Review

Helicobacter pylori: “A benign fellow traveler or an unwanted inhabitant”

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Abstract

The recent decades have witnessed an alarming increase in the Helicobacter pylori associated diseases worldwide. In spite of this, deficiencies in our knowledge still exist about its exact epidemiology, the optimum method of its diagnosis and indeed about the precise role it plays in gastric carcinogenesis. In the present article, we review the available literature in an attempt to assign a definite role to this unique gastric pathogen. The acquisition of the cag-PAI has undoubtedly altered the understanding of host-microbe interactions, and growing appreciation of other potential determinants viz: vacA, iceA, babA, hrgA etc., may enable us understand the role of this organism and its gradual transition from a commensal to a pathogen.

Keywords: Helicobacter pylori, commensal, pathogen.

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Helicobacter pylori is a human pathogen that causes chronic gastritis, plays a causative role in gastric and duodenal ulcer and is involved in gastric carcinogenesis. Indeed, the bacterium has been classified as a definite (Class I) carcinogen of humans1, 2. This gram negative gastric pathogen is also regarded as being a possible important factor in at least a subset of patients with functional dyspepsia3-5.

Although there appears to be a consensus of opinion that the majority of individuals become infected with H. pylori during early childhood (around 4 years), there are epidemiological differences between children and adults6, 7. In addition to the acquisition of H. pylori during childhood, young children also appear to be at increased risk of re-infection or recrudescence following antimicrobial eradication of the organism8.

Many aspects of this unique pathogen still remain elusive. For example, it is still not clear as to why only a subset of infected individuals present with clinically significant disease and related complications. The spectrum of H. pylori disease is so variable that it is sometimes difficult to predict clinical outcome (Fig 1). The extensive research on its molecular characterization and genomics was
initiated in different parts of the world in order to identify strain specific markers specific for overt manifestations of gastro-duodenal disease, but the equivalent distribution of the genotypes among normal and diseased subjects has not resolved this issue. So, is \textit{H. pylori} a benign fellow traveler that has been associated with humans since ages or is it an unwanted inhabitant of the gut biota? This article attempts to weigh the currently available evidence.

**Historical background of \textit{H. pylori}’s association with humans**

Though \textit{H. pylori} was discovered in 1983, this microbe has been associated with humans since the pre-historic era\textsuperscript{3}. Recent evolutionary studies have shown that \textit{Helicobacter pylori} has likely been a part of the primitive human biota of the gut\textsuperscript{10,11}. The gut of primordial beasts lacked acid secreting cells (parietal cells) in the stomach\textsuperscript{12}. With the evolution of the first acid secreting stomach around 350 million years ago, \textit{Helicobacter pylori} adapted to survive in the acidic milieu via subtle modifications, which allowed them to dwell in the mucus layer close to the mucosal cells, mostly through adaptations including urease production, spiral shape, flagella and microaerophily\textsuperscript{13}. Gradually to utilize the nutrients from the gastric mucosa \textit{H. pylori} acquired genes that induced inflammation, but in spite of this these organisms could not at this time pose any menace, as the life span of the host in which they resided was not long enough\textsuperscript{9,12}. In order to survive the inflammatory process in the gut \textit{Helicobacter pylori} gradually upgraded its mechanisms of survival principally through the elaboration of the enzymes catalase and superoxide dismutase (SOD) which protected the bacterium from the toxic effects of the compounds generated by the phagocytes.

**The transformation of \textit{H. pylori} from a silent bug to a gut pathogen**

About 150-200 years ago \textit{H. pylori} seems to have turned into a pathogen. The reasons for this have been a matter of intense debate. Some experts argue that disease of the upper gastrointestinal...
tract is not because of *Helicobacter pylori*, but it is a result of change in the host physiology that has occurred with civilization probably due to increased intake of processed food, excess meat, etc.\textsuperscript{14,15} and this selection pressure forced its adaptation to its particular ecological niche. It is also possible that it was acquisition of ‘alien’ DNA that altered this relationship\textsuperscript{8}. Other experts argue that gastroduodenal disease cannot be attributed solely either to *Helicobacter pylori* or host factors alone, but it is a complex and well coordinated interplay between *H. pylori*, host genetics, and environmental factors\textsuperscript{16,17}.

During its years as a normal gastric colonizer, *H. pylori* appeared to offer protection against lethal diarrhoeal diseases of the children\textsuperscript{18} by mechanisms such as the heightening of the gastric acid barrier\textsuperscript{19}, priming of the immune response in the stomach\textsuperscript{20}, etc. *H. pylori* is also believed to reduce the risk of gastro-esophageal reflux disease (GERD) and ultimately esophageal cancer in the infected subjects.

**H. pylori** virulence determinants involved in bacterial-epithelial interactions

The most accepted hypothesis underlying the gradual transition advocates the ‘acquisition of the *cag* pathogenicity island’ (*cag*-PAI) as the major evolutionary event that enabled the bacterium to become more virulent. Whole genome sequences of four different strains of *H. pylori* (J99 and ATCC 26695, G27 and HPAG1) isolated from different patients with different disease conditions have provided adequate evidences that *cag*-PAI has different G+C content (35%) in contrast to the rest of the genome (39%) thus justifying its foreign origin\textsuperscript{21}. This ~40kb DNA fragment (of unknown origin) is mainly comprised of 30 open reading frames (ORFs). Seven genes of this ‘pathogenicity island’ (namely *hp0524, hp0525, hp0527, hp0528, hp0530, hp0532* and *hp0544*) are known to share homology to the *vir* family of genes forming a multiprotein complex apparatus of Type IV secretory machinery (T4SS), that in other prokaryotic species, functions as a conduit for export of multimeric...

![Fig 2. An animated view of ‘good’ and ‘bad’ Helicobacters with arsenal of virulence factors](image-url)
proteins and nucleoproteins across both the inner and outer bacterial membrane. The cag-PAI in H. pylori is required for both translocation of bacterial proteins into host cells and induction of proinflammatory cytokine release thus validating the recent findings that the cagA island of genes has biological significance. This may provide an explanation for the observation that Helicobacter pylori with complete cag-PAI are more interactive with the host than those with partial and complete deletions. There are also reports that corroborate various genes of the cag-PAI in H. pylori with disease outcome thus contending that H. pylori with functional cag-PAI could be potentially more harmful to humans than those lacking them. If this indeed is the case, can we assume that pre-historic Helicobacters that existed before the acquisition of the cag-PAI rendered positive health benefits? Besides the cag-pathogenicity island there are other virulence determinants of H. pylori such as vacuolating associated cytotoxin gene A (vacA), flagellins (flaA & flaB), induced by contact with epithelium gene A (iceA), Helicobacter pylori restriction endonuclease replacing gene A (hrgA), and blood group antigen binding adhesin gene (babA) etc., that have been discovered, that influence disease outcome in infected individuals (Fig 2).

Unsolved conundrums

What was the role of these pathogenic markers? Were they potentially functional before the acquisition of cag-PAI or were they non-contributory to the causation of disease? Did the acquisition of this foreign DNA change the behavior of the other genes? In what way did the cag-PAI alter the expression of the toxins released by the above genes? Further research is required to validate or disprove the long-standing stance in favor of the ‘good’ Helicobacter pylori that might have existed in the past era. Though the genes of the cag-pathogenicity island are largely responsible for imparting a virulence trait to Helicobacter pylori they clearly do not tell the complete story. Epidemiological studies have already confirmed vacA, iceA, hrgA, flagellin genes and other virulence determinants as probable risk factors for various gastric diseases independent of the cag-pathogenicity island. Further screening of virulence genes such as vacA, iceA, babA, hrgA, and elucidation of their respective roles pre- and post-acquisition of cag-PAI in pre-historic human gut would enable us to understand the gradual transition of from a commensal to a hostile pathogen.

Conclusion

In conclusion, H. pylori, is a threat that extinguishes more than a million lives each year, and causes substantial distress to almost all infected individuals. In spite of its origins as a benevolent fellow traveler this fascinating spiral organism has now evolved as an undesirable commensal dweller of gastric mucosa. Though there exist studies that favor its positive health benefits are there is substantial evidence that implicates its role as a pathogen in gastro-duodenal disorders.

Conflict of interest: None

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References