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REVIEW

Strategies used by *helicobacter pylori* to establish persistent infection

Amin Talebi Bezmin Abadi

Amin Talebi Bezmin Abadi, Department of Bacteriology, Faculty of Medical Sciences, Tarbiat Modares University, Tehran 14115-111, Iran

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Correspondence to: Amin Talebi Bezmin Abadi, PhD, Assistant Professor, Department of Bacteriology, Faculty of Medical Sciences, Tarbiat Modares University, Tehran 14115-111, Iran. amin.talebi@modares.ac.ir
Telephone: +98-21-82884883
Fax: +98-21-82884883

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Abstract

Helicobacter pylori (*H. pylori*) is a Gram-negative and motile bacterium that colonizes the hostile microniche of the human stomach, then persists for the host's entire life, if not effectively treated. Clinically, *H. pylori* plays a causative role in the development of a wide spectrum of diseases including chronic active gastritis, peptic ulceration, gastric adenocarcinoma, and gastric mucosa-associated lymphoid tissue lymphoma. Due to the global distribution of *H. pylori*, it is no exaggeration to conclude that smart strategies are contributing to adaptation of the bacterium to its permanent host. Thirty-four years after the discovery of this bacterium, there are still many unanswered questions. For example, which strategies help the bacterium to survive in this inhospitable microniche? This question is slightly easier to answer if we presume the same clinical concept for both persistent infection and disease. Understanding the mechanisms governing *H. pylori* persistence will improve identification of the increased risk of diseases such as gastric cancer in patients infected with this bacterium. A well-defined and long-term equilibrium between the human host and *H. pylori* allows bacterial persistence in the gastric microniche; although this coexistence leads to a high risk of severe diseases such as gastric cancer. To escape the bactericidal activity of stomach acid, *H. pylori* secretes large amounts of surface-associated and cytosolic urease. The potential to avoid acidic conditions and immune evasion are discussed in order to explain the persistence of *H. pylori* colonization in the gastric mucosa, and data on bacterial genetic diversity are included. Information on the mechanisms related to *H. pylori* persistence can also provide the direction for future research concerning effective therapy and management of gastroduodenal disorders. The topics presented in the current review are important for elucidating the strategies used by *H. pylori* to help the bacterium persist in relation to the immune system and the many unfavorable features of living in the gastric microniche.

Key words: *Helicobacter pylori*; Gastric microniche; Persistent infection; Gastric cancer

Core tip: *Helicobacter pylori* (*H. pylori*) infections are thought to cause severe gastroduodenal disorders which are the main outcome of this interaction between the host and this microorganism. The bacterium has developed interesting strategies which allow it to efficiently colonize the gastric mucosa leading to persistent infection. In this review, we aim to look at the five major reported strategies leading to the persistent survival of *H. pylori* within gastric epithelial cells.

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INTRODUCTION

The groundbreaking discovery of a Gram-negative bacterium by Marshall and Warren changed the gastroenterologists' view regarding the historic dogma that the stomach was a sterile organ[1]. Phylogenetic analysis emphasized the global distribution of the bacterium from East Africa to other continents thousands of years ago[2-5]. *Helicobacter pylori* (*H. pylori*) which was previously called *Campylobacter pyloridis* is mostly acquired during childhood and it has been genetically proved that it can be transmitted within families[4]. *H. pylori* is a ε-proteobacterium that colonizes the human stomach with patchy distribution and is mainly found in the antrum rather than the fundus[6]. Many published international guidelines recommend treatment of the bacterium with effective antibiotics[7-11]. Both *in vitro* and *in vivo* evidence in addition to epidemiologic data have confirmed that *H. pylori* is the main cause of both gastric and duodenal ulcers, gastric adenocarcinoma and gastric mucosa-associated lymphoid tissue (MALT) lymphoma[12-15]. Due to the high prevalence of *H. pylori* worldwide and success of this long-term commensalism, it is no exaggeration to assume that complex strategies are involved in efficient colonization in the host. Virulence factors involved in the establishment of a persistent infection are shown in Table 1. As shown, an adhesion or secreted protein can be a determining factor in successful persistent colonization. This concept raises a challenging question concerning how *H. pylori* can persistently colonize the stomach in such unfavorable conditions. In the current review, we discuss the five observed strategies leading to persistent survival within gastric epithelial cells.

FIRST STRATEGY: ESCAPING GASTRIC ACIDITY

The human gastric lumen is known to consist of a large variety of physical and biochemical barriers to provide an unfavorable environment for all types of ingested microbes[16]. Successful gastric colonization by any microorganism in this microniche is due to the existence of various abilities to avoid hostile acidic conditions and the viscous mucosal layer[17,18]. To do this, *H. pylori* harbors specific features leading to successful colonization. In the following paragraphs, we discuss how this bacterium can cause persistent infection with a focus on acidity avoidance.

Table 1 Major virulence factors involved in the persistence of *Helicobacter pylori*

Virulence factors	Roles in persistent infection
OipA	Induces pro-inflammatory cytokines
	In combination with CagA, causes disruption of cell tight junctions
VacA	Increases IL8 expression and causes inflammation
	Contributes to long-term colonization
	Cell proliferation and elongation
	Increases the level of MAPK signaling
CagA	Stimulates the NF-κB pathway
	Induces apoptosis
	Induces pro-inflammatory cytokines
	Disrupts cell tight junctions
	Increases mucosal inflammation
BabA	Leads to effective cell adherence
	Mediates in the effective interaction between *H. pylori* and epithelial cells
DupA	Induces pro-inflammatory cytokines
	Induces apoptosis
GGT	Contributes to long-term gastric colonization
	Induces immune response tolerance
SabA	Mediates the effective interaction between *H. pylori* and epithelial cells

MAPK: Mitogen-activated protein kinase; NF-κB: Nuclear factor-κB; *H. pylori*: *Helicobacter pylori*.

UREASE AS THE FIRST WEAPON AGAINST ACIDITY

The acidity of the stomach (pH 1-2) is the first danger to threaten bacterial survival in the stomach[14,17,19]. *H. pylori* is able to survive at approximately pH 5 which can kill many digested organisms within a few minutes after acid exposure. This is the main adaptive feature of this bacterium which facilitates its survival in the gastric microniche. *H. pylori* growth is limited in neutral pH, but can survive in acidic pH due to an increase in periplasmic pH and secretion of a large amount of urease enzyme[18,20]. Urease is a key feature in the capacity of *H. pylori* to avoid gastric acidity. To avoid the bactericidal activity of acid, *H. pylori* secretes large amounts of surface-associated and cytosolic urease[6]. However, hydrolysis of urea (occurring in the gastric lumen) produces large amounts of ammonia, which is then protonated to create ammonium, thus creating a neutral bacterial microniche[21]. In the presence of urea, pH is shifted to 2-6 and *H. pylori* can

survive in the gastric microniche. In contrast, in the absence of urea, *H. pylori* can grow in the pH range of 6-8 and can even survive in the pH range of 4-8.5. Urea is imported through a specific channel, and with urease, ammonia will fill the entire cytosol and even bacterial periplasm[22,23]. *H. pylori* urease gene cluster consists of two major genes, ureA and ureB, and five accessory genes, ureI, ureE, ureF, ureG, and ureH. These accessory subunits are associated with urea absorption[16,18,21,24]. Urease is a nickel-binding hexamer of UreA and UreB. It has been reported that *H. pylori* can change the expression of certain genes (associated with the synthesis of ammonium ion) including arginase, urease and formamidase after exposure to hostile gastric acidic conditions[18]. The production of urease in 10% of bacterial proteomes enables it to hydrolyze large amounts of gastric urea to generate ammonia and CO2, causing a sharp increase in the pH around *H. pylori*[25]. However, in response to low pH by the ArsSR two-component system, production of ammonia can be continued by formamidase in addition to urease by the hydrolysis of short-chain amino acids, while arginase hydrolyzes L-arginine to L-ornithine and urea[26,27]. To establish persistent infection, after entering the gastric lumen, the bacterium should be able to penetrate and infiltrate the viscous mucosal layer[28,29]. Interestingly, mucosal viscosity is highly dependent on acidity. In general, in more acidic pH, mucus is stronger than at pH 4. Enzymatic activity governed by *H. pylori* facilitates bacterial penetration into the aggregated mucus. Subsequent diffusion of ammonia in the stomach provides an opportunity for *H. pylori* to penetrate deeply using corkscrew propulsion due to its flagella. The helical shape of the bacterium is another factor affecting its successful evasion of acid[30]. Due to low permeability of the mucosal layer, there is a scarcity of essential nutrients (for example Fe^{3+}) in the stomach for all ingested microorganisms[13,16,18,21,22]. The release of large amounts of urease is a smart strategy adopted by *H. pylori* to weaken the integrity of the mucus to facilitate deep penetration to reach the nutrient enriched region. Moreover, moving into deeper layers gives the bacterium the opportunity to avoid the acidic conditions on the surface of the lumen; another strategy which increases the viability of this bacterium[6,13,31]. Thus, *H. pylori* would not survive in the stomach without its potential to escape high acidity which is not observed in any other microorganisms.

Intracellular or extracellular life

During the time research had been undertaken on *H. pylori* colonization in the human stomach, no clear evidence has been published to indicate that *H. pylori* is an invasive organism in the human gastric microniche[4,6,19,32]. Following the assessment of a large number of *in vivo* and *in vitro* studies, we suggest that *H. pylori* is a noninvasive gastric pathogen[33,34]. Interestingly, *H. pylori* is able to repopulate the extracellular environment following bacterial clearance (for example with effective antibiotics) of the gastric lumen, suggesting it may be better described as a facultative intracellular microbe[35]. To date, no direct evidence on *H. pylori* replication in gastric cells has been reported[36]. However, despite the progress already achieved, more *in vitro* experiments are required before we can conclude that the intracellular effect of *H. pylori* is a strategy involved in long-term persistence in gastric epithelial cells. However, it can be assumed that *H. pylori* is a facultative intracellular bacterium rather than an extracellular organism. As a temporary strategy to avoid chemical and physical barriers, *H. pylori* can transiently enter the intracellular space for a short time to reduce exposure duration to antibiotics, acidic conditions and the immune response[37]. Moreover, as *H. pylori* is optimally evolved to reduce its exposure to acidic gastric conditions, it can localize in mucus close to the epithelial surface where acidity is tolerable for longer survival. This strategy adopted by the microbe further highlights the importance of research in finding effective antibiotics to treat this organism.

Direct contact with host cells

By involving various surface proteins, *H. pylori* can bind to epithelial cells[38]. BabA is a major outer membrane protein and is one of these contributing proteins (Figures 1-3)[39,40]. Interestingly, there are other adhesion molecules which facilitate attachment of the bacterium to epithelial cells[41]. Bacterial secreted lectin is another binding factor which binds to the sialic residues of laminin[42]. A cascade pathway allows the successful irreversible attachment of *H. pylori* to polarized epithelial cells (Figure 2)[43]. Small cytoplasmic changes can be observed following direct contact between *H. pylori* and host cells. Following first contact of the bacterium with the plasma membrane and rearrangement of the cellular cytoskeleton, an extension of the plasma membrane can engulf a part of the bacterium[38]. Undoubtedly, certain bacterial factors such as *cagA* and *dupA* are involved in the above processes; however, data regarding details of this contribution are lacking[44]. Interestingly, it was noted that only a small fraction of available *H. pylori* strains in the gastric mucosa can attach to the surface. Although *H. pylori* adherence is mediated by candidate surface proteins (*e.g.*, AlpA, AlpB, DupA, BabA, OipA, SabA and HopZ), no specific molecule has been shown to be essential in adhesive mechanisms[45,46]. For example, *H. pylori* SabA supports the release of nutrients in the apical side of epithelial cells for bacterial survival in the stomach. This nutrient release is in parallel with translocated CagA protein which can induce inflammation in infected cells[47]. Different expression of adhesion molecules occurs among *H. pylori* strains suggesting various adaptations induced by genetic recombination, on/off switching of gene

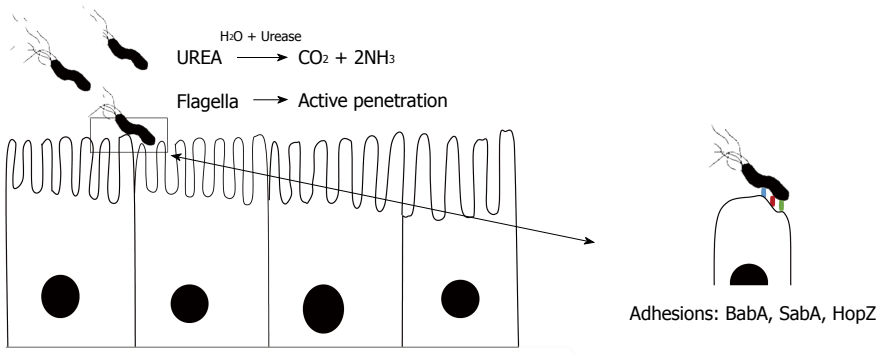

Figure 1 Basic overview of the events leading to the successful colonization of *Helicobacter pylori*.

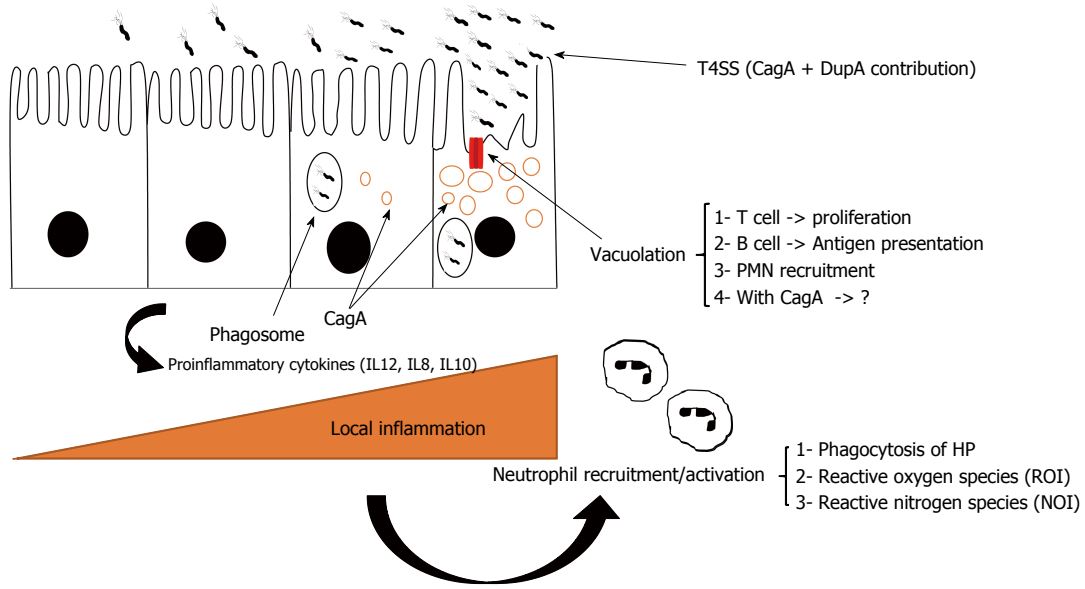

Figure 2 Subsequent activated events causing inflammation in chronic infection by *Helicobacter pylori*.

expression. It is clear that bacterial attachment is an inevitable step in the establishment of *H. pylori* infection, although determining the molecules involved is not easy. New technologies in the near future will reveal further details of the complex initial process in persistent *H. pylori* infection.

SECOND STRATEGY: HELICAL SHAPE

The helical shape of *H. pylori* has been suggested to provide a mechanical advantage for penetrating the viscous stomach mucus layer. Special cross-linkages in bacterial peptidoglycan can result in an efficient screw-like movement to facilitate *H. pylori* survival in the viscous environment of the stomach[48]. Consistent with this, *H. pylori* typically possesses a helical morphology and multiple uni-polar flagella. In an animal model, *H. pylori* cell shape mutants showed impaired stomach colonization indicating the importance of bacterial shape in motility and adherence[49]. The combination of a curved structure and cell elongation provides *H. pylori* with a suitable helical body shape. To date, our knowledge indicates that a certain number of genes such as Ccrp89, Ccrp58, Ccrp1142 and Ccrp1143 are involved in *H. pylori* morphology[48]. Thus, any mutations in these genes can cause a deficiency in bacterial motility and shape[50]. It should be noted that the helical shape in addition to flagella are a major part of the successful penetration process.

THIRD STRATEGY: THE PRESENCE OF FLAGELLA (MOTILITY)

To avoid elimination by regular gastric turnover, persistent infection is dependent on bacterial movement. *H. pylori* is mostly distributed within approximately 30 μm of mucosal epithelial cells and its histopathologic effects can be observed within the gastric crypts. During the last decade, *H. pylori* flagella have been widely investigated, and current knowledge demonstrates the critical role of these organelles in the colonization and establishment of persistent infection[43]. Extensive isogenic mutant studies have shown the role of intact flagellar apparatus in

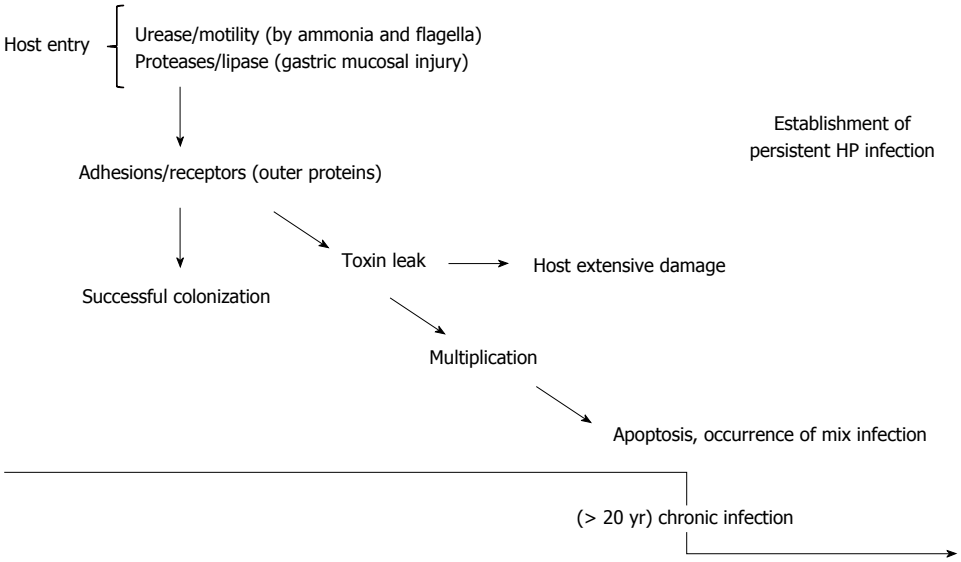

Figure 3 Flowchart of the strategies involved in persistent infection.

governing *H. pylori* infection, especially long-term infection[51]. *H. pylori* is an actively motile organism which has the ability to move between different regions of the stomach. Furthermore, flagella give the bacterium the potential for penetration which is necessary to avoid acidic pressure on the surface of the gastric mucosa[52]. Due to the combination of more than 39 genes in the *H. pylori* genome, 3-5 tuft-like flagella appear on the side of the bacterium. These flagella consist of a basal body, hook, and flagellar filament[53]. The deletion or any other changes in the genes related to the flagella can produce non-motile *H. pylori* which is unable to effectively colonize gastric mucosa[54]. In order to move both in counterclockwise (CCW) and clockwise (CW) directions, *H. pylori* requires a rotating movement around the filament[55]. The existence of polar flagella in *H. pylori* is a requirement for persistent infection. Following entry into the stomach, the bacterium has a durable acid-tolerance range[56]. *H. pylori* is tolerant to weakly acidic conditions in the stomach which occur after ingestion. Given that ammonia is produced by bacterial urease, the rheologic properties of the gastric mucin changes allowing penetration of *H. pylori* into the gastric mucosa using flagellated motility and its helical shape. The detailed mechanism by which *H. pylori* weakens mucus viscosity is not fully understood, but we now know that loss of tightness on the side of polarized epithelial cells may be involved leading to several gastroduodenal diseases. Thus, movement of *H. pylori* is necessary in order to attach to epithelial cells[57]. Taken together, these findings show that the presence of flagella is useful for *H. pylori* to produce infection in the gastric mucosa, and urease is an essential enzyme guaranteeing successful bacterial penetration.

FOURTH STRATEGY: *H. PYLORI* EVASION OF THE HUMAN IMMUNE SYSTEM

During the relatively long time that *H. pylori* has been recognized, it is clear that long-term bacterial persistence is necessary to maintain successful existence of *H. pylori* against both innate and adaptive immune responses (Figure 4)[57,58]. Following successful colonization of gastric mucosal cells by *H. pylori*, host immune responses (both innate and acquired branches) are stimulated generating specific antibodies and activated Th cells. Thus, *H. pylori* is required to avoid both branches of the immune system to colonize the stomach for several years[59]. In addition to long-term infection, other diseases are caused by this microorganism. Any digestive diseases related to prolonged colonization by *H. pylori* can be due to adaptation between the microbe and human host[60]. We now know that subsequent to colonization by *H. pylori,* a percentage of the infected population can develop autoimmunity or immune system abnormalities[61-64]. These findings show bilateral effects between *H. pylori* and the human immune system. During the thousands of years of commensalism between humans and *H. pylori*, the bacterium has learned to subvert the immune response and it may serve as an example of bacterial evolution in maintaining its micro-territory in humans[62]. Taken together, these findings suggest that we should use the word "equilibrium" to define this status. In this equilibrium, *H. pylori* induces immune cells which cause minimum cell damage to shed nutrients onto the surface of the gastric mucosa for survival[32]. Cell damage following local superficial

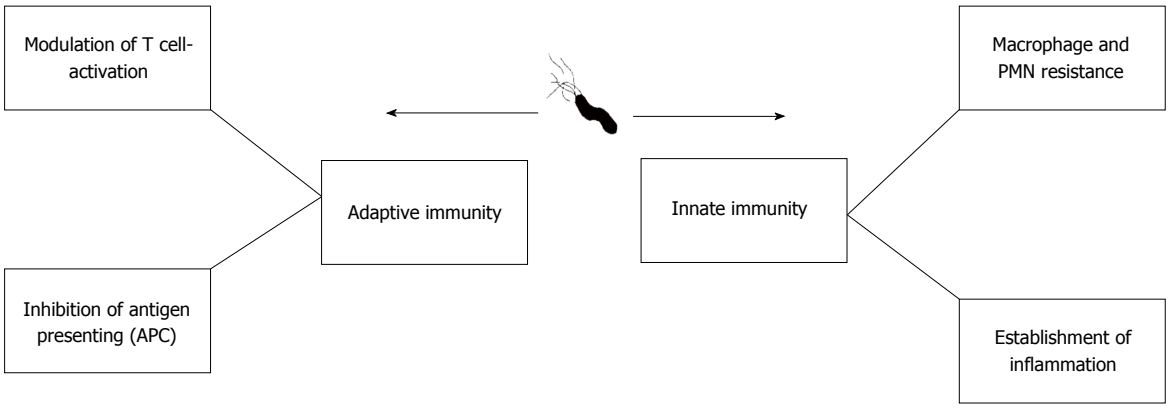

Figure 4 Different impacts of *Helicobacter pylori* on the two branches of the human immune system.

gastritis occurs, but seems necessary for governing long-term colonization as the infection can cause minimum nutrient shedding which is required for bacterial survival in the harsh stomach environment. It should be noted that the microbe will be immediately eliminated by active immune cells[65]. In conclusion, bacterial persistence only occurs if *H. pylori* and the immune system co-adapt following successful immune evasion. In the next section, we briefly describe how *H. pylori* effectively avoids innate and adaptive immune responses.

MECHANISMS OF IMMUNE EVASION BY *H. PYLORI* - INNATE IMMUNITY

Both components of the innate system (chemical and physical barriers) are involved in immune system responses against *H. pylori* in the stomach[66]. The gastric epithelial surface plays an active role in mucosal defense[67]. Immediately after entering the gastric epithelial cells, two major actions by the innate immune system work against *H. pylori*: (1) engulfment by phagocytes; and (2) chemical products of these cells include reactive nitrogen and oxygen[68,69]. Below, we focus on three different strategies adopted by *H. pylori* which facilitate establishment of persistent chronic infection in the gastric epithelium.

EVASION OF PHAGOCYTE KILLERS

Although *H. pylori* is usually phagocytosed by macrophages, in comparison to other Gram negative microbes, *H. pylori* is highly resistant to killing by these cells during phagocytosis[70-73]. A virulent *H. pylori* strain (type I: *cagA* $^{+}$ *vacA*$^{+}$) is more resistant to phagocytosis than other strains[74-76]. Accumulation of the bacterium in vesicles which produce megasomes is the main evidence for delayed phagocytosis[77,78]. Macrophage apoptosis can result in *H. pylori* escaping phagosomes[79]. As mentioned previously, *H. pylori* induces inflammation to provide nutrients, thus inflammation may be present for months or years. Therefore, *H. pylori* needs to be well prepared to confront large numbers of phagocytes in the stomach due to the high rate of cell damage.

There are three proposed strategies which can help the bacterium to survive in this phagocyte-rich environment: (1) *H. pylori* induces mitochondrial-associated cell death in macrophages (mitochondrial dependent apoptosis)[80,81]; and (2) production of peroxiredoxin by AhpC gene actively defends the bacterium against NO products available in the gastric microniche[82-85].

Similarly, *H. pylori* arginase due to substrate competition can reduce NO or $O2^{-}$ radicals[86]. *In vitro* studies have shown that *H. pylori* activates macrophage nitric oxide synthase and thus apoptosis[87-89]. It has been shown that arginase-deficient bacteria are more sensitive to oxidative stress caused by macrophages[90,91]. Finally, *H. pylori* has adopted a smart strategy to inhibit polymorphonuclear neutrophil (PMN) and monocyte activation by involving CagA proteins (type Ⅳ secretion system)[92]. Furthermore, *cagA* positive strains produce more IL8, a trigger cytokine for inducing infiltration of inflammatory cells. Isogenic mutant experiments suggest the participation of VacA toxins in escape of the microbe from phagosomes[93]. Subsequent deactivation of PMNs and monocytes can cause interference in the innate immune response which is favorable for *H. pylori*[94]. An alteration in phagocyte function is the main mission of *H. pylori* to facilitate persistent infection. Therefore, there are undoubtedly other mechanisms involved in the persistence of *H. pylori* against phagocytosis[95,96]. Further *in vitro* and *in vivo* experiments are necessary to fully elucidate the complex interactions in chronic *H. pylori* infection.

ADAPTIVE IMMUNITY

A successful pathogenic organism which aims to overcome innate immunity to establish colonization in an ecological niche leading to chronic infection should possess strategies to overcome adaptive immunity. *H. pylori* modulates adaptive immunity by affecting T

reg and T cell proliferation[97,98]. In the next paragraph, we describe the major reactions of *H. pylori* to adaptive immunity which include: (1) enhanced T and B cell functions; and (2) interference in the antigen presentation process.

EFFECTS ON B AND T CELLS AND THEIR PROLIFERATION

Recent data have demonstrated that *H. pylori* can modulate T cell responses[99-102]. Elegant *in vivo* experiments suggested that CD4 T lymphocytes are highly involved in the adaptive immune response against *H. pylori*, in contrast to the relatively inactive role of CD8 T cells. As shown previously, *H. pylori* stimulates the immune response using Th1[101,103]. The main interference due to *H. pylori* in the adaptive immune response is its inhibitory effect on T cell proliferation *via* three mechanisms: (1) binding the VacA toxin to the unknown surface ligand in T cells which results in actin rearrangement and then inhibition of cell proliferation[74,103]; (2) the VacA toxin is able to form an anion-selective channel in the host cell membrane. These specific channels can cause vacuoles in host cells leading to apoptosis[104]. This event starts following attachment of VacA to surface receptor alpha (RPTPα)[105]; and (3) VacA can bind to mitochondria and trigger the associated apoptotic pathway. This mechanism can induce inhibition of T cell proliferation. Moreover, VacA located in the membrane of anionic channels inhibits the release of cytochrome C, indicating the crucial role of channel formation in apoptosis induced by *H. pylori* VacA. The exact apoptotic role of VacA needs to be elucidated in the future. We noted that the antibody response is not sufficient to eliminate *H. pylori* infection in humans, as the bacterium has developed strategies to protect itself from the effects of antibodies[106]. Unfortunately, the data concerning the actual role of any specific bacterial product to inhibit B cell response are lacking although some experiments have shown that Janus kinase (JAK)-STAT (signal transducer and activator of transcription) suppression by CagA may be a major mechanism in reducing effective B cell response[107].

INTERFERENCE IN THE ANTIGEN PRESENTATION PROCESS

H. pylori has adopted various strategies to interrupt accurate antigen presentation in the host, which is the main method of interfering with late endocytic membrane trafficking. Inhibition of APC activation may be the key point in reducing B cell response to colonization of *H. pylori* in humans[108]. Inhibition of MHC-class Ⅱ export to the cell surface is the main reason for impaired antigen presentation in dendritic cells[109,110]. In a novel study, the inhibitory effect of CagA on IL3-dependent B cell proliferation was reported to be *via* the JAK-STAT signaling pathway, which can cause ineffective antibody secretion in humans[111,112]. JAK/STAT signaling is an important immune signaling pathway. Certain inflammatory molecules can activate different types of JAK and STAT. Phosphorylated STAT generates dimers that translocate to the nucleus, thereafter its binding to the promoter of specific genes involved in immune inflammatory response can be stimulated[112,113]. As mentioned previously, data regarding the actual role of *H. pylori* in limiting B cell response are scarce and more detailed studies are required to elucidate the complex mechanism responsible for the establishment of persistent infection[114].

SUBVERSION OF PATTERN RECOGNITION

Different Toll-like receptors (TLRs) corresponding to microbial components called pathogen-associated microbial patterns (PAMPs) are the main components which provide a new strategy for *H. pylori* to avoid involvement with the human immune system. Any interruption of this complex process can hamper bacterial clearance by the immune system. We now know that successful recognition of pathogens by TLRs is involved in both the innate and adaptive systems[115-118]. Subversion of TLRs is dependent on recognition by *H. pylori* which helps the bacterium to survive in the strongly immune cell-rich gastric microniche[119-122]. TLR4-mediated inflammatory response to LPS in *H. pylori* is largely different to other organisms (almost 1000-fold less reactogenic than other Gram negative bacteria)[123-129]. Indeed, co-evolution with humans has resulted in a reduction in immunogenic ligands[130]. TLR-dependent immune subversion is a strategy that works in both innate and adaptive immune responses to *H. pylori*; therefore, this adopted strategy should have an effect in hiding the bacterium in the human gastric microniche.

FIFTH STRATEGY: *H. PYLORI* GENETIC DIVERSITY: FACILITATING PERSISTENT INFECTION

The bacterium is relatively competent in DNA uptake from other *H. pylori* strains. The diversity of the *H. pylori* strains even within a single host is impressive[131]. *H. pylori* is a highly heterogeneous bacterium with more than 1600 genes[12,58,68,69]. *H. pylori* is a highly competent at taking up both environmental DNA and DNA from other *H. pylori* strains. *H. pylori* was identified as being heterogeneous by a large amount of evidence from experiments investigating (1) allelic variation; (2) SNP; (3) genome size; and (4) bacterial recombination[21,132-134]. Genetic recombination is a very important factor involved in adaptation of *H.*

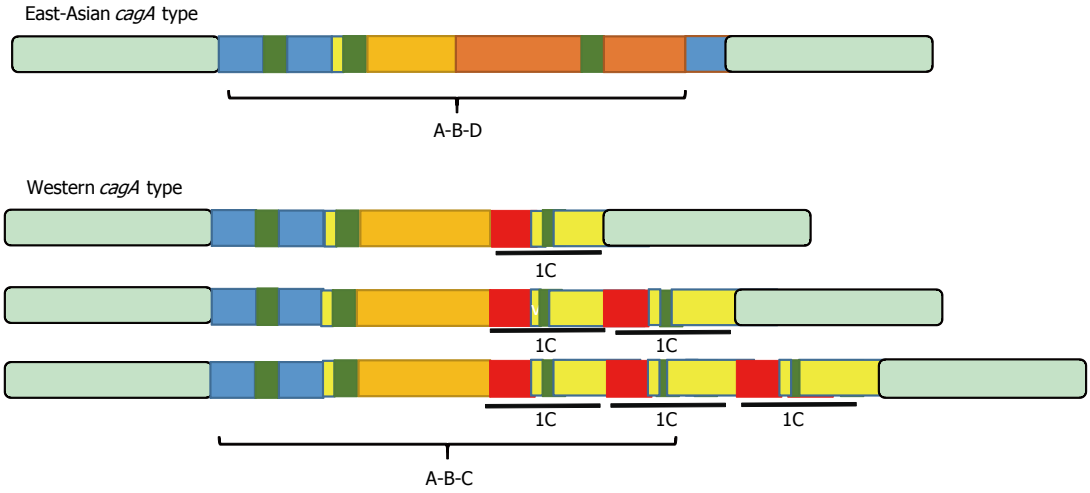

Figure 5 Polymorphism of the *cagA* gene reported in various regions of the world.

pylori in the human stomach[135]. CagA is a classic virulence factor of the bacterium and has been isolated in different regions of the world (Figure 5). It can be seen from this figure that reported polymorphisms can directly affect its clinical importance. *H. pylori* is considered to be a genetically diverse organism infecting individuals around the world[19]. Its high potential for DNA uptake results in *H. pylori* having one of highest recombination rates reported in human pathogenic bacteria. This high rate of recombination causes high genomic variability among the bacterial strains[134]. Due to natural selection after these genetic changes, *H. pylori* is more persistent in the gastric microniche. However, it should be mentioned that in addition to genetic recombination, bacterial mutation can have a role in generating highly variable strains observed in persistent infections[136]. Almost 10% of its genome consists of specific genes for *H. pylori*[12]. Scientists have suggested that chronic persistent infection cannot occur independently. Comparative analyses of full genome sequences of *H. pylori* strains J99 and 26695 in addition to the large amount of data on new sequencing techniques provide new insight into bacterial diversity and its potential to infect humans life-long[137]. The *H. pylori* genome is not diverse, but various changes in the third base of codons has resulted in specific strains called "quasi-species"[133,138,139]. Currently, both antigenic and phase variation contribute to *H. pylori* persistence against immune responses[140,141]. Indeed, wide diversification in the *H. pylori* genome increases the chance of survival in the hostile gastric environment. In order to answer a direct question on the possible mechanism of bacterial diversity to establish chronic persistent infection we need to look at the biology of *H. pylori*. Clearly, bacteria such as *H. pylori* which is exposed to the human immune response and PMNs, it is crucial to promote strategies to avoid these unfavorable conditions. Apart from bacteria such as *E. coli* which have a large genome, *H. pylori* has half the genome of these bacteria. The main genetic deficiency in *H. pylori* is its two-component regulatory system[142]. Deficiencies in mismatch-repair systems of *H. pylori* can increase the frequency of genetic variation, and may facilitate minimal genetic diversity. Thus, *H. pylori* can take advantage of diversity in genetic sequences following selective pressure. To compensate for the lack of genetic contents in the regulatory systems, *H. pylori* has adopted the strategy of remaining life-long in the gastric microniche. This strategy means nonstop recombination and genetic change in the genome and then natural selection to choose the fittest organisms to adapt and live in the gastric environment. This adaptation can also be translated into successful bacterial immune evasion during *H. pylori* persistence.

CONCLUSION

The beginning of the *H. pylori* era in 1984 was characterized by questions which require considerable attention; such as treatment, efficient vaccines, useful biomarkers and management of the infection[6,31,143]. For *H. pylori,* similar to most common gastric pathogens, we have information on its many molecular mechanisms, but its survival strategies in the human host are not well elucidated. The human stomach is a challenging niche for bacterial colonization; therefore, sophisticated strategies to aid survival of the bacterium would not be surprising. Bacterial genetic diversity and extensive polymorphism also facilitate the survival of *H. pylori* within the hostile gastric environment[14,63,144]. The potential for *H. pylori* to survive in the strong acidic conditions in the stomach is considered a major feature of bacterial persistence. Even with the five strategies described in this study, there is a big gap in the knowledge concerning the mechanisms involved in the persistent colonization of *H. pylori*. Initially, a useful buffering potential in addition to the presence of sufficient bacterial adhesion facilitate primary colonization and then continuous genetic diversification

in parallel with immune evasion are the main strategies used for persistent infection. Despite intensive studies, the molecular host - *H. pylori* interactions, particularly in symptomatic patients colonized by persistent *H. pylori* are obscure. Understanding the details of *H. pylori* persistence and its contributing elements will help identify better strategies to treat the infection or may design better drug targets.

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