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Stanniocalcin 2 contributes to aggressiveness and is a prognostic marker for oral squamous cell carcinoma

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ABSTRACT

Stanniocalcin 2 (STC2), a glycoprotein that regulates calcium and phosphate homeostasis during mineral metabolism, appears to display multiple roles in tumorigenesis and cancer progression. This study aimed to access the prognostic value of STC2 in oral squamous cell carcinoma (OSCC) and its implications in oral tumorigenesis. STC2 expression was examined in 2 independent cohorts of OSCC tissues by immunohistochemistry. A loss-of-function strategy using shRNA targeting STC2 was employed to investigate STC2 in vitro effects on proliferation, apoptosis, migration, invasion, epithelial-mesenchymal transition (EMT) and possible activation of signaling pathways. Moreover, STC2 effects were assessed in vivo in a xenograft mouse cancer model. High expression of STC2 was significantly associated with poor disease-specific survival (HR: 2.67, 95% CI: 1.37–5.21, p = 0.001) and high rate of recurrence with a hazard ratio of 2.80 (95% CI: 1.07–5.71, p = 0.03). In vitro downregulation of STC2 expression in OSCC cells attenuated proliferation, migration and invasiveness while increased apoptotic rates. In addition, the STC2 downregulation controlled EMT phenotype of OSCC cells, with regulation on E-cadherin, vimentin, Snail1, Twist and Zeb2. The reactivation of STC2 was observed in the STC2 knockdown cells in the in vivo xenograft model, and no influence on tumor growth was observed. Modulation of STC2 expression levels did not alter consistently the phosphorylation status of CREB, ERK, JNK, p38, p70 S6K, STAT3, STAT5A/B and AKT. Our findings suggest that STC2 overexpression is an independent marker of OSCC outcome and may contribute to tumor progression via regulation of proliferation, survival and invasiveness of OSCC cells.

1. Introduction

Oral squamous cell carcinoma (OSCC), the most common tumor in the head and neck region, displays high incidence (more than 350,000 new cases every year) and rates of mortality (approximately 177,000 deaths every year) [1]. Since OSCCs are asymptomatic at early stages, most patients are diagnosed at advanced stage of disease, resulting in a 5-year survival rate of approximately 50% [2]. Tumor invasion, lymph node metastasis and high rates of locoregional recurrence are the main factors leading to the death of patients with OSCC [3]. Therefore, biomarkers of early diagnosis, prognosis and post-therapeutic monitoring are essential to improve clinical management of OSCC. Indeed, several studies have reported potential biomarkers for predicting OSCC progression and prognosis, however, their practical usefulness remains very limited [4].

Stanniocalcins are glycoprotein hormones involved in calcium and

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