学 位 論 文 の 要 旨

氏名　　千貫　大介

学　位　論　文　名　　REG Iα Protein Expression in Barrett's Esophagus

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著　　者　　名　　Daisuke Chinuki, Yuji Amano, Shunji Ishihara, Nobuyuki Moriyama, Norihisa Ishimura, Hideaki Kazumori, Yasunori Kadowaki, Shin Takasawa, Hiroshi Okamoto, Yoshikazu Kinoshita

論 文 内 容 の 要 旨

INTRODUCTION

Over the last two decades, Barrett's adenocarcinoma arising from Barrett's esophagus has had one of the fastest growing incidence rates of any cancer in Western countries. Therefore, the establishment of a diagnostic strategy for pre-cancerous Barrett's esophagus with high malignant potential is an important objective. We have investigated the pathophysiology of Barrett's esophagus from the viewpoint of cellular proliferation related to cyclooxygenase-2 expression and mucin phenotyping, and showed that Barrett's adenocarcinoma is more likely to arise in cases of Barrett's esophagus with a predominant intestinal mucin phenotype that possesses higher rates of cellular proliferation, as reported by some investigators. Thus, one of the factors determining the malignant potential of Barrett's esophagus may be cellular proliferation activity, and growth factors may play a key role in the pathophysiology and malignant transformation of Barrett's esophagus.

Regenerating gene *(REG)*, an epithelial growth factor, has been reported to be involved in chronic inflammation-related carcinogenesis in the stomach, colon, bile duct and pancreas. There have been no reports investigating the expression of *REG* in patients with Barrett's esophagus, although several inflammatory cytokines that stimulate *REG* expression are found to be up-regulated in gastrointestinal tract. In the present study, we investigated the degree of expression of *REG* in Barrett's esophagus and the correlation between clinico-pathological characteristics of Barrett's esophagus and *REG* expression.

MATERIALS AND METHODS

Between July 2003 and June 2004, 266 patients with endoscopically and histologically proven Barrett's esophagus were enrolled in this study. Every patient had Barrett's esophagus and was endoscopically re-evaluated to determine whether or not newly developed squamous re-epithelialization had occurred at the biopsy sites 12 months after the first endoscopy. Before endoscopic examination, all participants answered structured questionnaires for gastro-esophageal reflux symptoms and drug usage. Mucin phenotype, cyclooxygenase-2 expression, cellular proliferation and apoptosis were investigated in the biopsy samples taken from the sites of Barrett's esophagus. Investigated growth factors were REG Iα, TGF-α and TGF-β. REG Iα protein expression was confirmed by immunohistochemical and RT-PCR methods. Clinico-pathological factors that correlated with REG Iα protein expression in patients with Barrett's esophagus were evaluated using multivariate logistic regression analysis.

RESULTS AND DISCUSSION

REG Iα protein expression was observed in 48 (18.0%) out of 266 patients with Barrett's esophagus. In univariate analysis, older age, presence of hiatal hernia, gastric mucosal atrophy, newly developed squamous re-epithelialization, intestinal mucin phenotype and lower apoptosis index were correlated with REG Iα protein expression. Among these factors, age, presence of hiatal hernia and newly developed squamous re-epithelialization in Barrett's esophagus were shown to be independent predictors of positive REG Iα protein expression by multivariate logistic regression analysis. Conversely, PCNA index and COX-2 expression did not show any correlation with REG Iα protein expression.

TGF-α and TGF-β protein were found to be expressed in 47.3% and 25.5% of patients with Barrett's esophagus, respectively. Presence of hiatal hernia, accelerated cellular proliferation and COX-2 protein expression were independent predictors for positive TGF-α protein expression. Presence of *H. pylori* infection and reflux esophagitis were also predictors for positive TGF-β protein expression.

Clinical management of Barrett's esophagus may benefit greatly from the investigation

of *REG* expression. Presence of hiatal hernia, aging and squamous re-epithelialization were found to be independent predictors for REG Iα protein expression. Hiatal hernia and aging in patients with Barrett's esophagus are thought to be closely correlated with the strong and longstanding inflammation induced by gastric acid and bile reflux. The inflammatory condition may consequently evoke REG Iα protein expression via proinflammatory cytokines. This is the first report to show that *REG* expression correlates significantly with newly developed squamous re-epithelialization of Barrett's esophagus after de-epithelialization. Squamous re-epithelialization has been demonstrated to occur more frequently in Barrett's esophagus with a gastric mucin phenotype that has a lower cellular proliferation rate. *REG* has been reported not only to posses a growth-promoting effect but also to activate cellular differentiation in the gastric mucosa. Thus, our results suggest that *REG* expression may have a dominant effect on the cellular differentiation of Barrett's epithelium to squamous epithelium, since expression of REG Iα protein has no significant effect on cellular proliferation or on epithelial apoptosis.

CONCLUSION

The present study is the first to examine REG expression in Barrett's esophagus. The presence of REG Iα was more frequently observed in cases that showed squamous re-epithelialization of Barrett's esophagus at biopsy sites.