Upregulation of SLC11A1 is associated with poor survival in head and neck cancer patients.

Aleena A[1], Smiline Girija AS[1], Balachander K[2], Vijayashree Priyadharsini J[2], Arumugam Paramasivam[2*]

[1]Department of Microbiology, Saveetha Institute of Medical and Technical Sciences, Chennai, India

[2]Department of Cellular and Molecular, Saveetha Institute of Medical and Technical Sciences, Chennai, India

Abstract

SLC11A1 upregulation has a significant impact on cancer development and metastasis. Several studies have found the upregulation of SLC11A1 associated with tumorigenesis and poor survival in patients with cancer. However, the expression and prognostic value of SLC11A1 remain largely unknown in HNSCC. The present study aimed to analyze the expression of SLC11A1 is associated with prognosis in HNSCC. In the present study, we used the large TCGA (The Cancer Genome Atlas) RNA sequencing (RNAseq) dataset to explore the SLC11A1 expression level in HNSCC. This study included a total of 564 tissue samples (520 samples from HNSCC and 44 as control tissues). The mRNA expression level of SLC11A1 in various kinds of cancers, including HNSCC, was analyzed *via* the UALCAN database. The mRNA expression level of SLC11A1 was increased in most cancers compared with normal tissues, especially in HNSCC. Besides, we also used a Kaplan-Meier plotter to evaluate the prognostic value of SLC11A1 in HNSCC patients. It showed highly expressed SLC11A1 was significantly related to poor Overall Survival (OS) in HNSCC patients. The SLC11A1 is highly expressed in HNSCC and associated with poor survival in HNSCC patients. Therefore, SLC11A1 could be a promising prognostic biomarker for HNSCC.

Keywords: SLC11A1, mRNA expression, HNSCC, Prognostic value, TCGA database

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Introduction

Head and Neck Squamous Cell Carcinoma (HNSCC), is a leading cause of oral cancer-causing oral cavity, lips, larynx, oropharynx, and nasopharynx, etc [1]. The lifestyle of the people, consumption of alcohol, using tobacco, human papilloma infections are leading to this cancer. HPV vaccination in the present study significantly reduces the risk factor of this cancer [2,3].

The progression of a suspected lesion into cancer is based on the growth in epithelial dysplasia not following a predictable progression in sequence from mild to moderate to severe dysplasia and can revert into normality in rare cases [4]. The etiological factors for HNSCC include tobacco use, consumption of alcohol, Human Papillomavirus (HPV) infection, and Epstein-Barr virus (EBV) infection [5,6]. Recent molecular genetic research has demonstrated the development of the majority of HNSCCs within a contiguous preneoplastic cell field in the head and the neck. Several studies can show that these alterations play a key role in the progression of the tumor and the overall survival of malignant cells in several cell molecules, including DNA, RNA, and proteins [7-9]. Our recent studies also showed that DNA, RNA, and protein alteration are associated with several diseases [10-19]. Consequently, treated patients often have 40–60 percent recurrence and do not respond to therapeutic interventions following treatment. Therefore, the 5-year Overall Survival (OS) rates of HNSCC have not changed greatly in the past decade, despite improvements in OS for patients with other tumor types. The prognosis in HNSCC patients remains poor despite numerous advances in therapeutic processes. The molecular mechanism behind HNSCC population growth was therefore urgent and ultimate and necessary to better understand and classify important genes which could serve as useful biomarkers and future treatment objectives [20-23].

The Solute Carrier Family 11 Member 1 (SLC11A1) gene is located on chromosome 2q.35 in humans, 14kb in length contains 15 exons which previously known as Natural Resistance Associated Macrophage Protein 1 (NRAMP1), it's linked with various infections, autoimmune diseases, and cancers [24]. Chronic inflammation is associated with cancer predisposition and autoimmunity. Leukocytes such as neutrophils, monocytes, macrophages, and eosinophils are part of the immune cells involved in inflammation. The soluble factors that are intended to mediate inflammation occur in these cells. If inflammation is uncontrolled it also contributes to diseases associated with chronic inflammation. SLC11A1 codes for a 10–12 transmembrane protein in mice which is only expressed in macrophages and leukocytes and neurons polymorphonuclear [25]. The SLC11A1 gene protein is located on the acidic endosomal and lysosomal compartments of the macrophage [26]. In the macrophages in which SLC11A1 resides, SLC11A1 is a divalent metal cation transporter that regulates the iron cell (Fe2+) levels and regulates the phagolysosome by activating the macrophage SLC11A1 [27,28].

SLC11A1 expression has a significant impact on angiogenesis, tumor metastasis and self-renewal, and other properties of cancer stem cells. Several studies are showing increased levels of SLC11A1 can promote tumor susceptibility and progression, or SNP/mutations in SLC11A1 gene may be responsible for cancer progression. But some of the researchers also stated that decreased levels of SLC11A1 can also lead to cancer progression. The expression of SLC11A1 and its association with cancer susceptibility and progression is a controversial topic. Hence more research in the area of SLC11A1 gene expression and analysis of the association between this SLC11A1 gene expression and tumor susceptibility progression of cancer should be promoted. This present study aimed to analyze the SLC11A1 gene expression and its prognostic value in HNSCC.

Materials and Methods

Gene expression analysis

The present study primarily evaluated the SLC11A1 expression in HNSCC (n=520) and normal tissues (n=44) using data from the TCGA dataset. We used the UALCAN to analyze the SLC11A1 expression in primary HNSCC and normal tissues.

Survival analysis by Kaplan-Meier plotter

In the present study, the prognostic values of SLC11A1 at mRNA level in HNSCC were analyzed using Kaplan-Meier plotter is an online database containing gene expression profiles and survival information of cancer patients.

Results and Discussion

The SLC11A1 gene encodes SLC11A1 exacts pleiotropic effects on macrophage function that include enhanced chemokine KC, inducible nitric oxide synthase, interleukin-1β, tumor necrosis factor-α, and MHC class II expression. All are significant in the induction and maintenance of autoimmunity and cancer. In pathologies, the preference of clinical and epidemiological variables is also important [29].

In the present study, SLC11A1 expression analysis using the UALCAN datasets showed the overexpression of SLC11A1 in various types of cancer including HNSCC than normal ($p<0.01$) (Figure 1). In addition, the overexpression of SLC11A1 is associated with sample types, patients age, individual cancer stages and tumor grade ($p<0.05$) (Figure 2).

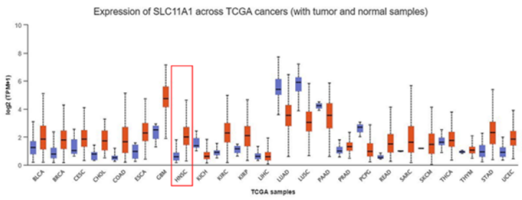

Figure 1. *SLC11A1 mRNA expression pattern in normal and tumor tissues (UALCAN database; $p<0.05$). X-axis shows the types of tissues SLC11A1 were expressed and Y- axis exhibits log2 fold change values of SLC11A1 expression. Red boxes represent tumor tissues; blue boxes represent normal tissues. SLC11A1 mRNA is highly expressed in different types of cancer including HNSCC.*

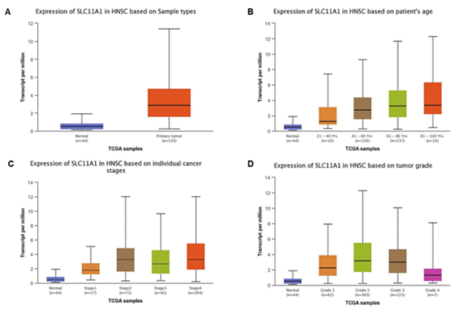

Figure 2. *Expression of SLC11A1 is based on sample types (A): Patients age (B): Individual cancer stages (C): Tumor grade. The Y axis: Transcript per million and X axis: Pathological cancer stages with the number of samples in each stage in parenthesis.*

SLC11A1 can also be considered as an expression in innate lymphocytes in anti-tumor responses. Expression IFN-γ is important for protecting tumors from innate lymphocytes [30,31]. DC cell stimulation is considered important for the optimal expression of NK cells to IFN-γ and is the objective of current cancer vaccine and therapeutic trials [32,33]. Since SLC11A1/−mouse tumor models are widely tested, it should be interesting to research the contribution of SLC11A1 in the NK expression of IFN-γ to help translate these treatments to humans [34].

In the present study, high expression of SLC11A1 was found, which is related to poor survival rate in HNSCC patients (p=047) (Figure 3). Apart from HNSCC, colorectal cancer, hepatocellular carcinoma also showed decreased overall survival rate associated with increased expression of the SLC11A1 gene. Overexpression of SLC11A1 is also associated with poor survival of glioblastoma [35]. Genetic variations of SLC11A1 are associated with esophageal cancer at high risk [36]. The present study results also agreed with the aforementioned literature in the case of increased SLC11A1 expression and decreased overall survival rate of HNSCC patients.

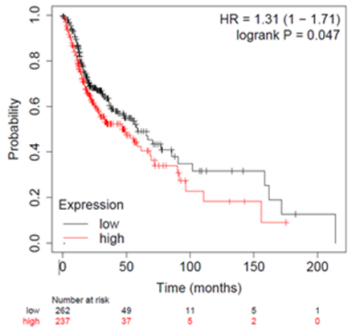

Figure 3. *Kaplan Meier curves indicated HNSCC patients had poorer survival in high expression of SLC11A1 (P=0.047). Red line shows the cases with highly expressed SLC11A1 and black*

line is indicated for the cases with lowly expressed SLC11A1. The Y-axis is the survival probability, and the X-axis represents time (months).

Conclusion

In conclusion, SLC11A1 mRNA was found to be overexpressed in HNSCC. Furthermore, high SLC11A1 expression was linked to a poor prognosis in HNSCC patients. As a result, SLC11A1 may be used as a prognostic biomarker for HNSCC.

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Conflict of Interest

The authors declare no conflict of interest.

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*Corresponding to:

Arumugam Paramasivam

Department of Cellular and Molecular Research

Saveetha Institute of Medical and Technical Sciences

Chennai

India

E-mail: kavithas.sdc@saveetha.com