Cytokine expressions and *H. pylori*-associated gastric mucosal lesion

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Abstract. To determine the role of host genetic factors in *Helicobacter pylori* infection, we examined the relation between gastroduodenal diseases and *IL-1B* polymorphisms in patients with *H. pylori* infection. In addition, we also compared gastric mucosal cytokine levels in those patients. We confirmed the findings that the *IL-1B*-31 C-to-T base transition was inverted in association with the -511 T-to-C base transition. There was no relation regarding to *IL-1B* polymorphisms and clinical outcomes. The gastric mucosal *IL-1B* level of the body of the stomach but not the antrum was significantly different among *IL-1B* genotypes. Furthermore, the *IL-8* levels in the body were also higher in *IL-1B*-511C/C/*IL-1B*-31TT than *H. pylori* negative patients. These findings suggested that *IL-1B* polymorphisms enhance not only *IL-1B* production but also *IL-8* production in the gastric body and may play an important role in the development of atrophic gastritis.

Key words: *H. pylori* infection, interleukin-1 gene polymorphisms, interleukin-1, interleukin-8

Helicobacter pylori has been recognized as a major cause of chronic gastritis,¹ and *H. pylori* infection is an important etiologic factor in the pathogenesis of peptic ulcers.^{2,3} Furthermore, *H. pylori* infection is associated with gastric cancer. The infection increases the risk of duodenal ulcer disease, a condition characterized by high acid secretion and antral predominant gastritis, while also increasing the risk of gastric cancer, a condition characterized by gastric atrophy and hypochlorhydria.⁴ These paradoxical divergent clinical outcomes in *H. pylori* infection have remained poorly understood.

H. pylori infection is histologically characterized by neutrophil infiltration. Moreover, recent evidence suggests that neutrophils have an important role in the development of peptic ulcers. Toxic metabolites and lysosomal enzymes released from neutrophils may be responsible for gastric mucosal injury.^{5,6} Being a potent chemoattractant for and activator of neutrophils, *IL-8* is thought to play a central role in gastric mucosal injury caused by *H. pylori*.⁷

IL-1β is a potent proinflammatory cytokine and is up-regulated in the presence of *H. pylori*.^{8,9} Recently, El-Omar *et al.* reported that *IL-1B* gene polymorphisms (*IL-1B*-511TT) and *IL-1RN**2/2* are associated with an increased risk of hypochlorhydria and gastric cancer.¹⁰ Machado *et al.* also reported that carriers of *IL-1B*-511T and *IL-1RN**2/2* had increased risk for develop-

ing intestinal-type gastric cancer with odds ratios of 2.7 and 3.1, respectively.¹¹

To determine the role of host genetic factors in *H. pylori* infection, we examined the relation between *IL-1B* polymorphisms and gastroduodenal diseases in patients with *H. pylori* infection. We confirmed the findings that the *IL-1B*-31 C-to-T base transition was inverted in association with the -511 T-to-C base transition¹² (Table 1). There was no relation regarding to *IL-1B* polymorphisms and clinical outcomes (Table 2). Gastric mucosal *IL-1β* levels tended to be higher in *H. pylori* positive patients but not significantly. In contrast, gastric mucosal *IL-8* levels were significantly higher in both the antrum ($p = 0.0116$) and body ($p = 0.0263$) of the stomach from *H. pylori* positive patients than in *H. pylori* negative patients. Furthermore, we found a significant association between *IL-1B* polymorphisms and *IL-1β* production (data not shown). The gastric mucosal *IL-1β* level of the body but not the antrum was significantly higher in genotype *IL-1B*-511CC-*IL-1B*31TT than *H. pylori* negative patients ($p > 0.001$). The present findings which showed gastric mucosal *IL-1B* levels were higher in the *IL-1B*-511C genotype do not agree with those studies that reported that *IL-1B*-511T homozygotes had increased risk for gastric cancer.^{10,11} However, conflicting findings were reported regarding an association of *IL-1B* polymorphisms with gastric cancer risk in Japanese. Kato *et al.* reported that there

Table 1 IL-1B (-31/-511) Genotype in Japanese Patients and Controls

	CC/CC	CC/TT	TT/CC	CT/CT
31/-511	1/86(1.1%)	20/86(23.3%)	20/86(23.3%)	48/86(55.8%)

Table 2 IL-1 β Gene Polymorphism (-31/-511) and Gastroduodenal Diseases

Disease	CC/CC	CC/TT	TT/CC	CT/CT
Gastric ulcer	1	3	3	2
Duodenal ulcer	0	2	4	4
Gastro-duodenal ulcer	0	0	0	4
Chronic gastritis	0	4	6	8
Gastric cancer	0	1	2	1
Gastric adenoma	0	0	0	3

were no associations between *IL-1B* specific genotypes with gastric cancer in the Japanese population.^{13,14} Furthermore, they reported that *IL-1B*-511C may be important for the mucosal atrophy of the stomach. This discrepancy may be explained by haplotype frequencies between *IL-1B* and *IL-1RN* gene polymorphisms among the Japanese population and a Western country population. Santtila *et al.* found that the IL-1RN*2 allele strongly increased *in vitro* production of IL-1B.¹⁴ Machado also reported that the frequency of the IL-1RN*2 allele in controls and gastric cancer are 20/220, 24/152, respectively.¹¹ In contrast, Hamajima *et al.* reported that the frequency of IL-1RN2*2* was one of 241 cases in Japanese.¹² *IL-1RN* may play a more important role in the development of gastric cancer in Western countries.

We found that the IL-8 levels in the body were also higher in *IL-1B*-511C/C than in *H. pylori* negative patients ($p < 0.003$). The mechanisms underlying the association between the *IL-1B* polymorphism and enhanced IL-8 production are unknown. Yamaoka *et al.* reported that the antral and the corporal musosal levels of IL-8 correlated with levels of IL-1B.¹⁵ Suppression of acid secretion leads to *H. pylori* re-distribution to the corpus and gastric atrophy.²⁴ Since IL-1B is a potent inhibitor of gastric acid secretion, IL-1 may enhance IL-8 production through re-distribution of *H. pylori*.

A recent prospective study by Uemura *et al.* showed that gastric cancer developed in 36 of 1246 *H. pylori*-infected patients but in none of the 280 uninfected patients.¹⁶ They also reported that among patients with *H. pylori* infection, those with sever gastric atrophy, corpus-predominant gastritis, and intesitinal metaplasia were at higher risk for gastric cancer.

These findings suggested that *IL-1B* polymorphisms enhance not only IL-1-B production but also IL-8 production in the gastric body and may play an important role for the development of atrophic gastritis.

References

1. Marshall BJ, Warren JR: Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. *Lancet* 1984; i: 1311-5
2. Blaser MJ: Hypothesis on the pathogenesis and natural history of *Helicobacter pylori*-induced inflammation. *Gastroenterology* 1992; 102: 720-7
3. Dixon MF: *Helicobacter pylori* and peptic ulceration: Histopathologic aspects. *J Gastroenterol Hepatol* 1991; 6: 125-30
4. McColl KE, El-Omar E: *Helicobacter pylori* and disturbance of gastric funtion associated with duodenal ulcer disease and gastric cancer. *Scand J Gastroenterol suppl* 1996; 215: 32-37
5. Suzuki M, Miura S, Suematsu M, *et al*: *Helicobacter pylori*-associated ammonia production enhances neutrophil-dependent gastric mucosal cell injury. *Am J Physiol* 1992; 263: G719-25
6. Murakami M, Asagoe K, Dekigai H, Kusaka S, Saita H, Kita T: Products of neutrophil metabolism increase ammonia-induced gastric mucosal damage. *Dig Dis Sci* 1995; 40: 268-73
7. Crabtree JE: The role of cytokines in *Helicobacter pylori* infection. *Mucosal Immunol. Update* 1994; 2: 5-7
8. Noach LA, Bosma NB, Jansen J, Hoek FJ, van Deventer SJ, Tytgat GN: Mucosal tumor necrosis factor-alpha, interleukin-1 beta, and interleukin-8 production in patients with *Helicobacter pylori* infection. *Scand J Gastroenterol* 1994; 29: 425-429
9. Peek RM, Miller GG, Tham KT, Perez-Perez GI, Zhao X, Atherton JC, *et al*: Heightened inflammatory response and cytokine expression *in vivo* to cagA+ *Helicobacter pylori* strains. *Lab Invest* 1995; 71: 760-770
10. El-Omar EM, Carrington M, Chow W-H, McColl KEL, Bream JH, Young HA, Herrera J, Lissowska J, Yuan C-C, Rothman N, Lanyon G, Martin M, Fraumeni JF Jr, Rabkin CS: Interleukin-1 polymorphisms associated with increased risk of gastric cancer. *Nature* 2000; 404: 398-402
11. Machado JC, Pharoah P, Sousa S, Carvalho R, Oliveira C, Figueiredo C, *et al*: Interleukin 1B and interleukin 1RN polymorphisms are associated with increased risk of gastric carcinoma. *Gastroenterology* 2001; 121: 823-829
12. Hamajima N, Matsuo K, Saito T, Tajima K, Okuma K, Yamao K, *et al*: Interleukin 1 polymorphisms, Lifestyle factors, and *Helicobacter pylori* infection. *Jpn J Cancer Res*
13. Kato S, Onda M, Yamada S, Matsuda N, Tokunaga A, Matsukura N: Association of interleukin-1B genetic polymorphism and gastric cancer risk in Japanese. *J Gastroenterol* 2001; 36: 696-699
14. Santtila S, Savinainen K, Hurme M: Presence of IL-1RA allele 2 (IL1RN*2) is associated with enhanced IL-1B production *in vitro*. *Scand J Immunol* 1998; 47: 195-198
15. Yamaoka Y, Kodama T, Kita M, Imanishi M, Kashima K, Graham DY: Relationship between clinical presentation, *Helicobacter pylori*, interleukin 1B and 8 production, and cagA status. *Gut* 1999; 45: 804-811
16. Uemura N, Okamoto S, Yamamoto S, Matsumura N, Yamaguchi S, Yamakido M, *et al*: *Helicobacter pylori* infection and the development of gastric cancer. *N Engl J Med* 2001; 345: 784-789