Effect of helicobacter pylori-induced cyclooxygenase-2 on gastric epithelial cell kinetics : implication for gastric carcinogenesis

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【 学位論文題目 】

Effect of Helicobacter pylori - Induced Cyclooxygenase-2 on Gastric Epithelial Cell kinetics: Implication for Gastric Carcinogenesis
(Helicobacter pylori により誘導される Cyclooxygenase-2 の胃上皮細胞回転に与える影響)

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INTRODUCTION:

Cyclooxygenase (Cox) plays a key role in the production of prostaglandins. Increased expression of the inducible isoform, **Cyclooxygenase-2** has been detected in the mucosa infected with *Helicobacter pylori* (*H. pylori*) and it is also known to be induced by a variety of cytokins, hormones and tumor promoters.

One aspect currently attracting much attention is the involvement of Cox-2 in the development of gastric cancer. Cox-2 is thought to enhance gastric carcinogenesis by affecting the maintenance of a balance between **proliferation** and **apoptosis** (programmed cell death), which are the essential kinetic events of epithelial homeostasis.

We investigated the expression of Cox-2 in subjects with non-ulcer dyspepsia (NUD) and in the background mucosa of *H. pylori* positive cancer subjects. Furthermore, we analyzed the relationship between Cox-2 expression and a balance between gastric epithelial cell proliferation and apoptosis.

METHODS:

Subjects: Endoscopic gastric biopsies from 160 subjects, 97 with NUD (47 *H. pylori* negative, 50 *H. pylori* positive) and 63 *H. pylori* positive with gastric cancer were examined immunohistochemically for Cox-2 expression, cell proliferation and apoptosis (Antibodies: Cox-2, Ki-67 and Single Stranded DNA, respectively). The extent of Cox-2 evaluation was graded in a 4-point scale: 0 (no staining), 1 (<25%), 2 (25-50%) and 3 (>50%). The intensity of Cox-2 in stained specimens was graded according to the comparison with the internal build-in control as 1 (weak), 2 (moderate) 3 (strong).

Indices for proliferation labeling (LI) and apoptosis (AI) were obtained from a ratio of positive cell to 600 total counted cells, respectively.

***H. pylori* status** was established on gastric biopsies using a combination of culture of two biopsies (greater curvatures of the antrum and mid corpus) and histology (warthin starry stain) of four sites (the greater and lesser curvatures of antrum and mid-corpus). Serum *H. pylori* antibody IgG test was also performed. The subject was considered infected if two or more of the tests were positive.

RESULTS:

Cox-2 expression in the corpus was significantly higher in *H. pylori* positive than that in *H. pylori* negative ($p<0.05$). Regardless of gastric site, gastric cancer subjects had significantly higher Cox-2 expression compared with those in the *H. pylori* negative and positive NUD subjects ($p<0.005$). **Proliferation Labeling Index** was higher in cancer and *H. pylori* positive than in *H. pylori* negative NUD ($p<0.0001$). Moreover, cancer had enhanced proliferation than *H. pylori* positive NUD in corpus greater ($p=0.0454$) and antrum lesser ($p=0.0215$) curvatures. **Apoptosis index** was higher in *H. pylori* positive than in negative NUD ($p<0.05$). However, both had a higher AI than the cancer subjects ($p<0.0001$). **Apoptosis to proliferation** (A:P) ratio was higher in corpus of *H. pylori* negative than in positive NUD in greater ($p<0.0122$) and lesser ($p<0.0009$) curvatures. However, both had a higher A:P ratio than cancer subjects ($p<0.0001$). A negative correlation between Cox-2 expression and A:P ratio was found in the corpus greater ($r = -0.176$, $p = 0.0437$) and lesser curvatures ($r = -0.188$, $p = 0.0312$).

DISCUSSION:

We detected Cox-2 expression in the gastric mucosa of *H. pylori* negative and positive NUD and in the mucosa of gastric cancer subjects. The background mucosa of cancer subjects had more prominent Cox-2 expression in both antrum and corpus, compared to *H. pylori* positive NUD. This significant finding which had not been previously reported, suggest that, the nonmalignant mucosa of cancer subjects had increased malignant potential than the *H. pylori* positive NUD.

Although proliferation was higher in *H. pylori* positive as compared to *H. pylori* negative, the increase was not correlated with the relatively low increase in apoptosis. Further, proliferation was more enhanced in cancer subjects in the presence of significantly reduced apoptosis. As a result, A:P ratio was reduced in *H. pylori* positive and even further in cancer subjects. The disproportionate increase in proliferation against apoptosis may be caused by the effect of Cox-2 expression on the gastric cell kinetics as we found an inverse correlation between Cox-2 expression and A:P ratio. As a results of reduced apoptosis, A:P ratio was lower in cancer than in *H. pylori* positive NUD.

CONCLUSION:

Over-expression of Cox-2 in *H. pylori* infection is associated with the disruption in gastric epithelial cell kinetics and therefore, may play a role in the early stages of gastric carcinogenesis.

論文審査の結果の要旨			
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（要旨は１，０００字～２，０００字程度）

シクロオキシゲナーゼ（COX）はプロスタグランジン産生にかかわる重要な酵素であるが、*Helicobacter pylori* (*H. pylori*) に感染している胃粘膜では、誘導型である COX-2 の発現増加がみられ、胃癌進展における COX-2 の役割が注目されている。胃癌や潰瘍性病変を認めない non-ulcer dyspepsia (NUD) 患者と胃癌を有する *H. pylori* 陽性患者を対象に COX-2 の発現を検討し、さらに COX-2 発現と胃上皮の増殖アポトーシスバランスの関係を検討した。

97 名の NUD 患者（*H. pylori* 陰性 47 名、陽性 50 名）と 63 名の胃癌患者、計 160 名を対象とした。非癌部の背景粘膜より生検を行い、抗 COX-2 抗体、抗 Ki-67 抗体、抗 Single Stranded DNA 抗体を用いて COX-2 発現、細胞増殖、アポトーシスを免疫組織学的に調べた。

COX-2 発現と増殖 Labeling index は、*H. pylori* 陰性者に比べ、陽性者や胃癌患者において亢進していた。Apoptosis index は、*H. pylori* 陰性者に比べ、陽性者で高かったが、胃癌患者では低かった。アポトーシス／増殖比は、*H. pylori* 陰性者に比べ、陽性者において低かったが、胃癌患者ではさら低く、また COX-2 発現とアポトーシス／増殖比は逆相関を認めた。

H. pylori 陰性者に比べ陽性者では、増殖が亢進しているが、アポトーシスも微増しており、アポトーシス／増殖比は微減に留まったが、胃癌患者ではさらに増殖が亢進するがアポトーシスは逆に減少しており、その結果としてアポトーシス／増殖比は有意に低下した。COX-2 発現とアポトーシス／増殖比は逆相関を示すことから、COX-2 発現によるアポトーシス抑制が胃上皮の細胞回転に影響を及ぼし、結果として胃癌患者の背景粘膜での潜在的悪性度を増加しているものと考えられた。

本研究は、COX-2 発現と増殖アポトーシスバランスを研究したものであるが、胃癌患者の非癌部背景粘膜における潜在的悪性度の増加について重要な知見を得たものとして価値ある集積であると認める。よって、本研究者は、博士（医学）の学位を得る資格があると認める。