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COL1A1 and *COL1A2* Alterations are Associated with Tumorigenesis in Head and Neck Squamous Cell Carcinoma

Research Article

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Abstract

Background and Aim: Recent studies have shown that alterations of *COL1A1 and COL1A2* are associated with various types of cancer, however, the potential oncogenic roles of *COL1A1 and COL1A2* in head and neck squamous cell carcinoma (HNSCC) remain largely unknown.
Objectives: The aim of the present study was to analyze the expression and genetic alterations of *COL1A1 and COL1A2* in HNSCC.
Materials and Methods: In the present study, we examined the genetic alterations and expressionof *COL1A1 and COL1A2* genes in HNSCC using openly available data from The Cancer Genome Atlas (TCGA). We also analyzed the interaction network, and functional enrichment of *COL1A1 and COL1A2*.
Results: Here, we found that *COL1A1 and COL1A2* were highly expressed in HNSCC compared to control tissues. In addition, we identified several pathogenic variants in *COL1A1 and COL1A2* genes in HNSCC patients. Therefore, these findings suggest that alterations of *COL1A1 and COL1A*2 play important roles in the development of HNSCC.
Conclusion: The *COL1A1 and COL1A2* were highly expressed and frequently altered in HNSCC patients. Therefore, *COL1A1 and COL1A2* may be closely related with HNSCC development.

Keywords: HNSCC; *COL1A; COL1A2*; Genetic Alterations and Expression; TCGA Database.

Introduction

Head and neck squamous cell carcinoma (HNSCC) is an aggressive life-threatening disease associated with high mortality rates. HNSCC has a multifactorial etiology, which includes chronic use of smoking and smokeless form of tobacco, alcohol, and HPV viruse. HNSCC is characterized by poor prognosis and a low survival rate despite sophisticated surgical and radiotherapeutic modalities [1-4]. Cancer cells exhibit multiple hallmarks of cancer progression, including the recruitment of various cells to form a tumour environment. The most abundant matrix protein polymers are collagen. Extensive collagen deposition is the main pathological characteristics of some carcinomas. The main functions of collagen are cancer cell invasion, cancer cell metastasis, cancer cell death resistance, anti-cancer immunity revelation, intratumoral vessel regulation, hypoxic condition regulation, tumorigenesis and cancer cell proliferation [1, 2].

There are several different types of collagen family, of which type I collagen is the most common and abundant. Type I collagen is a heterotrimeric protein consisting of two α1 chains (*COL1A1*) and one α2 chain (*COL1A2*) [5, 6]. *COL1A1 and COL1A2* are considered to influence tumor invasion and progression [7, 8]. Recent studies reported that abnormal expression *COL1A1* and *COL1A2* have involved in many types of cancer [9]. A study reported that *COL1A2* was downregulated in bladder cancer and melanoma, further *COL1A1 and COL1A2* transcripts levels were upregulated in colorectal cancer and medulloblastoma [6, 9, 10]. Another study reported that *COL1A2* gene methylation was an independent adverse prognostic factor in HNSCC [8]. In the pre-

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sent study, we examined the genetic alterations, and expression of *COL1A1* and *COL1A2* genes in HNSCC.

Materials and Methods

Oncomine and UALCAN Analysis

Gene expression data with clinical information from HNSCC projects (520 cases and 44 controls) were used from The Cancer Genome Atlas (TCGA). In the present study, Oncomine (https://www.oncomine.org/) dataset was used to analyze *COL1A1* and COL1A2 expression in various types of tumor [11]. We also used the UALCAN (http://ualcan.path.uab.edu) database [12] to analyze transcription levels of *COL1A1* and *COL1A2* in HNSCC and normal tissues.

cBioPortal Analysis

The cBioPortal (http://www.cbioportal.org/) is an open resource for interactive exploration of multiple cancer genomic datasets [13]. The genetic alterations *COL1A1* and *COL1A2* in HNSCC patients were assessed by cBioPortal.

STRING and Metascape analysis

We used STRING database (https://string-db.org/) [14] to search protein–protein interaction (PPI) network for *COL1A1* and *COL1A2*. We also used Metascape (http://metascape.org) to analyse the pathway and process enrichment of *COL1A1* and *COL1A2*.

Results

Overexpression of *COL1A1* and *COL1A2* in HNSCC patients

Our results showed that *COL1A1* and *COL1A2* were highly expressed in several types of cancer including HNSCC, colon cancer, breast cancer, liver cancer, lung cancer, and ovarian cancer (Figure 1A) UALCAN database analysis showed that *COL1A1* ($P < 0.001$, Figure 1B) and *COL1A2* ($P < 0.001$, Figure 1C) were highly expressed in HNSCC compared to control tissues.

The genetic alterations of C*OL1A1* and *COL1A2* in HNSCC patients

In this study, we screened the genetic alterations of *COL1A1* and *COL1A2* in HNSCC patients by using cBioPortal. We observed that *COL1A1* and *COL1A2* were altered in 11% of HNSCC patients (Figure 2A). We also found several point mutations in *COL1A1* (Figure 2B) and *COL1A2* (Figure 2C) in patients with HNSCC.

Protein-protein interactions and functional enrichment analysis of *COL1A1* and *COL1A2*

We identified interactions of *COL1A1* and *COL1A2* at the protein expression level by using STRING. The *COL1A1*was shown to interact with *COL1A2*, and other collagen proteins (Figure 3A). The GEPIA (http://gepia.cancer-pku.cn/) database analysis showed the correlation between *COL1A1* and *COL1A2* (Figure 3B). To study the functions of *COL1A1* and *COL1A2*, we analyzed GO and KEGG pathways using Metascape. The result showed top 7 enrichment (Figure 3C and 3D), molecular functions including collagen biosynthesis and modifying enzymes, assembly of collagen fibrils, extracellular matrix organization, and endodermal cell differentiation.

Discussion

Despite the advances in HNSCC research, it is still a major cause of morbidity and mortality worldwide. Previous studies revealed that type I collagen, the major component of fibrillar collagen family and involved in tumor development, invasion and progression [15, 16]. Although, *COL1A1* and *COL1A2* expression levels in malignant tumors remain controversial. Recent studies reported that *COL1A1* and *COL1A2* mRNA was increased in colorectal cancer and medulloblastoma [17, 18]. Aberrant *COL1A2* promoter methylation aberration also reported in various cancer types [19]. In the present study, our results showed that *COL1A1* and *COL1A2* was highly expressed in various types of cancer including HNSCC. Previous studies have shown that *COL1A1* and *COL1A2* plays prognostic roles in various cancers [20-22]

Figure 1. *COL1A1* and *COL1A2* expression in HNSCC. (A) mRNA expression of *COL1A1 and COL1A2* in different types of cancers compared with in the corresponding normal tissues (red, overexpression; blue, downregulation) using on the Oncomine. Boxplot showing relative expression of *COL1A1* (B) and *COL1A2* (C) in HNSCC and normal tissues.

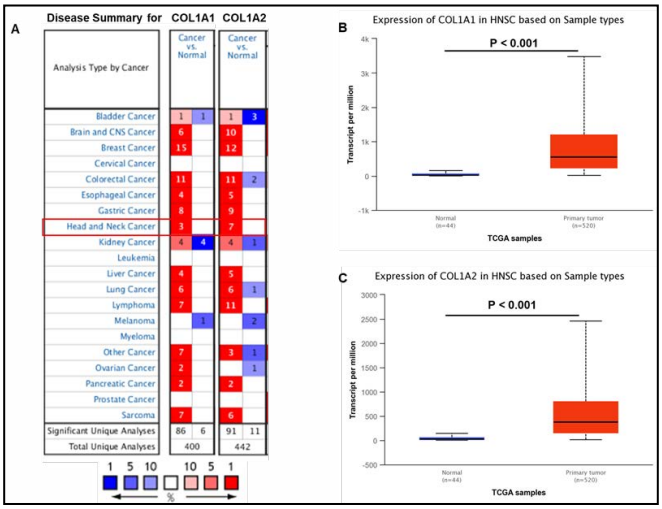


Figure 2. The genetic alterations of *COL1A1 and COL1A2* genes. (A) Oncoprint in cBioPortal database exhibited the proportion and distribution of genetic alterations in *COL1A1 and COL1A2* genes. variations in *COL1A1* (B) and *COL1A2* (C) proteins.

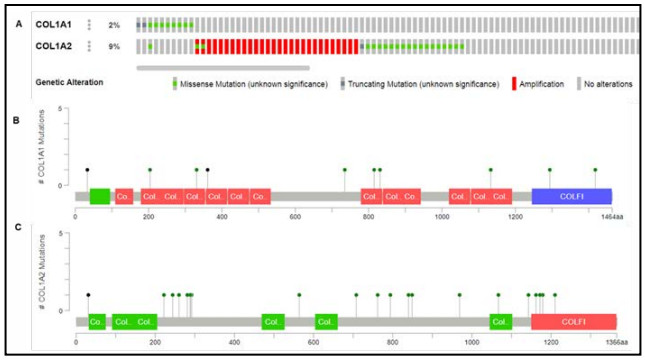
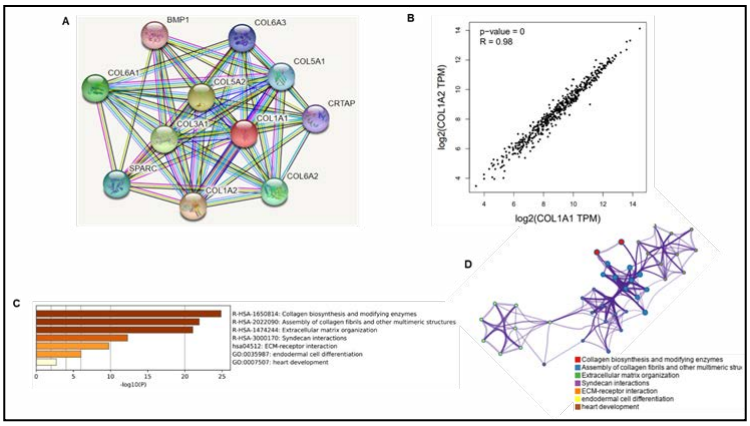


Figure 3. Co-expression, interaction, and functional analysis of *COL1A1 and COL1A2*. (A) Protein-protein interaction network among *COL1A1 and COL1A2* in the STRING dataset. (B) Pearson correlation between *COL1A1 and COL1A2*. (C) Kyoto Encyclopedia of Genes and Genomes (KEGG) functional analysis of 7 key genes in HNSCC. (D) Detailed net structure of key genes in HNSCC (Metascape).



In this study, we found that high expression of *COL1A1* and *COL1A2* were not significantly associated with prognosis in HNSCC patients.

Genetic alterations in *COL1A1* and *COL1A2* have been reported in osteogenesis imperfecta (OI) [23]. Our results demonstrated that *COL1A1* and *COL1A2* was altered in 11% of HNSCC patients. Our results also showed several pathogenic variants in *COL1A1* and *COL1A2* genes. In silico functional analyses predict these variants to be pathogenic with high probability scores. Therefore, our findings suggest that genetic alteration in *COL1A1* and *COL1A2* play important roles in the development of HNSCC.

Further, the protein functional enrichment and the mechanism of *COL1A1* and *COL1A2* studied by Metascape. The results revealed that the pathways involved in *COL1A1* and *COL1A2* might include collagen biosynthesis and modifying enzymes, assembly of collagen fibrils, extracellular matrix organization, and endodermal cell differentiation. Many studies have reported that these pathways are involved in the tumorigenesis. Therefore, these finding help to study the role of type I collagen and relevant signaling pathways in HNSCC development and progression.

Conclusion

The present study provides information on *COL1A1* and *COL1A2* alterations are associated with tumorigenesis in head and neck squamous cell carcinoma. In conclusion, this data demonstrates that *COL1A1* and *COL1A2* play important roles in the oncogenesis of HNSCC.

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