The role of persistence in *Helicobacter pylori* pathogenesis

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Purpose of review

Helicobacter pylori induces chronic gastritis and is the strongest known risk factor for peptic ulcer disease and distal gastric cancer, yet only a fraction of colonized individuals ever develop clinical disease. The aim of this article is to provide an overview of recent advances into mechanisms of *H. pylori* persistence and to incorporate these findings into our current understanding of *H. pylori* pathogenesis.

Recent findings

Recent studies have heightened awareness of the significance of bacterial persistence in *H. pylori*-associated diseases. Persistence is achieved through initial interactions between *H. pylori* adhesins and cellular receptors, after which *H. pylori* must avoid clearance by the immune system. This is accomplished by avoiding host recognition, by producing specific bacterial factors that stimulate selective expression of host genes, and by inducing an ineffective T-cell response. Further, it has become increasingly evident that the genetic diversity of *H. pylori* also plays a significant role in its persistence.

Summary

H. pylori persists in its acidic gastric niche, typically for the lifetime of the host. This persistence increases the risk of diseases such as peptic ulcer disease and gastric cancer. Delineation of mechanisms that regulate ongoing *H. pylori*–host interactions will not only improve targeted diagnostic and therapeutic modalities, but may also provide insights into other diseases that arise within the context of chronic pathogen infection.

Keywords

gastric cancer, *Helicobacter pylori*, immune regulation, oxidative stress

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Abbreviations

APE-1/Ref-1	AP endonuclease-1/redox factor-1
NFAT	nuclear factor of activated T cells
NF-κB	nuclear factor κB
TFF	trefoil factor family
TLR	Toll-like receptor
Le[b] antigen	Lewis[b] antigen

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Introduction

Helicobacter pylori is a Gram-negative pathogen that colonizes the stomach of approximately half of the world's population. Virtually all infected persons develop coexisting gastritis, which represents the strongest known risk factor for peptic ulcer disease and distal gastric cancer. Colonization typically occurs during childhood and persists for the lifetime of the host, and such persistence within the context of ongoing gastric inflammation is the signature feature of *H. pylori* infection. This is in marked contrast to infections by other mucosal pathogens, such as *Salmonella*, for which the inflammatory response results in either elimination of the pathogen or death of its host. Biological costs of the long-term relationship between *H. pylori* and humans include an increased risk of peptic ulceration, gastric adenocarcinoma, and non-Hodgkin's lymphoma of the stomach [1]. Many *H. pylori* factors known to be important for initial colonization or virulence also have the capacity to manipulate the host immune response, allowing long-term inhabitance of the stomach. The focus of this review will be to highlight and discuss recent studies which have provided insights into specific interactions that facilitate *H. pylori* persistence and pathogenesis in order to place the biological impact of *H. pylori* carriage in perspective.

Colonization of the gastric niche

Gastric acidity as well as peristalsis preclude bacterial colonization of the stomach. However, *H. pylori* has several mechanisms to elude these primary host defenses and establish persistent infection. Approximately 20% of the *H. pylori* population in colonized persons binds to gastric epithelial cells and adherence is required for prolonged inhabitance of the stomach. BabA is a membrane-bound *H. pylori* adhesin encoded by the strain-specific gene *babA2*. BabA binds the blood-group Lewis[b] (Le[b]) antigen on gastric epithelial cells and *H. pylori* strains expressing BabA confer an increased risk for gastric cancer precursor lesions and gastric adenocarcinoma. Recent work has demonstrated that nonbinding of Le[b] is a metastable phenotype; that is, within a population of non-Le[b]-binding *H. pylori* strains, cells with a Le[b]-binding phenotype are present and can be recovered [2•]. This usually occurs by recombination of a silent copy of *babA* into the closely related *babB* gene, resulting in the expression of a BabB/A chimeric adhesin that is additionally subject to phase variation due to frameshifts within the highly repetitive sequence motifs of *babB*. This suggests that adherence of *H. pylori* can be precisely modulated, which is likely important for both

initial colonization as well as long-term persistence. Sialyl-dimeric-Lewis^x glycosphingolipid, a marker of gastric dysplasia, is also expressed on gastric epithelial cells, and is upregulated by chronic gastric inflammation. Sialyl-Lewis^x is a receptor for the *H. pylori* adhesin SabA, which has a critical role in the nonopsonic activation of neutrophils [3].

H. pylori exhibits strict host and tissue tropism, naturally colonizing only gastric tissue of human and nonhuman primates. Further, human histopathologic studies have demonstrated that *H. pylori* colonizes specific microniches within the stomach; for example, bacterial binding and density are greatest in the upper region of gastric glandular units. Trefoil peptides belong to the trefoil factor family (TFF) and are secreted by mucus-secreting cells. TFF1 is a trefoil factor peptide for which the pattern of distribution mirrors the pattern of *H. pylori* colonization and *H. pylori* binds TFF1 avidly *in vitro*, suggesting that TFF1 may act as a receptor for *H. pylori in vivo* [4•]. In contrast, *H. pylori* is rarely found in deeper glandular regions where gastric mucous cells produce mucin containing α1,4-linked *N*-acetylglucosamine *O*-glycans. These *O*-glycans have been shown to exert an antimicrobial effect against *H. pylori* by inhibiting the biosynthesis of cholesteryl-D-glucopyranoside, a major component of the *H. pylori* cell wall [5••]. Together these data indicate that dynamic interactions between specific *H. pylori* adhesins and host receptors in conjunction with a naturally occurring antimicrobial agent dictate tropism for a particular gastric niche, which may in turn affect chronicity and disease.

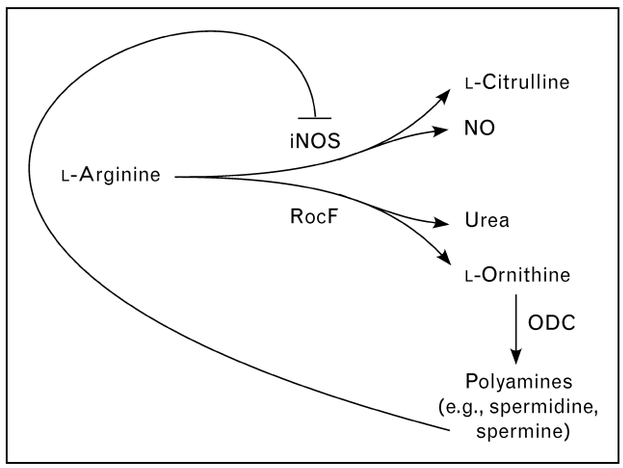
Helicobacter pylori and the host immune response

To succeed in persistent colonization of its host, *H. pylori* must be able to avoid clearance by the immune system and recent studies have utilized global transcriptional profiling to define and characterize host mediators of persistence. One study of the gastric transcriptional profile in the rhesus macaque model of *H. pylori* infection demonstrated upregulation of specific inflammatory and immune mediators including β-defensin 2, protease inhibitor 3, and chemokine receptor 2 [6]. In a separate study using a murine model of infection, investigators examined gene-expression profiles of three major gastric epithelial cell lineages in *H. pylori*-infected and uninfected mucosa by using laser capture microdissection coupled with microarray analysis. Each cell type exhibited a distinct transcription profile, but only gastric mucous cells were found to respond specifically to *H. pylori*. As expected, *H. pylori*-altered genes included genes related to proinflammatory and defense responses [e.g. interleukin-1β, tumor necrosis factor-α-inducible protein 6, and RANTES (regulated upon activation, normal T cells expressed and secreted)] [7•].

Reactive oxygen and nitrogen species that can induce oxidative DNA damage are generated by activated neutrophils present within inflamed gastric mucosa. These reactive species not only injure host tissue but additionally have the potential to harm infecting organisms; therefore, recent studies have investigated the ability of *H. pylori* to survive under conditions of oxidative stress. *H. pylori* upregulates the host inducible NO synthase while simultaneously producing an arginase, RocF, which siphons L-arginine away from the competing host inducible NO synthase, thereby limiting the production of bactericidal NO (Fig. 1) [8]. Further, recent studies have shown that *H. pylori* induces both arginase II and ornithine decarboxylase in macrophages and the induction of ornithine decarboxylase occurs via c-Myc [9•]. Arginase catalyzes the conversion of L-arginine to L-ornithine, which is in turn metabolized by ornithine decarboxylase to putrescine that is then converted to the polyamines spermidine and spermine (Fig. 1). Spermine can inhibit inducible NO synthase translation and, consequently, NO production [9•,10]. These two mechanisms of limiting NO production likely contribute to the persistence of *H. pylori*.

AP endonuclease-1/redox factor-1 (APE-1/Ref-1) is a host-cell protein that functions in the repair of oxidative DNA damage. Further, APE-1/Ref-1 has been implicated in the regulation of DNA-binding activity of transcription factors such as nuclear factor κB (NF-κB) and p53. APE-1/Ref-1 is increased after exposure of gastric epithelial cells to *H. pylori* due to increased protein synthesis *de novo* [11••], and the newly synthesized protein rapidly accumulates in the nucleus. These data also suggest a role for APE-1/Ref-1 in the persistence and pathogenesis of *H. pylori* infection.

Figure 1 Metabolism of L-arginine by inducible NO synthase (iNOS), *Helicobacter pylori* arginase (RocF), NO and ornithine decarboxylase (ODC)



The effect of *H. pylori* on Jurkat cells and normal human T lymphocytes has also been examined to identify mechanisms through which *H. pylori* might alter T-cell function [12•]. T cells incubated with wild-type *H. pylori* exhibited decreased proliferation as well as decreased expression of the TCR CD3ζ chain. In contrast, an *H. pylori* arginase mutant affected neither proliferation nor TCR CD3ζ-chain expression. The mechanism by which arginine depletion alters T-cell signaling, however, remains unclear.

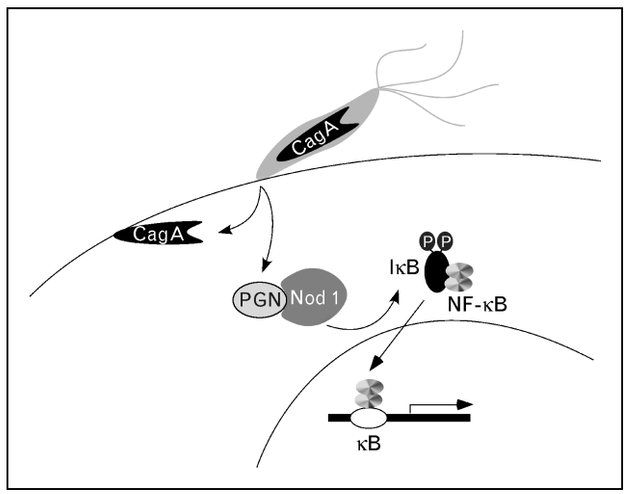
In humans and in animal models, infection with *H. pylori* leads to robust production of IgG and IgA antibodies, both in the serum and within the gastric mucosa. Using a B-cell-deficient mouse model, Akhiani *et al.* [13] demonstrated that, although initial colonization was comparable to that observed in wild-type mice, bacteria were completely cleared from mutant mice within the context of severe gastric inflammation. In contrast, wild-type mice remained colonized throughout the study, but developed only mild gastritis [13]. This suggests that the presence of antibodies results in less severe inflammation, but at the cost of persistent colonization. In further studies using interleukin-10-deficient mice, IgA-deficient mice, and interleukin-10/IgA-deficient mice, this same group found that the absence of both interleukin-10 and IgA resulted in lower colonization densities, but enhanced levels of inflammation [14•].

Toll-like receptors (TLRs) are a conserved family of eukaryotic receptors that function in innate immunity by recognizing invariant regions of bacterial molecules termed pathogen-associated molecular patterns (PAMPs). Eleven mammalian TLRs have been identified and, although the bacterial ligands for TLRs are distinct, the signaling pathways activated by these receptors all eventuate in NF-κB activation and proinflammatory cytokine expression. Interestingly, *H. pylori* has evolved strategies to avoid global activation of this system. Although the secreted flagellins of other Gram-negative mucosal pathogens robustly active proinflammatory responses through TLR5, *H. pylori* flagellin is not secreted and is noninflammatory [15–17]. Polarized expression of TLRs also play a role in modulation of immunity. In persons with noninflamed gastric mucosa, TLR4, TLR5, and TLR9 are located on both apical and basolateral epithelial surface. In the presence of *H. pylori*-induced gastritis, TLR5 and TLR9 are found exclusively at the basolateral surface [18•]. Interestingly, a recent report indicates that TLR2 may be the dominant TLR responsible for recognition for *H. pylori*. In this study it was determined that TLR2 was required for cellular cytokine responses to *H. pylori* and that the TLR2-mediated response was greater when *H. pylori* strains possessing the *cag* gene island were tested against *cag*$^-$ strains [19].

In spite of the strategies utilized by *H. pylori* to avoid immune clearance, significant immune activation still occurs. Recent data now indicate that *H. pylori* can utilize bacterial virulence factors to both downregulate and avoid acquired immune effectors. The *H. pylori cag* pathogenicity island encodes a type IV secretion system which delivers bacterial products into host cells. One such product is CagA, the product of the terminal *cag* island gene, which undergoes Src-dependent phosphorylation and activates SHP-2, a eukaryotic phosphatase that leads to dephosphorylation of host-cell proteins and cellular morphological changes. CagA can induce β-catenin activation and, in certain strains, interleukin-8 secretion [20,21]. Analysis of changes in gene expression in response to CagA revealed that this bacterial effector can also activate the nuclear factor of activated T cells (NFAT), independently of CagA phosphorylation [22••]. Another bacterial substrate that is translocated into host cells via the type IV secretion system is peptidoglycan, which is recognized by the intracellular receptor Nod1, and this results in NF-κB activation (Fig. 2) [23••]. *H. pylori* infection of Nod1-deficient mice leads to an augmented inflammatory response, suggesting that recognition of peptidoglycan by Nod1 is critical for host defense against *H. pylori* [23••].

An additional *H. pylori* factor linked with pathologic outcomes is VacA, a bacterial cytotoxin. *In vitro*, incubation of VacA with epithelial cells results in multiple effects including the formation of large intracellular vacuoles and depolarization of cellular membranes. The gene that encodes VacA is present in all *H. pylori* strains, although cytotoxic activity varies due to genetic variation. Recent evidence suggests that VacA may

Figure 2 Translocation of CagA and Nod-1-dependent activation of nuclear factor κB (NF-κB) by *Helicobacter pylori* peptidoglycan (PGN)



I-κB, inhibitor of κB.

contribute to evasion of the adaptive immune response [22••]. In contrast to CagA, VacA blocks activation of NFAT [24] and more recent data indicate that VacA inhibits the clonal expansion of CD4+ T cells independently of NFAT [25•]. Thus multiple mechanisms exist by which VacA inhibits T-cell activation and proliferation, which likely contribute to the capacity of *H. pylori* to evade the immune response and establish persistent colonization.

Helicobacter pylori induces ineffective T-cell polarization

CD4+ T lymphocytes can be divided into two functional subsets, type 1 (Th1) and type 2 (Th2) T-helper cells, which are defined by distinct patterns of cytokine secretion. Th1 cells secrete interleukin-2 and interferon-γ and promote cell-mediated immune responses, whereas Th2 cells produce interleukins 4, 5, 6, and 10 and induce B-cell activation and differentiation. Though the acquired immune response to *H. pylori* includes both Th1 and Th2 cells, cytokine profiles indicate a Th1 predominance, and studies now suggest that this Th1-predominant response is dysfunctional and may have an important role in persistence.

Infection of mice that lack the Th1 cytokine interferon-γ with *H. pylori* or the related organism *Helicobacter felis* leads to lower levels of gastric inflammation and atrophy in comparison with wild-type mice. Some strains of mice, such as C57/BL6, that mount a predominantly Th1-type response develop extensive gastritis in response to challenge with *H. felis*, whereas other strains of mice (Balb/c) that respond with a Th2 type of response develop minimal gastritis. Adoptive transfer of Th1-type cells from *Helicobacter*-infected mice into infected recipients results in enhanced gastritis, while transfer of Th2-type lymphocytes paradoxically reduces colonization density. Interestingly, coinfection with *H. felis* and the intracellular parasite *Toxoplasma gondii*, which induces high levels of interferon-γ, shifts the T-cell response toward a Th1-type cytokine profile and results in increased gastric injury [26]. In another report, investigators examined the role of childhood infection with helminths and *H. pylori* seropositivity in children and adults residing in regions of Columbia with distinct differences in risk for gastric cancer [27]. These results suggested that intestinal helminthiasis in children led to a Th2-predominant response to *H. pylori* and may result in decreased cancer risk. Together these data suggest that immune responses to unrelated organisms may have a significant impact on *H. pylori*-associated disease outcomes.

The role of *Helicobacter pylori* diversity in persistence

H. pylori is a remarkably diverse bacterial species for which every isolate from different individuals is unique, varying in genetic content, gene order, and allelic profile. Further, there is evidence that, even within a single host, diversity exists. Mechanisms through which diversity may be generated include the accumulation of spontaneous mutations over time, as well as frequent intra and inter-genomic recombination. A recent study examined sequence diversity among subclones obtained 9 years apart in two individuals. Though few differences were found within the 10 loci sequenced, analysis of the highly variable gene *amiA*, which encodes an amidase involved in cell-wall synthesis, revealed great variation in the size of this gene among subclones from each patient. It was further determined that both patients carried a single strain of *H. pylori* with clonal variants [28]. As described above, diversity is important for phase variation and modulation of adhesion, which likely have a role in *H. pylori* colonization and persistence. RuvC is an *H. pylori* enzyme required for resolution of Holliday junctions in the process of recombination. To investigate the role of recombination-dependent gene rearrangement on the host immune response, outbred CD1 mice were infected with either a wild-type strain of *H. pylori* or an isogenic *ruvC* mutant [29•]. The wild-type strain induced a Th2-type response and mice remained colonized until the conclusion of the experiment at 70 days. In contrast, the *ruvC* mutant elicited a Th1-type response and bacteria were completely cleared within 30 days. These findings provide evidence that *H. pylori* genetic recombination may dictate a specific type of host response that contributes to both the establishment of colonization as well as long-term survival within the stomach.

Conclusion

Despite a variety of host defenses, *H. pylori* is able to persist in the gastric niche which inherently increases the risk for pathologic outcomes such as peptic ulcer disease and distal gastric cancer. The mechanisms by which *H. pylori* is able to survive within its host and induce gastric inflammation are still not clear, though significant strides have been made. As this field becomes more refined and new tools become available, additional advances are highly anticipated. Improved understanding of the mechanisms and roles of *H. pylori* persistence will allow development of more effective therapies for diseases associated with gastric inflammation and may serve as a paradigm for the role of chronic inflammation in the initiation of other clinical sequelae of the gastrointestinal tract.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 60–66).

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This important article reports induction of APE-1/Ref-1, an enzyme that repairs damaged DNA and can activate transcription factors, in response to *H. pylori*, both *in vitro* and *in vivo*, suggesting a role for APE-1/Ref-1 in *H. pylori* pathogenesis.

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