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# Genetic factors determining the host response to *Helicobacter pylori*

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## INTRODUCTION

The strongest evidence that *H. pylori* infection is the cause of peptic ulcer is that treatment with antibiotics as the only regimen, is not only effective for the clearance and eradication of the infection, but more importantly for the healing of the ulcer or the remissi on of gastric lymphoma. However, it is still a matter of controversy and research as to why only a minority of people develop gastric ulcer, gastric lymphoma, gastric cancer or duodenal ulcer when half of the world's population is infected by *H. pylori*. Since bacteria and host form an interactive unit, the pathogenesis of gastric pathology is dete rmined and probably follows the same principles of any infectious disease.

First, the bacteria have to undergo evolutionary changes that are needed to survive the host response. This explains to a certain extent the highly diverse virulence of *H. pylori* strains which undoubtedly contribute to determining the development of disease[1].

Second, host factors, such as the age at which the host acquires the infection, appear to determine the outcome of the interaction between *H. pylori* and the host. It is well known that gastric and duodenal ulcer rates increase with age. The presence of a genetic predisposition is also important. The relative risk of developing gastric, duodenal ulcer or duodenitis in patients with a family history of gastric pathology, is higher than in patients without familial occurren ce. More convincingly still, several studies have established that the prevalence of peptic ulcer is higher in monozygotic twins than in dizygotic twins. Also, the concordance rates for *H. pylori* infection among pairs of twins reared apart is higher for monozygotic than for dizygotic twins[2] .

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Experimental animal models have provided evidence that the host response is an important determinant in the severity of gastritis[3].

## THE BIOLOGICAL BASIS OF THE IMMUNE RESPONSE

Therefore, it is justifiable to look for the biological basis of the susceptibility to acquire the infection and which determines the pattern of disease and severity. The host response is important for the immune defense against a variety of infections and the protection of the organism against the invasion of foreign material.

It is important to recognize that immunity to infection is mediated by two systems, the innate and the acquired. Innate immunity provides a rapid antimicrobial host defense. Innate immunity is the bridge between the recognition of an invading microorganisms and the mounting of an efficient acquired and adaptive immune reaction that should overcome the infection. At the first contact of bacteria and host, *Helicobacter* Lipopolysaccharide (LPS) activate cells of the innate immune system. The host defense systems are mobilized to eliminate the infection. LPS of many *H. pylori* strains express Lewis antigens (Lex, Ley, Lea, Leb) which are similar to the antigens expressed by gastric epithelial cells of the host. Recent studies in *H. pylori* strains isolated from Asian peptic ulcer patients have shown to express more Lewis antigens than strains from non-ulcer dyspepsia patients[4]. Since it is now known that Lewis antigens are involved in adhesion and colonization the increased adherence may lead to an increased bacterial burden. This will enhance the cross talk between the *H. pylori* and the host and leads to the activation of the transcription factor NF-κB and host signal transduction pathways. IL-8 production is enhanced and results in the characteristic neutrophil infiltr ation and inflammation of *H. pylori* gastritis. *H. pylori* induces also *IL-12* which in turn elicits interferon-gamma INFγ production. During the induction of cell-mediated immunity, T lymph ocytes expressing IFNγ and TNFα are generated. Macrophages are recruited and become activated. It is now known that *IL-12* also facilitates the development of T helper type 1 (Th1) lymphocytes required for protection against the bacteria [5]. In principle, the Th1 response is a normal adaptive immune response, however, when this response is too strong it will produce a severe chronic inflammation. In the stomach, locally produced IL-1β is an important mediator of hypochlorhydria

since IL-1β inhibits gastric acid and pepsinogen secretion . The levels of IL-1β in cultured antral biopsy specimens are significantly higher in *H. pylori* positive patients than in individuals with negative cultures for *H. pylori* with normal antral mucosa. There is evidence that other cytokines, such as TNF, are also increased in *H. pylori* positive patients.

## THE GENETIC CONTROL OF THE IMMUNE RESPONSE

During the inflammatory response a multitude of new genes encoding proinflammatory cytokines such as IL-1α, IL-1β, TNFα, and LTα as well as other proteins with pro-or anti-inflammatory properties are induced. Genetic control of the IL-1 family of cytokines and *TNF* appears to regulate the production and transcription of the respective cytokines. In healthy individuals, significant inter-individual variations were found in *in vitro* production of IL-1 proteins. This has been interpreted as inherited inter-individual differences.

The genes controlling the innate and the acquired immune response are different and probably work in a complementary way. Little is known of the genetic control of the innate immune response. With respect to the acquired immune response it is known that the *IL-1*A, *IL-1*B and *IL-1RN* genes are clustered on the long arm of human chromosome 2. Several functional polymorphisms have been described in these genes. This strongly suggests that individuals who produce high amounts of *IL-1*β and lower amounts of the IL-1ra have difficulty in controlling inflammation. Preliminary results of IL-1 gene polymorphisms in duodenal ulcer patients have shown that the simultaneous carriage of *IL-1*B + 3953 allele 2 and *IL-1RN* allele 2, is an independent factor associated with reduced risk of bleeding duodenal ulcers[6]. In a recent study supporting the role of the interleukin-1 gene cluster in the progression to disease, E1-Omar and co-workers[7] have reported the association of specific interleukin-1 gene polymorphisms with increased risk of gastric cancer. According to these authors, carriage of *IL-1B*-31 allele 2 and *IL-1RN** 2.2 homozygosity increase both the likelihood of a chronic hypochlorhydric response to *H. pylori* infection and the risk of gastric cancer, presumably by altering *IL-1*β levels in the stomach. *IL-1*B+3953 allele 2 homozygotes seemed to play a protective role in gastric cancer, although the effect did not reach statistical significance.

The localization of the tandemly arranged *TNF* and *LTA* genes, encoding respectively *TNF* and LTα in the central region of the MHC at the short arm of chromosome 6 (6p21.3) has prompted interest in the study of their contribution to diverse inflammatory processes. Recent studies have found that polymorphi sms in the *TNF* and *LTA* genes are associated with peptic ulcers. Recently, the *TNF*-308 polymorphism located in the promoter region of the *TNFA* gene has been found associated with susceptibility to the development of duodenal ulcer[8]. Thus, *H. pylori* positive individuals with the *TNFA*-308*G/G* genotype appeared to have a higher risk for the development of duodenal ulcer than individuals with the *TNFA*-308*G/A* or *A/A* genotypes.

## CONCLUSION

The data suggest that the normal physiological control of the gastric secretory function and the control related to the pathogenesis of *H. pylori* associated diseases, to a certain extent are dependent on the genetic control of the inflammatory response. It is clear that more work needs to be done to clarify the role of the genetic control. Studies of the interaction between virulent *H. pylori* strains and the genetic factors as described above need to be addressed.

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