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THE VERSATILITY OF *HELICOBACTER PYLORI* IN THE ADAPTATION TO THE HUMAN STOMACH

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A growing body of data indicates that *H. pylori* colonization of human is ancient, which is consistent with its high prevalence, chronicity of carriage, and generally low level of disease, which, when it occurs has only marginal or no effects on host reproductive capacity. All of these phenomena are markers for a relatively benign co-existence, which may include all of the entire spectrum of interactions from parasitism, through commensalism, to symbiosis. Recent studies suggest the emergence of “quasispecies” during prolonged colonization, and the presence of multiple strains colonizing individual hosts. Such observations suggest that concepts of competition between strains and mutualism will be important in understanding the ecology of colonization and its effects on hosts. The presence of particular pathologies in the host may in part be a function of the characteristics of the bacterial population present. At a genomic level, *H. pylori* appears to adapt to changing conditions by point mutation, genomic rearrangement, and horizontal gene transfer; the latter is favored by its natural competence. The ability of *H. pylori* to alter phenotypic properties including superficial Lewis antigen expression and secretion of proinflammatory molecules is evidence of its sensitivity to environmental signals from the host. In such a universe, disease outcomes such as ulceration or neoplasia may be considered as accidents secondary to microbial persistence.

Key words: *ecology, pathogenesis, parasitism, symbiosis*

INTRODUCTION

In attempting to understand why and how *Helicobacter pylori* causes disease, we must consider several facets of its biology. In the 15 years since the discovery of *H. pylori*, much has been learned about its epidemiology and relationship to clinical disease, but to move to a deeper understanding, several fundamental questions must be addressed (*Table 1*).

Table 1. Critical biological features of *H. pylori*

Criterion	<i>H. pylori</i> characteristic
Longevity in primates	ancient
Colonization of individual host	persistent
Population structure	diverse
Generation of variation	on-going

Historical association of H. pylori and the human stomach

First, we must understand the longevity of its relationship with humans. A wide and consistent body of evidence indicates that *H. pylori* is an ancient inhabitant of the human stomach (1). This evidence may be summarized as follows. Stomachs are highly conserved in vertebrate evolution (more than 300 million years), and *Helicobacter*-like organisms are found in stomachs across a broad phylogenetic distribution. *H. pylori* are found nearly universally in the stomachs of non-human primates, and among humans living under the conditions extant for most of human history. *H. pylori* are highly diverse at the genetic level and cause a low level of disease in relation to their prevalence. Such analyses indicate that to study the human stomach, we must understand *H. pylori*, since it has been part of us for a very long time. Similarly, co-evolution of *H. pylori* and the human stomach implies that to know the organism, we must have a detailed understanding of gastric physiology.

Persistence in the gastric milieu

Once *H. pylori* colonization is established in a human host, the organisms persist for decades, if not for the host's entire lifetime. This phenomenon must be regarded as one of the cardinal biological features of *H. pylori*, and distinguishes it from many intestinal pathogens important in human medicine. From a biological standpoint, the need to persist has forced the evolution of the organism into particular directions. For example, parasites that induce highly inflammatory responses either are quickly eliminated or kill their host. Infection with *Streptococcus pneumoniae* is an example of such an organism. Organisms that are persistent often find ways to minimize inflammation, such as by mimicking host antigenic structures. The expression of Lewis antigens by *Schistosoma* species is an example of this phenomenon (2). The recent description of *H. pylori* strains possessing Lewis antigens as part of the

polysaccharide chains of their endotoxin molecules (3—6), a superficial portion of the bacterial cell, is consistent with the latter type of pathogen.

Similarly, persistence in the stomach requires mechanisms for dealing with low pH. Interestingly, *H. pylori* has the means for raising the local pH, by producing urease, for example, resulting in enhanced ammonia production (7, 8), with neutralization of gastric acidity. In contrast, it has the means to lower its environmental pH, by producing N- α methylhistamine, which is a gastric secretagogue (9).

The ability of *H. pylori* to induce inflammation (10—12), but to possess a lipopolysaccharide (LPS) with low endotoxic activity (13—15) and cloaked with Lewis antigenic determinants, appears paradoxical. Similarly, the ability to both raise and lower gastric pH seems hardly necessary. Yet these apparent contradictions point to a greater truth. One hypothesis is that in order to persist in the gastric milieu, *H. pylori* must tightly regulate its interactions with the environment. Such regulation may involve expression of bacterial phenotypes, and/or host characteristics. In mathematical analyses, an unregulated model was not able to achieve steady-state (persistence) (17). *H. pylori* may be thought to be persisting through a finely-tuned, and probably well-balanced interaction with its host.

Diversity of H. pylori

From studies of restriction endonuclease digestion and restriction fragment length polymorphism, among other techniques, it became clear that *H. pylori* strains were highly diverse at the genetic level (18—21). Recent work by Go and colleagues, using multilocus enzyme electrophoresis confirmed these observations, and indicated that *H. pylori* were more diverse than any of the 11 other bacterial pathogens studied (22). The phenomena that contribute to its diversity are summarized in *Table 2*. These may be summarized by noting that at the level of the individual gene, there is extensive variability based on point mutations, that are predominantly non-coding (23), and on mosaic gene structures (24), that suggest recombination among strains. A large chromosomal segment (pathogenicity islands) is present in a subset of strains (25—27); examination of G+C content indicates that it entered the genome after the bulk of the chromosome was defined. *H. pylori* may have mobile DNA, including insertion sequences (25, 26) and plasmids (28—30). Although for certain organisms, such as *E. coli*, for example, gene order on the chromosome is relatively fixed from strain to strain, for *H. pylori* the order is highly variable (31).

Table 2. Types of diversity in *H. pylori*

Type	Example
Point mutations	<i>ure C</i> (23)
Mosaicism	<i>vac A</i> (24)
Non-conserved elements	<i>cag</i> island (25—27)
Mobile DNA	IS605 (25, 26)
genome order	map rearrangement (31)

Generation of variation

An important, and ultimately clinically relevant, question is whether the enormous variation merely reflects an ancient lineage, or whether it continues to occur. Studies of a series of *H. pylori* isolates from a Dutch family provides evidence that there is ongoing change (32). Recent work by Kuipers *et al.*, examining paired isolates obtained 7 to 10 years apart from the same host suggests the formation of “quasispecies”, presumably due to point mutations (33). If this model is correct, then an individual host is colonized by a “cloud” of closely related organisms. Such biology might reflect a strategy to maximize fitness by maintaining a diverse population in case of environmental changes in a given host. Such a strategy also might maximize transmission to and colonization of a new host.

H. pylori are naturally competent (34, 35), that is able to take up and be transformed by free DNA. This ability to be transformed, first observed in pneumococci, suggests that *H. pylori* can recombine with one another *in vivo*. Mosaic structures of genes are consistent with recombination, and a population structure analysis provided further evidence for this phenomenon (36).

Thus, the ability to change genotype by *H. pylori* appears to be on-going and is summarized in Table 3. Such changes provide models to understand the population biology of these organisms, and such phenomena as the emergence of antibiotic resistance (37).

Table 3. Genetic variation in *H. pylori*

Mechanism	Consequence	Type of genetic variation
Point mutation	→ quasispecies formation	Drift
Recombination	→ chimera formation	Shift

Exclusive niches for H. pylori variants?

Individuals may be colonized by more than one *H. pylori* strain (19, 38—41) a phenomenon that can be easily distinguished by virtually all genotyping methods, in contrast to “quasispecies”. The minimum estimate for this phenomenon is 15% of all hosts, but since biopsies sample a minute proportion (10^{-5}) of the gastric mucosa, and usually only single colonies are isolated, this is probably a substantial underestimation. In developing countries, the multiplicity of colonizing organisms may be even higher (42).

With two or more organisms occupying the stomach of a host, an important question is whether the strains are competitive, cooperative, or indifferent to one another. The presence of recombination, especially through conjugation (43), already suggests one potential form of cooperativity, the exchange of genetic material. Sexual reproduction offers many survival advantages over asexual replication. Whether further cooperativity exists, as has been observed among commensal populations in the oral cavity, remains to be determined. Strain differences imply the potential for competition for scarce resources, such as nutrients or binding sites. Bacteria use mechanisms such as bacteriocins to gain advantage over competitors; however, none have yet been described for *H. pylori*. Alternatively, different strains can co-exist because each colonizes a different, perhaps exclusive niche. Such a phenomenon may exist, for example, among *cagA*⁺ and *cagA*⁻ strains, in which differences in susceptibility to acidic pH may reflect the particular niches occupied by these organisms.

CONCLUSIONS

The major selective pressures on *H. pylori* appear to be directed toward ensuring persistence in particular hosts, and ultimately transmission to new hosts. In such a context, the development of disease may be regarded as an accident, or the “cost of doing business”. The emergence of peptic ulceration as a “disease of civilization”, may reflect changes in the ecology of the stomach. These may include introduction of new *H. pylori* strains, or alterations in the balances between host and microbes. Exploration of these questions will be of particular interest in the coming years.

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