

## Original Article

# Caveolin-1, E-cadherin and $\beta$ -catenin in Gastric Carcinoma, Precancerous Tissues and Chronic Non-atrophic Gastritis

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## ABSTRACT

**Objective:** To investigate the expressions of caveolin-1, E-cadherin and  $\beta$ -catenin in gastric carcinoma, precancerous gastric and chronic non-atrophic gastritis tissues, and evaluate the correlation of these expressions with the development of gastric cancer.

**Methods:** The expressions of caveolin-1, E-cadherin and  $\beta$ -catenin were detected by biotin-streptavidin-peroxidase (SP) immunohistochemistry on 58 gastric cancer tissues, 40 precancerous gastric tissues and 42 chronic non-atrophic gastritis tissues. The correlation between the expressions of caveolin-1, E-cadherin and  $\beta$ -catenin, and the clinicopathologic parameters of gastric cancer was analyzed retrospectively.

**Results:** The positive rates of caveolin-1 and E-cadherin expressions in gastric carcinoma were significantly lower than precancerous gastric and chronic non-atrophic gastritis tissues ( $P < 0.01$ ). An abnormal rate of  $\beta$ -catenin expression in gastric carcinoma was higher than precancerous gastric and chronic non-atrophic gastritis tissues ( $P < 0.01$ ). Moreover, low expressions of caveolin-1, E-cadherin and  $\beta$ -catenin correlated with tumor size, depth of invasion, lymph node metastasis and TNM stage ( $P < 0.05$ ). The positive rates of caveolin-1 and E-cadherin expressions decreased ( $P < 0.01$ ), while an abnormal rate of  $\beta$ -catenin expression increased inversely, with the degree of atypical hyperplasia ( $P < 0.01$ ). Caveolin-1 expression correlated positively with E-cadherin ( $r = 0.41$ ,  $P < 0.05$ ). Caveolin-1 ( $r = -0.36$ ,  $P < 0.05$ ) and E-cadherin ( $r = -0.45$ ,  $P < 0.05$ ) expressions negatively correlated with abnormal  $\beta$ -catenin expression.

**Conclusion:** These results suggested that dysregulated expressions of caveolin-1, E-cadherin and  $\beta$ -catenin correlated with the development of gastric cancer and its biological behavior.

**Key words:** Gastric carcinoma; Caveolin-1; E-cadherin;  $\beta$ -catenin; Immunohistochemistry

## INTRODUCTION

Cancer biology researches have demonstrated that a multi-step process and a lot of genetic alterations are involved in the development of malignant tumors. The loss of cell-cell adhesion is associated with tumoral progression, invasion and metastasis. A number of membrane molecules and genes, including caveolin-1, E-cadherin and  $\beta$ -catenin, are involved<sup>[1-8]</sup>. Caveolin-1

is an essential structural protein that acts as a tumor modulator regulating cells proliferation, differentiation, apoptosis, adhesion, and invasion by interacting with cell adhesion molecules and signaling receptors<sup>[3-4, 8-11]</sup>. E-cadherin and  $\beta$ -catenin as a complex are specifically involved in the regulation of epithelial cell-to-cell adhesion and they have a close relationship with the invasion and metastasis ability of cancer<sup>[6, 7, 12-15]</sup>. In many malignant tumors, down-expression or destruction of E-cadherin and  $\beta$ -catenin is one of the changes that characterize an invasive phenotype. These genes are considered to be invasion/tumor suppressor genes, and partial or complete loss of E-cadherin and  $\beta$ -catenin expression is reported to be associated with poor prognosis in malignant tumors<sup>[11, 14-17]</sup>.

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The aim of this study was to investigate the changes of caveolin-1, E-cadherin and  $\beta$ -catenin expressions in gastric carcinoma, precancerous, and chronic non-atrophic gastritis tissues by using immunohistochemical staining, and to explore their roles in gastric carcinogenesis and development.

## MATERIALS AND METHODS

### Patients and Specimens

Fifty-eight patients with gastric carcinoma underwent surgical resection at the First Affiliated Hospital of Wenzhou Medical College from January 2007 to October 2009. There were 49 males and 9 females. The median age was  $59.6 \pm 10.4$  years (range 29 to 78 years). The histopathological diagnosis was well differentiated adenocarcinoma in 14 patients, poorly differentiated adenocarcinoma in 42, and undifferentiated carcinoma in 2. The TNM staging based on International Union Against Cancer (UICC) classification (6th edition)<sup>[18]</sup> was stage I in 9 patients, stage II in 7, stage III in 17 and stage IV in 25. During the same study period, precancerous gastric tissues from 40 patients with a median age of  $60.8 \pm 12.6$  years (range 28.6 to 87 years) were collected. These included 19 patients with intestinal metaplasia and 21 with dysplasia. Also, chronic non-atrophic gastritis tissues were collected from 42 patients with a median age of  $46.3 \pm 10.7$  years (range 21 to 70 years). This study was approved by the Ethics Committee of the Hospital (No. 2006-06).

Moderately-differentiated tubular adenocarcinoma, and mucinous carcinoma, were regarded histologically as differentiated tumors. Solid poorly differentiated adenocarcinoma, non-solid poorly differentiated adenocarcinoma, and signet-ring cell carcinoma were regarded as undifferentiated tumors. The depth of invasion was classified as mucosal, submucosal, muscularis and subserosal involvement.

### Immunohistochemistry

Immunohistochemistry was performed by the standard biotin-streptavidin-peroxidase (SP) method on 4  $\mu$ m thick formalin-fixed, paraffin-embedded tissue sections. After deparaffinization in xylene and rehydration in descending concentrations of alcohol, an antigen retrieval step was performed by microwaving in 10 mmol/L citrate buffer (pH 6) for 20 min at boiling temperature. Endogenous peroxidase was blocked by 3% hydrogen peroxide. After blocking with 3% bovine serum albumin for 1 h, the sections were incubated with diluted primary antibody for an appropriate time as listed in Table 1. The 3, 3'-diaminobenzidine (DAB) solution was used as a

chromogen. The sections were then lightly counterstained with hematoxylin. The sections without primary antibody served as negative controls.

### Evaluation of Immunohistochemical Staining

The immunostaining was independently evaluated semiquantitatively by two pathologists who were unaware of the clinical data. Caveolin-1 expression was based on the presence of cytoplasmic and/or membranous staining. On the basis of the percentage of immunopositive cells, the data were subdivided into four categories: 0, no positive cell; 1, <25%; 2, 25%–50%; and 3, >50% positive cells. E-cadherin expression was based on the presence of membranous staining. The expression of E-cadherin was classified as more than 90% of cell membranes stained as positive, otherwise as reduced expression. The expression of  $\beta$ -catenin was classified as more than 70% of cell membranes stained as positive, otherwise as negative, and more than 10% of cells with cytosol or nuclei stained as ectopic expression. Ectopic expression and negative expression were considered to reflect abnormal expression.

### Statistical Analysis

The chi-square and Fisher's exact tests were used to analyze the statistical significance of the relationship between caveolin-1, E-cadherin,  $\beta$ -catenin expressions and the clinicopathological variables. SPSS 11.5 program package (SPSS Inc., IL, USA) was used for statistical analysis. A *P* value of less than 0.05 was regarded as statistically significant.

## RESULTS

### Caveolin-1 Protein Expression Correlated with Clinicopathological Variables

Caveolin-1 protein appeared at cell cytoplasm and/or membrane, and it was located at the base and neck of gastric pits within all fundic mucosal fragments in gastric intestinal metaplasia as well as the cells. The positive rates of caveolin-1 expression in chronic non-atrophic gastritis was 100% (42/42), but it was decreased in precancerous gastric tissues (80.0%, 32/40) and in gastric carcinoma (48.3%, 28/58) (Figure 1A–C). The difference between these groups was significant ( $\chi^2=34.40$ ,  $P<0.01$ , Table 2). The positive rates of caveolin-1 expression decreased with the degree of atypical hyperplasia ( $\chi^2=39.08$ ,  $P<0.01$ ). Moreover, the rate of positive caveolin-1 staining of smaller (<5 cm) tumors (66.7%, 14/21) was significantly higher than larger  $\geq 5$  cm in diameter) tumors (37.8%, 14/37) ( $\chi^2=4.46$ ,  $P<0.05$ ), and the expression in T3+T4 lesions (35.6%, 16/45) was

significantly lower than that in T1+T2 lesions (92.3%, 12/13) ( $\chi^2=13.01$ ,  $P<0.01$ ). The difference in caveolin-1 expression between tumors with lymph node metastases (38.1%, 16/42) and those without (75.0%, 12/16) was significant ( $\chi^2=6.32$ ,  $P<0.05$ ). Significant differences in caveolin-1 expression were found in patients with stage I+II diseases (93.8%, 15/16) than stage III+IV diseases (31.0%, 13/42) ( $\chi^2=18.30$ ,  $P<0.01$ ) (Table 3).

### E-cadherin Protein Expression Correlates With Clinicopathological Variables

E-cadherin immunohistochemical staining was located at cell membrane. The positive rates of E-cadherin expression in gastric carcinoma (27.6%, 16/58) and in precancerous gastric tissues (62.5%, 25/40) were significantly less than in chronic non-atrophic gastritis (100%, 42/42) ( $\chi^2=53.16$ ,  $P<0.01$ ) (Figure 1D–F, Table 2). The positive rates of E-cadherin

**Table 1.** Primary antibodies used for immunohistochemical analysis

Protein	Company	Antibody dilution/incubation time
Caveolin-1	Santa Cruz Biotechnology, Inc., USA	1:100/1 h
$\beta$ -catenin	Santa Cruz Biotechnology, Inc., USA	1:50/1 h
E-cadherin	ZSGB-BIO, Beijing, China	1:100/1 h

Incubation was at room temperature.

**Table 2.** Expressions of caveolin-1, E-cadherin and  $\beta$ -catenin in gastric cancer tissues

Groups	Caveolin-1 positive expression (n, %)	E-cadherin positive expression (n, %)	$\beta$ -catenin abnormal expression (n, %)
Chronic non-atrophic gastritis (n=42)	42 (100) <sup>a</sup>	42 (100) <sup>b</sup>	0 <sup>c</sup>
Precancerous lesion (n=40)	32 (80.0)	25 (62.5)	13 (32.5)
IM (n=19)	19 (100)	15 (78.9)	2 (10.5)
Dysplasia (n=21)	13 (61.9)	10 (47.6)	11 (52.4)
Gastric carcinoma (n=58)	28 (48.3) <sup>d</sup>	16 (27.6) <sup>e</sup>	40 (69.0) <sup>f</sup>

<sup>a</sup> $\chi^2=34.40$ ,  $P=0.000$ , vs. precancerous lesion and gastric carcinoma; <sup>b</sup> $\chi^2=53.16$ ,  $P=0.000$ , vs. precancerous lesion and gastric carcinoma; <sup>c</sup> $\chi^2=49.93$ ,  $P=0.000$ , vs. precancerous lesion and gastric carcinoma; <sup>d</sup> $\chi^2$  (trend of proportion)=39.08,  $P=0.000$ , vs. dysplasia, intestinal metaplasia (IM) and chronic non-atrophic gastritis; <sup>e</sup> $\chi^2$  (trend of proportion)=57.00,  $P=0.000$ , vs. dysplasia, IM and chronic non-atrophic gastritis; <sup>f</sup> $\chi^2$  (trend of proportion)=55.85,  $P=0.00$ , vs. dysplasia, IM and chronic non-atrophic gastritis.

**Table 3.** Relationship between the expressions of caveolin-1, E-cadherin and  $\beta$ -catenin and pathological variables in gastric carcinoma

Clinical variables	Caveolin-1 positive expression (n, %)	E-cadherin positive expression (n, %)	$\beta$ -catenin abnormal expression (n, %)
Age			
<60 (n=25)	11 (44.0)	8 (32.0)	18 (72.0)
$\geq 60$ (n=33)	17 (51.5)	8 (24.2)	23 (69.7)
Gender			
Male (n=49)	23 (46.9)	13 (26.5)	33 (67.3)
Female (n=9)	5 (55.6)	3 (33.3)	8 (88.9)
Tumor size			
<5 cm (n=21)	14 (66.7) <sup>*</sup>	9 (42.9) <sup>**</sup>	11 (52.4) <sup>*</sup>
$\geq 5$ cm (n=37)	14 (37.8)	7 (18.9)	30 (81.1)
Histopathological differentiation			
Differentiated Ad (n=14)	9 (64.3)	5 (35.7)	7 (50.0)
Undifferentiated Ad (n=44)	19 (43.2)	11 (25.0)	35 (79.5)
Depth of invasion <sup>#</sup>			
T1+T2 (n=13)	12 (92.3) <sup>*</sup>	9 (69.2) <sup>*</sup>	3 (23.1) <sup>*</sup>
T3+T4 (n=45)	16 (35.6)	7 (15.6)	38 (84.4)
Lymph node metastasis <sup>#</sup>			
No (n=16)	12 (75.0) <sup>*</sup>	12 (75.0) <sup>*</sup>	4 (25.0) <sup>*</sup>
Yes (n=42)	16 (38.1)	4 (9.5)	37 (88.1)
TNM stage <sup>#</sup>			
I+II (n=16)	15 (93.8) <sup>*</sup>	12 (75.0) <sup>*</sup>	4 (25.0) <sup>*</sup>
III+IV (n=42)	13 (31.0)	4 (9.5)	37 (88.1)

Statistical analysis was performed by chi-square test (<sup>\*</sup> $P<0.05$ ; <sup>\*\*</sup> $P=0.05$ ); Ad, adenocarcinoma. <sup>#</sup>TNM classification of malignant tumors (6th edition)<sup>[18]</sup>.

expression decreased with worsening degrees of atypical hyperplasia ( $\chi^2=57.00$ ,  $P<0.01$ ). Reduced E-cadherin expression correlated with tumor size 18.9% (7/37) vs. 42.9% (9/21) ( $\chi^2=3.84$ ,  $P<0.05$ ), depth of invasion 15.6% (7/45) vs. 69.2% (9/13) ( $\chi^2=14.55$ ,  $P<0.01$ ), lymph node metastasis 9.5% (4/42) vs. 75.0% (12/16) ( $\chi^2=24.87$ ,  $P<0.01$ ), and TNM stage 9.5% (4/42) vs. 75.0% (12/16) ( $\chi^2=24.87$ ,  $P<0.01$ ), but not with histopathological differentiation, age or gender ( $P>0.05$ ) (Table 3).

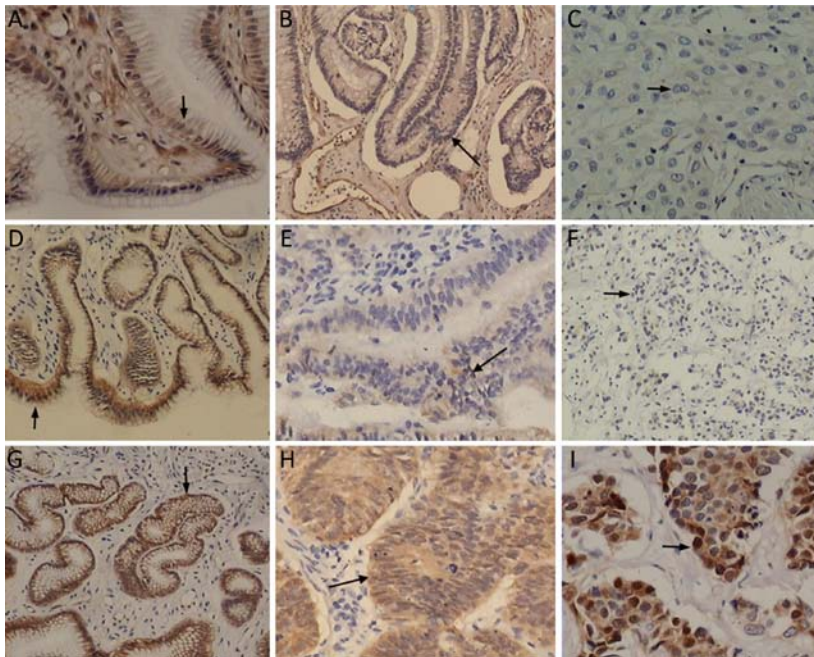
#### $\beta$ -catenin Protein Expression Correlated with Clinicopathological Variables

In this study,  $\beta$ -catenin protein was expressed in cytosol or nuclei, and no immunoreactivity of  $\beta$ -catenin was found in normal gastric mucosal tissues. The positive expression of  $\beta$ -catenin protein was 69.0% (40/58) in patients with gastric carcinoma and 32.5% (13/40) in precancerous gastric tissues. The difference was significant ( $\chi^2=49.93$ ,  $P<0.01$ ) (Figure 1G-I, Table

2). The positive rates of abnormal rate of  $\beta$ -catenin expression increased inversely with worsening degrees of atypical hyperplasia ( $\chi^2=39.90$ ,  $P<0.01$ ).  $\beta$ -catenin expression correlated with tumor size 81.1% (30/37) vs. 52.4% (11/21) ( $\chi^2=5.33$ ,  $P<0.05$ ), depth of invasion 84.4% (38/45) vs. 23.1% (3/13) ( $\chi^2=18.33$ ,  $P<0.01$ ), lymph node metastasis 88.1% (37/42) vs. 25.0% (4/16) ( $\chi^2=24.26$ ,  $P<0.01$ ) and TNM stage 88.1% (37/42) vs. 25.0% (4/16) ( $\chi^2=22.26$ ,  $P<0.01$ ), but not with histopathological differentiation, age or gender ( $P>0.05$ ) (Table 3).

#### Correlation among Expressions of Caveolin-1, E-cadherin and $\beta$ -catenin

Positive correlation ( $r=0.41$ ,  $P<0.05$ ) was observed by a Spearman correlation analysis between the expressions of caveolin-1 and E-cadherin, but they were negatively correlated with the expression of  $\beta$ -catenin ( $r=-0.36$  and  $r=-0.45$ , respectively,  $P<0.05$ ) (Table 4).



**Figure 1.** Immunohistochemical staining for caveolin-1, E-cadherin and  $\beta$ -catenin. **A:** The expression of caveolin-1 (arrow) in chronic non-atrophic gastritis (SP method,  $\times 200$ ); **B:** The expression of caveolin-1 (arrow) in precancerous lesion (dysplasia,  $\times 100$ ); **C:** The expression of caveolin-1 (arrow) in gastric carcinoma ( $\times 200$ ); **D:** The expression of E-cadherin (arrow) in chronic non-atrophic gastritis ( $\times 100$ ); **E:** The expression of E-cadherin (arrow) in precancerous lesion (dysplasia,  $\times 100$ ); **F:** The expression of E-cadherin in (arrow) in gastric carcinoma ( $\times 100$ ); **G:** The expression of  $\beta$ -catenin (arrow) in chronic non-atrophic gastritis ( $\times 200$ ); **H:** The expression of  $\beta$ -catenin in precancerous lesion (dysplasia,  $\times 200$ ); **I:** The expression of  $\beta$ -catenin (arrow) in gastric carcinoma ( $\times 200$ ).

**Table 4.** Correlation among expressions of caveolin-1, E-cadherin and  $\beta$ -catenin

Protein	E-cadherin		<i>r</i> value	$\beta$ -catenin		<i>r</i> values
	Positive	Negative		Positive	Negative	
Caveolin-1			0.407			-0.363
Positive	13*	15		15*	13	
Negative	3	27		26	4	
E-cadherin						-0.450
Positive				6*	10	
Negative				35	7	

Statistical analysis was performed by Spearman rank correlation test ( $*P<0.05$ ).

## DISCUSSION

In our study, we found (1) the positive rates of caveolin-1 and E-cadherin expressions in gastric carcinoma were significantly lower than those in precancerous gastric and chronic non-atrophic gastritis tissues; (2) the positive rate of  $\beta$ -catenin expression in gastric carcinoma was significantly higher than that in precancerous gastric and chronic non-atrophic gastritis tissues; (3) the positive rates of caveolin-1 and E-cadherin expression decreased with the degrees of atypical hyperplasia; and (4) the positive rates of abnormal rate of  $\beta$ -catenin expression increased inversely with the degrees of atypical hyperplasia. All these suggested that a reduction or loss of expression of caveolin-1 and E-cadherin, and an over-expression of  $\beta$ -catenin were implicated in the pathogenesis of oncogenic cell transformation and promoted the occurrence of gastric cancer. Williams et al.<sup>[19]</sup> found disruption of the caveolin-1 gene in transgenic mice promoted mammary tumorigenesis. Burgermeister, et al.<sup>[9]</sup> reported that the overall caveolin-1 mRNA and protein were decreased in 74% and 54% gastric carcinoma patients, respectively. Furthermore, recent evidences showed that caveolin-1 was implicated in the pathogenesis of oncogenic cell transformation and tumorigenesis through Wnt signaling pathway by regulating  $\beta$ -catenin location<sup>[9-12]</sup>. In this study, we have also found that gastric intestinal metaplasia as well as the cells at the base and neck of gastric pits within all fundic mucosal fragments showed caveolin-1 immuno-staining, suggesting a histogenetic derivation of these lesions from the trans-differentiation of chief cells or from a cryptic progenitor population at the base of fundic glands.

Chu, et al.<sup>[16]</sup> discovered a decreased E-cadherin expression was related to invasion and metastasis of gastric carcinoma. Utsunomiya, et al.<sup>[15]</sup> also discovered that a decrease of E-cadherin or  $\beta$ -catenin or both could weaken cell-cell adhesion and resulted in cell dissipation that made cancer cell infiltration and metastasis easier. Our study showed that down-regulated expressions of caveolin-1 and E-cadherin were related to the depth of invasion, lymph node metastasis and TNM stages, and up-regulated expression of  $\beta$ -catenin was correlated to the depth of invasion, lymph node metastasis and TNM stage. These suggested that a reduction or loss of expression of caveolin-1 and E-cadherin and an over-expression of  $\beta$ -catenin promoted the development of gastric cancer and its malignant biological behaviors such as invasion and metastasis.

A report from Zhou, et al.<sup>[7]</sup>, suggested that the abnormal expressions of  $\beta$ -catenin and E-cadherin

were 43.2% and 44.6% in gastric cancer, respectively. Abnormal  $\beta$ -catenin and E-cadherin staining occurred more frequently in poorly differentiated tumors than in well differentiated tumors ( $P < 0.005$ , respectively). However, in our study, the difference in the expression of  $\beta$ -catenin and E-cadherin between the differentiated and undifferentiated groups was not significant ( $P > 0.05$ ). The possible reason may be related to our small sample size.

Our study also showed that (1) the expressions of caveolin-1 and E-cadherin in the  $\beta$ -catenin (+) group were significantly lower than those in the  $\beta$ -catenin (-) group in gastric cancer tissues; (2) the expressions of caveolin-1 and E-cadherin were negatively correlated with the expression of  $\beta$ -catenin, respectively; (3) the expression of caveolin-1 in the E-cadherin (+) group was significantly higher than that in the E-cadherin (-) gastric cancer tissues; (4) the expression of caveolin-1 was positively correlated with the expression of E-cadherin; (5) the expression of  $\beta$ -catenin in the gastric cancer patients with lymph node metastasis was significantly higher than that in patients without lymph node metastasis; and (6) the expressions of caveolin-1 and E-cadherin were negatively correlated. These suggested that a reduction or loss of the expressions of caveolin-1 and E-cadherin worked in coordination with an over-expression of  $\beta$ -catenin to promote the development of gastric cancer and its malignant biological behaviors. Recent studies revealed that the cytoplasmic domain of E-cadherin is associated with catenins, and  $\beta$ -catenin directly connects the E-cadherin to  $\beta$ -catenin, which in turn links up with the actin-based cytoskeleton<sup>[20, 21]</sup>. These associations are essential for the intercellular adhesive function of E-cadherin. Any significant change in the expression or structure of one of these components may lead to an adhere junction disassembly, which has been implicated in the loss of tumor differentiation and the development of invasive phenotype of tumor cells<sup>[22-24]</sup>. Taking these into account, we can say that there may be a close link among these three indicators during the occurrence and development of gastric cancer.

Utsunomiya, et al.<sup>[15]</sup> reported that a disordered  $\beta$ -catenin expression pattern was significantly correlated with diffuse type adenocarcinoma and deep tumor infiltration ( $P < 0.05$ ), and its expression was significantly associated with reduced E-cadherin expression ( $P < 0.01$ ). Joo, et al.<sup>[14]</sup> reported that abnormal expressions of E-cadherin and  $\beta$ -catenin were correlated with poorly differentiated and diffuse-type carcinoma and poor survival. However, no significant difference was found between poorly differentiated and well differentiated adenocarcinoma

in our study.

In summary, our results suggested that dysregulated expressions of caveolin-1, E-cadherin and  $\beta$ -catenin may be correlated with the development of gastric cancer and its biological behaviors.

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