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Original research

Expression of claudin-7 and loss of claudin-18 correlate with poor prognosis in gastric cancer

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ABSTRACT

Background: The purpose of this study was to evaluate the expression of claudin-3, claudin-7, and claudin-18 in gastric cancer and to determine the significance of these proteins for patient outcome.
Materials and methods: A total of 134 samples were obtained from surgically resected specimens from patients who were diagnosed with gastric carcinoma at a single institution. Paraffin tissue sections from tissue microarray blocks were examined with immunohistochemistry for the expression of claudin-3, claudin-7, and claudin-18.
Results: In normal gastric tissues, positive immunoreactivity was detected for claudin-18 but not for claudin-3 or claudin-7. Claudin-3 and claudin-7 were expressed in 25.4% and 29.9% of the gastric cancer tissues, respectively. However, 51.5% of gastric cancer tissues exhibited reduced expression of claudin-18. Claudin-7 expression was significantly lower in cases with diffuse histologic type and positive lymphatic invasion. There was a significant inverse correlation between claudin-18 expression and perineural invasion. In the survival analysis, the overall survival time was shorter in patients with claudin-7 expression than in those without claudin-7 expression. However, the overall survival was longer in patients with claudin-18 expression than in those without claudin-18 expression.
Conclusions: Our data suggest that the up-regulation of claudin-3 and claudin-7 and the down-regulation of claudin-18 may play a role in the carcinogenesis of gastric cancer. Furthermore, the expression of claudin-7 and the loss of claudin-18 may be independent indicators of a poor prognosis in patients with gastric cancer.

1. Introduction

Gastric cancer is the fourth most frequent malignancy and the second most frequent cause of cancer death in East Asia and the world.[1] Although overall survival has improved in the last few decades, the prognosis of patients with advanced gastric cancer remains poor because tumor progression and metastasis of gastric cancers occur frequently. Advancements have been made in the molecular and histological analysis of most of the cancers arising from the gastrointestinal tract including esophageal, gastric, and colon cancer.[2,3] Despite these remarkable achievements, little diagnostic or therapeutic improvement for patients with cancer recurrence or metastasis has resulted. Therefore, there is a dire need for the identification and characterization of novel molecular markers that can be exploited for determining prognosis.

Claudins, a crucial component of tight junctions, are transmembrane proteins with extracellular loops that are potential targets for diagnostic and therapeutic modalities.[4–6]The alteration in claudin expression might lead to impaired functioning tight junction, have an influence on signaling pathways, and act as a tumor promotional event in some epithelial cancer.[7–9] Recent gene expression profiling analyses have indicated that claudin gene expression is altered in various cancers and claudin protein expression may have significant clinical relevance.[10] Several members of claudin family including claudin-3 and claudin-7 have been reported to be more highly expressed in gastric cancer

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Table 1
Baseline clinical characteristics.

Basic characteristics	Values (%)
Age (year)	63.47 ± 11.64
Gender	
Male	82 (61.2)
Female	52 (38.8)
Histologic type	
Differentiated	71 (53.0)
Less-differentiated	63 (47.0)
Lauren classification	
Intestinal	70 (52.2)
Diffuse	51 (38.1)
Mixed	13 (9.7)
Lymphatic invasion	
Positive	81 (60.4)
Negative	53 (39.6)
Venous invasion	
Positive	30 (22.4)
Negative	104 (77.6)
Perineural invasion	
Positive	55 (41.0)
Negative	79 (59.0)
T stage	
T1	17 (12.7)
T2	24 (17.9)
T3	46 (34.3)
T4	47 (35.1)
N stage	
N0	44 (32.8)
N1	20 (14.9)
N2	29 (21.6)
N3	41 (30.6)
M stage	
M0	122 (91.0)
M1	12 (9.0)
TNM stage	
I	25 (18.7)
II	42 (31.3)
III	55 (41.0)
IV	12 (9.0)
Total cases	134

compared to normal gastric mucosa.[11,12] However, claudin-18 has been reported to be more reduced in gastric cancer compared to normal gastric mucosa.[13] Claudin-low colon cancer is associated with poor survival and this may be also true for gastric cancer.[14]Low claudin-3 and claudin-18 protein expression was associated with poorer survival in an analysis of 94 primary gastric adenocarcinomas.[15] In contrast, in another study high claudin-3 expression in gastric cancer was correlated with longer survival in both univariate and multivariate analyses.[16] Thus, definite correlation between expression and clinical significance of the claudin proteins in gastric cancer remains controversial.

Unfortunately, studies on the prognostic significance of these claudins in gastric cancer have not been extensively studied. In this study, we investigated the expression patterns of claudin-3, claudin-7, and claudin-18 in gastric cancer. In addition, we evaluated the association of the expression of these proteins with the clinicopathological characteristics of gastric cancer and assessed their clinical significance and prognostic value.

2. Patients and methods

2.1. Patients

A total of 134 samples of primary gastric adenocarcinoma were acquired from St. Vincent's Hospital, The Catholic University of Korea from March 2004 to May 2012. An additional 34samples of non-cancerous gastric mucosa were included. The study protocol was approved by the Institutional Review Board of St. Vincent's Hospital, The Catholic University of Korea. The tumors were divided into two histological subgroups: a differentiated type consisting of papillary and well to moderately differentiated tubular adenocarcinomas, and a less-differentiated type consisting of poorly differentiated adenocarcinomas, signet ring cell carcinomas, and mucinous adenocarcinomas. The stages of all of the patients were evaluated in accordance with the guidelines of the Japanese Classification of gastric carcinoma.[17]The surgical treatment comprised gastric resection, according to the localization of the primary tumor, and lymph node dissection following the recommendations of the Japanese Research Society for Gastric Cancer. After surgery, clinical follow-up data were obtained from all of the patients. Survival time was measured as the time from the date of the initial surgery to the date of death.

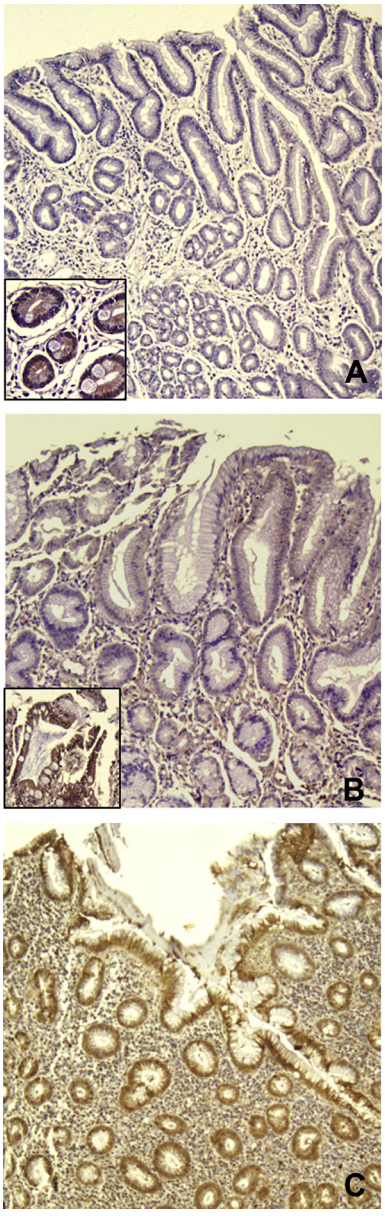

Fig. 1. Immunohistochemicalanalysis of claudin-3, claudin-7, and claudin-18 in normal gastric mucosa. Claudin-3 (A) and claudin-7 (B) are not detected in normal gastric mucosa, however, intestinal metaplastic glands are positive for claudin-3 and claudin-7 (inset)(×100). (C) Expression of claudin-18 is preserved in gastric mucosa (×100).