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Downregulation of PRKAR1A Expression in Oral Squamous Cell Carcinoma

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ABSTRACT

Introduction: Oral squamous cell carcinoma is an uncommon and potentially aggressive malignant tumor arising from Oral epithelial remnants. Identification of molecular alterations involved in Oral squamous cell carcinoma may contribute to the discovery of reliable diagnostic and prognostic biomarkers and potential therapeutic targets. PRKAR1A encodes the regulatory subunit type I-alpha of protein kinase A (PKA) and may play an important role in cellular signaling and tumor development. This study aimed to evaluate PRKAR1A gene expression in peripheral blood samples from patients with Oral squamous cell carcinoma compared with healthy individuals and to investigate its association with clinicopathological characteristics of the disease.

Materials and Methods: In this case-control study, peripheral venous blood samples were collected from 30 patients with histopathologically confirmed Oral squamous cell carcinoma and 30 healthy individuals matched for age and sex. Total RNA was extracted from blood samples using the Viva 2-Step RNA extraction method. Following reverse transcription, quantitative real-time polymerase chain reaction (qRT-PCR) was performed to determine PRKAR1A mRNA expression. GAPDH was used as the internal reference gene, and relative gene expression was calculated using the $2^{-\Delta\Delta Ct}$ method. Statistical analyses were selected according to the distribution and type of the variables. Independent-samples t-test or Mann–Whitney U test was used for comparison between the two study groups, as appropriate. Associations between PRKAR1A expression and clinicopathological characteristics were evaluated using appropriate parametric and non-parametric tests.

Results: PRKAR1A mRNA expression was significantly lower in peripheral blood samples from patients with Oral squamous cell carcinoma compared with healthy controls ($P < 0.05$). Reduced PRKAR1A expression was also associated with more advanced tumor stage, poorer histological grade, and the presence of metastasis ($P < 0.05$).

Conclusion: The findings suggest that reduced PRKAR1A expression in peripheral blood may be associated with Oral squamous cell carcinoma and with clinicopathological indicators of tumor progression. PRKAR1A may have potential as a molecular biomarker of Oral squamous cell carcinoma. However, the relatively small sample size and absence of HPV assessment should be considered when interpreting these findings. Larger, adequately powered studies are required to validate the diagnostic and prognostic value of PRKAR1A in Oral squamous cell carcinoma.

Keywords: PRKAR1A; Oral squamous cell carcinoma; Gene expression; PKA signaling.

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Introduction

Oral squamous cell carcinoma is a rare epithelial malignancy originating from Oral tissues. It is known for its invasive behavior and tendency to recur locally. Despite progress in imaging and histopathology, identifying the disease at an early stage remains a challenge, and prognosis often relies on late diagnosis. The PRKAR1A gene encodes the regulatory subunit I-alpha of protein kinase A (PKA), a central enzyme in the cyclic AMP (cAMP) signaling cascade [1]. This gene functions as a tumor suppressor and contributes to vital cellular mechanisms, including proliferation control, cell differentiation, and apoptosis regulation [1,2]. Disruption in PRKAR1A expression or activity has been associated with various neoplasms, such as those affecting the adrenal glands, thyroid, and bones [2,3]. Considering its role in tumor suppression, this research focuses on evaluating PRKAR1A expression in Oral squamous cell carcinoma patients and determining its potential clinical relevance in diagnosis and prognosis [4,5].

Materials and Methods

Study Design and Participants

This case-control study included 30 patients with histopathologically confirmed Oral squamous cell carcinoma and 30 healthy individuals matched for age and sex. Patients were eligible for inclusion if they had a histopathologically confirmed diagnosis of and provided an adequate peripheral blood sample for molecular analysis. Individuals with a history of previous chemotherapy or radiotherapy, other malignancies, or underlying systemic conditions according to the predefined exclusion criteria were excluded. The control group consisted of healthy individuals without a history of malignancy or major systemic disease who were matched to the patient group according to age and sex. No formal a priori power analysis was performed before recruitment. The sample size was based on the available eligible participants during the study period. Therefore, the relatively small sample size was considered when interpreting the findings and is acknowledged as a limitation of the study.

Ethical Considerations

The study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval was obtained under approval IR.TUMS.AMIRALAM.REC.1403.040. Written informed consent was obtained from all participants before enrollment and blood collection.

Blood Sample Collection and RNA Extraction

Peripheral venous blood samples were collected from all participants into sterile blood collection tubes and stored at −80°C until RNA extraction. Total RNA was extracted from peripheral blood samples using the Viva 2-Step RNA extraction method according to the manufacturer's instructions. All procedures were performed under RNase-free conditions. The concentration and purity of extracted RNA were assessed using spectrophotometry. RNA samples with adequate concentration and purity were used for subsequent reverse transcription and quantitative real-time PCR analysis [8,9].

cDNA Synthesis and Quantitative Real-Time PCR

For mRNA expression analysis, complementary DNA (cDNA) was synthesized from the extracted total RNA using RTPL12). Cat. no) Viva 2-steps RT-PCR Kit according to the manufacturer's instructions. Quantitative real-time PCR was performed using SYBR Green master mix and primers specific for PRKAR1A. GAPDH was used as the endogenous reference gene. Relative PRKAR1A mRNA expression was calculated using the $2^{-\Delta\Delta Ct}$ method, with GAPDH used as the endogenous control [10,11,12,13,14].

Statistical Analysis

Statistical analyses were performed using SPSS version 26 (IBM Corp., Armonk, NY, USA). The normality of continuous variables was assessed using the Shapiro–Wilk test. For comparison of PRKAR1A expression between the two independent groups, namely patients with Oral squamous cell carcinoma and healthy controls, an independent-samples t-test was used when the data were approximately normally distributed. When the normality assumption was not met, the Mann–Whitney U test was applied. For comparisons involving more than two clinicopathological groups, one-way analysis of variance (ANOVA) was used for normally distributed data when the relevant assumptions were satisfied. For non-normally distributed data, the Kruskal–Wallis test was applied. For categorical variables, the chi-square test or Fisher's exact test was used, as appropriate. Associations between PRKAR1A expression and continuous or ordinal clinicopathological variables were assessed using Spearman's rank correlation coefficient when appropriate. For binary clinicopathological variables, an independent-samples t-test or Mann–Whitney U test was used according to the distribution

of the data. All statistical tests were two-sided, and a P value < 0.05 was considered statistically significant.

Results

As shown in Figure 1, relative PRKAR1A mRNA expression was significantly lower in peripheral blood samples from patients with oral squamous cell carcinoma (SCC) compared with healthy controls (P < 0.05). The comparison between the two groups was performed using an independent-samples t-test or Mann–Whitney U test according to the distribution of the data.

Association Between PRKAR1A Expression and Clinicopathological Characteristics

Reduced PRKAR1A expression was associated with more advanced tumor stage, poorer histological grade, and the presence of metastasis (P < 0.05). PRKAR1A expression was significantly lower in patients with metastasis than in those without metastasis. The comparison between patients with and without metastasis was performed using an independent-samples t-test or Mann–Whitney U test according to the distribution of the data.

Study Limitations

Several limitations should be considered when interpreting the findings of this study. First, no formal a priori power analysis was performed, and the study included a relatively small sample of 30 patients with Oral squamous cell carcinoma and 30 healthy controls. Accordingly, the study should be considered exploratory, and the limited sample size may have reduced the statistical power to detect associations between PRKAR1A expression and individual clinicopathological characteristics.

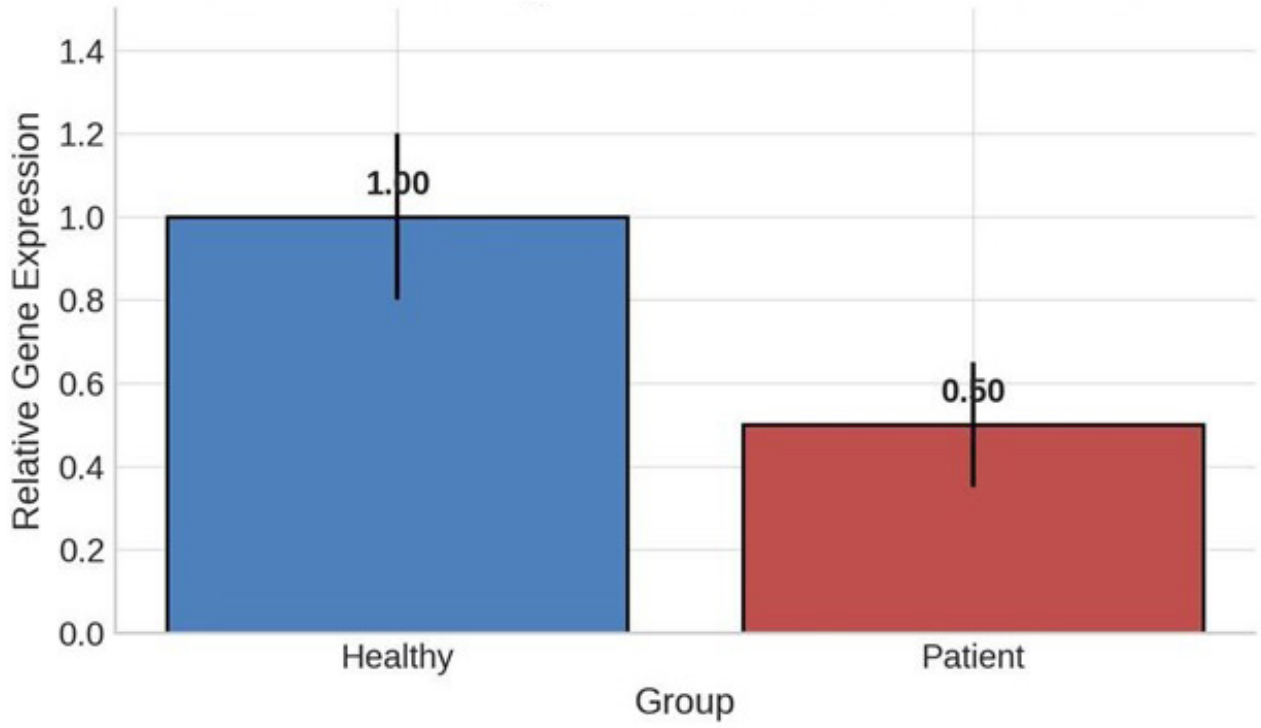


Figure 1. Comparison of PRKAR1A gene expression between healthy individuals and SCC patients.

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Discussion

The present findings reveal a significant decrease in PRKAR1A gene expression among individuals diagnosed with Oral squamous cell carcinoma. As a key component in cAMP/PKA-mediated signaling, loss of PRKAR1A function may disturb normal cell regulation and encourage cancer progression through mechanisms like enhanced proliferation and invasion [1]. Earlier research has highlighted similar tumor-suppressive functions for PRKAR1A in other cancers, particularly in adrenal and skeletal tumors [1,5]. Its diminished expression has been implicated in epithelial-mesenchymal transition (EMT), reduced cell death, and increased cell motility—hallmarks of aggressive tumor biology [5,6]. The correlation between decreased PRKAR1A expression and poor clinical indicators such as high tumor grade, advanced stage, and metastasis underscores its potential utility as a prognostic marker [4,6,7]. Moreover, targeting PRKAR1A pathways may offer a new strategy for treatment, especially in malignancies resistant to standard therapies [4,5]. Nonetheless, the study is limited by a relatively small sample size and the absence of protein-level validation. Future research using broader samples, along with immunohistochemical techniques and mechanistic studies, is recommended to establish PRKAR1A's precise role in Oral squamous cell carcinoma [4,5].

Conclusion

The findings of this study showed that PRKAR1A gene expression was decreased in patients with squamous cell carcinoma (SCC) compared to healthy individuals. Decreased expression of this gene could lead to dysregulation of PKA-dependent signaling pathways and thereby contribute to the growth and invasion of cancer cells. These results suggest that PRKAR1A could be used as a potential molecular biomarker in predicting disease progression or as a target for targeted therapies in SCC. Further studies with larger sample sizes and more detailed molecular mechanisms are recommended to confirm these results.

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Conflict of Interest

There is no conflict of interest to declare.

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