Experimed 2022; 12(3): 119-24

ORIGINAL ARTICLE

DOI: 10.26650/experimed.1189327

Assessing E-Cadherin and Connexin 43 Gene Expressions in Colorectal Cancer

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Cite this article as: Surmen S, Arikan S, Timirci Kahraman O, Surmen MG, Cacina C, Yaylim I. Assessing E-cadherin and connexin 43 gene expressions in colorectal cancer. Experimed 2022; 12(3): 119-24.

ABSTRACT

Objective: Dysregulation of cellular adhesion is one of the main mechanisms responsible for tumor initiation, proliferation, and survival. E-cadherin is a cell adhesion molecule associated with tissue invasion and metastasis in most epithelial cancers. Gap junctions are known as small molecular channels that allow communication between neighboring cells and consist of connexin molecules. Connexin 43 (Cx43) is a gap junction protein that plays a central role in cell-cycle regulation and has an important function in carcinogenesis. The present study aimed to evaluate the expression levels of E-cadherin and Cx43 in colorectal cancer patients using clinical and prognostic parameters.

Materials and Methods: The quantitative real-time polymerase chain reaction (qRT-PCR) method was utilized to characterize the expression patterns of the E-cadherin and Cx43 genes in tumor and adjacent non-tumoral colon tissues from 32 colorectal cancer patients. Analysis of gene expression data was carried out using the delta-CT method.

Results: The results show the expression level of Cx43 to decrease 14-fold in tumor tissue compared to normal tissue ($p<0.05$). However, the study could find no significant difference with regard to E-cadherin expression.

Conclusion: The research provides valuable clues to the elucidation of tumor development and metastatic processes for further studies.

Keywords: Colorectal cancer, cell adhesion, connexin 43, E-cadherin, qRT-PCR

INTRODUCTION

Colorectal cancer (CRC) is a multifaceted and therapeutically challenging disease. The development, progression, and metastatic spread of CRC have been comprehensively investigated in terms of characterizing the genomic and proteomic alterations of the disease in different populations. The different stages of tumor onset and progression involve irregularities in both intracellular and intercellular communication networks. The systematic literature review by Nalewajska et al. (1) emphasized targeting the connexins that connect the cytoplasm of neighboring cells to possibly be an effective way for treating specific tumors.

Gap junction intercellular communication (GJIC) is defined as intercellular channels allowing small molecules (e.g., ions, metabolites and second messengers such as cAMP) to pass between cells and has an important role in apoptosis, cell growth, cell cycle control, tissue differentiation, and homeostasis. GJIC consists of the protein subunits of connexin, which has more than 20 isoforms. As the most commonly known isoform of the family member, connexin 43 (Cx43) has been named according to its molecular weight and is encoded by the GJA1 gene (1, 2).

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Submitted: 16.10.2022 **Revision Requested:** 03.11.2022 **Last Revision Received:** 09.11.2022 **Accepted:** 21.11.2022 **Published Online:** 27.12.2022

Studies have shown a negative correlation to exist between Cx43 expression and tumor growth. Accordingly, both the cell surface and cytoplasmic Cx43 may have a suppressive role in tumor growth through their C-termini tails that bind to signaling molecules (3). However, some reports have stated increased Cx43 expression to appear to be associated with poor prognosis and poor patient survival (2). According to the STRING database, the GJA1 protein, which interacts with tight junction protein ZO-1, vinculin, and E-cadherin, is involved in the regulation of cell-cell junction assembly and cell migration (Figure 1). Decreased Cx43 and E-cadherin expression have been reported to contribute to the presence of primary gastric cancer, while concurrent elevated expression levels of these proteins can contribute to metastatic lymph nodes (4). The cytoplasmic domains of Cx43 may interact with cell adhesion molecules that play a pivotal role in invasion and metastatic processes. E-cadherin is a member of the calcium dependent cell adhesion molecules that are thought to have a crucial role in maintaining epithelial tissue integrity (5). Researchers have demonstrated a loss of the E-cadherin protein to be related to a decrease in intercellular adhesion. Accordingly, the aberrant E-cadherin expression triggers the invasion and metastasis abilities of cells (6, 7). Several alterations of regulation that have adverse impacts on E-cadherin can arise during the progression of cancer in ways such as decreased transcriptional activities, mutations, and promoter methylation (8). Previous reports have highlighted E-cadherin expression to be downregulated in certain cancers (e.g., gastric, colorectal, cervical, and breast) (9-11). In addition, decreased expressions of Cx43 and E-cadherin in lung cancer cells have been reported to be significantly correlated with one another (12).

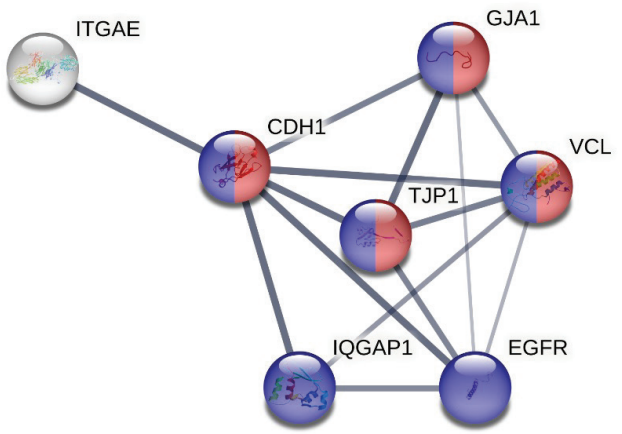

Figure 1. Protein interaction network. GJA1: Gap junction alpha-1 protein; CDH1: Cadherin-1; TJP1: Tight junction protein ZO-1; VCL: Vinculin. Purple and red colors indicate proteins involved in cell-cell junction assembly and the regulation of cell migration, respectively.

When considering the relation between gap junctions and adhesion molecules, the expression patterns of these two genes may play a significant role in tissue homeostasis, differentiation, and proliferation and thereby contribute to carcinogenesis. The aberrant expression of Cx43 or E-cadherin has been reported in different cancer types (1, 6). However, the relationship between E-cadherin and Cx43 expressions in colon cancer has yet to be fully explained, with studies evaluating both genes together still being needed. This study aims to examine both the mRNA expression of Cx43 and E-cadherin in tissue samples from colorectal cancer patients and to evaluate their relationship with the patients' clinical and pathological features.

MATERIALS AND METHODS

Case Information

The study protocol was approved from the ethical committee of the Istanbul University Faculty of Medicine (16.04.2012/665). For expression analysis, 32 tumor and 32 non-tumor tissues were obtained from CRC patients at the surgery clinic of Istanbul Research and Education Hospital between 2012 and 2013. A written informed consent was obtained from each participant. These CRC patients had not undergone any chemotherapy, radiotherapy, or other treatment pre-operation.

RNA Isolation

All tissue samples were collected as fresh frozen within 30 min after tissue resection. PureLink RNA Mini Kit was used according to standard kit protocol for total RNA isolation (Ambion-Life Technologies™, USA). Tissue samples of approximately 100 mg in 1000 µL TRIzol Reagent (Ambion-Life Technologies™, USA) were homogenized with RNAse-free mortars and pestles. The lysate (up to 0.6 mL) was transferred to the spin cartridge and the binding, washing, and elution steps were applied in that order. Following RNA purification, DNAse I digestion procedure was performed to remove DNA contamination. The purity and concentration of all RNA products were detected by measuring the absorbance ratio at A260/A280 nm. Finally, the purified RNA yields were stored at -80 ^{0}C until further analysis.

cDNA Synthesis

High-capacity RNA to cDNA master mix was used for single-stranded cDNA synthesis (Applied Biosystems, Foster City, CA, USA). The cDNA conversion procedure was as follows: 20 µL of the reaction mix was added to the master mix and diluted to an RNA ratio of 1:5. The mix was run on a PCR thermal cycler under optimized conditions (Step 1: 25 ^{0}C for 10 min; Step 2: 42 ^{0}C for 2 h; Step 3: 85 ^{0}C for 5 min).

Quantitative Real-time Polymerase Chain Reaction (qRT-PCR)

The expression levels of Cx43 (UniGene ID Hs.700699) and E-cadherin (UniGene ID Hs.461086) were evaluated by qRT-PCR using the Stratagene Mx3005P System (Agilent Technologies, USA). cDNA products were amplified using TaqMan Gene Expression Master Mix (Applied Biosystem, CA, USA) and

TaqMan gene expression assay, which includes the target gene-specific primer and probe sets (Applied Biosystems, Foster City, CA, USA). TaqMan assays with the following IDs were purchased: Assay ID Hs01023894_m1 for the E-cadherin and Assay ID Hs00748445_s1 for Cx43. As a result of the literature review, β-actin (Assay ID: Hs99999903_ m1) was chosen as a housekeeping gene to normalize the levels of Cx43 and E-cadherin. The PCR mix was prepared in a final volume of 20 µL, and the cycling conditions were as follows: hot start 10 min at 95 ^{0}C, next 40 cycles of 15 s at 95 ^{0}C, and lastly 1 min at 60 ^{0}C. All reactions were run in duplicate. The quantification results have been evaluated using the comparative CT method, in which $2^{-\Delta\Delta CT}$ values were calculated.

Statistical Analyses

Statistical analyses were examined using the program IBM SPSS version 20.0 for Windows (IBN Corp., Armonk, NY, USA). Data were given as means and standard deviations (± *SD*).

Statistical comparisons of the differences between the two groups were carried out with the Mann-Whitney U test, with a $p < 0.05$ being assumed to show statistical significance.

RESULTS

This study compared the obtained gene expression data from the tumor tissue and corresponding normal tissue of the same patients. Of the 32 patients, 24 (75%) were male and eight (25%) were female, with the mean age of all CRC patients being 63.19 ± 10.55 years (range= 36-80 years). The patients' clinicopathologic characteristics were determined according to the American Joint Committee on Cancer (AJCC) 7th TNM stage. The distribution of tumor stages I and II among all patients was 18.8%, with 81.3% having tumors in an advanced stage. The patients were equally distributed according to the presence of metastasis. A total of 43.8% of patients had no lymph node involvement, while 37.5% had N1, and 18.8% had N2. When evaluating the specimens histopathologically, 25.9% of the tumors were noticed to be poorly differentiated, 55.6% to be moderately differentiated, and 18.5% to be well differentiated. The majority of tumor was localized to the sigmoidal colon (44.8%), with other tumors being located in the right colon (24.1%), in the left colon (3.4%), in the transverse colon (10.3%), in the cecum (3.4%), and in the rectum (13.8%).

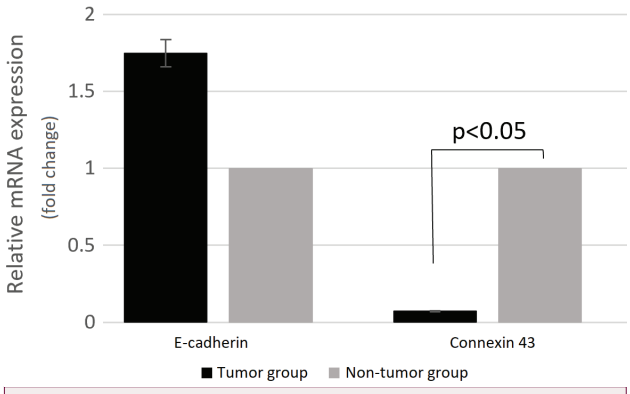

Figure 2. Comparison of E-cadherin and Cx43 mRNA levels in tumor and non-tumor tissues from CRC patients.

The mRNA expression levels of the Cx43 and E-cadherin genes were observed to change in tumor tissue compared to the normal tissue of patients diagnosed with CRC (Figure 2), with the expression of Cx43 having significantly decreased 14-fold in the tumor tissue ($p < 0.05$). Although the study has found no statistically significant difference in expression levels of the E-cadherin gene, a 1.75-fold increase was found in the expression of the E-cadherin gene within tumor tissue ($p > 0.05$). When comparing tumor stages, the study detected E-cadherin expression to have increased 1.33-fold in advanced-stage tumors ($p > 0.05$). The expression patterns of both genes are summarized in Table 1. In addition, when evaluating the expression of both Cx43 and E-cadherin in terms of clinical pathological features such as tumor stage, lymphatic invasion, differentiation grade, and metastasis, no significant differences were found ($p > 0.05$). The relations between the pathologic features of the tumor samples and expression patterns of two genes are given in Table 2.

DISCUSSION

The spread of cancer cells beyond the origin of the tumor to surrounding tissues and organs is tightly associated with molecules involved in cell-cell and cell-matrix adhesion (13). In this process, epithelial tissue cells acquire the mesenchymal phenotype through loss of adhesion and increased migration. To the best of the study's knowledge, epithelial mesenchymal transition (EMT) contributes to cancer progression and promotes cells to metastasize in removed regions. In many types of epithelial cancers, several steps are involved in

Table 1. Fold change value of E-cadherin and Cx43 genes in tumor tissue compared to normal tissue.

Gene	Log2 Fold Change	95%CI	Fold Change	95%CI	*p* Value	Fold Regulation
Cx43	-3.816	(-5.643- -3.058)	0.071	(0.02-0.12)	0.039*	-14.052
E-Cadherin	0.807	(0.88-1.56)	1.750	(0.54-2.96)	0.336	1.750

*p values less than 0.05 denoted statistical significance.

Table 2. Fold change value of Cx43 and E-cadherin genes according to clinical pathological features.

		Log2 Fold Change	95%CI	Fold Change	*P-value*
E-Cadherin Gene Expression	Distant Metastases	-0.049	(-2,556 - 0,81)	0.966	p>0.05
	Lymphatic Invasion	-0.125	(-2.058-0.669)	0.9171	
	Differentiation	0.177	(-5.058-0.97)	1.131	
	Grade	-0.418	(-4.321-0.536)	0.748	
Cx43 Gene Expression	Distant Metastases	1.658	(-0.64 - -2.503)	3.157	
	Lymphatic Invasion	1.183	(-0.971-2.014)	2.2726	
	Differentiation	-4.921	(-16.609- -0.234)	0.330	
	Grade	0.820	(-16.609-1.933)	1.766	

*p values less than 0.05 denoted statistical significance.

tumor metastasis, including the genetic reprogramming and transitioning of cancer cells (14). E-cadherin is a tumor suppressor gene and one of the crucial molecular markers that trigger EMT. In addition, E-cadherin expression has been associated with cell migration, poor differentiation, and metastasis (15,16). This study has investigated the mRNA levels of E-cadherin and Cx43 genes in 32 patients with CRC. Unlike most previous studies, this one has shown E-cadherin gene expression to be 1.75 times higher in tumor tissue compared to normal tissue. However, this difference detected in tumor tissue was not statistically significant. Two studies were published by El-Bahrawy et al. (17, 18) revealed the mRNA levels of E-cadherin and catenin (α,β,γ) to increase in colorectal carcinomas compared to non-neoplastic mucosa. The reason for the increased expression of E-cadherin has been attributed to its accumulation in the cytoplasm.

Furthermore, this study has also evaluated the relation between the E-cadherin expression levels and the pathological parameters of CRC patients. Although a negative correlation does exist between E-cadherin expression and pathological features (i.e., stage, distant metastasis and grade of differentiation) of colorectal carcinoma patients, it was not statistically significant ($p > 0.05$). The literature contains various results regarding the impact of E-cadherin expression on CRC progression. Mădălina Palaghia et al. (19) conducted a study on 65 patients who'd undergone a colectomy for CRC and concluded E-cadherin expression abnormalities to be an important marker of tumor aggressiveness and spread potential. Gao et al. (20) showed the expression of E-cadherin to be lower in colon cancerous tissues during metastasis. In addition, one meta-analysis showed the downregulation of E-cadherin to be significantly related to poor prognosis in Asian patients with CRC (21). Previous studies have led to the conclusion that decreased E-cadherin expression is associated with invasive colorectal cancer (16).

In addition to epithelial tissue integrity, E-cadherin also plays a pivotal role in ensuring communication between adherent cells by means of Cx43. E-cadherin facilitates the formation of gap junctions by playing a role in the cell membrane transport of Cx43 (22, 23). A positive correlation has been reported to exist between E-cadherin and Cx43 protein expression with regard to gastric, lung, and colorectal cancer (4, 12, 24). Xu et al. (12) showed the pattern of E-cadherin expression to be related to Cx43 expression levels and reported overexpression of Cx43 to induce E-cadherin expression in lung cancer cells. Their same study also found concurrent reduction of expressions in both genes to be associated with lymph node metastasis. Similarly, Tang et al. (4) showed the concurrent reduction of Cx43 and E-cadherin in primary gastric cancer using immunostaining. In addition, Zhao et al. (25) investigated E-cadherin and Cx43 with regard to both mRNA and protein levels in Chinese patients with non-small cell lung cancer (NSCLC). They found decreased E-cadherin and Cx43 protein levels to correlate to NSCLC progression, clinic stage, and lymph node metastasis. However, E-cadherin and Cx43 mRNA levels significantly increased with regard to advanced tumor stages, poor differentiation, and lymph node metastasis. These results reveal the need to explain the cause of variability in mRNA and protein levels.

According to the literature review, Cx43 acts as a tumor suppressor, with its low expression contributing to colon carcinogenesis. Sirnes et al. (26) examined the clinical significance of the irregular expression of Cx43 in CRC tissue and cell lining. They reported Cx43 to regulate cell growth negatively in HT29 colon cancer cells by inducing apoptosis. Decreased expression of Cx43 was related to overall survival for patients in the early stages. Furthermore, the study results implied that Cx43 may also cause different clinical effects according to its subcellular localization. The present study has found Cx43 expression to be reduced 14-fold in tumors compared to adjacent normal tissue, and this data

was statistically significant. Ismail et al. (27) examined Cx43 expression by immunohistochemical analysis and reported downregulation of Cx43 to be significantly related to the histological features of the colon cancer. The current study observed an increase in Cx43 expression for patients in advanced stage who were metastasis-positive; however, the differences were not significant. Kanczuga-Koda et al. (24) examined the correlation among the expressions of E-cadherin, β-catenin, and the three Cx proteins (i.e., Cx26, Cx32, and Cx43) in colorectal cancer tissues using immunohistochemistry. According to their study, a significant positive correlation was found between E-cadherin and Cx26 in the total patient group and between E-cadherin and Cx43 protein expression levels in patients with metastatic lymph nodes and tumors in advanced stages. Despite the decrease in Cx43 expression found in the current study, this was not correlated with E-cadherin expression. In addition, when examining the mRNA levels of Cx43 and E-cadherin in terms of tumor size, lymph node involvement, remote metastasis, and differentiation, the study found no significant differences.

CONCLUSION

Although a wide range of data is available about the linkage between E-cadherin and Cx43 protein levels, less is known about the mRNA levels for both E-cadherin and Cx43 genes with respect to colorectal cancer. Our study findings suggest that Cx43 may play a crucial role in the progression of colorectal cancer. However, the current study also has limitations. It evaluated only the mRNA expressions of these genes and not protein levels through the immunohistochemical method or western blotting. The cause of the malfunction of E-cadherin and Cx43 remains unclear. This is a preliminary study for CRC, which has a complex pathogenesis. Thus, a large-scale study that comprehensively investigates mRNA and protein levels is needed. In future studies in particular, revealing the relationship between E-cadherin and Cx43, which help maintain cell-to-cell communications, will contribute to the clear elucidation of tumor development and metastasis.

Ethics Committee Approval: The study protocol was approved from the ethical committee of the Istanbul University Faculty of Medicine (16.04.2012/665).

Peer-review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study - I.Y., O.T.K., S.S.; Data Acquisition - S.S., S.A.; Performing experiments - O.T.K., S.S., M.G.S., C.C.; Data Analysis/Interpretation - S.S.; Drafting Manuscript - I.Y., C.C., M.G.S., O.T.K., S.A.; Critical Revision of Manuscript - I.Y., S.S., S.A., O.T.K., M.G.S., C.C.; Final Approval and Accountability - I.Y.

Conflicts of Interest: The authors declare no conflict of interest.

Financial Disclosure: This study was funded by The Scientific Research Projects Coordination Unit of Istanbul University (Project number:24522).

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