-binding transcription factor 4 (OCT4), a member of the POU domain transcription factor family, plays a key role in the regulation of self-renewal and pluripotency in embryonic stem cells, germ cells and adult stem cells. OCT4 is a potential biomarker forecasting poor prognosis in patients with several malignancies including OSCC.[8,9] A potential biomarker that can help to predict oral leukoplakia that is more likely to undergo MT is needed, and this study intends to evaluate the significance of OCT4 as predictors for MT in oral leukoplakia.

SUBJECTS AND METHODS

Overall, twenty cases of formalin-fixed tissues with a clinical diagnosis of oral leukoplakia were obtained from Oral Cancer Research and Coordinating Centre, Malaysian Oral Cancer Database and Tissue Bank System, University of Malaya, Malaysia. The approval for the study was obtained by the Medical Ethics Committee, Faculty of Dentistry, University of Malaya, Reference number: DF OS1823/0077(L). Immunohistochemistry was performed on 5 μm thick sections from twenty formalin-fixed and paraffin-embedded tissue samples After deparaffinization and rehydration procedures, epitope retrieval was executed in heated citrate buffer for 30 min as recommended. The primary antibodies such as OCT4 (1:50, Santa Cruz) were applied to manifest a specific marker, and counterstaining was performed with hematoxylin. The immunostaining staining levels were evaluated as negative with no stain and/or weakly positive, moderately positive and strongly positive.

RESULTS

The immunostaining expressions for staining were evaluated as no stain and/or weakly positive for all the tissues evaluated.

DISCUSSION

Squamous cell carcinoma of the oral cavity is among the sixth most occurring cancers with a global incidence of roughly 275,000 new cases. Unfortunately, developing countries like India have the highest incidence, about 30% of all new cases annually.[10,11]

The terminology for oral lesions that may have the potential to progress to malignancy has been varied over the years. The World Health Organization (WHO) workshop held in 2007 recommended that the distinction between potentially malignant lesions and conditions is abandoned in favor of a common term "oral potentially malignant disorders (OPMDs)" which have been accepted in the latest WHO classification.[2,3,12,13]

The MT of the oral surface epithelium is a result of the accumulation of mutations in critical control genes which occur over a period of time from years to decades, and the underlying genetic defects do not show obvious clinical and histopathologic phenotypic changes until later in the process, and the majority of the literature supports the view that oral epithelial dysplasia carries a significant risk for malignant transformation.[13,14] The development of tissue markers to enhance the detection of these lesions with a high potential for malignant change is, therefore, paramount.[15] OCT4 is a member of the POU domain transcription factor family and functions as one of the most important stem cell transcription factors in regulating cancer invasion, migration and self-renewal properties. OCT-4 has been recognized as a predictive biomarker for poor prognosis in several carcinomas; a large amount of evidence indicates that OCT4 expression acts as a tumor biomarker and promoter in hepatocellular carcinoma (HCC), lung adenocarcinoma and many other tumors, and its expression has been described as an important step in tumorigenesis.[16-18,26,27]

Rates of MT of oral leukoplakia to squamous cell carcinoma are varied and may be due to differences in the underlying pathology, use of putative carcinogens and the location of oral leukoplakia. The geographic differences in the transformation rate are likely related to the differences in tobacco habits in various parts of the world. In the US populations, a majority of oral leukoplakia probably never become malignant, and the statistical analysis from several studies on the Indian subcontinent concluded the prevalence of leukoplakia ranging from 0.2% to 5.2% and the MT rate of 0.13%–10%. Wide ranges in the risk of transformation have been observed from one anatomic site to other, for example, the floor of the mouth – the transformation rates are comparatively higher than others, although, paradoxically, many show only minimal amounts of epithelial dysplasia.[19-21] Clinical or histologic biomarkers

are needed to improve the ability to distinguish lesions that may progress to cancer from those that will not.[12,22]

It is generally accepted that the histologic assessment is the gold standard to determine MT, but this is also subjective, with wide inter- and intra-observer variability. Currently, there are no microscopic, biological or molecular methods that can predict which individual dysplasia, irrespective of the grade, will progress to squamous cell carcinoma. It is not inevitable that the dysplastic lesion will transform into cancer, and nondysplastic lesions may also progress, thus literature at times is confusing and conflicting, which ultimately delays the treatment and the prevention strategies. Identifying the cancer stem cells (CSCs) population can be a reliable prognostic indicator in OPMDs with or without epithelial dysplasia. Multimarker panel investigation for CSCs in OPMDs may assist in curtailing new cases of oral cancer to a great extent; a large amount of work remains to be done, as cure rates have remained constant over the 30 years.[19,23-28]

It is also hypothesized that cancer formation is the result of uncontrolled reprogrammation. A number of markers have been claimed to identify CSCs such as CD133, Oct4 and Sox 2, CD44 Nanog and many other stemness genes.[16,17,27-30]

Various studies have shown that Oct4 and Sox 2 were expressed in transforming oral mucosa of rat, precancerous lesions of human, epithelial noncancer tissues adjacent to the OSCCs and primary sites of OSCCs which suggests that Oct4 and Sox 2-positive profile can be the biomarker of stem cells which drive epithelial cells to OSCCs.[31] The stem cell transcription factors Oct4 and Nanog are increased in HCC with aggressive tumor behavior.[32] It is well documented that overexpression of Oct4, Sox 2 and Nanog, together or separately, led to tumorigenicity, tumor metastasis and even distant recurrence after chemoradiotherapy in different types of cancer data suggests that Oct4 may be a critical regulator of head-and-neck squamous carcinoma CSCs.[33]

The results of Qiao *et al*.[31] study showed that Oct4 and Sox2-positive profile can be the biomarker of stem cells which drive epithelial cells to OSCCs. Vijayakumar et al.,[34] SOX2 itself can act as a potential marker for proliferation in tumor cells while OCT4 has non-significant role in regulation of tumor behavior in oral squamous cell carcinoma as well as in oral epithelial dysplasia.[35] A larger prospective study with a multimarker panel investigation for CSCs could be advocated to determine which oral leukoplakia has the potential risk of developing oral cancer.

CONCLUSION

The molecular mechanisms of Oct4 regulation and, in particular, of its switch on and off in tissues depend on its microenvironment, which makes it challenging in fundamental and applied research fields of regenerative medicine and cancer therapy. It is better that patients should undergo multiple biopsies for the early detection of MT with close follow-up during the first 2–3 years; a large amount of work remains to be done with multimarker panel investigation, as cure rates have remained constant over the three decades.[28,35-37]

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Conflicts of interest

There are no conflicts of interest.

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