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Effect of *Helicobacter pylori* on Cell Gap Junction Ultrastructure of Gastric Epithelial Cells

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Abstract To observe the effect of *Helicobacter pylori*(*H. pylori*) on cell gap junction ultrastructure of gastric epithelial cells, and to explore carcinogenic mechanism of *H. pylori* from the changes of cell gap junction, BGC-823 cells were co-cultured with different *H. pylori* strains for 24 h and 48 h. The cell gap junction ultrastructure was observed under transmission electron microscope with sample preparation of fixation and embedding *in situ*. In 70 patients with gastric cancer(GC), *H. pylori* was detected by rapid urease test, basic fuchsin stain and ^{14}C-urea breath test. The CagA gene of *H. pylori* was determined by PCR and the cell gap junction ultrastructure was observed under transmission electron microscope. More cell gap junctions and junction complexes of BGC-823 cells were found in control group without *H. pylori*. Groups with *H. pylori* had less number of cell gap junctions, less number of junctions/ unit perimeter, shorter length of junctions /unit perimeter, and bigger width of the intercellular space, comparing to control groups without *H. pylori* ($P < 0.001$ or $P < 0.005$). The number of cell junctions and the number of junctions/unit perimeter in the groups co-cultured with NCTC J99, GC 01 and NCTC 11639($CagA^+$) were less than that in the groups co-cultured with NCTC 12908($CagA^-$) ($P < 0.001$ or $P < 0.05$), and the length of junctions/unit perimeter in the groups co-cultured with NCTC J99 and GC 01 was shorter than that in the groups co-cultured with NCTC 12908 ($P < 0.001$). In patients with GC, the number of cell junctions, the number of junctions/unit perimeter and the length of junctions/unit perimeter in group *H. pylori* infection were all less than those in group without *H. pylori* infection($P < 0.001$), and that in $CagA^+$ *H. pylori* group were less than that in $CagA^-$ *H. pylori* group, but its smallest width of the intercellular space was longer than that in $CagA^-$ *H. pylori* group. The above results showed that the changes of cell gap junction of gastric epithelial cells were associated with *H. pylori* infection especially $CagA^+$ *H. pylori* infection.

Key words *Helicobacter pylori*, CagA gene, gastric epithelial cell, cell gap junction, ultrastructure
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Helicobacter pylori (*H. pylori*) infection is an important risk factor of gastric cancer. $CagA^+$ *H. pylori* of them has a close relationship with gastric cancer and its precancerous lesions. However, its carcinogenic mechanism is still not entirely clear. From recent report at abroad, some experts considered that *H. pylori* might cause gastric cancer by destroy the cell junction of gastric epithelial cells. They observed that *H. pylori* strains localized at epithelial cell junctions, and changed the structure and functions of apical-junctional complex and resulted in damage on cell integrity. They also found that $CagA^+$ *H. pylori* with CagA gene caused the more severely damage, comparing to $CagA^-$ *H. pylori*. And knockout of its CagA gene could prevent the damage to the cell junctions of gastric epithelial cells[1].

Cell junctions include tight junction, gap junction, chemical synapse, desmosome and etc. Cell gap junction is an important way of cell junction. The inhibition of gap junctional intercellular communication (GJIC) of gastric epithelial cells was associated with gastric cancer[2]. *H. pylori* could significantly inhibit the GJIC function of the gastric epithelial cells, and the effect of inhibition in cells with $CagA^+$ *H. pylori* was more significant than that with $CagA^-$ *H. pylori*[3]. This suggested that *H. pylori* infection might play an important role in the pathogenesis of gastric cancer by inhibition of GJIC function of gastric epithelial cells.

This study used *in-situ* cell fixation and *in-situ* embedding methods and transmission electron microscope to observe the effect of *H. pylori* on cell gap junction of gastric epithelial cells cultured *in vitro*.

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This method could fully maintain the cell growing state and truly reflected the neighboring relations of cells. At the same time, this research also observed the changes of cell gap junction ultrastructure of gastric epithelial cells in gastric cancer patients and the relationship between these changes and *H. pylori* infection, especially $CagA^+$ *H. pylori* infection. It explored the carcinogenic mechanism of *H. pylori* from the aspect of cell gap junction of gastric epithelial cells. It would be valuable for further to study the role and mechanism of *H. pylori* eradication therapy in the prevention and treatment of gastric cancer.

1 Materials and methods

1.1 Materials

International standard *H. pylori* strains NCTC J99 ($CagA^+$ and $VacA^+$), NCTC 11639($CagA^+$ and $VacA^-$) were provided by Epidemiology and Microbiology Institute of National Academy of Preventive Medicine, and NCTC 12908($CagA^-$) was purchased from Shanghai Institute of Digestive Disease, while GC 01($CagA^+$) was isolated from the gastric mucosa of gastric cancer patients at Third Xiangya Hospital. BGC-823 cells (human gastric poorly differentiated adenocarcinoma cell line) were provided by Cancer Research Institute, Xiangya School of Medicine, Central South University.

1.2 Methods

1.2.1 Experimental grouping of *H. pylori*. Group①: control group, cultured without *H. pylori* for 24 h; Group②:cultured with $CagA^+$ standard strains NCTC 11639 for 24 h; Group③: cultured with $CagA^+$ clinical strain GC01 for 24 h; Group④:cultured with $CagA^+$ standard strain NCTC J99 for 24 h; Group⑤: cultured with $CagA^-$ standard strain NCTC 12908 for 24 h; Group⑥: cultured with $CagA^+$ standard strain NCTC J99 for 48 h. Meanwhile, 70 samples of gastric cancer patients during February, 2005～December, 2006 were collected according to the diagnostic criteria of gastric cancer classification standard set up by WHO. *H. pylori* was detected by rapid urease test, basic fuchsin stain and ^{14}C-urea breath test. *H. pylori* infection was confirmed if 2 or more tests showed positive results. No *H. pylori* infection was confirmed if all test results were negative. The CagA gene of *H. pylori* was determined by PCR. The results of these tests listed as follow: the number of patients with *H. pylori* infection was 48 and that of no *H. pylori* infections was 22. And among 48 patients with *H. pylori* infection, 39 of them were $CagA^+$, the rests were $CagA^-$.

1.2.2 BGC-823 cells co-cultured with *H. pylori*. BGC-823 cells in exponential growing phase were digested with 2.5 g/L trypsin. They were then inoculated on culture plate at 1×10^6 cells/hole with embedded glass coverslip, cultured in incubator with saturation humidity, containing 50 ml/L CO_2, at temperature 37℃, and became adherent overnight. Different *H. pylori* suspensions were added according to the bacteria/cell ratio of 100∶1. Only RPMI 1640 medium with 100 ml/L fetal calf serum was added into control group.

1.2.3 Electron microscopy specimen preparation. BGC-823 cells were prepared *via in-situ* fixation and *in-situ* embedding methods. After cultured for 24 h and 48 h, cells were washed twice by a little mixture of 20 g/L glutaraldehyde and 40 g/L paraformaldehyde precooled at temperature 4℃. After adding 5 ml mixture of 20 g/L glutaraldehyde and 40 g/L paraformaldehyde, samples were stored in refrigerator setting to 4℃. *In-situ* fixation was used continuously for twice, 30 min each time. After washed 8 times by PBS, cells were fixed by 20 g/L osmium acid for half an hour, and washed 8 times by double distilled water, 5 min each time. Used 20 g/L uranyl acetate to cover cell layer for 20 min, washed 8 times by double distilled water, dehydrated Seriatim by acetone gradient (500 g/L, 700 g/L, 900 g/L, 1 000 g/L) for 3 times, 5 min each grade. Immersed by Epon 812 epoxy resin mixture and pure acetone at ratio of 1∶1 at temperature 37℃ for 24 h. Embedded for 24 h at 60℃. Each sample was embedded for 5 blocks. 5 pieces of ultrathin section each block were observed by electron microscope after fixation of semi-thin section. Biopsy tissue under gastroscope was fixed by 25 g/L glutaraldehyde, washed 3 times by PBS, 5 min each time, and fixed by 10 g/L osmium acid for 1.5 h. After washed by PBS, tissue was dehydrated Seriatim by acetone gradient (500 g/L, 700 g/L, 900 g/L, 1 000 g/L) for 3 times, 5 min each grade. Immersed by Epon 812 epoxy resin mixture and pure acetone at ratio of 1∶1 at temperature 37℃ for 24 h. Embedded by Epon 812.

1.2.4 Observation of cell gap junction ultrastructure. Lead and uranium electron staining were used after ultrathin sectioning. Gap junction ultrastructures of gastric epithelial cells were observed *via* Hitachi H-600 transmission electron microscope (TEM). 5 views were randomly selected under 4 000 times

magnification. The number of cell junctions, length of junctions, and smallest width of the intercellular space were counted for more than 30 cells. The number of cell junctions/unit perimeter and length of junctions/unit perimeter (10 μm) were calculated by cell morphology three-dimensional metrology square test grid method[4].

1.3 Statistical analysis

All data were presented as the $\bar{x} \pm s$ and analyzed by SPSS11.0 statistical software. SNK-q test of two samples means was used. $P < 0.05$ was taken as significant criterion.

2 Results

2.1 Effect of different *H. pylori* strains on cell gap junction ultrastructure of BGC-823 cells

After 24 h cultured without *H. pylori*, BGC-823 cells had distributed more intensively, cell gap was smaller, and adjacent cell membrane moved closer to each other and more cell junctions were formed. Conjunctions between two cell membranes were still 2 ～4 nanometers, which was called gap junction (Figure 1). Sometimes we could even see the forming of the junctional complex(Figure 2). After 24 h cultured with $CagA^-$ *H. pylori*, a few cell gap junctions were visualized (Figure 3). After 24 h cultured with $CagA^+$ *H. pylori*, the intercellular space of BGC-823 cells obviously broadened, the number of cell gap junctions reduced， even they had no cell gap junction, and junctional complex didn't appear (Figure 4). Groups with *H. pylori* had less number of cell gap junctions, less number of junctions /unit perimeter, shorter length of junctions /unit perimeter, comparing to control groups without *H. pylori*. But smallest width of the intercellular space in groups with *H. pylori* was bigger than that in control groups ($P < 0.001$ or $P < 0.005$). And group NCTC J99, group clinical strain GC01 and group NCTC 11639 all had less number of cell junctions, and number of junctions/unit perimeter than that group NCTC 12908 had ($P < 0.001$ or $P < 0.05$). The length of junctions/unit perimeter in both group NCTC J99 and group clinical strain GC01 was shorter than that in group NCTC 12908 ($P < 0.001$, Table 1).

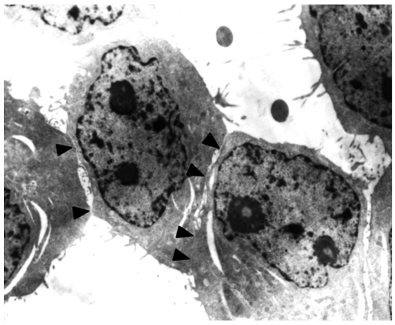

Fig. 1　The changes of cell gap junction ultrastructure of BGC-823 cells after cultured 24 h without *H. pylori*

There were more cell gap junctions in some BGC-823 cells. Sign "▲" indicated the cell gap junctions (×4 000).

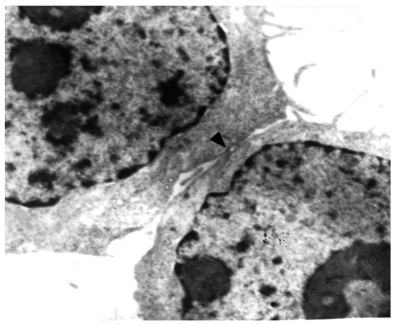

Fig. 2　The changes of cell gap junction ultrastructure of BGC-823 cells after cultured 24 h without *H. pylori*

Some BGC-823 cells had the forming of the junctional complex. Sign "▲" indicated the junctional complex formation (×10 000).

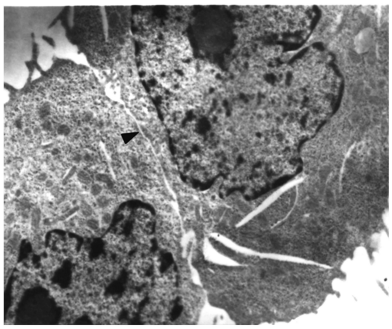

Fig. 3　The changes of cell gap junction ultrastructure of BGC-823 cells after co-cultured 24 h with $CagA^-$ NCTC 12908

A few cell gap junctions were visualized. Sign "▲" indicated the cell gap junction(×10 000).

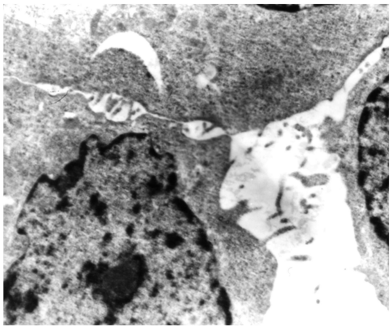

Fig. 4　The changes of cell gap junction ultrastructure of BGC-823 cells after co-cultured 24 h with $CagA^+$ NCTC J99

The intercellular space of BGC-823 cells broadened and no cell gap junction was seen(×10 000).

Table 1 Effect of different *H. pylori* strains on gap junction ultrastructure of BGC-823 cells

Group	*n*	*J*	*J*/Pi	*L*/Pi	*D*
Group①	30	2.267 ± 0.295	1.546 ± 0.251	1.000 ± 0.162	0.127 ± 0.075
Group②	30	0.433 ± 0.092[1)]	0.181 ± 0.053[1)]	0.130 ± 0.043[1)]	2.103 ± 0.364[1)]
Group③	30	0.100 ± 0.056[1,3)]	0.042 ± 0.024[1,3)]	0.019 ± 0.012[1,3)]	1.850 ± 0.399[1)]
Group④	30	0.100 ± 0.074[1,3)]	0.031 ± 0.023[1,3)]	0.017 ± 0.013[1,3)]	1.649 ± 0.339[2)]
Group⑤	30	0.500 ± 0.150[1,4,5,6)]	0.291 ± 0.070[1,4,5,6)]	0.177 ± 0.042[1,5,6)]	1.296 ± 0.366[1)]

n means the number of cells had been observed, *J* means average number of cell junctions, *J*/Pi means the number of cell junctions/unit perimeter (10 μm), *L*/Pi means the length of cell junctions/unit perimeter (10 μm), *D* means smallest width of the intercellular space(μm). [1)]$P<0.001$, [2)]$P<0.005$ *vs* group①; [3)]$P<0.001$, [4)]$P<0.05$ *vs* group②; [5)]$P<0.001$ *vs* group③; [6)]$P<0.001$ *vs* group④.

2.2 Effect of different co-culture time with *H. pylori* on cell gap junction ultrastructure of BGC-823 cells

After 24 h co-cultured for BGC-823 cells with NCTC J99, comparing to control group, no cell internal structure difference was detected. Meanwhile, observation by transmission electron microscope showed rare microvilli of cell surface, broadened cell gap, and less cell junctions. Only few focal gap junctions between two adjacent cells were found. After 48 h co-cultured, some cells were necrosis and *H. pylori* could be seen in cytoplasm of some cell. Comparing to 24 h co-cultured, distribution of cells was sparser, cell gap was wider, no any cell junctions was found (Figure 5). After co-cultured with NCTC J99 for 48 h, the number of cell junctions, the number of junctions/unit perimeter and the length of junctions/unit perimeter were all less than those for 24 h ($P < 0.01$), while their smallest width of the intercellular space was longer than that for 24 h ($P < 0.001$, Table 2).

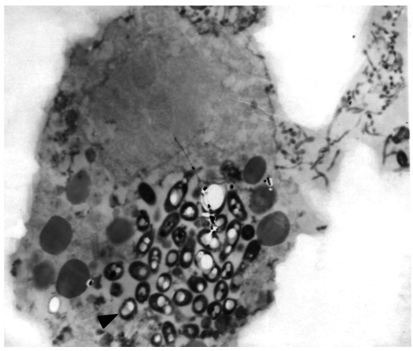

Fig. 5 The changes of cell gap junction ultrastructure of BGC-823 cells after co-cultured 48 h with CagA$^+$ NCTC J99

Distribution of cells was sparser, cell gap was wider, no any cell junctions was found. Sign "▲" indicated the large quantity of ingested *H. pylori* in cells (×10 000).

Table 2 Effect of different co-culture time with *H. pylori* NCTC J99 on cell gap junction ultrastructure

Group	*n*	*J*	*J*/Pi	*L*/Pi	*D*
Cultured 24 h	30	0.100 ± 0.074	0.031 ± 0.023	0.017 ± 0.013	1.649 ± 0.339
Cultured 48 h	30	0.000 ± 0.000[1)]	0.000 ± 0.000[1)]	0.000 ± 0.000[1)]	4.959 ± 0.804[2)]

n means the number of cells had been observed, *J* means average number of cell junctions, *J*/Pi means the number of cell junctions/unit perimeter (10 μm), *L*/Pi means the length of cell junctions/unit perimeter(10 μm), *D* means smallest width of the intercellular space (μm). [1)]$P < 0.01$, [2)]$P < 0.001$ *vs* cultured 24 h group.

2.3 Changes of cell gap junction ultrastructure in gastric cancer patients

For gastric cancer without *H. pylori* infection, some cancer cells had more cell gap junctions and longer junction length (Figure 6). Gastric cancer with CagA$^-$ *H. pylori* infection had a few cell junctions (Figure 7). But in gastric cancer with CagA$^+$ *H. pylori* infection, intercellular space obviously broadened, cell junction lost or only very few and short cell gap junctions could be found (Figure 8).

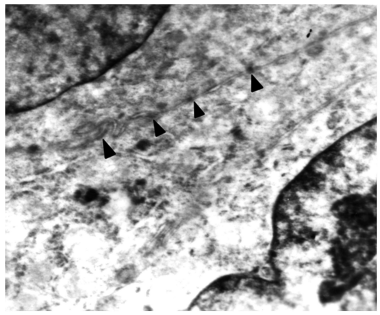

Fig. 6 The changes of cell gap junction ultrastructure of gastric epithelial cells in GC patients without *H. pylori* infection

Some cells had more cell gap junctions and longer junction length. Sign "▲" indicated cell gap junctions(×13 000).

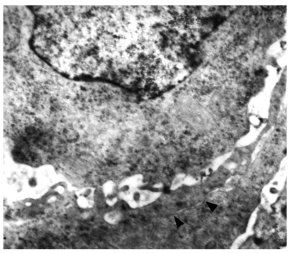

Fig. 7 The changes of cell gap junction ultrastructure of gastric epithelial cells in GC patients with CagA⁻ *H. pylori* infection

There were a few cell gap junctions in some cells. Sign "▲" indicated cell gap junctions(×13 000).

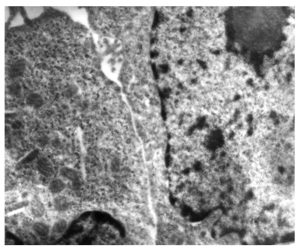

Fig. 8 The changes of cell gap junction ultrastructure of gastric epithelial cells in GC patients with CagA⁺ *H. pylori* infection

The intercellular space of cells became obviously large, and the number of cell gap junction became less or no cell junction was discovered (×4 000).

2.4 Effect of *H. pylori* infection on the changes of cell gap junction ultrastructure in gastric cancer patients

The number of cell junctions, the number of junctions/unit perimeter and the length of junctions/unit perimeter in group GC with *H. pylori* infection were all less than those in group GC without *H. pylori* infection($P < 0.001$, Table 3).

2.5 Effect of CagA⁺ *H. pylori* infection on the changes of cell gap junction ultrastructure in gastric cancer patients

For GC patients with CagA⁺ *H. pylori* infection, cell junctions were reduced and the length of cell junctions became significantly shorter. Some cells had no cell junctions. The number of cell junctions, the number of junctions/unit perimeter and the length of junctions/unit perimeter were all less than those in GC patients with CagA⁻ *H. pylori* infection, while the smallest width of the intercellular space was longer than that in CagA⁻ *H. pylori* group($P < 0.001$, Table 4).

Table 3 Effect of *H. pylori* infection on the changes of cell gap junction ultrastructure in gastric cancer patients

Group	*n*	*J*	*J*/Pi	*L*/Pi	*D*
H. pylori infection	150	1.647 ± 0.149	0.307 ± 0.027	0.199 ± 0.020	0.556 ± 0.075
No *H. pylori* infection	150	0.433 ± 0.064[1)]	0.093 ± 0.014[1)]	0.058 ± 0.009[1)]	1.218 ± 0.101[1)]

n means the number of cells had been observed, *J* means average number of cell junctions, *J*/Pi means the number of cell junctions/unit perimeter (10 μm), *L*/Pi means the length of cell junctions/unit perimeter(10 μm), *D* means smallest width of the intercellular space (μm). [1)]$P < 0.001$ *vs* no *H. pylori* infection group.

Table 4 Effect of CagA⁺ *H. pylori* infection on the changes of cell gap junction ultrastructure in gastric cancer patients

Group	*n*	*J*	*J*/Pi	*L*/Pi	*D*
CagA⁻ *H. pylori*	60	0.700 ± 0.110	0.156 ± 0.026	0.098 ± 0.016	0.761 ± 0.124
CagA⁺ *H. pylori*	90	0.256 ± 0.072[1)]	0.051 ± 0.015[1)]	0.032 ± 0.009[1)]	1.523 ± 0.138[1)]

n means the number of cells had been observed, *J* means average number of cell junctions, *J*/Pi means the number of cell junctions/unit perimeter(10 μm), *L*/Pi means the length of cell junctions/unit perimeter(10 μm), *D* means smallest width of the intercellular space(μm). [1)]$P < 0.001$ *vs* CagA⁻ *H. pylori* group.

3 Disscussion

H. pylori infection is one of the important risk factors that cause gastric cancer. However, there is no proportional relationship between *H. pylori* infection incidence and gastric cancer incidence. It might have something to do with crowd of genetic susceptibility, environment, and difference of *H. pylori* strains. Among these, differences of *H. pylori* strain might play a decisive role. CagA is an important virulence factor of *H. pylori*. Comparing to CagA⁻ *H. pylori* strain, CagA⁺ *H. pylori* has more virulence, causing more intense inflammatory reaction. As indicated by epidemiological studies, CagA⁺ *H. pylori* infection was closely related to atrophic gastritis and gastric

cancer [5]. Comparing with the patients with CagA⁻ *H. pylori* infection or no *H. pylori* infection, risk or possibility of having gastric cancer for those with CagA⁺ *H. pylori* infection was highly increased.

Our clinical study showed that gastric cancer patients with CagA⁺ *H. pylori* infection had less cell junctions, shorter length of junctions and wider intercellular space than those gastric cancer patients with CagA⁻ *H. pylori* infection. This suggested that gastric cancer patient's cell junction reduction and junction length shortening had more to do with CagA⁺ *H. pylori* infection [6]. Our experimental study used *in-situ* cell fixation and *in-situ* embedding methods and transmission electron microscope to observe the effect of *H. pylori* on cell gap junction of the gastric epithelial cells cultured *in vitro*. This method could fully maintain the cell growing state and truly reflected the neighboring relations of cells. There were more cell gap junctions and junctional complexes in gastric epithelial cells cultured without *H. pylori*. After co-cultured with *H. pylori*, cell gap widen, the number of cell junctions reduced or lost, the length of cell junctions was shorter. And CagA⁺ *H. pylori* strain had stronger influence on the change of cell gap junction ultrastructure than CagA⁻ *H. pylori* strain. This suggested that CagA⁺ *H. pylori* might play an important role in the pathogenesis of gastric cancer. It might affect the formation of cell gap junction, and reduce the GJIC function of cell so that cell loses its contact signal of growth regulation and cell differentiation, finally lead to occurrence and progression of gastric cancer.

At current stage, the mechanism how *H. pylori* affects the cell junction remains unknown. The possible mechanisms are listed as follows: (1) Direct effect caused by *H. pylori*. *H. pylori* can intrude deeply along cell gap of gastric epithelial cell, grow in intercellular space, cause mechanical damage and lead to the destruction of cell junction between the neighboring cells.(2) Affected by cytokines. Cytokines can mediate the down-regulation of Cx protein expression, impact GJIC function, and take effects on cell proliferation, transformation and aberration [7]. (3) Affected by oxygen free radicals. Once *H. pylori* was infected, ascorbic acid, CuZnSOD and other antioxidants in stomach reduce, resulting in decline of free radical scavenging capacity of organism. And this causes the accumulation of oxygen free radicals. Free radicals can act on gap junction [8]. (4) E-cadherin reduction: After *H. pylori* infection, E-cadherin protein expression decreases in gastric tissue [9]. E-cadherin can regulate intercellular adhesion and contact. Less E-cadherin can decrease adhesion function between gastric epithelial cells [10]. From recent report by Amieva, CagA⁺ *H. pylori* strains concentrated in the junction place of MDCK cells, its CagA acted on the epithelial tight-junction scaffolding protein ZO-1 and the transmembrane protein junctional adhesion molecule, caused ectopic aggregation of tight junction structure at bacterial attachment sites. It changed the structure and functions of apical-junctional complex and resulted in damage on cell integrity. Meanwhile, *H. plyori* of its CagA gene knocked out did not concentrate on junction place. Cell junction remained intact [1]. Recently another report also said that *H. pylori* could significantly suppress GJIC function of gastric epithelial cells. And CagA⁺ *H. pylori* had more suppressing effect than CagA⁻ *H. pylori* [3]. In our study, CagA⁺ *H. pylori* strains also had more effects than CagA⁻ *H. pylori* strains on the number of cell junctions, the number of junctions/unit perimeter and the length of junctions/unit perimeter. This suggested that influence of *H. pylori* on gap junction of gastric epithelial cells is related to CagA.

In conclusion, *H. pylori* can affect cell gap junction of gastric epithelial cells. It may decrease the cell GJIC function and result in occurrence and development of gastric cancer. If we can early eradicate *H. pylori* infection at the promotion stages in gastric carcinogenesis, and recover the GJIC function, then we may have good chance to stop the further development of gastric cancer.

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幽门螺杆菌对胃上皮细胞间隙连接超微结构的影响

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摘要 通过实验和临床观察幽门螺杆菌(*Helicobacter pylori*)对胃上皮细胞间隙连接超微结构的影响，从细胞间隙连接角度探讨 *H. pylori* 致癌机制. 将不同 *H. pylori* 菌株与 BGC-823 细胞共培养 24 h 或 48 h，用原位固定与原位包埋法透射电镜观察细胞间隙连接超微结构变化. 对 70 例胃癌患者，用快速尿素酶试验、碱性品红染色和 ^{14}C 尿素呼气实验检测 *H. pylori*，PCR 法检测 *H. pylori* CagA 基因，及透射电镜观察胃上皮细胞间隙连接超微结构变化. 结果显示，未加 *H. pylori* 组 BGC-823 细胞可见较多细胞连接及连接复合体，加 *H. pylori* 各组细胞的连接数、单位周长连接数与单位周长连接长度均小于未加 *H. pylori* 组，而细胞间隙最小宽度大于未加 *H. pylori* 组($P < 0.001$ 或 $P < 0.005$)，且 $CagA^+$的 NCTC J99 组、临床株 GC 01 组和 NCTC 11639 组细胞连接数、单位周长连接数均小于 $CagA^-$ 的 NCTC 12908 组($P < 0.001$ 或 $P < 0.05$)，NCTC J99 组与临床株 GC 01 组细胞单位周长连接长度短于 NCTC 12908 组($P < 0.001$). 胃癌患者 *H. pylori* 感染组细胞连接数、单位周长连接数与单位周长连接长度均小于无 *H. pylori* 感染组，细胞间隙最小宽度大于无 *H. pylori* 感染组($P < 0.001$)，且 $CagA^+$ *H. pylori* 感染者细胞连接数、单位周长连接数与单位周长连接长度均小于 $CagA^-$ *H. pylori* 感染者，细胞间隙最小宽度大于 $CagA^-$ *H. pylori* 感染者. 上述结果表明，胃上皮细胞间隙连接改变与 *H. pylori* 感染，特别是 $CagA^+$ *H. pylori* 感染有关.

关键词 幽门螺杆菌，CagA 基因，胃上皮细胞，细胞间隙连接，超微结构
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