SPANDIDOS PUBLICATIONS

Association of polymorphisms in myeloperoxidase and catalase genes with precancerous changes in the gastric mucosa of patients at inner-city hospitals in New York

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Received January 31, 2007; Accepted March 9, 2007

Abstract. Gastric carcinogenesis is a multistep process progressing from chronic gastritis, through glandular atrophy (GA), intestinal metaplasia (IM) and dysplasia. We have previously demonstrated that minority patients at New York City hospitals are infected with a relatively virulent strain of *H. pylori* (Hp) and that Hp infection is associated with an increased incidence of precancerous changes in the gastric mucosa. Nevertheless, precancerous changes are not observed in every Hp-infected individual, suggesting that environmental and genetic factors may also play a role in the formation and appearance of precancerous lesions. In the present study, the association between polymorphisms in the promoter regions of human myeloperoxidase (MPO -463G→A) and catalase (CAT -262C→T) genes and the appearance of precancerous changes in the gastric mucosa of our patient population were examined. Patients enrolled in this study were undergoing endoscopy for gastrointestinal complaints. Samples were collected from 126 patients at Kings County Hospital in Brooklyn and St. John's Episcopal Hospital in Queens. One antral biopsy was taken for genotyping, while additional biopsies were taken from the antrum and fundic region for histological analysis and were scored with respect to acute and chronic inflammation, GA, IM and Hp infestation according to the Sydney classification. MPO and CAT genotypes were determined by PCR and RFLP. CAT genotypes did not influence the incidence or severity of precancerous lesions in the fundic or antral regions of the stomach, whereas the MPO -463A allele was associated with an increase in intensity of gastric atrophy in the fundic mucosa. In Hp-infected individuals, the MPO -463G/G genotype was associated with an increase in the incidence of IM in the antrum, whereas the A allele was associated with an increase in IM in the fundic region. These paradoxical findings suggest that different MPO genotypes are associated with the appearance of IM in distinct anatomical regions of the stomach. However, since the majority of gastric cancer (GC) cases in our patient population occurred in the antrum, the MPO -463G/G genotype, which is associated with increased MPO expression and antral IM, may be considered a risk factor for GC.

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Key words: myeloperoxidase, catalase, gastric atrophy, intestinal metaplasia, gastric cancer, *Helicobacter pylori*

Introduction

Helicobacter pylori (Hp) is a gram-negative spiral shaped organism that is an important etiological factor in gastroduodenal disorders including chronic gastritis, peptic ulcer disease, MALT-lymphoma and gastric cancer. The factors that determine which individuals will develop symptomatic disease in response to Hp are unclear but probably include the bacterial strain, genetic, environmental and dietary factors. Hp infection is believed to be a crucial factor in the multistep carcinogenic process of gastric cancer (1,2). Initially, Hp infection causes chronic active gastritis which may progress in severity and distribution throughout the stomach. In later stages of infection, a reduction in the inflammatory infiltrate is observed and mucosal atrophy may occur. This may progress further to intestinal metaplasia, dysplasia and eventually gastric cancer.

The acute and chronic inflammation induced by Hp causes an increase in the formation of reactive oxygen species (ROS) that are mutagenic and carcinogenic to the gastric mucosa. The increased oxidative stress may lead to cell damage and alterations in the mechanisms that control cell proliferation and apoptosis (3-5). Myeloperoxidase (MPO) and Catalase (CAT) are two enzymes that play important roles in regulating the level of ROS in humans. MPO is expressed in monocytes and neutrophils and functions as an antimicrobial agent by catalyzing the formation of hypochlorous acid from H_2O_2 and chloride. Moreover, ammonia generated by the urease enzyme of Hp reacts with hypochlorous acid to form monochloramine

in the gastric mucosa, a powerful and potentially damaging oxidizing agent (5,6). CAT is a heme enzyme that provides primary defense against oxidative damage by converting H_2O_2 into H_2O and O_2. CAT is located in the peroxisomes of nearly all animal cells. In MPO and CAT expression levels may affect ROS formation during the inflammatory response and, therefore, susceptibility to inflammation-related diseases including gastric cancer. Single nucleotide polymorphisms (SNPs) have been identified in the promoter regions of the CAT and MPO genes and these SNPs alter the expression levels of these genes. A frequent SNP in the MPO gene promoter is -463G→A (7). The MPO A variant allele confers lower transcriptional activation than the G common allele and, therefore, the A allele may lower levels of ROS formation during inflammation. The A allele is associated with a decreased risk for lung cancer (8-10), but not Alzheimer's disease (11). An SNP in the CAT gene promoter (-262C→T) has also been described and characterized (12). The less common T allele is associated with lower levels of red blood cell CAT activity (13,14) which may increase ROS formation and oxidative stress.

Variations in the occurrence of gastric cancer have been observed among different ethnic groups within a given region. For example, the incidence of gastric cancer in Black and Hispanic groups in the United States was found to be three- and two-times as high as that observed in Caucasians, respectively (15). It was suggested that the increased incidence of gastric cancer in Blacks and Hispanics reflects the higher Hp infection rate in these ethnic groups. We have previously examined the prevalence of Hp infection, as well as the expression of putative virulence factors in patients undergoing upper endoscopy at inner city hospitals in New York City (16). We found that Hp infection rates were significantly higher in Black patients (43%) when compared with Caucasians (11%) and that the Hp strain infecting these patients is relatively virulent. More recently we have demonstrated an association between Hp infection and the appearance of precancerous lesions in the gastric mucosa in this population (17).

Gastric cancer often manifests at an advanced stage and, therefore, most patients who develop this cancer do not survive. As with other cancers, prevention may be the key to reducing mortality. Chronic inflammation, gastric atrophy and intestinal metaplasia are considered precursor lesions to gastric cancer. The aim of the present study was to examine the relationship between Hp infection, polymorphisms in the MPO and CAT genes and the appearance of precancerous lesions in the gastric mucosa of patients at inner-city hospitals.

Materials and methods

Study subjects. Subjects included patients at King's County Hospital (KCH) and St. John's Episcopal Hospital (SJEH) undergoing upper endoscopy for gastrointestinal complaints. Inclusion criteria included: i) age >18 years, ii) pre-selection for esophagogastroduodenoscopy (EGD) with signed consent for EGD including gastric biopsy. Exclusion criteria included: i) acute upper gastrointestinal bleeding, ii) unstable hemodynamic state, iii) coagulopathy, i.e., prothrombin time >14, platelet count <90,000 and history of bruising or bleeding. The protocols were approved by the Internal Review Boards at King's County Hospital, St. John's Episcopal Hospital and Hunter College.

Patient data. A patient data sheet was completed and filed for each patient enrolled in the study and included medical information such as the indication for EGD, where the procedure was performed, past and current medical conditions (gastrointestinal and other), medications the patient was taking and had taken over the last 12 months, histological and endoscopic diagnoses.

Endoscopic procedures. Standard EGD was performed in an endoscopy suite. A gastric biopsy was taken from the antrum for analysis by the rapid urease test (CLOtest). Additional biopsy specimens were taken from the antrum and fundic regions of the stomach for analysis of Hp infection and genotyping of MPO and CAT by PCR (antral biopsy) and for histological assessment (antral and fundic biopsies).

Preparation of biopsy specimens for PCR. Gastric antral biopsies were placed in a cryogenic tube and stored at -20˚C until they were processed for PCR. DNA from biopsy specimens was extracted by incubating samples in 150 μl lysing buffer (20 mM Tris-HCl, pH 8.0) containing 0.5% Tween-20 and proteinase K (0.5 mg/ml) for 3 h at 55˚C and 98˚C for 10 min to inactivate proteinase K. Following centrifugation (10,000 x g for 5 min), the supernatant was removed and stored at 4˚C. Aliquots (5 μl) were used for analysis by PCR.

Genotyping of MPO and CAT genes. Polymorphisms in the promoter regions of the MPO and CAT genes were detected by PCR and RFLP. A nested PCR approach was required for genotyping of the MPO polymorphism at -463. A 1129-bp fragment was amplified with the following primers: NMPO-F GCT GCC CAT TGG GTG GCT GTT GGA and NMPO-R AGA GGG CTG GGG CGT GGC CAG AAT. The product was used as a template for the second PCR with the following primers: MPO-F CGG TAT AGG CAC ACA ATG GTG AG and MPO-R GCA ATG GTT CAA GCG ATT CTT C. The 350-bp fragment was digested with *Aci*1 (New England Biolabs, MA) for 2 h at 37˚C. The genotypes and fragments for the various MPO alleles were as follows: G/G 169 and 120 bp; G/A 289, 169 and 120 bp; and A/A 289 bp.

The region of the CAT promoter containing the polymorphism was amplified using the following primers: CAT-F AGA GCC TCG CCC CGC CGG ACC G and CAT-R TAA GAG CTG AGA AAG CAT AGC T. The 185-bp product was digested with *Sma*1 (Invitrogen, CA) for 2 h at 37˚C. The genotypes and fragments for the various CAT alleles were as follows: C/C 150 and 30 bp; C/T 185, 150 and 30 bp; and T/T 185 bp. PCR products and restriction fragments were detected by agarose gel electrophoresis and ethidium bromide staining. Gel images were documented using the DigiGenius Documentation System (Syngene, MD).

Histologic assessment of gastric biopsies. For each of the 126 patients that underwent endoscopy, two biopsies were sent for histologic review, one from the antrum and one from the fundus. Two slides were prepared from each biopsy. One was stained with hematoxylin and eosin, and the other with

Association between MPO genotype and histological scores for *H. pylori* infestation, inflammation, gastric atrophy inal metaplasia in the antrum and fundic mucosa.

	H. pylori infestation	Acute inflammation	Chronic inflammation	Atrophy	Metaplasia
Antrum					
G/G	0.536±0.122	0.536±0.088	1.527±0.088	0.340±0.066	0.327±0.089
G/A	0.688±0.162	0.575±0.113	1.538±0.110	0.333±0.076	0.175±0.071
A/A	0.267±0.153	0.533±0.215	1.267±0.175	0.100±0.100	0.067±0.067
G/A + A/A	0.573±0.128	0.564±0.108	1.464±0.094	0.268±0.063	0.146±0.055
Fundic					
G/G	0.602±0.138	0.480±0.090	1.286±0.089	0.000±0.000	0.020±0.021
G/A	0.516±0.130	0.500±0.143	1.288±0.123	0.152±0.078	0.125±0.059
A/A	0.333±0.188	0.333±0.142	1.125±0.152	0.000±0.000	0.083±0.083
G/A + A/A	0.465±0.109	0.456±0.109	1.244±0.097	0.114±0.059[a]	0.114±0.049

Values represent the mean ± SEM. [a]Significantly different when compared with the MPO G/G allele ($p<0.05$).

Giemsa. Each hematoxylin and eosin slide was evaluated microscopically for the presence of acute inflammation, chronic inflammation, gastric atrophy and intestinal metaplasia. These parameters were graded on a scale of 0-3 (0, none; 1, mild; 2, moderate; 3, severe) according to the Updated Sydney System (18). The degree of Hp infestation was judged and graded using the Giemsa-stained slide. The slides were evaluated by a single pathologist (J. Schneller) without prior knowledge of the endoscopic diagnosis or PCR results.

Data analysis. Statistical analysis was performed using the Fisher's exact test or the Student's t-test. In some cases, data was stratified with respect to gender and age. Statistical significance was set at the 0.050 level.

Results

Study population and H. pylori infection. Samples were collected from 115 patients at KCH and SJEH. Fundic biopsies were not obtained from 19 subjects. With respect to the ethnicity of the study subjects, 61.1% were Black, 13.5% were Hispanic and 25.4% were Caucasian. Of the study subjects, 69.8% were female and 30.2% were male, and the average age was 54.9 years old. With respect to socioeconomic status, the annual income of 85% of the individuals enrolled in the study was <25,000 dollars. Hp DNA was detected in 34.1% of the biopsies by PCR using the URE primers as described previously (16). Hp infection was highest in Blacks (41.6%) and Hispanics (29.4%), and lowest in Caucasians (18.8%).

Association of MPO genotypes with Hp infestation, inflammation, atrophy and intestinal metaplasia in the gastric mucosa. With respect to the expression of the MPO alleles, 47.5% of the subjects were genotyped as G/G, 36.9% were G/A, and 13.9% were A/A. The G/A and A/A genotypes were considered separately and in combination. As shown in Table I, the only significant change in histological scores was observed between the G/G and G/A + A/A genotypes for atrophy in the fundic region. In this case, a small but significant increase in atrophy score was observed in the fundic region with the G/A + A/A genotypes when compared with the G/G genotype. Histological scores for intestinal metaplasia and atrophy were lower in the antrum when the A/A genotype was compared with G/G (Table I). However, these differences were not statistically significant. Similarly, Hp infestation scores were lower for the A/A genotype when compared with G/G in both regions of the stomach. Again, these differences were not statistically significant.

Next, the relationship between MPO genotypes and the incidence of Hp infestation, atrophy or intestinal metaplasia were examined (Table II). For this analysis, incidence is defined as any sample in which Hp, atrophy or intestinal metaplasia is observed, regardless of severity. Although no statistically

Table II. Association between MPO genotype and the incidence of Hp infection, gastric atrophy and intestinal metaplasia. Values represent percentage of biopsies in which *H. pylori*, gastric atrophy or intestinal metaplasia were observed.

	n	Hp infestation	Atrophy	Metaplasia
Antrum				
G/G	54	33.3	33.4	25.9
G/A	40	35.0	33.3	15.0
A/A	15	20.0	6.7	6.7
G/A + A/A	54	31.5	25.9	12.7
Fundic				
G/G	49	32.7	0	2
G/A	31	38.7	12.5	12.5
A/A	12	25.0	0	8.3
G/A + A/A	43	34.9	9.3	11.4

Table III. Association between CAT genotype and histological scores for Hp infestation, inflammation, gastric atrophy and intestinal metaplasia in the antrum and fundic mucosa.

	H. pylori infestation	Acute inflammation	Chronic inflammation	Atrophy	Metaplasia
Antrum					
C/C	0.535±0.094	0.547±0.075	1.459±0.070	0.277±0.050	0.227±0.060
C/T + T/T	0.607±0.195	0.482±0.126	1.589±0.132	0.346±0.096	0.232±0.096
Fundic					
C/C	0.579±0.103	0.493±0.083	1.300±0.072	0.069±0.036	0.069±0.030
C/T + T/T	0.409±0.186	0.364±0.126	1.159±0.152	0.000±0.000	0.046±0.047

Values represent the mean ± SEM.

Table IV. Association between CAT genotype and the incidence of Hp infestation, gastric atrophy and intestinal metaplasia. Values represent percentage of biopsies in which *H. pylori*, gastric atrophy or intestinal metaplasia were observed.

	n	Hp infestation	Atrophy	Metaplasia
Antrum				
C/C	86	32.6	27.1	17.4
C/T + T/T	28	32.1	34.6	21.4
Fundic				
C/C	72	38.6	5.6	6.9
C/T + T/T	22	22.7	0	4.6

Table V. Association between MPO genotype and the incidence of gastric atrophy and intestinal metaplasia in Hp infected (+) and non-infected (-) individuals.

	MPO genotype (n)	Atrophy (%)	Metaplasia (%)
Antrum			
H. pylori (-)	G/G (38)	27.0	10.8
	G/A, A/A (40)	22.9	8.3
H. pylori (+)	G/G (19)	43.8	58.8
	G/A, A/A (23)	31.6	15.8[a]
Fundic			
H. pylori (-)	G/G (40)	0	3.2
	G/A, A/A (38)	3.5	0
H. pylori (+)	G/G (19)	0	0
	G/A, A/A (23)	18.8	33.3[a]

[a]Values are significantly different when compared with the MPO G/G allele ($p<0.05$).

significant differences were detected, the incidence of atrophy and metaplasia associated with the A/A genotype was decreased 4- and 3-fold in the antrum, respectively, when compared with the G/G genotype (Table II).

Association of CAT genotypes with Hp infestation, inflammation, atrophy and intestinal metaplasia in the gastric mucosa. With respect to the CAT alleles, 74.8% of the subjects were genotyped as C/C, whereas 25.2% were C/T or T/T. The C/T and T/T CAT genotypes were combined because only three subjects (2.6%) expressed the T/T genotype. No significant differences in the histological scores or incidence of Hp infestation, atrophy or intestinal metaplasia were observed between the C/C and C/T + T/T genotypes (Tables III and IV).

Association between MPO genotype and the incidence of gastric atrophy and intestinal metaplasia in Hp-infected and non-infected individuals. Finally, we examined the association between MPO and CAT genotypes and the incidence of atrophy and intestinal metaplasia in Hp-infected and non-infected individuals. In non-infected individuals, the incidences of atrophy and metaplasia were not different with respect to MPO genotypes (Table V). However, in Hp-infected individuals, the incidence of metaplasia in the antrum was nearly 4-fold lower in individuals with the G/A + A/A MPO genotype when compared with the G/G genotype. In contrast, the incidence of intestinal metaplasia in the fundic region was significantly higher for G/A + A/A MPO genotypes when compared with the G/G MPO genotype (Table V). Hence, in Hp-infected individuals, the A allele has a protective effect with respect to intestinal metaplasia in the antrum, whereas this allele increases the likelihood of metaplasia developing in the fundic region. These observations were seen when the data was adjusted for gender and age. No differences in the incidences of intestinal metaplasia or atrophy of the gastric mucosa were observed with the various CAT genotypes in either the Hp-infected or non-infected individuals (data not shown).

Discussion

In the present study, we examined the association between precancerous changes in the gastric mucosa and common

phisms in two genes that are involved with the n of free radical formation, MPO and CAT. Our population, which is predominantly Black and Hispanic, consisted of patients at two inner city hospitals in New York City undergoing upper endoscopy for gastrointestinal complaints. The MPO -463 genotype distribution in our population was similar to that observed in Caucasian populations in previous studies in that the A allele was present in approximately 40-50% of the individuals genotyped (19,13). In contrast, the A allele was present in only 20-25% of the subjects in studies performed with Asian populations (20-22). With respect to genotyping of the CAT -262 polymorphism, the T allele (C/T or T/T) was observed in 25% of our population. In contrast to these findings, the T allele was observed less frequently in a Korean population (5-6%), yet was more common among Swedes (48%) (12,23).

Production of ROS by neutrophil-associated MPO activity is an important defense mechanism against bacteria. Therefore, one may propose that the G/G MPO genotype may have a protective effect with respect to Hp infection because of the higher level of MPO expression associated with this genotype. However, we did not observe any differences with respect to Hp infection rates or Hp infestation and MPO genotypes. In fact, the incidence of Hp infection and Hp density was decreased in A/A MPO genotypes (Tables I and II, respectively), although these changes were not significant. Similarly, in a study performed in Japan, the G/G MPO genotype was associated with an increased risk for Hp infection (20). In contrast to these findings, carriers of the MPO A allele displayed higher Hp density scores than non-carriers in a more recent study (22). Hence, the association between MPO genotype and Hp infection is ambiguous.

As proposed by Correa's model of gastric carcinogenesis, chronic inflammation, gastric atrophy and intestinal metaplasia are considered precursor lesions to gastric cancer (24). With respect to the MPO -463 polymorphism, we observed an increase in the histological score for atrophy in the fundic region of the stomach for carriers of the A allele (A/G + A/A) when compared with the G/G allele. In contrast to these findings, the MPO A/A genotype was associated with a decrease in the incidence of Hp infestation, atrophy and intestinal metaplasia in the antrum, although these changes were not statistically significant (Table II). Others have demonstrated a correlation between neutrophil infiltration and the severity of gastric atrophy in patients with the MPO -463 G/G genotype, but not the G/A genotype (21). As mentioned previously, expression of the MPO -463 A allele results in decreased MPO expression which would be consistent with observed decreases in inflammation, atrophy and intestinal metaplasia in the gastric mucosa. Hence, the increase in severity of fundic atrophy associated with the MPO -463 A allele is difficult to explain. How could a decrease in MPO expression be associated with an increase in atrophy in the fundic region and decreased atrophy and intestinal metaplasia in the antrum? Moreover, these changes are more pronounced in Hp-infected individuals (see below).

In the present study, CAT -262 genotypes were not associated with differences in any of the parameters measured. With respect to other diseases, the CAT -262 C/C genotype, which is associated with higher CAT activity, was associated with a 17% reduction in the risk of breast cancer when compared with having at least one T allele (25). This is most likely due to the ability of CAT to neutralize ROS involved with carcinogenesis. In contrast, CAT genotypes were not associated with the development of rheumatoid arthritis (23) or lupus erythematosus (27). It has been previously demonstrated that the CAT -262 T allele is associated with lower CAT activity (12). However, it was recently discovered that the effect of the T allele on CAT activity is observed only in Caucasians, especially women, and that the CAT -262 genotypes do not appear to affect CAT activity in African-Americans (25). Hence, the fact that CAT -262 genotypes were not associated with changes in histological scores or incidences of precancerous lesions in the present study is probably due to the fact that 75% of the subjects in our study were Black.

Our findings indicate that the CAT -262 polymorphism is not associated with an individual's susceptibility to developing gastric atrophy or intestinal metaplasia, whereas marginal associations are observed with respect to the MPO polymorphism. However, when the data are analyzed with respect to Hp infection status, a different story emerges. In Hp-infected individuals, the MPO -463 G/G genotype is associated with a 4-fold increased risk of developing intestinal metaplasia in the antrum when compared with the G/A or A/A genotypes. The increased risk for intestinal metaplasia in the antrum with the G/G genotype is not observed in non-infected individuals. Paradoxically, the G/G MPO genotype is also associated with a decreased incidence of intestinal metaplasia in the fundic region of Hp-infected individuals. Hence, our findings indicate that all three MPO -463 genotypes are associated with an increase in the incidence of intestinal metaplasia in the gastric mucosa, albeit at different anatomical sites. In a recent study, the MPO -463 genotypes G/A and A/A were found to be associated with a reduced risk for gastric cancer in Chinese males (27). These findings are consistent with the reduced incidence of intestinal metaplasia in the antrum that we have observed in Hp-infected individuals with the G/A or A/A genotypes. Moreover, in the present study, we observed a decreased incidence of intestinal metaplasia in the antrum of both males and females with the G/A or A/A genotypes, while the protective effect of these genotypes against gastric cancer was observed only in males in the Chinese study (27). This may have been due to genetic differences between the ethnic groups studied.

The reduced risk for gastric cancer in Chinese individuals with the G/A and A/A genotypes is not consistent with the increased incidence of intestinal metaplasia we observed in the fundic region of the stomach with the G/A or A/A genotypes in our population. Again, this may be due to ethnic differences. Another possible explanation is that when intestinal metaplasia develops in the antrum, it is more likely to develop into gastric cancer as opposed to the development of intestinal metaplasia in the fundic region of the stomach. In fact, the anatomical site of the majority of gastric cancer cases at KCH is the antrum (J. Schneller, unpublished data). Therefore, the MPO -463 G/G genotype, which is associated with an increase in IM in the antrum, may have been a risk factor for gastric cancer in our patient population.

In conclusion, in the patient population examined in the present study, the CAT genotype was not associated with an

increased risk in the development of precancerous changes. However, in Hp-infected individuals, the various MPO genotypes increased the risk of developing intestinal metaplasia at different anatomical sites of the stomach. Are different MPO genotypes associated with an increased risk for gastric cancer in different anatomical locations? Further studies are required to answer this question.

Acknowledgements

This study was supported by grants from The Cancer Research and Prevention Foundation, The Rosalyn Yalow Foundation for Medical Research and The City University of New York, PSC-CUNY Research Award program. The authors would like to thank Dr Edward Binkowski for assisting with the statistical analysis of the data.

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