

Update on the Association of CD44 Expression with Esophageal Squamous Cell Carcinoma Invasion

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Abstract

Background: Esophageal cancer (EC) is an aggressive gastrointestinal tumor necessitating novel prognostic, diagnostic, and therapeutic strategies. It is essential to identify important markers for diagnosing malignancy and predicting outcomes. Understanding gene functions in signaling pathways and early cancer detection are vital for reducing EC mortality. CD44 upregulation is linked to cancer stem cells (CSC), metastasis, poor prognosis, and treatment response. CD44v6, a variant of CD44, plays a pivotal role in tumor invasion and metastasis by influencing the extracellular matrix, promoting cell motility, and suppressing cancer cell apoptosis.

Methods: This study investigated CD44v6 expression in tumor and tumor-free tissues of the esophagus in 50 esophageal squamous cells carcinomas (ESCC) patients using real-time PCR. The aim was to assess its prognostic value and its correlation with tumor invasion.

Results: Significant overexpression of CD44v6 mRNA was detected in 9 out of 50 tumor specimens (18%, $p = 0.0001$). CD44v6 expression showed an inverse correlation with tumor cell metastasis to lymph nodes ($p = 0.047$). Among the 21 patients with lymph node metastasis, 5 (23%) exhibited CD44v6 overexpression. Additionally, CD44v6 expression was linked to the tumor stage ($p = 0.008$). Specifically, 2 out of 9 patients with stage I tumors (22.2%), 4 out of 9 with stage II tumors (44.4%), and 3 out of 9 with stage III tumors (33.3%) showed CD44v6 overexpression.

Conclusion: Our findings suggest that lower CD44v6 expression at the RNA level correlates with increased tumor invasion and more advanced stages in ESCC.

Keywords: CD44v6, Esophageal squamous cell carcinoma, Gene expression, Invasion.

Introduction

Esophageal cancer (EC) is the eighth most common cancer and the sixth leading cause of cancer-related deaths globally. It is often diagnosed at an advanced stage, leading to a poor prognosis with a 5-year survival rate of approximately 20% (1-3). These cancers are mainly categorized into two histological

subtypes: esophageal adenocarcinomas (EACs) and esophageal squamous cell carcinomas (ESCCs), which make up most cases (2). It is the sixth most common cancer globally, with the highest mortality rates in Asia (4). Despite advancements in diagnosis and treatment, mortality rates for ESCC have not significantly

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improved (5-7). This persistent trend is largely due to the late-stage detection of ESCC and the limited comprehension of the underlying cellular and molecular mechanisms governing its initiation and progression (8, 9). Due to the poor prognosis, most cases of ESCs are diagnosed at late stages, resulting in a low overall 5-year survival rate of 9%. Early detection of malignancy can significantly improve survival rates (10). Research has focused on understanding the molecular mechanisms underlying ESCC to identify key molecules involved in tumor growth, which could serve as prognostic markers or treatment targets (11).

Several studies have emphasized the prognostic significance of CD44, a stem cell surface marker, in gastrointestinal cancers (12-14). CD44 is an 85 to 90-KD transmembrane glycoprotein involved in various physiological processes such as leukocyte homing, wound healing, tumor progression, and metastasis (15, 16). As the primary marker for cancer stem cells (CSCs), CD44 is closely linked to their self-renewal abilities and tumorigenic potential, playing a crucial role in tumorigenesis (17). The CD44 family is encoded by a gene located on chromosome 11 and consists of 20 exons. Exons 1-5 and 16-20 combine to form the standard isoform (CD44S), while exons 6-15 create alternative isoforms through splicing. This results in multiple variant isoforms of CD44 (18). Studies have demonstrated that CD44 expression is associated with tumor progression in various human cancers, including breast cancer (19), colon cancer (20), melanoma (21), gastric cancer (22), and lung cancer. Specifically, isoform V6 of CD44 has been shown to play a crucial role in promoting metastasis in adenocarcinoma in rat models (23). CD44 is activated by the phosphatidylinositol 3-kinase (PI3K)/Akt pathway, leading to increased proliferation and resistance to apoptosis. CD44, along with membrane-bound receptor tyrosine kinases such as c-ErbB-2 and c-Src, promotes the proliferation of tumor cells (24). Additionally, CD44 plays a role in tumor cell

binding, stimulation of cell growth, and proliferation in gastric and colorectal cancer, as well as in metastasis (25, 26).

The high prevalence of ESCC in developing countries and rising mortality rates underscore the critical need for further research to identify biomarkers that can predict treatment response, resistance, and prognosis. This study examined CD44v6 expression in 50 ESCC patients using comparative real-time PCR to investigate its correlation with invasion in ESCC.

Materials and Methods

Tissue Specimens

Fresh tumor and distant tumor-free esophageal tissue samples were obtained from 50 patients with histologically confirmed esophageal squamous cell carcinoma (ESCC) who underwent surgical resection at Omid Hospital, affiliated with Mashhad University of Medical Sciences. Inclusion criteria were as follows: histologically confirmed ESCC, no prior history of chemotherapy or radiotherapy, and the ability to provide informed consent. Exclusion criteria were history of other malignancies, prior esophageal surgery, or inadequate clinical data. Tumor specimens were verified histologically to contain at least 70% tumor cells. The study protocol was approved by the Institutional Ethics Committee of Birjand University of Medical Sciences (BUMS), and written informed consent was obtained from all participants. Detailed histopathological characteristics, including tumor size, anatomical location, and differentiation grade, were recorded (27).

cDNA synthesis and quantitative real-time-PCR

After collection, specimens were immediately treated with RNAlater solution (Qiagen, Hilden, Germany) and stored at -20 °C until RNA extraction. Total RNA was isolated from fresh tumor and normal tissues using the RNeasy Mini kit (Qiagen, Hilden, Germany). cDNA was synthesized with oligo dT primers in the First-Strand Synthesis kit (Fermentas, Lithuania) in 20 µL reactions following the manufacturer's

instructions. Quantitative real-time RT-PCR was performed using SYBR Green PCR Master Mix (Fermentas, Lithuania) with ROX as a reference dye on a Stratagene Mx3000P real-time thermocycler (Stratagene, La Jolla, CA) with primers listed in Table 1. The thermal cycling program included an initial denaturation step at 95 °C for 10 min, followed by 40 cycles of 15 sec at 95 °C, 10 sec at 60 °C, and 1 min at 72 °C. Data were normalized to glyceraldehyde 3-phosphate dehydrogenase (GAPDH) expression (28).

The PCR efficiencies for GAPDH and CD44v6 were determined by generating standard curves. The relative levels of CD44v6 gene expression were analyzed based on fluorescence intensity changes in tumor versus normal tissues using the comparative threshold cycle method. mRNA expression levels over two-fold were considered overexpression, under twofold as underexpression, and within the two-fold range as normal expression. All reactions were performed in triplicate.

Table 1. Primer sequences used for quantitative real-time RT-PCR.

Primer	Accession numbers	Forward	Reverse
CD44v6	NM_001202555	AGGAACAGTGGTTTGGCAAC	CGAATGGGAGTCTTCTCTGG
GAPDH	NM_001289745	GGAAGGTGAAGGTCGGAGTCA	GTCATTGATGGCAACAATATCCACT

Statistical analysis

The data were analyzed using SPSS version 19.9 statistical software (SPSS, Chicago, IL). The associations between CD44 mRNA expression levels and various histopathological characteristics of patients were assessed using the χ^2 test. Results were presented as mean \pm standard deviation (SD), with p-values < 0.05 considered statistically significant.

Results

Patients and tissue specimens

A total of 50 esophageal tumor specimens, along with their matched adjacent normal tissues, were analyzed for CD44v6 mRNA expression using quantitative real-time RT-PCR. The mean age of the patients was 61.73 \pm 12.14 years, and the tumor size averaged 4.16 \pm 1.88 cm. Among the patients, 24 (48.0%) were male and 26 (52.0%) were female, with no significant difference in CD44v6 expression between genders (p = 0.909).

Tumor localization was predominantly in the middle (50.0%) and lower (42.0%) regions of the esophagus. Histologically, 64.0% of tumors were moderately differentiated (Mod. D), while 16.0% were poorly differentiated (Poor D), and 10.0% were well differentiated (Well D). No statistically significant association was observed between CD44v6 expression and tumor grade (p = 0.494) or location (p = 0.44).

Lymph node involvement was observed in 23 patients (46.0%), and a significant correlation was found between CD44v6 expression and lymph node metastasis (p = 0.047, r = 0.077). Additionally, CD44v6 expression was significantly associated with tumor stage (p = 0.008, r = 0.0201). Most patients were in stage II (56.0%) or III (40.0%).

Regarding tumor depth, 41 patients (82.0%) had T2 invasion, while 9 patients (18.0%) were T1, showing no significant difference in CD44v6 expression between the two (p = 0.494). The clinicopathological features of the patients are detailed in Table 2.

Table 2. Correlations between CD44 isoforms V6 gene expression and clinicopathological characteristics of the ESCC patients.

Patients	50	CD44v6 overexpression (P value)	Correlation r value
Mean age (mean±SD)	61.73±12.14 years	0.873	
Size (mean ± SD)	4.158±1.88 cm	0.948	
Sex			
Male	24(48.0%)	0.909	
Female	26(52.0%)		
Location			
Lower	22(42.0%)	0.44	
Middle	25(50.0%)		
Upper	3(8.0%)		
Grade			
PD	8(16.0%)	0.494	
MD	32(64.0%)		
WD	10(10.0%)		
Lymph node			
Yes	23(46.0%)	(0.047)	0.077
No	27(54.0%)		
Stage			
I	2(4.0%)	(0.008)	0.0201
I	28(56.0%)		
III	40(40.0%)		
Depth of tumor invasion (T)			
T1	9(18.0%)	0.494	
T2	41(82.0%)		

WD: Well differentiated; MD: Moderately differentiated; PD: Poorly differentiated.

*Significant correlation between CD44v6 mRNA expression and clinicopathological feature.

Upregulation of CD44v6 in ESCC

Relative expression of CD44v6 mRNA in 50 paired tumor and adjacent normal esophageal tissue samples. Each dot represents the fold change (tumor vs. normal) in one patient, measured by quantitative real-time RT-PCR. Fold change values were calculated using the $2^{-\Delta\Delta Ct}$ method. A fold change ≥ 2 (red

horizontal line) was considered upregulation, while a fold change ≤ 2 (blue horizontal line) indicated downregulation. Red dots represent samples with significant upregulation. Most samples show mild variation around baseline (fold change = 1), with a few cases of strong downregulation or upregulation (Fig. 1).

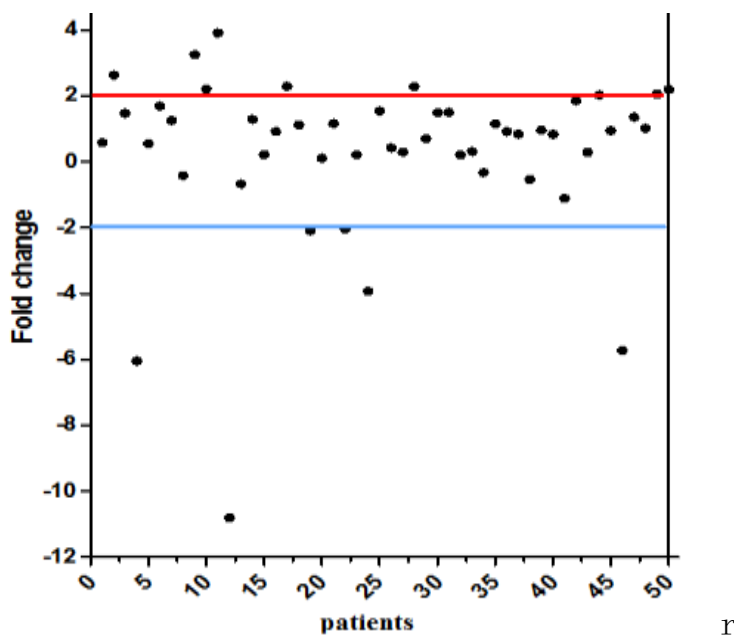


Fig. 1. A scatter plot illustrating the level of CD44v6 mRNA expression in ESCC patients. The Y-axis represents the fold change in gene expression, while the X-axis indicates the number of patients. A two-fold increase in gene expression in tumor samples was classified as overexpression, while a two-fold decrease was categorized as underexpression. Expression levels falling between these two values were considered within the normal expression range.

We found significant overexpression of CD44v6 mRNA in 9 (18%) patients ($p = 0.0001$). The fold changes in mRNA

expression ranged from -10.80 to 3.91 times (mean \pm SD: 0.328 ± 2.475). In contrast, 41 (82%) patients exhibited normal or underexpression of CD44v6 (Fig. 2).

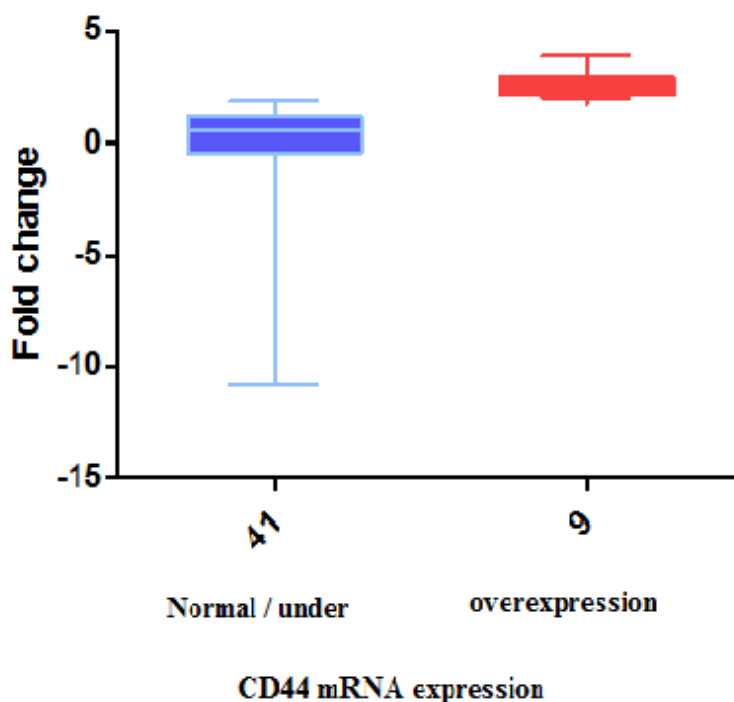


Fig. 2. A box plot illustrating the relative mRNA expression of CD44v6 in ESCC patients. The Y-axis displays the fold change of relative mRNA expression, while the X-axis indicates the patient groups. The box plots depict the lowest, median, and highest observations of fold changes in patients with normal/underexpressed or overexpressed CD44v6 ($P = 0.0001$).

Association of CD44v6 expression with clinicopathological variables

We analyzed the correlation between CD44v6 gene expression and clinicopathological variables (Table 2) to estimate the clinicopathological outcomes of CD44v6 expression in ESCC. CD44v6 expression was inversely associated with tumor cell metastasis to lymph nodes ($P = 0.047$). Out of 21 patients with lymph node metastasis, 5 of 21 (23%) overexpressed CD44v6. Additionally, CD44v6 expression was associated with the stage of the tumor ($P = 0.008$). 2 out of 9 (22.2%) stage I, 4 out of 9 (44.4%) stage II, and 3 out of 9 (33.3%) stage III patients overexpressed CD44v6. No significant associations were observed between CD44v6 expression and other clinicopathological variables, such as tumor grade or depth of tumor invasion.

Discussion

Several studies confirmed that *CD44* is a crucial CSC marker in ESCC and they have shown upregulation of *CD44* in ESCC, colon, glioma, ovarian, breast, kidney, and gastric cancers, which was related to CSCs, metastasis, poor prognosis, and poor treatment outcomes (29). CD44v6 is considered a significant contributor to tumor invasion and metastasis, functioning by modulating the extracellular matrix, facilitating cell motility, and preventing apoptosis in neoplastic cells (30). Moreover, it is proposed that CD44v6 is positively associated with both invasive growth and the advancement of metastasis in specific tumor types (31). There are some similar studies reporting the overexpression of *CD44v6* in different malignancies. It has been shown that the expression of this gene and its isoforms is increased significantly in different malignant tissues, including breast cancer (32), certain types of leukemia (33), head and neck SCC (34), oral cancer (35), and Barrett's esophagus (36). Studies show that *CD44* isoforms and, particularly *CD44v6* are important in tumorigenesis, particularly in the metastatic process. To further substantiate the hypothesis

pertaining to the role of CD44v6 in tumor growth and invasion, empirical research has revealed that the inhibition of CD44v6 through the application of the A5G27 polymer is associated with a significant attenuation of cancer cell invasion and migration (37). This discovery reinforces the role of CD44v6 in the processes associated with tumor invasion.

Additionally, *CD44v6* regulates Met transcription and activates the PI3K-Akt pathway through its binding to the extracellular matrix. This result indicates the involvement of *CD44v6* in the invasive phenotype of ESCC. In line with previous studies, our finding suggests that the reduced expression of *CD44v6* is associated with a higher probability of invasion in Esophageal squamous cell carcinoma (ESCC). Expression analysis of *CD44v6* in normal and esophageal tumor tissues showed overexpression of *CD44v6* in nearly 18% of ESCC samples. Even though this does not appear to be a common characteristic for all tumors (38). In our study, the decreased expression of *CD44v6* was correlated with the tumor invasion, similar to what was reported by Hiroaki Suzuki. He studied expression of CD44 isoforms V3 and V6 in 93 Japanese lung adenocarcinoma patients using immunohistochemistry and found that reduced expression of CD44 V3 and V6 is linked to invasion in lung adenocarcinoma, supporting our findings (39). Nonetheless, the involvement of CD44 in cancer progression remains ambiguous; while certain studies indicate that an increase in CD44 levels may facilitate tumor invasion and dissemination, other research suggests that a decrease or lack of CD44 expression is associated with more aggressive tumor characteristics (40). Recent investigations have increasingly focused on the CD44v6 splice variant, which has been identified as a valuable prognostic marker across various cancers, including gastric, head and neck, prostate, and lung cancers (41). Unlike the standard CD44 form, which is generally expressed in many tissues, CD44 splice variants containing the variant exon v6 demonstrate a more limited expression profile

in normal tissues (42). Thus, the findings delineated in the present study indicate that the standard isoform of CD44 (CD44s) is ubiquitously expressed across both normal and pathological gastric epithelial cells. In contrast, the variant isoform CD44v6 demonstrates a preferential expression in premalignant gastric lesions and is identified in approximately 70% of gastric cancer (GC) cases. These insights suggest a potential role for CD44v6 as a biomarker in the early detection and diagnosis of gastric malignancies (43). Previous studies have shown that co-expression of *CD44v6* and *CD44s* was associated with tumor grade, and *CD44v6* / *CD44v3* was associated with sex, lymph node involvement, tumor stage, and metastasis. Thus, co-expression of *CD44* isoforms seems to be a potential marker to predict the invasiveness of ESCC (44).

The present study demonstrates a correlation between CD44v6 expression levels and tumor invasion, thus indicating that the expression of CD44 isoforms could serve as a potential marker for predicting invasiveness in esophageal squamous cell carcinoma (ESCC). It is recommended that future research investigate the individual contributions of the various CD44 isoforms in patients with this

malignancy.

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Authors' Contribution

AF., M.N., and R. K. K. participated in data collection and manuscript writing. S. A. E and A. M. designed and drafted the article. All authors have fully read and approved the final manuscript.

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Conflicts of interest

The authors affirm the absence of any conflicts of interest.

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