**Overexpression of HNRNPA2B1 is Associated with Poor Prognosis in Head and Neck Squamous Cell Carcinoma**

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**ABSTRACT**

Introduction: Head and neck squamous cell carcinoma (HNSCC) is an aggressive life-threatening disease associated with high mortality rates. Heterogeneous nuclear ribonucleoprotein A2B1 (HNRNPA2B1) is tightly linked to tumorigenesis. Recent studies have shown that HNRNPA2B1 is a mediator of N6-methyladenosine (m6A)-dependent nuclear RNA processing events. However, the role of HNRNPA2B1 in head and neck squamous cell carcinoma (HNSCC) is largely unknown.

Objective: To check the expression profile for HNRNPA2B1 in HNSCC using the Oncomine datasets and TIMER database.

Methods: Therefore, in the present study, we used the large TCGA RNA sequencing (RNAseq) dataset to explore the HNRNPA2B1 expression level in HNSCC. We also used Kaplan-Meier plotter to evaluate the effect of HNRNPA2B1 on clinical prognosis.

Results: HNRNPA2B1 was significantly upregulated in HNSCC compared to normal tissues (p<0.05). Moreover, the increased expression of HNRNPA2B1 mRNA was closely associated with reduced overall survival (OS) (p=0.0099) in HNSCC patients.

Conclusion: Our findings systematically elucidate the expression profiles and instinct prognostic value of HNRNPA2B1 in HNSCC, which might provide a novel therapeutic target and potential prognostic biomarker for HNSCC patients.

Key Words: HNRNPA2B1, HNSCC, Prognostic value, m6A, m6A regulator, TCGA database

**INTRODUCTION**

Head and neck squamous cell carcinoma (HNSCC) is aggressive and it is an epithelial-derived from mucosal linings of the oral cavity, oropharynx, larynx, or hypopharynx.¹,² According to the recently published report GLOBOCAN 2018 (global cancer statistics) more than 8 lakhs new HNSCC cases are diagnosed every year.¹³ Main etiological factor for HNSCC is alcohol, tobacco, and HPV infection.⁴,⁵,⁶ Therefore, the treated patients often have a recurrence experience of 40-60% and are unresponsive to subsequent therapeutic interventions.⁷,⁸ Therefore, despite the improvement in overall survival (OS) for patients with other tumor types, the 5 year OS rate of HNSCC has not changed much over the past decade.⁹,¹⁰ Despite numerous advances in therapeutic methods, the prognosis of HNSCC patients still remains poor. Therefore, there was an ultimate and an urgent need to have a better understanding of the molecular mechanism underlying HNSCC population progression and to identify essential genes that could serve as effective biomarkers and potential treatment targets.¹⁰,¹¹

Heterogeneous nuclear ribonucleoproteins(H2/B1) is a protein-coding gene that has abundant RNA binding proteins expressed in most human tissues.¹² Increasing evidence suggests that some HNRNPA2B1 play a direct role in tumor development and progression.¹³,¹⁴

Previous research showed overexpression of HNRNPA2B1 in lungs,¹⁵,¹⁶ breast cancers¹⁷, and liver cancers.¹⁸ Furthermore, knockdown of this gene in breast cancer cells induced apoptosis and HNRNPA2B1 plays an important role as a driver oncogene in glioblastoma development and acts as a predictor of glioblastoma patient survival.¹⁷ Recent studies have found that HNRNPA2B1 modulates hypoxia via alternative splicing glycolytic pyruvate kinase isozyme 2 (PKM2) enzyme in cancer cells.¹⁹ However, some reports had pointed
out that HNRNPA2B1 could promote tumorigenesis. The role of HNRNPA2B1 in HNSCC remains largely unknown.

**MATERIALS AND METHODS**

**Gene expression analysis**

In the current study, ONCOMINE, Tumor Immune Estimation Resource (TIMER) and UALCAN databases were applied to analyze the HNRNPA2B1 expression in primary HNSCC and normal tissues.

**Survival analysis by Kaplan-Meier plotter**

In the present study, the prognostic values of HNRNPA2B1 at mRNA level in HNSCC was analyzed using Kaplan-Meier Plotter (http://kmplot.com/analysis/) is an online database containing gene expression profiles and survival information of cancer patients.

**Statistical analysis**

It was performed on the bioinformatics database online or using SPSS 21.0 software. The differential mRNA expression of HNRNPA2B1 gene for HNSCC was analyzed by student t-test. Kaplan-Meier plots were generated with course, bye-bye lock-rank tests. For all analyses, differences considered statistically significant P-values are less than 0.05.

**RESULTS**

**Overexpression of HNRNPA2B1 in various type of cancer**

We first used Oncomine and TIMER databases to analyze the transcriptional level of HNRNPA2B1 in various types of cancers and corresponding normal tissues. The results showed that HNRNPA2B1 increased in most types of cancers, including HNSCC, breast, brain, bladder, cervical, colorectal cancers (Figure 1A, 1B).

**Overexpression of HNRNPA2B1 correlated with poor survival in HNSCC**

We also used UALCAN database to analyze the mRNA level of HNRNPA2B1 in HNSCC and corresponding normal tissues. Box plot showed that HNRNPA2B1 mRNA levels were significantly higher in HNSCC compared with control tissues (P = 1.624e-12, Figure 2A). By using the KM plotter, we found that high HNRNPA2B1 expression was associated with poor overall survival (P = 0.0099, Figure 2B).

**DISCUSSION**

HNSCC is the sixth leading cancer by incidence worldwide and cancers of the oral cavity, and oropharynx is the most common HNSCC. Tobacco chewing is a major cause of oral and oropharyngeal cancers.1,2,23 The hnRNP A/B protein families are overexpressed or downregulated in various cancers and likely account for the oncogenic effects of several types of cancer.17,24 Recent studies have shown that HNRNPA2B1 plays a critical role in carcinogenesis and the progression of cancer.25,26,27 Increased expression of HNRNPA2B1 protein was observed in pancreatic cancer, lung cancer and may act as a biomarker for early detection.15,28 Moreover, overexpression of HNRNPA2B1 was reported in glioblastoma,17 breast cancer, hepatocellular carcinoma,29 and neurodegenerative.30 Studies regarding the HNRNPA2B1 gene in HNSCC is minimal and largely unknown. Even the prognosis of HNSCC is also poor. Therefore, it is an urgent need to have a better understanding of the molecular mechanism underneath the HNSCC progression and to identify the essential genes that could serve as effective biomarkers and potential treatment targets.

Therefore, in the present study, the expression profile for HNRNPA2B1 in HNSCC was first determined using the Oncomine datasets and TIMER database. We demonstrated that HNRNPA2B1 was highly expressed in various types of cancer including HNSCC. Recent studies reported that high expression of HNRNPA2B1 was correlated with poor prognosis. In this study, we employed Kaplan-Meier plotter to evaluate the prognostic value of HNRNPA2B1 in HNSCC patients and the result showed a high expression of HNRNPA2B1 was significantly associated with poor overall survival (OS) of HNSCC patients. Overexpression of HNRNPA2B1 gene in HNSCC, which is similar to the overexpression in breast cancer,17,31,32 glioblastoma,10,13 neurodegeneration,30 lung cancer34, and pancreatic cancer (27).

**CONCLUSION**

HNRNPA2B1 mRNA expression level was increased in HNSCC. In addition, HNRNPA2B1 increased expression was significantly related to poor survival in HNSCC patients. These findings suggest that HNRNPA2B1 may be used as a prognostic biomarker for HNSCC. The results may be validated and analyzed using in vitro and in vivo studies.

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Aswani et al.: Overexpression of Hnmpa2b1 is associated with poor prognosis in head and neck squamous cell carcinoma

Figure 1: HNRNPA2B1 expression levels in human cancers: (A) HNRNPA2B1 in data sets of different cancers in the Oncomine database (red, overexpression; blue, downexpression). (B) HNRNPA2B1 expression levels in different tumor types from TCGA database were determined by TIMER (*P < 0.05, **P < 0.01, ***P < 0.001).

Figure 2: (A) Boxplot showing HNRNPA2B1 expression in patients with HNSCC and normal tissues (P=1.624e-12). (B) Kaplan-Meier curves indicated HNSCC patients had poorer survival in high expression of HNRNPA2B1 (P=0.0099).