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BRIEF ARTICLE

Inflammatory cytokine gene polymorphisms increase the risk of atrophic gastritis and intestinal metaplasia

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Abstract

AIM: To investigate the effects of interleukin-8 (*IL-8*), macrophage migration inhibitory factor (*MIF*) gene polymorphisms, *Helicobacter pylori* (*H. pylori*) infection, on the risk of developing severe chronic atrophic gastritis (SCAG) and intestinal metaplasia (IM).

METHODS: A total of 372 cases were selected from a cohort study in Linqu County, a high risk area for gastric cancer (GC) in northern China. To obtain a sufficient group size, patients with normal or superficial gastritis were included. Based on an average follow-up period of 56 mo, the 372 cases were divided into no progression group (no histological progression from normal or superficial gastritis, *n* = 137), group Ⅰ (progressed from normal or superficial gastritis to SCAG, *n* = 134) and group Ⅱ (progressed from normal or superficial gastritis to IM, *n* = 101). *IL-8*, *MIF* gene polymorphisms were detected by polymerase chain reaction-based denaturing high-performance liquid chromatography analysis and DNA sequencing.

RESULTS: An increased risk of SCAG was found in subjects with IL-8-251 AA genotype [odds ratio (OR) = 2.62, 95% CI: 1.23-5.72] or IL-8-251 A allele carriers (AA + AT) (OR = 1.81, 95% CI: 1.06-3.09). An elevated risk of IM was found in subjects with IL-8-251 AT genotype (OR = 2.27, 95% CI: 1.25-4.14) or IL-8-251 A allele carriers (OR = 2.07, 95% CI: 1.16-3.69). An increased risk of SCAG was found in subjects with MIF-173 GC genotype (OR = 2.36, 95% CI: 1.38-4.02) or MIF-173 C allele carriers (GC + CC) (OR = 2.07, 95% CI: 1.21-3.55). An elevated risk of IM was found in subjects with MIF-173 CC genotype (OR = 2.27, 95% CI: 1.16-4.46) or MIF-173 C allele carriers (OR = 3.84, 95% CI: 1.58-9.34). The risk of SCAG and IM was more evident in subjects carrying IL-8-251 A allele (OR = 6.70, 95% CI: 1.29-9.78) or MIF-173 C allele (OR = 6.54, 95% CI: 2.97-14.20) and positive for *H. pylori* infection.

CONCLUSION: *IL-8-251* and *MIF-173* gene polymorphisms are significantly associated with the risk of SCAG and IM in a population with a high risk of GC in Linqu County, Shandong Province, China.

Key words: Chronic atrophic gastritis; Gene polymorphisms; *Helicobacter pylori*; Interleukin-8; Intestinal metaplasia; Macrophage migration inhibitory factor

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INTRODUCTION

Atrophic gastritis (AG) and intestinal metaplasia (IM) are two important precursor lesions of intestinal type gastric cancer (GC)[1]. These precursor lesions may significantly elevate the risk of intestinal type GC[2,3].

Some bacterial factors, such as the pathogenic island of *Helicobacter pylori* (*H. pylori*) including cagA, sIm1 vacA, babA2, sabA, and oipA, are correlated with the severity of atrophic gastritis and occurrence of IM[4-9]. However, bacterial factors alone are not sufficient to explain the diverse results of *H. pylori*-related diseases. Our previous study has shown that the proportion of cagA + *H. pylori* strains in children living in Linqu County, an area with a high risk of GC in China, is very high (88.5%)[10]. It has also been demonstrated that almost 100% of *H. pylori* strains isolated from Chinese population are cagA positive[11].

There is increasing evidence that host inflammation-related cytokines and their gene polymorphisms are related with atrophic gastritis and IM[12,13]. Interleukin-8 (IL-8), a member of Cys-X-Cys (CXC) chemokine family, is an activator and chemoattractant of neutrophils and lymphocytes[14]. Gastric mucosal levels of IL-8 increase significantly after *H. pylori* infection and parallel to the severity of gastritis[15]. Macrophage migration inhibitory factor (MIF), an important activator of T lymphocytes and macrophages, plays a pivotal role in inflammatory and immune diseases[16,17]. *H. pylori* infection is associated with an increased expression of MIF mRNA and protein in gastric epithelial and inflammatory cells. Increased expression of the MIF protein correlates with histological severity of GC and its precursor[18].

As these inflammatory cytokines and their gene polymorphisms may potentially influence the outcome of *H. pylori* infection, a few studies have investigated the association of gene polymorphisms in these inflammatory cytokines with the risk of atrophy and IM[15,19,20].

However, these studies were limited by their single time-point assessment for pathological diagnosis. Therefore, we conducted a prospective study to investigate the association of *IL-8* gene polymorphisms with the risk of atrophic gastritis, and *MIF* gene polymorphisms with IM, showing that the high expressing genotypes of IL-8 are significantly associated with the increased risks of severe chronic atrophic gastritis, and MIF is significantly associated with IM.

MATERIALS AND METHODS

Study protocol

The initial study included over 3399 people from Linqu County, a rural area of Shandong Province, China, which has one of the highest GC mortality rates in the world (70/10000 males and 25/10000 females per year)[21]. In brief, we launched an endoscopic-pathological screening program for GC and precancerous lesions of GC in 3399 residents from 14 randomly selected villages of Linqu County in autumn of 1989 or in spring of 1990. In 1994, a follow-up endoscopic screening was performed in 83% of eligible members. People, diagnosed as normal or superficial gastritis in 1989 or in 1990, were subsequently genotyped for IL-8 and MIF. We analyzed the relation between genotypes and progression of gastric disease. The study design received approval from the Institutional Review Board of Peking University School of Oncology, and was conducted in accordance with the Helsinki Declaration. Informed consent was obtained from all participants.

Endoscopy and pathological diagnosis

Seven biopsies were taken from standard locations in each subject. The procedures and histopathologic criteria have been described elsewhere[22,23]. We reviewed all slides of 372 patients in our study according to the updated Sydney system[24]. Each subject was assigned a global diagnosis based on the most severe diagnosis among the seven biopsies. Independent examinations were performed by three experienced gastroenterologists. If there was any disagreement, the final decision was made based on the majority or subsequent discussion of the case.

Grouping

After the first examination in 1989, 372 of the 3399 subjects including 172 males and 200 females with a mean age of 42.2 years (range: 24-65 years) were enrolled in this study. All these 372 subjects were initially diagnosed as normal or as superficial gastritis (baseline). After a 56-mo follow-up, theses 372 subjects were subdivided into group Ⅰ (n = 134), group Ⅱ (n = 101) and no progression group (n = 137). Lesions in patients of group Ⅰ were progressed from baseline to severe chronic atrophic gastritis (SCAG). According to the updated Sydney system, recognition of minor degrees of atrophy without intestinal metaplasia in the antrum was difficult, marked degrees of atrophy without intestinal metaplasia in the antrum were selected as the presence of atrophic gastritis. Lesions in patients of group Ⅱ were progressed from baseline to IM, and lesions in patients of no progression group did no progress from baseline lesion.

Blood sample collection

In 1994, blood samples were collected and allowed to clot for 30-40 min at room temperature in the dark. Serum was harvested, the clot was frozen immediately at -20℃, and stored at -70℃ for 2 or 3 d. During the transfer, dry ice was used.

Diagnosis of H. pylori infection

The detailed serologic assay has been described elsewhere[22]. Serum level of *H. pylori*-specific IgG and IgA in all samples was measured by enzyme-linked

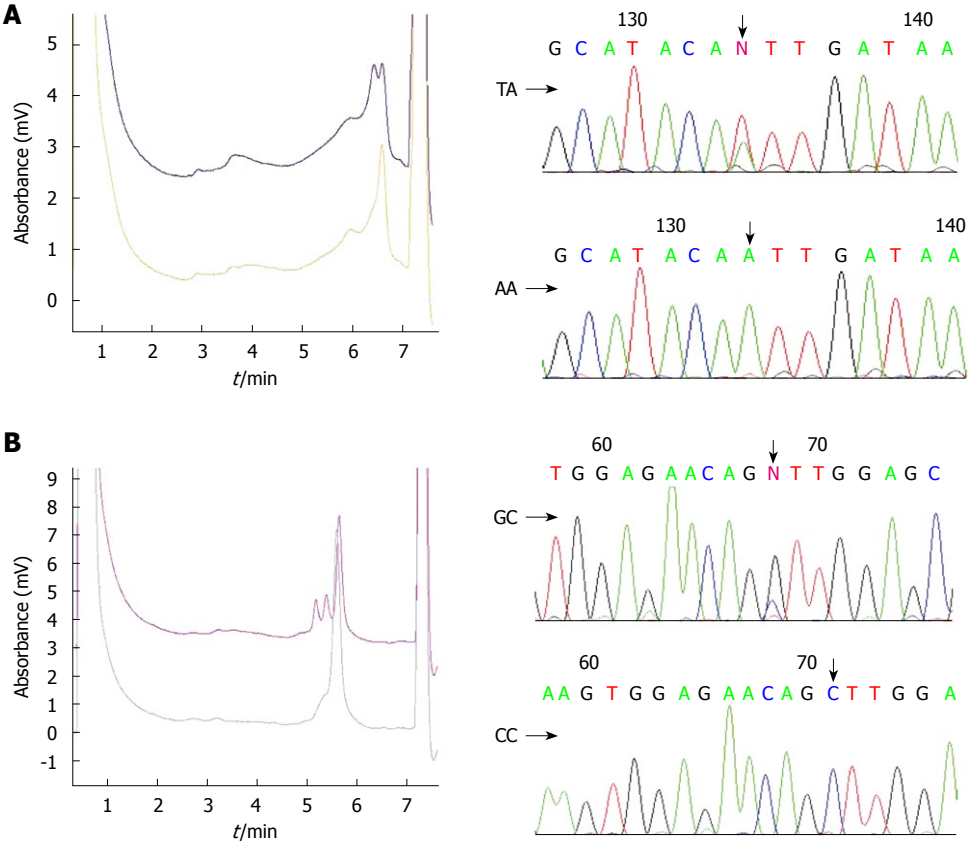

Figure 1 Denaturing high-performance liquid chromatography (DHPLC) and sequence analysis. A: Interleukin-8 (IL-8)-251 A/T polymorphism; B: Macrophage migration inhibitory factor (MIF)-173 C/G polymorphism.

immunosorbent assay (ELISA). Quality-control samples were assayed at Vanderbilt University (Nashville, TN). An optical density ratio (ODR) value > 1.0 and < 1.0 was considered seropositive and negative, respectively.

The presence of *H. pylori* was further confirmed by immunohistochemistry (IHC). Briefly, paraffin-embedded tissue sections were stained using IHC with an avidin-biotin complex immunoperoxidase kit. Polyclonal rabbit anti-*H. pylori* (ab7788, Abcam, Cambridge, UK) was used as a primary antibody as previously described[25].

DNA preparation

Blood clots were thoroughly washed with Tris-EDTA (TE) buffer containing 50 mmol/L Tris-HCl (pH 8.0) and 1 mmol/L EDTA. After centrifugation, pellets were incubated with rotation in a lysis buffer (TE buffer containing 2 g/L SDS and 200 μg/mL proteinase K) overnight at 37℃. Lysate was then extracted with phenol and precipitated with isopropanol. The precipitate was washed with 70% ethanol, dried, and dissolved in TE buffer. Concentration and purity of DNA were determined by spectrophotometry at $A_{260\ nm}$ and $A_{280\ nm}$. Then, DNA was aliquoted and stored at -80℃ until use.

Cytokine genotyping

Polymerase chain reaction (PCR) was performed in a 25 μL reaction mixture containing 100ng of DNA, 0.1 μmol/L of each primer, 0.2 mmol/L of deoxynucleosidetriphosphate, 1.0 U of *Taq* DNA polymerase (Promega, Madison, WI), and 1 × reaction buffer. The primer sequences of MIF-173, IL-8-251 have been described elsewhere[26]. PCR-based denaturing high-performance liquid chromatography (DHPLC) and single nucleotide polymorphisms (SNP) were further confirmed by direct sequencing.

DHPLC analysis was performed on a transgenomic WAVE system (Transgenomic Inc., Omaha, NE). The detailed genotyping process has been described elsewhere[27]. In brief, PCR products were denatured for 1 min at 94℃ and then gradually re-annealed by decreasing the sample temperature from 94℃ to 45℃ for 30 min to form homo- and/or hetero-duplexes. The PCR products were then applied to the DHPLC column at an optimal oven temperature and eluted with a linear acetonitrile gradient at a flow rate of 0.9 mL/min. The results of DHPLC were further confirmed by DNA sequencing with an ABI Prism 377 DNA sequencer (Applied Biosystems, Foster City, CA) (Figure 1).

Statistical analysis

Data were analyzed using the SPSS 13.0 (SPSS Inc., Chicago, IL, USA). Multiple linear regression analyses were performed with gender, age, smoking, and drinking as explanatory variables to determine which factors influence the progression of gastric lesions. Genotypes of IL-8-251 and MIF-173 loci were also included as explanatory variables when difference in groups I and Ⅱ and no progression group was detected. Odds ratios (OR) with 95% confidence interval (CI) were computed. $P < 0.05$ was considered statistically significant.

RESULTS

Demographic characteristics and *H. pylori* infection with

Table 1 Parameters of patients with or without progression *n* (%)

	No progression group (*n* = 137)	Group Ⅰ (*n* = 134)	*P* value	Group Ⅱ (*n* = 101)	*P* value
Age (yr)					
≤ 40	32 (23.4)	45 (33.6)[a]	0.045	35 (34.7)[b]	0.027
40-50	76 (55.5)	60 (44.8)		42 (41.6)	
≥ 50	29 (21.1)	29 (21.6)	0.330	24 (23.7)	0.200
mean ± SD	44.2 ± 0.7	43.8 ± 0.6		46.7 ± 0.7	
Sex			0.600		0.260
Male	59 (43.1)	62 (45.9)		51 (50.5)	
Female	78 (56.9)	72 (54.1)		50 (49.5)	
H. pylori infection			< 0.001		0.100
Negative	59 (43.1)	30 (22.4)		33 (32.7)	
Positive	78 (56.9)	104 (77.6)[c]		68 (67.3)	

[a]*P* = 0.045 *vs* patients at the age of 40-50 years (χ^2 = 4.04); [b]*P* = 0.027 *vs* patients at the age of 40-50 years (χ^2 = 4.87); [c]*P* < 0.001 *vs* patients with no progression (χ^2 = 13.13). *H. pylori*: *Helicobacter pylori*.

Table 2 Cytokine genotype frequencies in patients with or without progression *n* (%)

	No progression group (*n* = 137)	Group Ⅰ (*n* = 134)	Group Ⅱ (*n* = 101)
IL-8-251			
TT	59 (43.1)	39 (29.1)	25 (24.8)
TA	64 (46.7)	70 (52.2)	65 (64.4)
AA	14 (10.2)	25 (18.7)	11 (10.9)
MIF-173			
GG	100 (73.0)	71 (53.0)	62 (60.4)
GC	34 (24.8)	54 (40.3)	29 (28.7)
CC	3 (2.2)	9 (6.7)	10 (10.9)

IL-8: Interleukin-8; MIF: Migration inhibitory factor. GC: Gastric cancer.

progression and no progression are listed in Table 1. The number of patients under the age of 40 years was greater in groups Ⅰ and Ⅱ than in no progression group. The percentage of *H. pylori* infection was significantly higher in group Ⅰ than in no progression group.

The patients expressed Alleles at the individual loci were expressed in patients showing no progression of the lesions, with no significant χ^2 values.

Effect of IL-8-251 polymorphism on development of SCAG and IM

Multivariate analysis showed that the frequencies of IL-8-251 in groups Ⅰ and Ⅱ were significantly different from those in no progression group (Table 2). Compared with IL-8-251 TT genotype, IL-8-251 AA genotype and IL-8-251 A allele carriers exhibited a significantly increased risk for progression from baseline lesions to SCAG (Table 3). The patients with IL-8-251 TA genotype or IL-8-251 A allele carriers had an increased risk for progression from baseline lesions to IM.

Effect of MIF-173 polymorphism on development of SCAG and IM

Multivariate analysis showed that the MIF-173 GC genotype or MIF-173 C allele carriers were significantly associated with an increased risk for progression from baseline lesions to SCAG and IM (Table 3).

Table 3 Relation between cytokine gene polymorphisms and development of precursory lesions of GC *n* (%)

Genotype	Group Ⅰ (*n* = 134) OR (95% CI)	Group Ⅱ (*n* = 101) OR (95% CI)
IL-8-251		
TT	1.00	1.00
TA	1.64 (0.96-2.79)	2.27 (1.25-4.14)
AA	2.62 (1.23-5.72)	1.20 (0.76-1.90)
TA + AA	1.81 (1.06-3.09)	2.07 (1.16-3.69)
MIF-173		
GG	1.00	1.00
GC	2.36 (1.38-4.02)	1.50 (0.57-3.94)
CC	1.92 (0.95-3.87)	2.27 (1.16-4.46)
GC + CC	2.07 (1.21-3.55)	3.84 (1.58-9.34)

OR and 95% CI were calculated by logistic regression, with no progression group as a reference group and adjusted for age, sex. OR: Odds ratio.

The risk for SCAG in association with IL-8-251 and MIF-173 genotypes was further examined with stratification by *H. pylori* infection. The OR for development of SCAG in subjects carrying IL-8-251 A allele or with *H. pylori* infection alone was 2.34 (95% CI: 0.95-2.83) or 3.28 (95% CI: 1.09-9.78), respectively. However, the OR was significantly elevated in subjects carrying the AA genotype and with *H. pylori* infection (OR = 6.70, 95% CI: 1.29-9.78) (Table 4). There was an interaction between IL-8-251 A allele carriers and *H. pylori* infection, with a relative risk for development of SCAG due to the interaction of 6.70, and a synergy index of 1.57.

A similar trend to develop SCAG was observed between the MIF-173 C allele carriers and *H. pylori* infection. The OR of developing SCAG significantly increased in subjects carrying at least one MIF-173 C allele and with *H. pylori* infection (OR = 6.54, 95% CI: 2.97-14.20) (Table 4). An interaction between the MIF-173 C allele carriers and *H. pylori* infection was observed (OR = 2.26, synergy index = 3.15).

The association of IM and IL-8-251 with MIF-173 genotypes was further examined with stratification by *H. pylori* infection. However, the OR for IM in subjects carrying MIF-173 C allele and with *H. pylori* infection was elevated significantly (OR = 2.93, 95% CI: 1.28-6.60) (Table 5). There was also an interaction between the MIF-173 C allele carriers and *H. pylori* infection (OR = 2.20, synergy index = 1.25).

DISCUSSION

In this study, all tested genetic polymorphisms in IL-8 and MIF increased the risk of SCAG and IM. IL-8 and MIF are inflammatory cytokines expressed in injured mucosa after *H. pylori* infection. IL-8 is an important mediator of the inflammatory response and increases mucosal injury in *H. pylori* infected patients because IL-8 is a major activator and chemokine for neutrophils which

Table 4 Risk of SCAG in patients with IL-8-251 and MIF-173 genotypes and *H. pylori* infection

H. pylori infection	IL-8-251 genotype				MIF-173 genotype			
	TT	OR (95% CI)[1]	TA + AA	OR (95% CI)[1]	GG	OR (95% CI)[1]	C carriers	OR (95% CI)[1]
Negative	5/22	1.00	25/37	2.34 (0.95-2.83)	17/40	1.00	13/19	1.60 (0.64-3.97)
Positive	34/34	3.28 (1.09-9.78)	70/44	6.70 (1.29-9.78)	54/60	2.11 (1.07-4.13)	50/18	6.54 (2.97-14.20)

[1]OR and 95% CI were calculated by logistic regression, with no progression group as a reference group and adjusted for age, sex. SCAG: Severe chronic atrophic gastritis.

Table 5 Relation between risk of IM and MIF-173 genotypes infection

H. pylori infection	MIF-173 genotype			
	GG[1]	OR (95% CI)[2]	C carriers[1]	OR (95% CI)[2]
Negative	19/40	1.00	14/19	1.55 (0.63-3.72)
Positive	43/60	1.51 (0.76-2.94)	25/18	2.93 (1.28-6.60)

[1]Group Ⅱ/No progression, "Group Ⅱ" means lesions were progressed from normal or superficial gastritis to IM after follow up; [2]OR and 95% CI were calculated by logistic regression, with no progression group as a reference group and adjusted for age, sex.

contribute to mucosal damage by secreting NO and H_2O_2[28] and significantly augments T helper 1 (Th1) immune response by inducing proinflammatory cytokines such as TNF-α, interferon-γ, and IL-1β secretion. It has been shown that Th1 predominant immune responses inhibit acid secretion from gastric glands, and cause gastric atrophy and metaplasia in a *H. pylori* infected mouse model[29,30].

The transcript activity is significantly higher in the IL-8-251 A promoter than in the IL-8-251 T promoter[31]. Furthermore, the DNA sequence around the IL-8-251 A allele region may produce a potential binding site for C/EBP, and induce IL-8 expression through the nickel subsulphide dependent pathway[32].

In this study, the risk of progression from baseline lesions to SCAG and IM was significantly increased in patients carrying the IL-8-251 AA and IL-8-251 AT genotype or the IL-8-251 A allele, which is consistent with the reported findings[19,31]. Furthermore, SCAG occurred due to the interaction between IL-8-251 A allele carriers and *H. pylori* infection. A previous study on the same population also demonstrated that the IL-8-251 AA genotype significantly increases the risk of GC[33]. In the present study, IL-8-251 A allele carriers were positively correlated with the development of SCAG and IM, implying that *IL-8-251* gene polymorphism plays an important role in the development of GC.

MIF promotes the recognition of Gram-negative bacteria by the innate immune system[34]. The *MIF* gene appears to be a strong candidate susceptibility gene for *H. pylori* -related diseases. Xia *et al*[17] reported that both mRNA and protein levels of MIF are up-regulated in *H. pylori* -infected patients and parallel to the severity of gastritis. Moreover, the expression level of MIF protein is markedly different in patients with gastritis, IM, DYS, GC[17,18].

Functional studies, both *in vivo* and *in vitro*, demonstrated that the mutant allele MIF-173 C is associated with an increased MIF protein production[31,35]. The presence of MIF-173 C allele stimulates protein 4 (AP-4) transcription factor binding site that may up-regulate MIF expression[36].

In our study, the MIF-173 C allele was found to be associated with the high risk of SCAG and IM. Moreover, an interaction occurred between MIF-173 C allele carriers and *H. pylori* infection, thus promoting progression from baseline lesions to SCAG and IM. Other studies found that MIF not only modulates the expression of proinflammatory mediators such as TNF-α, IL-1β, IL-8, IFN-γ, but also regulates the activation of T cells[35,37].

Therefore, we hypothesize that variants of *MIF* gene polymorphism may contribute to the different outcomes of *H. pylori* -related gastritis. Moreover, *MIF* gene polymorphisms may be another important candidate gene marker for the outcomes of patients infected with *H. pylori*.

The fact that the population in our study lived in a relatively closed society and had similar living conditions or habits, may minimize the effects of other mixed factors such as intake of fresh vegetables, salt consumption, water intake. Furthermore, the subjects in our study were followed up for an average period of 56 mo, and the final pathological diagnosis was made in 1994. Although more recent pathological assessments may provide additional insights, an average follow-up period of 4-5 years provides a more dynamic process for the assessment of risks than a single time point analysis[15,19,20].

In summary, *H. pylori* infection and variants in IL-8-251 or MIF-173 polymorphisms influence the occurrence of SCAG and IM. Because of the high prevalence of *H. pylori* infection, antibiotic resistance, and some potential drawbacks associated with *H. pylori* eradication therapy (e.g. reflux esophagitis), our study may provide a reasonable basis for therapeutic decisions even at the early stage of GC.

COMMENTS

Background

Atrophic gastritis and intestinal metaplasia are two important precursory lesions of intestinal type gastric cancer (GC), except for factors of *Helicobacter pylori* (*H. pylori*). Host gene polymorphisms also play a very important role in the development of GC.

Research frontiers

To date, a few studies are available on the relation between gene polymorphisms of inflammatory cytokines and risk of atrophy and intestinal metaplasia (IM).

Innovations and breakthroughs

In this study, the authors conducted a prospective study using the data obtained during the 56-mo follow-up (including both gastroscopic and histopathological information). The relation between interleukin-8 (IL-8), migration inhibitory factor (*MIF*) gene polymorphisms and risk of atrophic gastritis and IM was also studied.

Applications

Because of the high prevalence of *H. pylori* infection, antibiotic resistance, and some potential drawbacks in *H. pylori* eradication therapy (e.g. reflux esophagitis), the result of this study may provide some new evidence for the selection of patients infected with *H. pylori* and for the prevention of progression of *H. pylori*-related gastritis.

Terminology

IL-8, a member of Cys-X-Cys (CXC) chemokine family, is an activator and chemoattractant of neutrophils and lymphocytes, thus playing an important role in the development of gastritis and GC. Macrophage MIF, an important activator of T lymphocytes and macrophages, plays a pivotal role in inflammatory and immune diseases. The expression of MIF is increased after *H. pylori* infection and related with histological severity of GC and its precursor.

Peer review

The authors studied the role of different IL-8 and MIF genotypes in the development of precancerous gastric lesions, severe atrophic gastritis or intestinal metaplasia, in a cohort of 372 patients. The study defined *H. pylori*-infected patients at the risk for GC.

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