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View Point

Helicobacter pylori: enemy, commensal or, sometimes, friend?

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Abstract

Helicobacter pylori is a Gram-negative ε-proteobacterium that colonizes about 50% of humans. Some pertinent characteristics are that it can survive the acid of the stomach, produces urease to neutralize it and is motile due to apical flagella. Not surprisingly given its wide distribution, it has long colonized mankind and its genome encodes many features that allows this. Consequently, it frequently has a persistent lifelong association with humans and, differently from most pathogens that are transmitted horizontally, it is preferentially transmitted vertically, often from mother to child. A variety of genes and polymorphisms, both in *H pylor*i and in humans, mediate the complex host-bacterium relationship, and can also determine if and what pathologies will be triggered by the species. *H. pylori* is naturally transformable, very recombinogenic and has a high mutation rate. Microbiota studies of the stomach have shown it to be an important species with a potentially regulatory role for the gastric microbial community. Likewise, epidemiological work has suggested that, while it clearly increases the risk of peptic ulcers and gastric cancer in some populations, it is also associated with lower risk of esophageal cancer and several other important pathologies. More recently, antibacterial resistant strains have been isolated, posing a problem for public health officials who called for its eradication. Hence, study of *H. pylori* and how it interacts with us can help revealing mutualistic or pathogenic interactions and the immune response in the digestive niche.

Key words: *H. pylori*; *cagA*; genome plasticity; immunity; antibiotic resistance.

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Introduction

Helicobacter pylori is a Gram-negative ε-proteobacteria that colonizes about 50% of humans. Its discovery was reported in 1984, about a century after its initial sighting in pathology examinations of the stomach [1]. It causes gastritis upon infection and leads to peptic ulcer formation in about 10% of persons colonized by it, with about 1% ultimately developing gastric cancer, although the prevalences vary by population [2].

The DNA sequencing revolution has unveiled the molecular basis of some of the ways in which *H. pylori* is well-equipped for its lifestyle of colonizing the human stomach and interacting with the resident epithelial and immune cells [3], while sequence information from different clinical isolates has also revealed genome plasticity and polymorphisms that mediate variation in our response to its infections [4,5]. A major determinant of colonization and virulence is the presence of the approximately 40 kbp pathogenicity island, which is not present in all strains and is also often distinct between isolates in different populations [6]. The island contains several important colonization-related genes and the genes encoding a bacterial type IV secretion system, to allow insertion of bacterial proteins into host cells, some of which can directly mediate host cell function. The most characterized of the bacterial genes involved in this activity is *cagA*, the product of which alters phosphorylation status of a number of host genes, including the anti-oncogenic p53 gene [7]. This provides the molecular explanation of why *H. pylori* is classified as a carcinogenic agent and the importance of CagA is such that it forms the main classification element of human associated *H. pylori* strains, *i.e.*,*cagA*+/*cagA*-. Some of the important factors involved in *H. pylori*-human interactions are listed in Table 1.

DNA sequencing has also provided information not just about the diseases that *H. pylori* may promote but also about the significant variation between different human populations, in terms of frequencies of the respective pathologies and their trends. Sequence studies have suggested that the ancestral *H. pylori* strain, HpAfrica2, has colonized humans since about 88,000 ybp [8]. It has also revealed that the main

mode of transmission of *H. pylori* is vertical, usually from mother to child [9]. Transmission is so stable, that its presence and identity can be a highly informative phylogenic marker, with an accuracy similar to using human mitochrondial DNA (mtDNA) or non-recombinogenic Y chromosome, and its presence is usually established early in life [10]. Furthermore, the closest relative to *H. pylori* found in other mammals is *Helicobacter acinonychis*, which colonizes large felines and apparently jumped from its human host around 50,000 ybp. A study has suggested that *H. acinonychis* is a direct descendant of an *H. pylori* strain that was introduced into the large felines from man, possibly by a predation event [11]. It seems that many of the genetic changes to render *H. acinonychis* better able to survive in its new niche have involved inactivation of genes encoding outer membrane proteins (OMPs), probably to avoid recognition and opsonization by the new host's immune defenses. Remarkably, some similar changes have been documented in spousal transmission of *H. pylori* in humans, providing some clues on the differences between early (vertical) *versus* late (horizontal) transmission [10]. Even in cosmopolitan cities with large immigrant populations, the *H. pylori* strains were found to accurately indicate the ethnic origin [12] and the infection rates, while decreasing for all groups within populations in developed cities, remain higher in the immigrant populations compared to resident ones [13]. However, it is precisely these differences that are key to understand if *H. pylori* can be considered friend or foe and can provide us insight on how we interact with it.

In contrast to other bacterial species that live in intimate contact with humans, but are clearly pathogens, *H. pylori* colonization can be asymptomatic, with different effects, beneficial and deleterious, emerging in certain populations and in age-specific fashion.

In this minireview, we will discuss some of the aspects involved in the complexity of *H. pylori*-human relationships in health and disease.

H. pylori in health and disease

The combination of *H. pylori* and host genetic variation is what led to the first suggestions of its existence and opened other questions. Studies in the UK in the 1950's suggested a greater susceptibility to peptic ulcers in persons who had blood type O [14,15]. Likewise, in the mid 1980's when work on *H. pylori* was beginning, an important reduction in cases of gastric cancer in a number of developed countries was noted, although the reasons behind this were not known [16].

As the role of *H. pylori* in peptic ulcers and gastric cancer became established, its importance in public health risk became clearer. Using the rate of *H. pylori* infection in different populations, together with the projected risk of gastric pathologies, indicated that there were major discrepancies in the incidence of the *H. pylori*-linked diseases between developed countries and undeveloped ones, like Africa and East Asia, the so-called Africa and Asia mystery [17], raising the possibility that the interaction between *H. pylori* and humans may have evolved differently also depending on the host.

Nevertheless, a mounting effort to eradicate *H. pylori* started to gather support in developed countries, particularly in view of the aforementioned fall off in gastric cancer that coincided with the widespread use of antibiotics in the study populations [16]. The unintentional side effect was that, in addition to curing the primary infection, antibiotic treatment was also eliminating *H. pylori* from the stomach in many

Table 1. Some of the principal bacterial and human loci that mediate interactions.

Gene locus	Role
CagA (Cytotoxin associated gene A)	Injected into host epitheleal cells. Modulates host signalling
VacA (Secreted toxin)	Removes epithelial barriers
BabA (Blood group antigen binding adhesin)	Binds to fucosylated epithelial cells
FlaA (Flagellin polymer)	Motility. Evokes low level response from TLR5
ABO blood antigens	Targets on epithelial cells for binding
TLR5 (Toll-like receptor 5)	Binds to flagella to activate host innate immune response
Il1B (Interleukin 1 β-subunit)	Host inflammatory cytokine. Activates TH1 cells
Il-8 (Interleukin 8)	Host pro-inflammatory cytokine expression polymorphisms
Il-10 (Interleukin 10)	Host pro-inflammatory cytokine
TNFα (Tumor necrosis factor α)	Host pro-inflammatory acid-suppressing cytokine

members of at-risk the population. Moreover, despite an initially high rate of sucessful therapy in people suffering of *H. pylori* related diseases, combining proton pump inhibitors with antibiotics, *H. pylori* drug resistance was soon observed [18] and is now a problem in many populations in both the developing world [19,20] and in several countries in southern Europe, although considerably less in countries where antibiotic use is more strictly controlled [21].

H. pylori and antibiotic resistance

The most current international guidelines have proposed to eradicate *H. pylori* in symptomatic patients using a standard triple therapy, consisting of a proton-pump inhibitor and two antibiotics with complementary modes of action, selected from amoxicillin, clarithromycin, levofloxacin and metronidazole [22]. Combined therapy was initially very effective, although mutations in 23S RNA [23], *pbp1A* [24], *gyrA* [25], *frxA* or *rdxA* [26], conferring resistance to each of the above mentioned antibiotic have been described, and in some populations has become so common, that the Maastricht IV consensus report urges local monitoring of *H. pylori* resistance [22].

Genomic studies of *H. pylori* and its DNA metabolism have given some explanation for how antibiotic resistance can arise rapidly. Short-term mutation rate is considerably higher than the median value seen in other enteric bacterial species and much genome variability is seen when different isolates from the same population are sequenced [22]. Likewise, the combination of a lack of mismatch DNA repair genes [27] and a high number of repeated sequences and inverted elements indicate that *H. pylori* can easily undergo phase variation to alternate gene expression [28-30]. This is apparently a crucial factor in mediating its survival and persistence in the face of the mammalian adaptive immune system and therapies [31].

H. pylori colonization *vs* infection

Lifelong association of *H. pylori* with the human host involves a balance between the two sides. However, this delicate equilibrium is largely mediated and can be altered by strains producing CagA. In fact, beyond the clear importance of *cagA* as a determinant in the pathogenic risk for human health, genomic surveys of the stomach microbiota have shown a strong correlation of the presence of *cagA*+ strains with a defined composition of bacterial species in this niche [32]. The study also revealed that *cagA*- strains can frequently be missed, as about 37% of the human hosts that tested negative for *H. pylori* where found to harbor these strains when their microbiota was examined [33]. In contrast, the most crucial delimiting factor is apparently the presence of *cagA*+ strains, as they had the most important impact on the diversity of the microbiota present, possibly also because of their ability to interact with and modify the activity of the gastric epithelium [32]. This suggests that *H. pylori cagA*+ is an important director, perhaps playing a keystone species role in the stomach of many persons. Given the rising appreciation of the importance of the microbiota in determining health and disease, *H. pylori* may thus represent a key to understanding the multidimensional activities that go on at the human-bacterial interface [33-42]. For this reason, *H. pylori* presents a number of important opportunities toward gaining better insight into both bacterial and host biology and interactions.

A number of unanswered questions that *H. pylori* can help to address are listed in Table 2. From the initial observations and molecular biology studies, it would seem to indicate that *H. pylori* is a dreaded noxious pathogen. However, a number of studies, notably epidemiological ones, have also indicated inverse correlations, odds ratios significantly less than one, for a number of serious health problems, in persons harboring *cagA*+ strains [39]. Further studies in selected populations may help to shed light on these

Table 2. Some yet unanswered questions regarding *H. pylori* and its association with humans.

H. pylori HpAfrica2 strain in its natural hosts**:** what complains are most common and rare compared to other populations? In particular how frequent are the traits like allergic asthma, celiac disease and stroke, in which there has been observed a negative association with infection in some populations?
H. pylori strains in recently colonized populations in South America and the Pacific islands**:** is there evidence of competition by different strains in the same individuals stomach? Also how do metabolic parameters, like levels of leptin and ghrelin compare in infected and non-infected youth?
H. pylori in the stomach: how diverse is the population? Do strains live together?
H. pylori genome: how open is the genome? Is it less open in any particular population, for example where it has longer lived with humans? This could indicate that the relationship is becoming more a symbiotic one.
H. pylori over the course of life: colonization is only bad after a certain age? It has been suggested that the species does not have a uniform effect during life, but rather can, at least in some populations. It will be vital to know if this is the case, so as to better deal with *H. pylori*.
H. pylori and host sequence variation: what are the likely risks for the host? What would be the most appropriate antibiotic therapy?

relationships, and also help to clarify if *H. pylori* is merely a bellwether or an active agent in positive as well as negative health outcomes, while also providing an ordering principle to one of the most particular microbial communities in our body and one which has important consequences also for the communities in the intestine, while being much less complicated. Answers to some of these questions will shed light on the *H. pylori*-human interactions and the processes of pathogenicity, commensality or mutualism as well.

Conclusive remarks

While it may seem regressive to suggest epidemiological studies in the post-genomic era, many important clues, including the paradoxes that suggested *H. pylori* presence, blood group affinity and role in ulcer and gastric cancer risk, came from such studies [14,15,16]. The HpAfrica2 strain has lived, apparently in peace, with specific human populations considerably longer than any other *H. pylori* strain [8] and perhaps in these populations this relationship, with both health risks and health advantages, will be clearer to verify. Additionally, the microbial ecosystem of the stomach, and its impact on other more complex systems, like the gastrointestinal tract and overall health throughout life, may be more discernible starting from knowledge of these interactions.

A better understanding of the clonality and role of transformation between *H. pylori* strains could also give insight into how important natural transformation plays in other more clearly pathogenic species and the interplay between *H. pylori* and it co-inhabitants of the gastrointestinal tract.

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