

## EDITORIALS

### Gastric Cancer and *H. pylori*: Host Genetics Open the Way

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Gastric cancer remains a major health problem with an estimated 21,700 new diagnoses in the United States in 2001 and 12,800 patients expected to die in the same year.<sup>1</sup> On a global scale, gastric cancer remains the world's second most common malignancy, having only been overtaken by lung cancer in the late 1980s.<sup>2</sup> There is substantial international variation in gastric cancer incidence with the highest rates reported from Japan and eastern Asia. Other high incidence areas include Eastern Europe and parts of Latin America, whereas Western Europe and the United States generally have low incidence rates.<sup>2</sup> The discovery of *Helicobacter pylori* in the early 1980s has proved a turning point in understanding the pathogenesis of this malignancy. Although the link between *H. pylori* and peptic ulcer disease was established soon after successful culture of the bacterium, the association with gastric cancer lagged almost a decade before credible evidence was presented. The major reason for this delay was inability to demonstrate the presence of active infection in gastric tissue of cancer patients. A major advance in this field came with the recognition that chronic *H. pylori* infection induces physiologic and morphologic changes within the gastric milieu that increase the risk of neoplastic transformation. It is widely accepted that chronic *H. pylori* infection induces hypochlorhydria and gastric atrophy, both of which are precursors of gastric cancer. Presence of the infection in the final stages of this cascade is therefore not necessary for cancer to develop because irreversible damage had already occurred.

The major paradox in *H. pylori* research has been the apparent association of the infection with divergent and mutually exclusive clinical outcomes. Thus the infection increases the risk of duodenal ulcer disease, a condition characterized by antral-predominant gastritis, high acid secretion, and absence of corpus atrophy, while also increasing the risk of gastric cancer, a condition characterized by corpus-predominant gastritis, gastric atrophy, and hypochlorhydria.<sup>3</sup> Yet the majority of infected individuals lie somewhere between these 2 extreme phenotypes, and they develop no significant clinical disease. The reasons for these divergent clinical outcomes have remained poorly understood. There is no doubt that *H.*

*pylori* virulence factors play a part in this process, because the virulent strains are associated with more aggressive tissue damage and increased risk of an extreme clinical outcome. On their own, however, bacterial virulence factors have failed to explain why the ulcer or the gastric cancer phenotype develops. This highlighted the need to explore host genetic factors as determinants of clinical outcome of the infection, including gastric cancer.

The pursuit of potential candidate genes in the context of *H. pylori*-induced gastric cancer had to stem from a profound understanding of gastric physiology and how this is disrupted by the infection. A key concept that has emerged during the 1990s is the 2-way interaction between acid secretion and *H. pylori*-induced gastritis.<sup>4</sup> Thus acid secretory capacity is crucial in determining the distribution and natural history of *H. pylori* infection,<sup>5</sup> while pharmacologic inhibition of acid secretion leads to a shift in the distribution of gastritis from antral to corpus-predominant, with the risk of development of gastric atrophy.<sup>6</sup> The key components in this process are acid secretion, *H. pylori*, and inflammation, and a gene product that interacted with all 3 was clearly a prime candidate to study.

The interleukin (IL)-1 $\beta$  gene satisfied the above criteria very amply: it is up-regulated by the infection, it is profoundly proinflammatory, and it is the most powerful acid inhibitor known.<sup>7</sup> Fortunately, the *IL-1* gene cluster (*IL-1B* encoding IL-1 $\beta$  and *IL-1RN*, encoding its naturally occurring receptor antagonist) also had a number of functionally relevant polymorphisms that could be correlated with high or low IL-1 $\beta$  production, enabling an association study with a case-control design. Our group studied the correlation of proinflammatory IL-1 $\beta$  genotypes (2 polymorphisms in the *IL-1B* and *IL-1RN* genes) with hypochlorhydria and gastric atrophy in a white population of gastric cancer relatives. These relatives are known to be at increased risk of developing the same cancer and have a higher prevalence of the precancerous abnormalities, but only in the presence of *H. pylori* infection.<sup>8</sup> We found that the high IL-1 $\beta$  genetic markers significantly increase the risk of these precancerous conditions. In a logistic regression model including both genotypes, the estimated age-adjusted odds ratios for *IL-1B-511T+/-31C+* and *IL-1RN\*2/\*2* were 7.5 (95% confidence interval [CI], 1.8-31) and 2.1 (95% CI, 0.7-6.3), respectively.<sup>9</sup> We proceeded to examine

the association between the same IL-1 $\beta$  genetic polymorphisms and gastric cancer itself using another white case-control study comprising 366 gastric cancer patients and 429 population controls. We confirmed the same positive association between these genotypes and gastric cancer. In a logistic regression model including both genotypes, the estimated odds ratios for *IL-1B-511T+/-31C+* and *IL-1RN\*2/\*2* were 1.6 (95% CI, 1.2–2.2) and 2.9 (95% CI, 1.9–4.4), respectively.<sup>9</sup> We have since confirmed the positive association of the same markers with gastric cancer in another white population from the United States.<sup>10</sup>

In this issue of GASTROENTEROLOGY, Machado et al.<sup>11</sup> have produced the first independent confirmation of the role of *IL-1* genetic markers in gastric cancer in a white population. Their case/control study was set in Portugal, a country with a higher incidence of gastric cancer compared with the rest of Western Europe or the United States. Their data confirm that the same proinflammatory *IL-1* gene cluster polymorphisms increase the risk of intestinal type gastric cancer. The odds ratios they report are very similar to the ones reported by our group (2.7 for *IL-1B-511T+*, and 3.1 for *IL-1RN\*2\*2*) and suggest that these markers impart only a modest risk, as would be expected of polygenic and complex human diseases. The independent confirmation of the role of *IL-1* in gastric cancer is a significant step forward and adds further confidence in the role of host genetic factors in the pathogenesis of this disease.

Machado et al. found that the association between proinflammatory *IL-1* genotypes and gastric cancer was confined to the intestinal type with only a nonsignificant risk being shown for the diffuse type. The investigators speculate that this may exclude a role for IL-1 $\beta$  in diffuse gastric cancer, because this type does not progress through the classical gastritis-atrophy-intestinal metaplasia-dysplasia-carcinoma sequence. Although this may be a valid explanation, it would be wise to exercise some caution before this interpretation is accepted for a variety of reasons. First, the number of diffuse gastric cancer cases studied was very small ( $n = 37$ ), and findings could certainly differ if the sample size were increased. In our study, we had double the number of diffuse cases and found a positive association. Secondly, one could argue that IL-1 $\beta$  could legitimately be considered a candidate gene for this subtype as it is for the intestinal type of gastric cancer. Diffuse gastric cancer arises in the setting of severe corpus gastritis, with or without atrophy, and progresses to cancer without the intestinal metaplasia or dysplasia stages. It is preceded, however, by 2 key abnormalities, namely severe gastritis and hypochlorhydria, which could clearly be induced by an excessive IL-1 $\beta$  and

other proinflammatory cytokine responses to *H. pylori*. Diffuse gastric cancer has the same association with *H. pylori* infection as intestinal cancer, and because the initial response is inflammation, it is reasonable to argue that the cytokine could be involved in both pathways at the outset. Why the 2 pathways diverge remains unclear, but it is likely that other genetic and environmental factors will contribute differentially to the histogenesis of the subtypes.

In addition to the independent confirmation of the role of *IL-1* markers in gastric cancer by Machado et al., other workers have recently confirmed the association with precursors of gastric cancer, namely hypochlorhydria and gastric atrophy. Furuta et al.<sup>12</sup> showed that the proinflammatory *IL-1B-511T+* genotype increased the risk of both conditions in a Japanese population. Furthermore, the same genotypes were associated with a reduced recurrence rate for duodenal ulcers with increasing age, suggesting that the mechanism involves a progressive loss of acid secretory capacity induced by the severe corpus inflammation and progressive gastric atrophy. The association of the *IL-1B* gene polymorphism with similar outcomes of *H. pylori* infection across geographic and ethnic differences underscores the key role played by IL-1 $\beta$  in the cascade of events leading to gastric cancer.

Although IL-1 $\beta$  was the perfect candidate gene, other genes involved in the *H. pylori*-induced gastritis cascade are also legitimate targets. We have recently confirmed a positive but weaker role for polymorphisms in the *TNF-A* gene that correlate with high tumor necrosis factor (TNF)- $\alpha$  levels.<sup>10</sup> The TNF- $\alpha$  polymorphism increases the risk of gastric cancer and its precursors in a similar fashion to the IL-1 $\beta$  polymorphisms. This proinflammatory cytokine is also up-regulated in *H. pylori* infection and has acid inhibitory properties, albeit weaker than IL-1 $\beta$ . It is very likely that several other polymorphic genes, encoding proinflammatory and anti-inflammatory mediators, will also contribute to the host genetic constitution that determines the outcome to *H. pylori* infection and risk of gastric cancer.

It is useful to have a working hypothesis for the role of cytokine gene polymorphisms in *H. pylori*-induced gastric cancer. It seems that the effect of these polymorphisms operates early in the disease process and requires the presence of *H. pylori* infection. When *H. pylori* infection challenges the gastric mucosa, a vigorous inflammatory response with a high IL-1 $\beta$ /TNF- $\alpha$  component may seem to be beneficial in driving the infection out, but concomitant inhibition of acid secretion may allow the infection to extend its colonization and damaging inflammation to the corpus mucosa, an area that is usually well protected by secretion of acid. A decreased flow of

acid may also undermine attempts to flush out mutagenic and genotoxic byproducts of inflammation, causing further damage to the mucosa and the risk of DNA damage. More inflammation in the corpus leads to sustained inhibition of acid secretion and a vicious cycle that accelerates glandular loss and onset of gastric atrophy. It is apparent that this vicious cycle ultimately succeeds in driving the infection out, but at a very high price for the host. The hypochlorhydric milieu is ideal for growth of non-*H. pylori* bacteria, some of which will no doubt contribute to further damage to the mucosa<sup>13</sup> and production of carcinogenic N-nitroso-compounds.

A proinflammatory host genetic makeup therefore facilitates the development of a hypochlorhydric, atrophic phenotype that increases the risk of gastric cancer, but the ultimate neoplastic transformation is clearly dependent on many other genetic and environmental factors. Progression of severe gastritis or atrophy towards cancer depends on other components of the host genetic constitution acting epistatically, as well as by dietary and other factors in the environment. For example, a high intake of fresh fruits and vegetables containing antioxidants such as vitamin C may retard the progression of atrophy, whereas smoking and a high salt intake may accelerate it.

The accumulating data on the role of IL-1 gene markers raise important issues about the role of host genetic factors in predicting the clinical outcome to *H. pylori* infection. The study of these host genetic factors will greatly enhance our understanding of the pathogenesis of gastric cancer. Furthermore, it is apparent that *H. pylori*-associated gastric carcinogenesis is a superb model of gene-environment interaction. This model is relatively simple and all its components are amenable to hypothesis-driven research. It will offer great insight into the pathogenesis of many other human cancers whose etiology is far more complex. The pursuit of host genetic factors that determine the outcome to this common infection will pave the way to unraveling other human diseases in which chronic inflammation plays a major role.

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## References

- Greenlee RT, Hill-Harmon MB, Taylor Murray T, Thun M. Cancer Statistics, 2001. *CA Cancer J Clin* 2001;51:15-36.
- Parkin DM, Pisani P, Ferlay J. Estimates of the worldwide incidence of 25 major cancers in 1990. *Int J Cancer* 1999;80:827-841.
- McCull KE, El-Omar E. *Helicobacter pylori* and disturbance of gastric function associated with duodenal ulcer disease and gastric cancer. *Scand J Gastroenterol Suppl* 1996;215:32-37.
- McCull KE, El-Omar E, Gillen D. *Helicobacter pylori* gastritis and gastric physiology. *Gastroenterol Clin North Am* 2000;29:687-703.
- Lee A, Dixon MF, Danon SJ, Kuipers E, Megraud F, Larsson H, Mellgard B. Local acid production and *Helicobacter pylori*: a unifying hypothesis of gastroduodenal disease. *Eur J Gastroenterol Hepatol* 1995;7:461-465.
- Kuipers EJ, Lundell L, Klinkenberg-Knol EC, Havu N, Festen HP, Liedman B, Lamers CB, Jansen JB, Dalenback J, Snel P, Nelis GF, Meuwissen SG. Atrophic gastritis and *Helicobacter pylori* infection in patients with reflux esophagitis treated with omeprazole or fundoplication. *N Engl J Med* 1996;334:1018-1022.
- El-Omar EM. The importance of interleukin 1beta in *Helicobacter pylori* associated disease. *Gut* 2001;48:743-747.
- El-Omar EM, Oien K, Murray LS, El Nujumi A, Wirz A, Gillen D, Williams C, Fullarton G, McCull KE. Increased prevalence of pre-cancerous changes in relatives of gastric cancer patients: critical role of *H. pylori*. *Gastroenterology* 2000;118:22-30.
- El-Omar EM, Carrington M, Chow WH, McCull KE, Bream JH, Young HA, Herrera J, Lissowska J, Yuan CC, 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.
- El-Omar EM, Chow WH, Gammon MD, Vaughan TL, Risch HA, Fraumeni JF Jr. Pro-inflammatory genotypes of IL-1 $\beta$ , TNF- $\alpha$ , and IL-10 increase risk of distal gastric cancer but not of cardia or esophageal adenocarcinoma. *Gastroenterology* 2001;120(suppl 1):A86.
- Machado JC, Pharoah P, Sousa S, Carvalho R, Oliveira C, Figueiredo C, Amorim A, Seruca R, Caldas C, Carneiro F, Sobrinho-Simoes M. Interleukin 1B and interleukin 1RN polymorphisms are associated with increased risk of gastric carcinoma. *Gastroenterology* 2001;121:823-829.
- Furuta T, Shirai N, Xiao F, Takashima M, Sugimura H. Effect of genotypic differences in interleukin-beta on gastric acid secretion, gastric atrophy, and recurrence of peptic ulcer disease. *Gastroenterology* 2001;120(suppl 1):A649.
- Sanduleanu S, Jonkers D, De Bruine A, Hameeteman W, Stockbrugger RW. Double gastric infection with *Helicobacter pylori* and non-*Helicobacter pylori* bacteria during acid-suppressive therapy: increase of pro-inflammatory cytokines and development of atrophic gastritis. *Aliment Pharmacol Ther* 2001;15:1163-1175.

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