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Helicobacter Pylori: Revisiting the Role of Host Genetics in Susceptibility to Infectious Diseases

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Abstract

Infectious diseases continue to be the leading reason of mortality across the globe.It has been put forward recently that host factors plays a key role in disease pathogenesis apart from the contributing pathogens. Helicobacter pylori is the major cause of inflammatory gastroduodenal and neoplastic diseases in human stomach. The deadly gastric pathogen infects more than half the world population and is of major concern especially in developing country like India. In this article we have briefly reviewed the different virulence factors of Helicobacter pylori and analyzed the role of host genetics in susceptibility to infectious diseases, considering Helicobacter pylori as an organism of major focus.

Keywords: Pathogen; Infection; Gastric; Helicobacter; Host

Introduction

Infectious diseases prove to be a major cause of mortality throughout the whole world especially in the developing and underdeveloped countries. These infective agents include a wide variety of pathogens, including virus, parasites and a wide variety of bacteria. Host defense against these intercellular and intracellular pathogens depends on effective cell mediated as well as humoral immune response which is again mediated by a wide variety of cytokines and chemokines. (Ottenhoff et al 2002).

Until recently, it was considered that pathogens are the sole contributors to

infectious diseases. However, recent evidence suggests that the host factors play a significant role in the various aspects of disease manifestation following infection. Host genetic factors explain, at least in part, why some people resist infection more successfully than others. Rare gene disruptions cause fatal vulnerability to specific microbes(Kwiatkowski, 2000), but more subtle differences are common and arise from minor variation in many genes. Recent advances in the Human Genome Project have made it possible to screen the whole genome for genetic factors that determine susceptibility to several infectious diseases such AIDS, malaria, and tuberculosis(Kwiatkowski, 2000). This has helped to identify critical pathways of host defense and generate novel strategies for disease prevention.

To what extent does the host genetic make up determine the different ways that one responds to the same infectious agent? Epidemiological analysis of the genetic component is confounded by environmental factors that cause familial clustering and is further complicated by the many different genes that are likely to be involved (Hill, 1998; Segal and Hill, 2003). Nevertheless, there is compelling evidence for a genetic component, including twin studies of tuberculosis, leprosy, malaria and Helicobacter pylori infection and a large survey that found that individuals adopted in childhood had a markedly increased risk of death from infection if a biological parent had died prematurely of infection (Hill, 1998). Unraveling the genetic and environmental determinants of infectious disease has been made possible with the increasing knowledge about the human genome. The human genome sequence provides the starting point for a systematic analysis of human genetic diversity (www.wellcome.ac.uk/en/genome) with respect to common infectious diseases.

Helicobacter pylori is a gastric pathogen that chronically infects more than half the world population. It is the major cause of inflammatory gastroduodenal as well as neoplastic diseases of the stomach. (Parsonnet, 1999) H. pylori infection and associated gastric diseases are common in developing countries including India. (Graham DY, 1991) The majority of the infected individuals do not develop any clinically apparent disease but there is compelling evidence that 6-20% of the infection results in duodenal ulceration and a smaller proportion are associated with gastric cancer. (Miwa H, 2002) Genetic predisposition to differential clinical outcomes upon H. pylori infection has been suspected over a long period of time. Thus it has been proposed that the complex interactions between the bacterial and host genetic factors along with the environment play a significant role in determining such differential clinical outcome among various individuals (Go, 2003;Konturek et al, 2002).

Helicobacter pylori: A brief overview

The organism began life as Campylobacter pyloridis (Marshall and Warren, 1984)and then became Campylobacter pylori (Marshall, 1987) and eventually Helicobacter pylori(1989). H. pylori is a Gram-negative bacterium with a number of features that enable it to be classified in the new genus, Helicobacter; the presence of sheathed flagella which give the organism its motility an external glycocalyx and a G+C content of chromosomal DNA of 35-44mol%.As the cultures age, the organism changes its shape from the classic bacilliary form to the coccoid form (Owen et al., 1985).

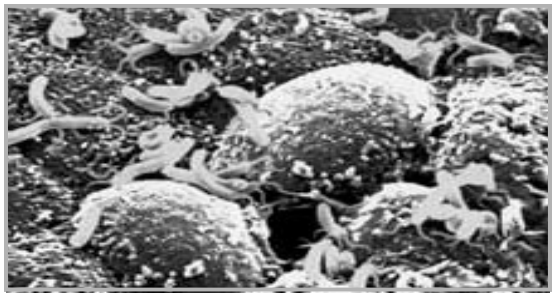


Figure 1: Electron micrograph of *Helicobacter pylori* infection in the human gastric epithelium

Humans appear to be the major host of H. pylori but there is a marked genetic diversity within the genus sufficient to allow classification of the isolates into distinct species. Seven species of Helicobacter have been reported to be associated with the gastric mucosa (Figure 2) of a variety of mammalian species and ten species have been associated with the intestinal mucosa (Eaton, 1993; Hanninen, 1996; Mendes, 1994).

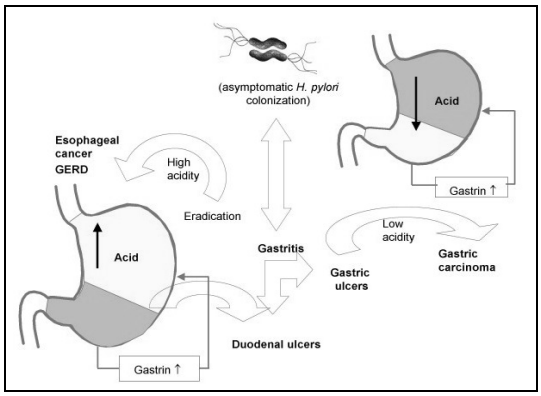


Figure 2: Infection of the gastric mucosa by *Helicobacter pylori* leads to either asymptomatic colonization or development of gastritis. Infection in the antrum leads to hyperacidity, stimulation of the hormone gastrin and subsequently hyperacidity and duodenal ulcer. Infection in the corpus progresses towards gastric ulcer or gastric carcinoma, which involves hypoacidity.

The inhabitation of the gastric mucosa by H. pylori required specialization of properties of this micro-aerophilic bacterial species to enable survival and growth on the gastric surface and within the antral glands. The bacteria had to adapt by gaining the ability to maintain its bioenergetic capacity over an unusual pH range. Although a variety of factors were involved, a major factor was the acquisition of a high level of constitutive urease activity, which is possessed by virtually all the strains of H. pylori (Luck and Seth, 1924; Mobley, 1991).

The H. pylori genome (1.65 Mbp) codes for about 1500 proteins. One of the remarkable features that the genomic analysis has revealed is the extent of molecular mimicry that exists between H. pylori and the human host (Taylor et al., 1992). This might explain the organism's ability to avoid immunological clearance from the host gastric mucosa.

The infection is acquired by oral ingestion of the bacterium and is mainly transmitted within families in early childhood. It seems likely that in industrialized countries, direct transmission from person to person by vomitus, saliva or feces dominates; additional transmission routes such as water may be important in developing countries(Megraud, 1995; Megraud and Broutet, 2000). H. pylori infection in adults is usually chronic and will not heal without specific therapy; on the other hand, spontaneous elimination of the bacterium in childhood is relatively common, aided by the administration of antibiotics(Ernst et al., 2006).

H. pylori Infection: Gastric Ulcer and Duodenal Ulcer

Helicobacter pylori infection induces various upper gastrointestinal diseases including peptic ulcer disease (Nervi et al., 2006). A peptic ulcer is a breach in the gastric or duodenal epithelium associated with acute and chronic inflammation.

Duodenal ulcer is characterized by a high gastric acid output. This is accompanied by a decrease in somatostatin or the D cell population and hypergastrinemia. The latter is thought to be trophic for the parietal cells, thus accounting for the higher acid output in duodenal ulcer patients. The presence of acid is as important as that of the organism in the generation of peptic ulcers, and given that the apical membranes of the gastric cells are relatively acid impermeable, it is likely that the first site of damage is the tight junction between the epithelial cells. This effect may well be due to inflammation. Once the tight junction is damaged allowing acid back diffusion, further damage can result in the back diffusion of the gastric hormone pepsin. The combination of infection, inflammation, acid and pepsin diffusion result in the ulcer development (Modlin, 1998).

Helicobacter pylori Virulence factors

Virulence or pathogenicity is related to the ability of a microbe to induce disease. The large population of rapidly multiplying bacteria ensures a high likelihood that a small population of mutated organisms is generally available that can take advantage of changes in the environment (e.g. progressively severe hypochlorhydria) and thus maintain infection. As a general rule, all bacterial genes serve a function.

The cag Pathogenicity Island (CagA)

The cytotoxin-associated-gene (cag) pathogenicity island (PAI) is an approximately 40-kb cluster of genes in the H. pylori chromosome and is divided into two regions, cagI and cagII. There are at least 14and 16 open reading frames (ORFs) in cagI and cagII, respectively. (Censini et al., 1996). The cag PAI qualifies as an important virulence factor in that its presence is associated with an increased risk of peptic ulcer and gastric cancer.

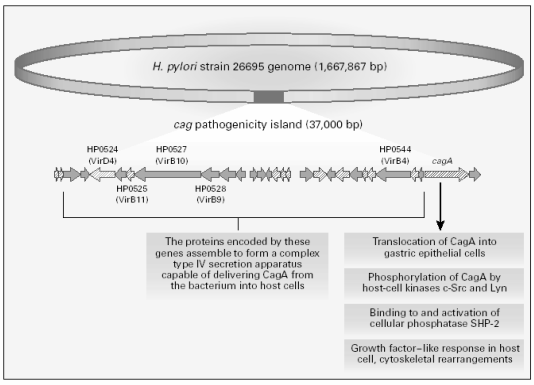


Figure 3: The cag pathogenicity island of *Helicobacter pylori.*

Vac A, the gene for vacuolating cytotoxin

The vacuolating cytotoxin (VacA) of H. pylori was one of the first potential bacterial virulence factor identified, with about 50% of strains expressing VacA with associated eukaryotic cell vacuolation (Lu et al., 2005c).Elegant studies using in vitro models have suggested that VacA may have multiple roles (Kim et al., 2004). One role for VacA might be to supply the organism with nutrients(Gebert et al., 2004). The gastric mucosa is a tight epithelium, which does not permit the diffusion of soluble H. pylori toxins. However, there are studies showing that H. pylori infected gastric mucosa has increased permeability to molecules such as luminal sucrose. The increased permeability may be due to brief opening of tight junctions to permit the passage of polymorphonuclear cells (Goodgame et al., 1997; Graham, 2000). Thus, the only important in vivo effect of VacA is related to its ability to selective increase the permeability of the epithelial paracellular pathway and thus enhances nutrient flow to the bacteria.

Discussion and Conclusion

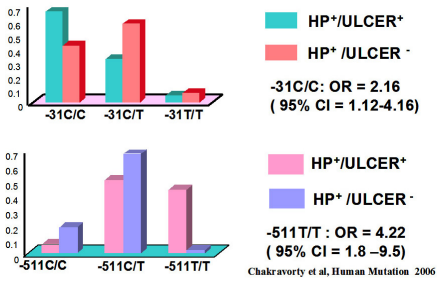
The two gastroduodenal diseases with distinct clinical profiles, resulting from the bacterial infection, are inversely associated with respect to gastric acid secretion-duodenal ulcers tend to be associated with high degree of acid secretion whereas gastric cancers are associated with low acid secretion due to loss of parietal cell mass. (El-Omar, et al., 1997; Hansson, et al., 1996; Troost, et al., 2003) Host factors related to gastric acid secretory pathways thus seem to play an important role in the distinct pathogenesis of the two H. pylori mediated diseases. The immune system also plays an important role in the pathogenesis of gastroduodenal diseases by regulating the nature and intensity of the inflammatory response to H. pylori infection.

The pro inflammatory cytokines Interleukin-1, and TNFα expressed in the gastric mucosa, play a key role in initiating and amplifying the immune-inflammatory response to H. pylori infection. (El-Omar, et al., 2000a) The Interleukin-1 gene cluster on chromosome 2q contains three related genes within a 430 Kb region, IL1A, IL1B

and IL1RN, which code for IL1A, IL1B and the endogenous receptor antagonist IL1-ra, respectively (Dinarello, 1996).

IL1B, a potent inhibitor of gastric acid, is speculated to be responsible for the modulations in the gastric milieu upon H. pylori infection. (Beales and Calam, 1998; Wallace, et al., 1991) Three biallelic polymorphisms have been reported in IL1B, all representing C>T base transition at positions -511, -31 and +3954 from the transcriptional initiation site. (Di Giovine, et al., 1992; Stokkers, et al., 1998). These polymorphisms have been shown to significantly affect gastric mucosal IL1B production in response to H. pylori infection. (Hwang, et al., 2002). The effect of these polymorphisms is therefore most likely mediated through the regulation of IL1B expression.

A case control study with 310 individuals was previously reported from Eastern India (Chakravorty et al, 2006) that depicted significant differences in genotype distribution at the IL1B -511 and -31 loci between the two groups of H. pylori positive individuals with and without duodenal ulcer. Among the H. pylori infected individuals, those with duodenal ulcers had a significantly higher frequency of the -511T/T homozygotes with an age and sex adjusted odds ratio of 4.22 (95% CI 1.8-9.5) and -31 C/C homozygotes with an odds ratio of 2.16 (95% CI 1.12-4.16), when compared with individuals with normal mucosa (Figure 4). The differences in genotype frequencies between the other two groups without H. pylori infection were statistically non-significant. All these loci were in Hardy-Weinberg equilibrium in all the groups except for the -511 locus of IL1B in the Hp^{-} $Ulcer^{-}$ group ($p<0.02$; data not shown). This was in agreement to the other populations, where it was also found that the IL1B-511 locus was in strong linkage disequilibrium (LD) with IL1B-31.



Haplotype	Hp $^{+}$Ulcer^{+}	Hp $^{+}$Ulcer^{-}	Odds ratio
IL1B -511T/-31C	0.59	0.237	2.47 (1.27-4.80)
IL1B -511C/-31T	0.12	0.413	0.196 (0.08-0.4)

Chakravorty et al, Human Mutation 2006

Figure 4: Comparative studies of Hp $^{+}$Ulcer^{+} and Hp $^{+}$Ulcer^{-} (Chakravorty et al, Human Mutation 2006).

As it has been proposed that the IL1B alleles responsible for increased IL1B production result in enhanced suppression of gastric acid leading to gastric atrophy (El-Omar, et al., 2000b) it is expected that the alleles that down regulate IL1B production and hence induce gastric acid secretion, would be the risk alleles for duodenal ulcer.

Thus, altered expression of IL1B due to a specific polymorphism in its promoter might have its effect on the expression genes that regulate gastric acid secretion. Since earlier findings in of this lab (chakravorty et al,2006) suggest the differential transcriptional role of the IL1B promoter upon the presence of promoter polymorphisms, an on going study further elucidated the role of this differential expression of IL1B upon the actual gastric acid secretion. For this purpose the acid secreting gene gastrin was selected for study. Gastrin is a major physiological regulator of gastric acid secretion. It also has an important trophic or growth-promoting influence on the gastric mucosa. Gastrin is synthesized in G cells, which are located in gastric pits, primarily in the antrum region of the stomach and binds receptors found predominantly on parietal and enterochromaffin cells. A 20-fold downregulation of gastrin upon increasing concentrations of IL1B in the gastric cell line, AGS was observed. The minimal promoter of the gastrin gene was next scanned and an NFKB binding site was reported. It is known that IL1B stimulates various target genes through NFKB pathway. Thus the involvement of NFkB pathway in this gastrin repression by IL1B was looked into. It was found that IL1B induced a dose dependent increase of NFkB activity in AGS cells and blocking of NFKB translocation released the IL1B mediated gastrin repression to about 40 %.This partial release on inhibition of NFKB indicated simultaneous involment of other pathways.

Gastrin is known to be a gene that is regulated by TGF beta pathway. The transcription factors Smad 2/3 are involved in expression of gastrin . It is known that IL1B can down regulate Smad 2/3 by either inhibiting translocation of the complex or by differential phosphorylation that renders the complex inactive. In this case, it was found that upon IL1B treatment in AGS cells,there was decreased nuclear translocation of Smad 2/3 , and upregulation of Smad7. Thus upregulation of smad 7 that inhibits formation of active Smad2/3 complex also participates in repression of gastrin by IL1B.

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