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Changes in Claudin-4 expression and tight junction integrity in human esophageal cancer: A Systematic Review

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Abstract

Background: Esophageal cancer is one of the most common cancers worldwide. Because this disease is usually diagnosed in advanced stages, its treatment is challenging and the survival rate of patients is relatively low. One of the parts that is disturbed in the tumor tissue of esophageal cancer is the tight connections between cells. Claudin-4 (CLDN-4) is one of the tight junction regulatory proteins whose changes are involved in cancer formation. In this systematic review, we examine the changes in CLDN-4 and the factors that affect its level in samples and cell lines related to esophageal cancer.

Methods: Scopus, PubMed, and Web of Science databases were searched for articles that examined CLDN-4 gene and protein expression in patients with esophageal cancer or cell lines related to esophageal cancer. A number of 202 manuscripts were obtained in the beginning, and after screening and applying the inclusion and exclusion criteria, six studies remained.

Results: Six studies, including 596 patients and seven cell lines related to esophageal tissues, were included in this systematic review. The studies were related to Japan, South Korea, China, and Finland. In these studies, the level of CLDN-4 in cancer samples related to esophageal cancer and their location in esophageal tissue cells have been examined.

Conclusion: In summary, it can be concluded that the change in the level of CLDN-4 in the tumor tissues of esophageal cancer altered the tight junctions from the normal state in the normal esophageal tissues, leading to a change in normal barrier function. However, considering the conflicting results in the reports, more studies are needed to accurately interpret the role of CLDN-4 in esophageal cancer.

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Highlights

What is current knowledge?
Changes in gene expression or changes in CLDN-4 protein levels play a role in the formation and progression of esophageal cancer.

What is new here?
Considering the conflicting results in the studies that have been published so far, more studies with a larger statistical population are needed to determine the exact role of CLDN-4

Introduction

Esophageal cancer is the eighth most prevalent cancer globally (1). There are two main histological subtypes of esophageal carcinoma: esophageal adenocarcinoma (EAC), originating from the columnar epithelia of the esophagus, and esophageal squamous cell carcinoma (ESCC), originating from the stratified squamous epithelia of the esophageal mucosa (2,3). The location of the tumor in the esophagus is different in EAC and ESCC subtypes (4). The ESCC, especially takes place in the proximal two-thirds of the esophagus, while EAC specifically occurs in the distal third of the esophagus (4). More than 90% of esophageal cancers in the world are of ESCC type and this cancer is mostly seen in countries with poor economic status and low income (2). The ESCC is associated with a poor prognosis, and its diagnosis usually occurs in the advanced stages of the disease (5). The incidence of EAC in Western countries has been increasing in recent decades (1). Despite advances in treatment and surgical techniques, the 5-year survival rate for EAC is 20.2% and 22.8% for ESCC (1). Considering the low survival rate in esophageal cancer patients, it is necessary to recognize the mechanisms of esophageal tumor progression (6).

Epithelial and endothelial cells form a protective barrier in the tissue and participate in maintaining homeostasis (7). The protective barrier requires proteins, including tight junction proteins, to function properly (8). Tight junctions (TJ) play a role in intercellular communication and cell polarity, maintenance of intercellular space in the epidermis, paracellular transport, and overall tissue maintenance (7,9,10). Components of TJ regulate gene expression, cell migration, and cell apoptosis by affecting signaling pathways (11). Studies show that TJ, in addition to maintaining the barrier function, is effective in the formation of various cancers (11).

Claudin family (CLDN) is one of the important structural and functional components of TJ (12). CLDNs are a family consisting of 27 genes, and CLDN proteins weigh approximately 20-27 kDa. They cross the cell membrane four times and their C-terminal and N-terminal are located in the cytoplasm (7,13). CLDNs have essential functions such as the barrier and the fence function (14). Also, they regulate cell adhesion, and their dysfunction (Upregulation or downregulation) is observed in tumorigenesis and cell invasion of different cancers (7,12,13).

CLDN-4 is a member of the claudin family and its gene is expressed in all human tissues (7). Its N-terminal is short and its C-terminal is variable length in different species and has approximately 27 amino acids. The cell membrane is connected to parts of the cytoskeleton through the C-terminal of the CLDN-4 (15). CLDN-4, as a regulator of tight junctions, is involved in the development of cancer and the invasion and cancer cell metastasis (12). This systematic review aims to investigate CLDN-4 changes in esophageal cancer. We aimed to investigate the effect of changes in the CLDN-4 gene and protein expression on cancer cells' growth by reviewing the available studies.

Methods

Eligibility criteria

Inclusion criteria for this systematic review are as follows: Examination of gene expression or examination of CLDN-4 protein in esophageal cancer cell lines and esophageal tumor (Mostly EAC and ESCC) samples as well as investigating the effect and relationship of different markers on the level of CLDN-4. Exclusion criteria consist of Barrett's esophagus, gastroesophageal adenocarcinoma, gastrointestinal cancer, methylation of the CLDN gene or its promoter, microarray data analysis, microarray data analysis, other CLDN family genes, review articles, articles that did not have relevant and extractable information, animal studies, and non-English language studies.

Information sources

A total of 202 studies were obtained from searching the databases (PubMed (n = 12), Scopus (n = 177), and Web of Science (n = 13)), and after removing duplicate articles, 176 articles remained.

Search strategy

The systematic search was performed on February 13, 2024, according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement. In this systematic review, the search language in the databases was

English. Search strategy in PubMed: ("CLDN4"(Title/Abstract) OR "CLDN 4"(Title/Abstract) OR "CLDN-4"(Title/Abstract) OR "Claudin4"(Title/Abstract) OR "Claudin 4"(Title/Abstract) OR "Claudin-4"(Title/Abstract)) AND ("Esophageal cancer"(Title/Abstract) OR "Esophageal tumor"(Title/Abstract) OR "Esophageal neoplasm"(Title/Abstract) OR "Esophageal carcinoma"(Title/Abstract) OR "Esophageal malignant"(Title/Abstract) OR "Oesophageal cancer"(Title/Abstract) OR "Oesophageal tumor"(Title/Abstract) OR "Oesophageal neoplasm"(Title/Abstract) OR "Oesophageal carcinoma"(Title/Abstract) OR "Oesophageal malignant"(Title/Abstract) OR "Esophagus cancer"(Title/Abstract) OR "Esophagus tumor"(Title/Abstract) OR "Esophagus neoplasm"(Title/Abstract) OR "Esophagus carcinoma"(Title/Abstract) OR "Esophagus malignant"(Title/Abstract) OR "esophageal adenocarcinoma"(Title/Abstract) OR "esophageal squamous cell carcinoma"(Title/Abstract)). Search strategy in Scopus: (TITLE-ABS-KEY ("cldn" OR "CLDN 4" OR "CLDN-4" OR "claudin" OR "Claudin 4" OR "Claudin-4") AND TITLE-ABS-KEY ("Esophageal cancer" OR "Esophageal tumor" OR "Esophageal neoplasm" OR "Esophageal carcinoma" OR "esophageal malignant" OR "Oesophageal cancer" OR "Oesophageal tumor" OR "Oesophageal neoplasm" OR "Oesophageal carcinoma" OR "oesophageal malignant" OR "Esophagus cancer" OR "Esophagus tumor" OR "Esophagus neoplasm" OR "Esophagus carcinoma" OR "esophagus malignant" OR "esophageal adenocarcinoma" OR "esophageal squamous cell carcinoma"). Search strategy in Wen of Science: “CLDN4” OR “CLDN 4” OR “CLDN-4” OR “Claudin4” OR “Claudin 4” OR “Claudin-4” (Topic) AND “Esophageal cancer” OR “Esophageal tumor” OR “Esophageal neoplasm” OR “Esophageal carcinoma” OR “Esophageal malignant” OR “Oesophageal cancer” OR “Oesophageal tumor” OR “Oesophageal neoplasm” OR “Oesophageal carcinoma” OR “Oesophageal malignant” OR “Esophagus cancer” OR “Esophagus tumor” OR “Esophagus neoplasm” OR “Esophagus carcinoma” OR “Esophagus malignant” OR “esophageal adenocarcinoma” OR “esophageal squamous cell carcinoma” (Topic).

Selection process

A total of 202 articles were extracted from Scopus, PubMed, and Web of Science databases, remaining 176 articles after removing duplicate articles. Then, 60 review articles and 102 unrelated articles were excluded from the collection of articles. Also, two articles with microarray analysis, and three non-English articles were excluded. In two articles, esophageal cancer tissue was examined along with some samples of other cancers, which were excluded. The initial screening was done based on the title and abstract of the articles by two reviewers (Jafari and Mahdizadeh) independently until February 2024. Afterward, the full text of the articles was reviewed according to the inclusion and exclusion criteria. Subsequently, each of the reviewers read all articles separately and finally shared their selected studies. If there were a difference of opinion in cases, such as articles with microarray analysis, they would reach an agreement by re-examining the article.

Data collection process

After identifying the final six studies, one reviewer read three of them in full, while another reviewer read the remaining three. Both reviewers worked independently. All the published reports and their tables and figures were studied and the desired information was extracted.

Quality assessment

Two distinct research experts assessed the quality level of the eligible studies utilizing the Cochran scoring methodology. This comprises seven criteria to gauge the risk of bias, which are as follows: random sequence generation, blinding of participants and staff, blinding of evaluators, allocation concealment, selective reporting, incomplete outcome data, and other probable biases.

Results

Study selection

Eventually, relevant articles were reviewed and sorted for final analysis. Figure 1 represents the flow diagram for searching and extracting. Montgomery's study was published in 2006 (16) and Langbein's study was published in 2003 (17), which met the criteria for entering this systematic review, but the cancer samples in these studies were a collection of different types of tissues, including esophageal cancer. As a result, because the samples were not limited to esophageal cancer, they were excluded from our study.

Study characteristics

The main characteristics of the six selected studies are described in Table 1. Two studies were conducted two studies in Japan, two studies in South Korea, one studies in China, and one study in Finland. Studies were published between 2007 and 2022. Altogether, the number of esophageal cancer patients included in each study varied from 20 to 164. A total of 479 patients (401 ESCC and 78 esophageal carcinoma) were included in these studies. Also, TE5, TE8, TE10, TE11, Eca109, and A431 esophageal cancer cell lines were used in these studies.

Table 1. Characteristics of the eligible studies

Author	H. Takala (22)	Chang Ohk Sung (20)	Keun-Woo Lee (25)	Mo Shi (21)	Yunyan Wu (23)	Shusuke Toda (24)
Year of publication	2007	2010	2012	2014	2016	2022
Country	Finland	Korea	South Korea	China	Japan	Japan
Types of studies	Clinical	Clinical	Clinical, in vitro	Clinical, in vitro	In vitro	Clinical
Cell line	-	-	TE8, TE10	Eca109, TE-1	TE-10, TE-11, TE-5, A431(Control)	-
Total patients	ESCC: 54 EAC: 20 Other histology: 4	164 ESCC	198 ESCC	119 ESCC	-	20 ESCC
Female / Male	NR	6 / 158	NR	20 / 89	NR	4 / 16
Average age	NR	68.8	NR	56	NR	69.5
Tumor size	Not associated	72 cases < 4cm, 92 cases ≥ 4cm	86 cases < 5 cm, 112 cases ≥ 5 cm	NR	NR	NR
Invasion depth	NR	T1: 33 T2: 27 T3: 94 T4: 10	T1: 40 T2: 34 T3: 112 T4: 12	NR	NR	NR
Tumor grade	Not associated	W/D: 26 M/D: 109 P/D: 29	W/D: 32 M/D: 131 P/D: 35	NR	NR	LVL grade A B B
Tumor stage	0: 1 I: 9 IIA: 33 IIB: 2 III: 23 IVA: 5 IVB: 5 Not associated	NR	I: 32 II: 68 III: 73 IV: 25	NR	NR	NR
Metastasis	Not associated	Lymph node metastasis (N1): 99, Distant metastasis (M1): 23	Absent: 79 Present: 119	40 patients	NR	NR
Follow-up	NR	31.5 months	NR	3 years	NR	NR
Survival analysis	Not associated	Low CLDN4: 44% High CLDN4: 77.3%	NR	Low CLDN4: 52.5% High CLDN4: 27.8%	NR	NR
Survival time examination	NR	5 years	NR	5 years	NR	NR
Recurrence	NR	NR	NR	Low CLDN4: 58.2% High CLDN4: 35.0%	NR	NR
Recurrence time examination	NR	NR	NR	3 years	NR	NR
Lymph nodes	NR	N0: 65 N1: 99	NR	N0: 0.00168 ± 0.00258 N1: 0.00104 ± 0.00183	NR	NR

Abbreviations: NR, Not Reported; WD, Well Differentiated; MD, Moderately Differentiated; PD, Poorly Differentiated.

In one study, the P-value was considered < 0.001 and in the other studies, P-value was considered < 0.05. Five studies reported clinicopathologic parameters, such as length of the tumor, tumor stage, TNM Stage, TNM classification, tumor grade, histological grade, LVL grade, nodal status, and depth of invasion. Three studies reported survival analysis. In four studies, metastasis was investigated using terms, such as lymphatic metastasis, distant metastasis, and nodal metastasis. Additionally, one study reported on participants' smoking and alcohol consumption histories. The follow-up of esophageal cancer patients was published in two studies. Only one study monitored recurrence in esophageal cancer patients.

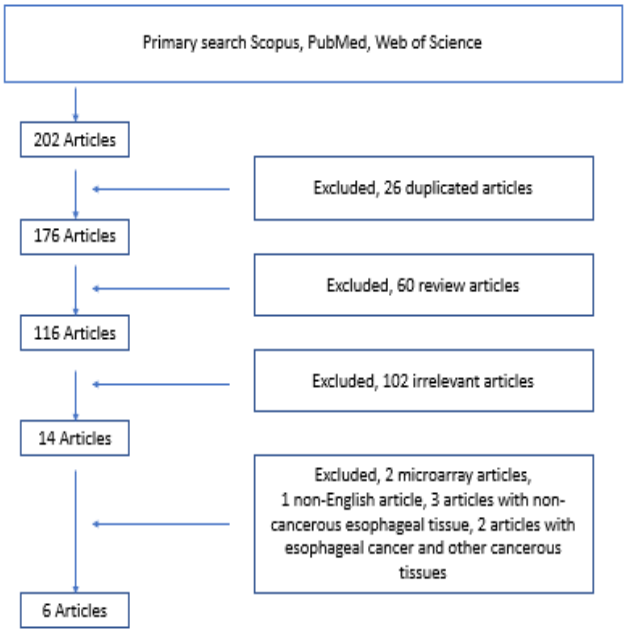

Figure 1. The selection process of the studies.

Discussion

Esophageal cancer has the 7th highest incidence rate and the 6th highest mortality rate among cancers, and there were about 544,000 deaths related to esophageal cancer in 2020. Despite the useful advances in drug treatment and surgical methods, the survival rate of patients is less than 25% (18). These statistics point to the need for more studies to understand the exact mechanism of this disease. Claudins as important members of TJ, are involved in maintaining epithelial cells in a polarized state (19). One of the members of this family is CLDN-4, whose expression changes have been reported in various cancers. Studies have been published so far to clarify the role of CLDN-4 in the progression of esophageal cancer, the pattern of CLDN-4 changes level, and the effect of various factors and genes on CLDN-4.

In normal squamous epithelium, Sung et al. observed strong CLDN-4 staining in cell-to-cell (IS; mean, 8.0 ± 2.739); however, cytoplasmic and nuclear staining was not observed. Staining in tumor samples was mainly membranous and 122 samples out of 164 patients had membrane staining (Mean IS, 2.533 ± 3.5). In general, immunoreactivity scores of CLDN-4 in the patient group were significantly lower than normal cases (Respectively 2.533 ± 3.5, 8.0 ± 2.739) (P-Value <0.001). According to the obtained results, it can be seen that the expression of CLDN-4 in esophageal cancer cells was lower than in normal cells. Spearman correlation coefficient showed a moderate positive correlation between CLDN-4 mRNA expression level and immunoreactivity scores (Spearman correlation coefficient (q) = 0.480, P-Value = 0.028) (20).

In 2014, Shi and colleagues investigated the role of CLDN-4 as an indicator of recurrence in ESCC after Ivor Lewis esophagectomy. In 119 patients, the level of CLDN-4 was examined by immunohistochemistry. Forty samples showed positive expression and 79 samples showed negative expression of CLDN-4. In 40 patients with positive expression of CLDN-4 protein, the CLDN-4 mRNA level was higher than in the other 79 patients. It can be concluded that in this study, the level of CLDN-4 was downregulated in most of the patients. Regarding invasion depth, it was observed that T1 group patients had the highest relative expression of CLDN-4 mRNA (0.00286 ± 0.00230). The relative expression of CLDN-4 decreased in T2 (0.00213 ± 0.00131) and T3+T4a (0.00177 ± 0.00083) patients, respectively (P-Value =0.002). According to these results, the decrease in the level of CLDN-4 leads to an increase in the depth of invasion.

Patients with lymphatic metastasis had significantly (P-Value < 0.001) lower relative expression of CLDN-4 mRNA than patients without lymphatic metastasis (0.00183 ± 0.00104 and 0.00258 ± 0.00168, respectively). The Kaplan-Meier survival analysis showed that 3-year recurrence in patients with decreased expression of CLDN-4 was higher than in patients with increased expression of CLDN-4 (58.2 Vs. 35.0%, P-Value = 0.009). Moreover, 5-year survival in patients with decreased CLDN-4 expression was lower than in patients with increased CLDN-4 expression (52.5 Vs. 27.8%, P-Value = 0.006) (21). These conflicting results show the importance of further studies on the level of CLDN-4 and the survival rate of patients.

Takala et al. stated that positive staining for CLDN-4 in normal epithelium is rare and CLDN-4 reactivity in esophageal cancer is more limited to the membrane. Immunohistochemical expression of CLDN-4 was observed in 47 out of 76 tumors. There was no significant correlation between CLDN-4 with tumor grade and tumor size and tumor T stage and metastasis (P-Value >0.05). They reported weak reactivity of CLDN-4 compared to CLDN-1 and CLDN-7 in esophageal tumors. In addition, CLDN-4 expression was higher in EAC samples than ESCC (42.1% and 18.9%, respectively). However, no significant difference was observed between strong and weak immunoreactivity of CLDN-4 in EAC and ESCC.

Apoptotic index in tumor samples with moderate and strong expression of CLDN-4 were significantly higher than samples with weak expression (2.22% ± 2.43 and 0.93% ± 0.95, respectively) (P-Value =0.026). Also, the number of caspases 3 was significantly higher in tumor samples with medium and strong expression of CLDN-4 than in samples with weak expression (4.51±5.08%, 2.81±2.34%) (P-Value =0.047) (22). The presence of CLDN-4 in esophageal cancer cells, compared to its absence in cancer cells, strengthens the apoptosis pathway and the factors involved. WU et al. investigated CLDN-4 gene expression in A431, TE-10, TE-11, and TE-5 cell lines. In the TE11 cell line, CLDN-4 expression was reported to be relatively low and Podoplanin (A glycoprotein with the ability to promote metastasis in all types of cancers) expression was strong by reverse transcription-quantitative polymerase chain reaction method. In this study, a negative correlation was observed between Podoplanin and CLDN-4.

When the cell lines were treated with TGF-β, Podoplanin expression was strongly induced but CLDN-4 expression was reduced. By blocking TGF-β receptors, they observed an increase in CLDN-4 expression. To better determine the relationship between these epithelial markers (CLDN-4), Podoplanin was knocked down and the result was an increase in CLDN-4 expression (23). It can be concluded that there is an inverse relationship between the level of CLDN4 and TGF-β. The reduction of CLDN-4 as a protein that plays a role in creating tight junctions was observed in these cell lines. Toda et al. investigated the expression of the CLDN-4 gene before and after exposure to acetaldehyde (AaH) and ethanol (EtOH) in esophageal cancer tumors. CLDN-4 mRNA level in non-exposed ESCC samples was lower than in non-ESCC samples (P-Value < 0.05).

After exposure of ESCC samples to AcH and EtOH, the CLDN-4 mRNA level tended to decrease (P-Value >0.05). CLDN-4 mRNA level after exposure to AcH and EtOH was not significantly different between LVL grades (P-Value > 0.05) (24). In this way, the expression of CLDN-4 in ESCC samples before exposure was significantly lower than in healthy samples. Since the results obtained after contact with ethanol and acetaldehyde were not significant, more studies with a larger population are needed to clarify the relationship of these compounds with CLDN-4 in esophageal cancer. In 2012, Lee et al. investigated the relationship between Twist1 and CLDN-4 in esophageal cancer cell lines and 198 patients with ESCC. When the expression of Twist1 was increased using lentivirus infection in the TE8 cell line, it binds to the endogenous CLDN-4 promoter and reduces the expression of CLDN-4. Further, the results also showed a decrease in CLDN-4 protein levels.

To investigate the inhibitory effect of Twist1 in the tumor tissue of patients with esophageal cancer, they used immunohistochemistry. Nineteen patients who had Twist1 upregulation had lower CLDN-4 immunoreactivity scores. CLDN-4 immunoreactivity scores were significantly higher in 179 patients who had Twist1 downregulation. Immunostaining results show inverse correlation patterns for Twist1 and CLDN-4. A significant inverse correlation between Twist1 and CLDN-4 was determined by Fisher's exact test (P-Value =0.012). In the study of survival rate, the worst result significantly belonged to patients with low CLDN-4 and high Twist1 (25). So, in this study, 179 patients had higher CLDN-4 protein in the esophageal tumor tissue than 19 other patients. Twist1 can lead to the induction of cancer by inducing epithelial to mesenchymal transition, i.e. reducing epithelial characteristics and increasing mesenchymal characteristics. The results of this study were not consistent with this assumption and only 19 patients out of 179 patients had positive regulation of Twist1 and most patients had upregulation of CLDN-4. No risk of bias or applicability concern was found in the reference standard domain, and the flow and timing domain. Limitations of this systematic review, such as sample size and small number of studies including inclusion criteria, provide an opportunity for future clinical research to understand the role of CLDN-4 in esophageal cancer formation and progression.

Conclusion

The results obtained from the published studies regarding changes in CLDN-4 levels among esophageal cancer samples and also comparing it with normal tissue were contradictory. From the review of studies, it can be concluded that there is an inverse relationship between CLDN-4 and TGF-β levels, and more information is needed to clarify the effect of TGF-β signaling on CLDN-4. Also, an inverse relationship between CLDN-4 and Twist-1 levels has been observed. These conflicting results can be interpreted in several ways. Assuming that cell junctions are destroyed in the formation of tumors, we can expect a decrease in CLDN-4 in esophageal cancer samples, which has been mentioned in some

studies. On the other hand, CLDN-4 can be involved in carcinogenesis by affecting different signaling pathways.

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Ethical statement

Not applicable.

Conflicts of interest

The authors declare that they have no competing interests.

Author contributions

Jafari and Arab designed the research and edited the manuscript. The search in databases was done by Jafari and Mahdizadeh. The manuscript was written by Mahdizadeh. All authors read and approved the final manuscript.

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