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# *Helicobacter pylori* evasion strategies of the host innate and adaptive immune responses to survive and develop gastrointestinal diseases

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ABSTRACT

*Helicobacter pylori* (*H. pylori*) is a bacterial pathogen that resides in more than half of the human population and has co-evolved with humans for more than 58,000 years. This bacterium is orally transmitted during childhood and is a key cause of chronic gastritis, peptic ulcers and two malignant cancers including MALT (mucosa-associated lymphoid tissue) lymphoma and adenocarcinoma. Despite the strong innate and adaptive immune responses, *H. pylori* has a long-term survival in the gastric mucosa. In addition to the virulence factors, survival of *H. pylori* is strongly influenced by the ability of bacteria to escape, disrupt and manipulate the host immune system. This bacterium can escape from recognition by innate immune receptors via altering its surface molecules. Moreover, *H. pylori* subverts adaptive immune response by modulation of effector T cell. In this review, we discuss the immune-pathogenicity of *H. pylori* by focusing on its ability to manipulate the innate and acquired immune responses to increase its survival in the gastric mucosa, leading up to gastrointestinal disorders. We also highlight the mechanisms that resulted to the persistence of *H. pylori* in gastric mucosa.

## 1. Introduction

*Helicobacter pylori (H. pylori)* as a Gram-negative bacteria is the first formally recognized bacterial carcinogen and is one of the most successful human pathogen, as it infects approximately 4.4 billion (~59%) of the world's population (Hooi et al., 2017). *H. pylori* infection is typically acquired in early childhood (Gold, 2001), although precise estimation of age of occurrence is difficult to obtain in young children. Despite severe innate and adaptive immune responses of human to this pathogen, it can survive in the gastric mucosa for a long time (Abadi, 2017). *H. pylori* infection is the main cause of chronic gastritis, which is an asymptomatic disorder in most infected people. This bacterium is also a major cause of gastric and duodenal ulcers known as peptic ulcer and two malignant cancers such as gastric adenocarcinoma and mucosa-associated lymphoid tissue (MALT) lymphoma (Kusters et al., 2006). The potential of *H. pylori* to survive and to cause chronic infection is more than other Gram-negative bacterial pathogens in the stomach (Testerman and Morris, 2014). The presence of *H. pylori* in the gastric tissue is often observed in gastric mucosa close to the underlying epithelial cells (Ebrahimpour et al., 2017). The initial colonization of the bacterium in the gastric mucus depends on several factors including the expression of the bacterial urease enzyme (to overcome the acidic conditions of the gastric lumen), possession of polar flagella (for motility), and the changes in the bacterial cell morphology to effectively penetrate the gastric mucosal barrier and gain access to the underlying epithelial cells. A number of bacterial virulence factors such as cytotoxic-associated gene A (CagA) and vacuolating cytotoxin (VacA), environmental factors, and host factors (host gene polymorphism) at the epithelium would increase the *H. pylori* colonization and susceptibility to the associated diseases (Dunne et al., 2014). The survival of *H. pylori*

*Abbreviation:* H. pylori, Helicobacter Pylori; PAI, Pathogenicislands; CagA, Cytotoxin-associated gene A; VacA, Vacuolating cytotoxin gene A; MALT, Mucosa-associatedlymphoid tissue

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is also strongly influenced by the ability of these bacteria to escape, disrupt and manipulate the host immune responses. This bacterium can escape from being recognized by innate immune receptors via altering its surface molecules (Peek et al., 2010). *H. pylori* can also block other innate recognition receptors by inhibiting downstream signaling pathways. On the other hand, *H. pylori* is able to escape from the host adaptive immunity by modulating the function of the T lymphocytes (Wen and Moss, 2009). In this review article, we mainly discussed the considerable ability of this bacterium to manipulate and escape the innate and adaptive immune responses.

## 2. Data collection

A systematic review of studies evaluating the immune escape mechanisms of *H. pylori* from 1999 to 2018 was carried out in multiple databases. It should be noted that the related keywords, including "*H. pylori,*" "intrinsic and specific immune responses," "immune escape" and "virulence factors" were used to find these articles. Of the extracted articles that were related to the subject, 105 articles were reviewed. According to results of the mentioned studies, *H. pylori* escapes innate immune responses through various mechanisms such as escape from recognition by Toll-like receptors (TLRs) and RIG-I-like receptors (RLRs) along with activation of inflammasome complex. Furthermore, *H. pylori* modulated adaptive immune responses through suppressing the development of Th1 and Th17. Therefore, each of these mechanisms is explained in more details.

## 3. *H. pylori* colonization in the gastric mucosa

### 3.1. Continuous colonization in the stomach mucosa and escape from the acidic lumen

The stomach lumen with acidic pH is not an appropriate environment for bacterial colonization. Thus, the highest bacterial density is visible in the lower bowel with neutral or slightly alkaline pH. Production of gastric acid in the stomach resulting in the creation of pH 1–2 limits bacterial colonization in this region. *H. pylori* can persist for just a few minutes in the lumen of the stomach and must quickly migrate to the epithelial cells crossing the mucosal barrier (Schreiber et al., 2005, 2006). The mucous membrane layer of the stomach acts as a physical barrier against bacterial infiltration and traps host antimicrobial compounds to prevent bacterial infection (Hansson, 2012). *H. pylori* produces urease enzyme responsible for gastric acid- resistance of bacteria via generation of ammonium ions, and movement of bacteria and penetration into the gastric mucosa by altering the viscosity of gastric mucins content (Sidebotham et al., 2003). At low pH, mucins convert into a gel status that effectively traps bacteria, but in the presence of urease activity, pH will increase and subsequently, viscosity of the mucins will decrease, leading to the bacteria being able to swim in mucous layer (Celli et al., 2009). Another mechanism that influences *H.pylori* colonization is chemotaxis. *H. pylori* expresses several chemotactic receptors and mutation in these chemotactic factors can reduce the number of bacteria that are in close proximity to gastric epithelial cells (Williams et al., 2018). *H. pylori* deficient in chemotactic factors are also associated with reduced inflammation and defective effector T cell responses, possibly due to lack of intimate contact with gastric epithelial cells (Johnson and Ottemann, 2018). So, keeping *H. pylori* away from direct contact with gastric epithelium will decrease the infection risk, while increasing the inflammation related to the close contact with epithelium simultaneously. In fact, high inflammation is inversely correlated with the low density of bacteria (Basir et al., 2017). These conditions highlight the fact that *H. pylori* should effectively manage its contact with gastric epithelium until it is able to prevent clearance by the host immune responses and survive in this position (Suarez et al., 2006).

Some *H. pylori* strains constitutively express DNA repair proteins such as RecA and thereby eliminates the need for classical SOS response to DNA damage. DNA damage in *H. pylori* likely increases bacterial genetic diversity, instead of natural sustainability resistance. Most of the DNA repair pathways have been identified in *H. pylori* and are involved in the effective colonization of bacteria (Dorer et al., 2011). Furthermore, all *H. pylori* strains express catalase and superoxide dismutase proteins that are important for the detoxification of reactive oxygen species (ROS) (Benoit and Maier, 2016). Along with these enzymes, arginase limits the production of nitric oxide (NO) from monocyte, neutrophil, and epithelial cells (Lewis et al., 2010) and thus promoting bacterial survival. *H. pylori* also subverts autophagy of infected cells through inhibition of lysosomal clearance of autophagosomes. Inhibition of lysosomal function can promote accumulation of autophagosomes in gastric epithelial cells leading to bacterial survival (Zhang et al., 2018). The mentioned strategies increase survival and colonization of *H. pylori* in stomach.

### 3.2. Major cytotoxin associated gene pathogenicity island (cagPAI) products

The cytotoxin-associated gene A (CagA) and Vacuolating cytotoxin A (VacA) molecules as two major toxins, which are encoded by pathogenicity island (PAI) genetic locus, are required for bacterial persistence in the stomach. Both CagA and VacA are known to affect multiple host cellular processes for the successful establishment of the pathogen (Nejati et al., 2018). In addition to CagA and VacA expression, *cag* PAI encodes several proteins that form the structural components of the bacterial type IV secretion system. In some strains of *H. Pylori*, the cag PAI is completely absent (Nilsson et al., 2003). The cag PAI-positive H. pylori strains in comparison to cag PAI-negative strains, stimulate epithelial cells to produce high levels of IL-8 (Guillemin et al., 2002). In addition, peptic ulcer and gastric cancer occur more frequently in individuals infected with cag PAI-positive strains than cag PAI-negative strains (Algood and Cover, 2006).

CagA, is a highly immunogenic protein encoded by the cag PAI and is associated with cell injury, duodenal ulcers, and gastric adenocarcinoma. CagA is transmitted to the host cell after attachment of bacteria to epithelial cell surface through the type IV secretion system (T4SS). CagA can act in both phosphorylated and unphosphorylated states. CagA when phophorylated, interacts with a tyrosine phosphatase, SHP-2, and modulates migration, spreading, and adhesion of bacteria to the epithelial cells (Yamazaki et al., 2003). In recent years have shown that CagA positive strains of bacteria increase the risk of cancer (Pormohammad et al., 2018). Consequently, CagA was introduced as a bacterial oncoprotein that critically involved in gastric carcinogenesis. (Hatakeyama, 2003).

Another product of PAI is CagL that is expressed on the pilus of the T4SS and is required for CagA translocation. The CagL interacts with α5β1 integrin through its arginine-glycine-aspartate (RGD) motif on epithelial cells that translocate bacterial CagA (Cherati et al., 2017).

VacA is a secreted pore-forming toxin that enters the host epithelial cells by endocytosis and affects a variety of biological processes. Many strains of *H. pylori* carry the VacA gene which show a considerable amount of diversity in DNA sequences among different strains. As a consequence, different isoforms are associated with differential cell toxicity and severity of gastrointestinal disease (Palframan et al., 2012). VacA through several mechanisms may contribute to H. pylori persistence in the stomach. VacA showed direct cell-damaging effects including cytoskeletal changes and suppression of epithelial cell proliferation (Pai et al., 1999). VacA as a pore-forming toxin causes apoptosis of epithelial cells (Nejati et al., 2018). Besides these mechanisms that may provide H. pylori persistence, VacA blocks phagosome maturation in macrophage cells (Zheng and Jones, 2003). Furthermore, VacA inhibits antigen presentation process to T cells, blocks T cell proliferation, and downregulates Th1 functions via interacting with calcineurin signaling pathway (Gebert et al., 2003).

## 4. *H. pylori* as a new challenge for the immune system

Besides multiple virulence factors of *H. pylori* leading to its survival, bacterium manipulates host immune responses as a successful strategy in the development of gastrointestinal disorders. The main defensive barriers against *H. pylori* are the mucus secreted by epithelial cells and the innate immune cells in the lamina propria (Chmiela et al., 2017; Mejias-Luque and Gerhard, 2017). The immune responses against *H. pylori* are initiated by the recognition of the highly conserved pathogen-associated molecular patterns (PAMPs) by pattern recognition receptors (PRRs) on epithelial and innate immune cells, followed by initiation of the adaptive immune responses. This bacterium applies many evasion pathways to escape the innate and adaptive immunity for the survival in the stomach to cause different gastrointestinal disorders (Mogensen,

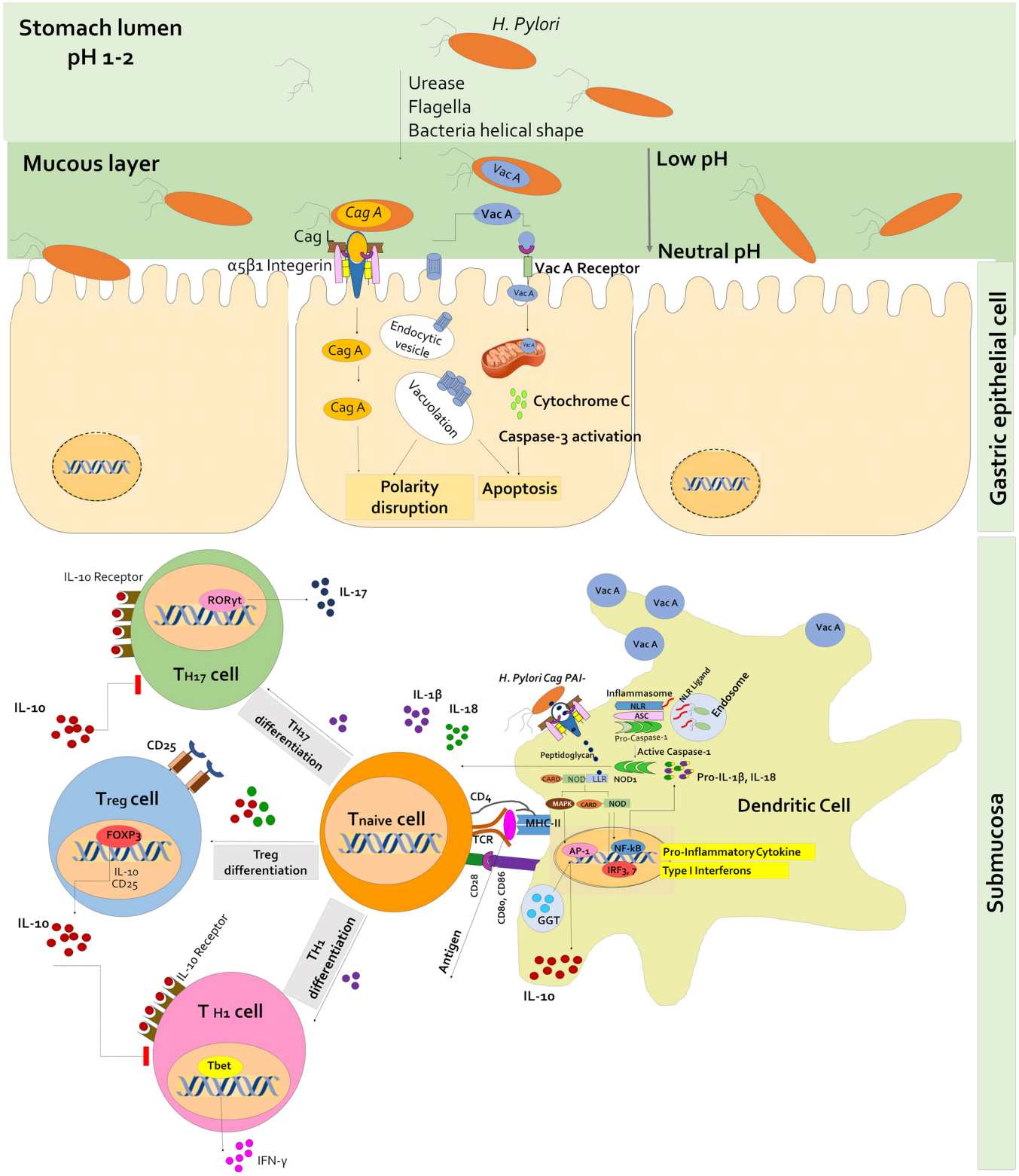


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**Fig. 1.** *H. pylori* evasion mechanisms from immune responses. After *H. pylori* enters into the lumen of stomach, urease activity locally raises the pH, and promotes bacterial persistence and motility. After bacterial attachment to the epithelial cells, VacA and CagA virulence proteins are injected to the host cells causing a number of changes including disruption of cell polarity and apoptosis. When the bacterium arrives to submucosa, DC act as the main antigen presenting cells and determine the fate of immune responses. The peptidoglycan of *H. pylori* is delivered to the NOD1 through T4SS. Activated NOD1 induces expression of pro-inflammatory cytokines through AP-1 and NF-κB. In addition, NOD1 signaling results in type I IFNs expression via IRF3 and IRF7. Furthermore, *H. pylori* NLR ligands in endosomes activate the inflammasome that conduct the IL-1β and IL-18 processing. Also, GGT exposed DCs produce IL-10. IL-18 and Il-10 binds to its receptor on naive T cells and induce FOXP3 dependent $CD4^+CD25^+$ Treg cell that followed by persistent colonization of *H. pylori*. On the other hand, IL-1β binding to its receptor induces Th1 and Th17 differentiation via Tbet and RORγt transcription factors, respectively. Bacterial clearance increases in the presence of Th1 and Th17 dependent immune responses. In contrast, secreted IL-10 from DCs or Tregs further suppresses Th1 and Th17 effector functions. ASC, apoptosis-associated speck-like protein containing a CARD; CARD, caspase activation and recruitment domain; GGT, γ-glutamyl-transpeptidase; LRR, leucine-rich repeat domain; IL-1β, interleukin-1β; IL-18, interleukin-18; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor-κB; NOD1, nucleotide-binding oligomerization domain-containing 1; RORγt, retinoid-related orphan receptor γt; PAI, pathogenicity island; Tbet, T-box transcription factor; Th1, T helper 1; Th17, T helper 17; Treg, regulatory T cells; T4SS, type IV secretion system.

2009). These mentioned mechanisms have been summarized in Fig. 1.

### 4.1. Innate immunity evasion strategies

The innate immunity is evolutionarily conserved in higher eukaryotes and is known as the first line of defense against infections. Toll like receptors (TLRs) are the main cluster of PPRs that recognized PAMPs. Bacterial lipopolysaccharides (LPS), peptidoglycan, lipoprotein, lipoteichoic acid and un-methylated CpG rich regions of DNA are the main targets of TLRs (Takeda and Akira, 2004). The TLRs signaling applies adaptor proteins and then activate nuclear factor (NF)-kB, interferon regulator factor (IRF) and activator protein-1 (AP-1). Activation of these transcription factors results in inflammatory cytokines and chemokines along with IFN-α and IFN-β production (Kawasaki and Kawai, 2014). On other hand, TLRs signaling in dendritic cells (DC) pave the way for adaptive immune responses against *H. pylori*. *H. pylori* escapes from detection by a large variety of PRRs that are essential for the recognition of other intestinal Gram-negative pathogens (Peek et al., 2010).

#### 4.1.1. Evasion from recognition by TLRs

Currently, 11 members of TLRs family have been identified in mammals. TLRs are expressed on the surface of the plasma membrane or endosomes and bind to the different classes of PAMPs (Satoh and Akira, 2016). Among the different TLRs, TLR2, TLR3, TLR4, TLR5, and TLR9 are characterized in the context of *H. pylori* infection and are recognized by lipoteichoic acid /or lipoprotein, double-stranded RNA (dsRNA), LPS, flagellin, and un-methylated CpG motifs, respectively (Akira and Takeda, 2004). Studies showed that *H. pylori* successfully escapes from recognition by the TLRs. For example, the TLR4 escapes of LPS recognition is well described. *H. pylori* LPS activity is 1000 times less than LPS of *Escherichia coli (E. coli)*. This less activity of LPS in *H. pylori* is related to tetra acylated form in comparison to hexa acylated LPS of *E. coli* (Stead et al., 2008). In addition, removal of phosphate groups from the 1′ and 4′ positions of lipid A in LPS induce the low negative charge to this molecule and increase the chance of escaping TLRs recognition. The responsible phosphatase for changes in lipid A was identified via site directed mutagenesis in this gene, as the colonization of *H. pylori* remarkably failed in infected mice (Cullen et al., 2011). Recognition of the LPS by TLRs is a controversial issue. Although many studies suggested the TLR4 is the main TLR for LPS binding, but other studies suggested TLR2 as a key TLR in LPS recognition. In recent years, both TLR4 and TLR2 have been introduced for recognition of the remaining PAMPs other than LPS of *H. pylori* (Rad et al., 2009). The recognition of non-LPS ligands by TLR2 exploits of innate immune responses for induction of anti-inflammatory responses that are associated with IL-10 production (Peek et al., 2010). Flagellin, another famous PAMP, is recognized by TLR5. Flagellin can modify the N-terminal recognition domain of TLR5 and, then escape from innate immune responses. Manipulation of amino acid 89–96 of the recognition domain of TLR5 results in low affinity to flagellin binding (Gewirtz et al., 2004). The experiments performed on DC cells showed that the innate immune system also recognizes the nucleic acid of *H. pylori* (Rad et al., 2009). Intracellular released DNA of *H. pylori* into DCs activates the endosomal accumulation of TLR9 leading to anti-inflammatory responses. A recent mouse model also showed that TLR9 signaling has anti-inflammatory effects in the early stages of *H. pylori* infection (Varga and Peek, 2017). Additionally, an experimental study confirmed that DNA of *H. pylori* could even inhibit inflammatory bowel disease (IBD) development in the mouse. Later, this unique sequence of *H. pylori* with immune-regulatory properties was introduced and had a short specific sequence (TTTAGGG) of *H. pylori* genome (Hansen et al., 2011).

#### 4.1.2. Evasion from RLR recognition

The RNA of *H. pylori* can be recognized via endosomally localized TLR8 on DC (Pachathundikandi et al., 2015). The study has suggested that Retinoic Acid Inducible Gene 1 Protein (RIG-1), a cytoplasmic nucleic acid sensor, is involved in sensing the RNA. The RIG-I like receptors (RLRs) as a subfamily of PRRs, have been studied in *H. pylori*infection. RLRs act as cytoplasmic sensors of PAMPs. The RLR family has three members: RIG-I, which is the best characteristic of this family, melanoma differentiation associated factor 5 (MDA5), and laboratory of genetics and physiology 2 (LGP2) (Matsumiya and Stafforini, 2010). It is well known that RLRs induce type I IFN in response to RNA viruses, but the role of RLRs in recognition of RNA from intracellular bacteria is unclear. Rad et al. showed that *H. pylori* 5′-triphosphorylated RNA can be recognized by RIG-I in DCs and can contribute to the type I IFN response (Rad et al., 2009). Further, MDA-5 expression significantly increased in the gastric antral mucosa of *H. pylori*-infected individuals (Tatsuta et al., 2012). It is currently unknown whether the production of type I IFNs in response to *H. pylori* via RIG-1 has pro-inflammatory or anti-inflammatory effects (Sayi et al., 2011).

#### 4.1.3. Evasion from CLR recognition

C-type lectin receptors (CLRs) as the third class of PRRs bind to glycans present on viruses, bacteria, and fungi to induce immune responses. The well characterized receptor in this class is DC-specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN) that expressed on the surface DCs and macrophages (van Kooyk and Geijtenbeek, 2003). The fucosylated ligands of *H. pylori* recognized by DC-SIGN strongly dissociate the signaling complex downstream of DC-SIGN leading to suppression of pro-inflammatory cytokine production. In contrast, most pathogens comprised DS-SIGN mannosylated ligands causing activation of the pro-inflammatory pathways. The different biological effects of mannosylated and fucosylated ligands of DS-SIGN are applied via acetylation of NF-kB (Wu et al., 2014). Acetylation of the P56 subunit of NF-kB has been shown to prolong and increase the transcription of the IL-10 to enhance anti-inflammatory responses (Takeshima et al., 2009). Moreover, anti-DC-SIGN significantly suppressed *H. pylori* induced IL-10 production in monocyte-derived DCs before *H. pylori* stimulation. In fact, these strategies will justify the persistence of the organism (Chang et al., 2012).

#### 4.1.4. The challenge of new players of innate immunity with H. pylori; NLRs and inflammasome

Nucleotide-binding and oligomerization domain (NOD) -like cytoplasmic receptors (NLRs) are the fourth and the last family of PRRs. The NLRs detect a wide range of damage-associated molecular patterns (DAMPs) that are created after disturbing tissue homeostasis (Land, 2015). Generally, NLRs are divided into two groups including NOD1 and NOD2. The NOD1 recognizes *H. pylori* peptidoglycan in the cytoplasm of epithelial cells and activates NF-kB signaling and its translocation to the nucleus. The NOD1 signaling causes *H. pylori* killing in the activated epithelial cell through β-defencin 2 as an antimicrobial peptide. Overall, H. pylori was reported to be recognized via NOD1 in epithelial cells and via NOD2 in bone marrow–derived DCs. Recently, experiments have shown that blocking of NOD1 cannot influence the NF-kB translocation (Minaga et al., 2018).

The second category in NLRs strengthens the formation of a complex containing several proteins called inflammasome, which activates the cysteine protease of caspase-1 that control the processing of pro-IL-1β and IL-18 (Tourani et al., 2018). The inflammasome involves a cytoplasmic sensor protein (NLRP1 (NLR family, pyrin domain–containing 1), NLRP3, or NLR family, CARD domain–containing 4 (NLRC4) of the NLR family), the adaptor protein apoptosis-associated speck-like domain containing CARD (caspase recruitment domain) (ASC) and procaspase-1. Establishment of the inflammasome complex is induced by a signal with specific aspects for the different types of inflammasome (Guo et al., 2015; Schroder and Tschopp, 2010). The inflammasome ligands and NLRs involved in *H. pylori* recognition are unknown. However, *in vivo* and *in vitro* studies indicated that caspase-1 is activated after co-culture with *H. pylori* in DCs and IL-1β and IL-18 processed and released into the gastric mucosa (Hitzler et al., 2012b). Recently following *H. pylori* infection has shown that potassium efflux, reactive oxygen species (ROS) and lysosomal destabilization are the key cellular targets responsible for activation of NOD and NLRP3 inflammasome. In addition, VacA and CagPAI were introduced as the bacterial virulence factors that are involved in inflammasome complex. Moreover, *in vivo* experiments indicated a key role of the inflammasome in the beginning and establishment of the inflammatory response to H. pylori infection (Semper et al., 2014).

There is no evidence indicating that *H. pylori* escape of the inflammasome or caspase-1. A study showed that caspase-1 deficient mice could clear the *H. pylori* experimental infection more effectively than the wild-type mice, and have more pathogen-specific T cell responses with more damages (Hitzler et al., 2012b). This unexpected observation was explained by IL-18 or IL-18R deficient mice that indicated the critical role of IL-18 in CD4+ CD25+ Foxp3+ Regulatory T Cells induction in response to *H. pylori.* Accompanied by the presence of Treg cells, the activity of effector T cells will be limited and result in the persistence of the infection (Oertli et al., 2012). In contrast, IL-1β deficient mice were unable to develop the specific *H. pylori* Th1 and Th17 that lead to expansion of experimental infections and mice were only protected against mildest forms of infection associated with immunopathology (Hitzler et al., 2012b). IL-1β and IL-18 are important in the context of H. pylori infection. Both cytokines have been extensively linked to gastric carcinogenesis. Polymorphisms in the IL-1βandIL-18 genes result in elevated levels of these cytokines that increase the risk of gastric cancer (Ramis et al., 2017). A study showed that specific expression of IL-1β in the stomach of a transgenic mouse model in response to H. pylori infection resulted in inflammation, dysplasia and enhanced gastric carcinogenesis. Whereas, IL-18 has been associated with increased metastasis and immune escape in gastric cancer cells (Huang et al., 2013; Kang et al., 2009).

Consequently, recognition of *H. pylori* with NLRs, activation of inflammasome complex and the downstream signaling pathways are essential for controlling *H. pylori* infection. Yet, these signaling pathways will limit the immunopathological tissue damages with effector T cell responses. Therefore, these observations suggest a dual role for the inflammasome during H. pylori infection (Mak'Anyengo et al., 2018).

### 4.2. Effector T cell response to H. pylori

$CD4^+$ T cells are the key effector cells of adaptive immunity in the immune response to *H. pylori* compared to the relatively inactive role of CD8 T cells.The immune response was originally considered as a Th1 response but other $CD4^+$ T cell subsets including Th17 and Tregs have been introduced in *H. pylori* infection (Bagheri et al., 2018b). Generally, activation of Th1 and Th17 cells follows with consequent production of IFN- γ, IL-17, and TNF-α (Bagheri et al., 2018a). Neutrophils and monocytes in response to the neutrophil activating protein of *H. pylori* (HP-NAP) produce IL-12 that promote Th1 responses. Furthermore, Th1 cells in response to HP-NAP producing IFN-γ in the gastric mucosa cause chronic gastric inflammation (Amedei et al., 2006). In addition, Th17 cells appear to be essential in the clearance of *H. pylori*. IL-17 facilitates the release of IL-8 that promote gastric inflammation. On the other hand, IL-8 recruits neutrophils that are critical for the clearance of the bacteria (Luzza et al., 2000). Moreover, in the distal gastric adenocarcinoma, a part of Th cells show significant proliferation to the peptidyl-prolyl cis-trans isomerase of *H. pylori* (HP0175). HP0175 induces high level of IL-17 and IL-21 production by lymphocytes, thus promoting Th17 responses (Amedei et al., 2014). IL-21 is a complicated cytokine that modulates the differentiation of $CD4^+$ and $CD8^+$ T cells in context dependent manner. Although, IL-21 promotes Th17 differentiation and IL-10 production, but inhibits the generation of potentially pathogenic Th1 and Th17 effector cells (Tian and Zajac, 2016). These Th17 cells had reduced cytolytic activity, while helping to monocyte matrix metalloproteinase-2 (MMP-2), matrix metalloproteinase-9 (MMP-9), and vascular endothelial growth factor (VEGF) production. Hence, HP0175 provides a link between *H. pylori* related inflammation and gastric cancer. Th1 and Th17 cells are involved in enhancing the immunopathologic and histopathologic changes of the gastric mucosa that result in gastric inflammation, atrophic gastritis, epithelial hyperplasia, and intestinal metaplasia in chronic infections (Hitzler et al., 2012a; Larussa et al., 2015). In contrast, Tregs that produced during *H. pylori* infection contribute to bacterial persistence. Tregs protect the host cells infected with *H. pylori* against excessive gastric inflammation and may also promote bacterial colonization which may lead to gastric tumor progression (Laur et al., 2016).

#### 4.2.1. Evasion of Th1 and Th17 cells

A prominent feature of *H. pylori* infection is that effector T cell responses are mostly impaired during infection leading to hyporesponsivity or anergy of T cells. *H. pylori* virulence factors contributing in interfering with T cell responses are VacA, γ-glutamyltranspeptidase (GGT), and arginase (Rimbara et al., 2013). VacA inhibits the proliferation of T cells. First, VacA binds to an unknown receptor on T cells which inhibits cell proliferation through actin rearrangement. Secondly, VacA binds to the mitochondria and leading to apoptosis. This mechanism is able to induce inhibition of T cell proliferation (Abadi, 2017). Furthermore, VacA inhibits the proliferation of T cells via interfering with the signaling pathway of TCR-IL-2 and upstream molecules such as calcium/calmodulin-dependent phosphatase calcineurin. VacA also prevents nuclear translocation of the nuclear factor of activated T cells (NFAT) transcription factor and consequently inhibits transcription of specific T cell genes (Gebert et al., 2003). Further studies identified integrin β2 (CD18) on T cells act as VacA receptor. The integrin β2 along with CD11a creates lymphocyte function-associated antigen-1 (LFA-1) on the surface of the T cell (Sewald et al., 2008).

In addition to Vac A, GGT is able to inhibit T cell proliferation. The GGT mediates the extracellular cleavage of glutathione and through ROS production leading to cell cycle arrest in lymphocytes. GGT disrupts Ras signaling pathway that result in G1 cell cycle arrest and then inhibits T cell proliferation (Lina et al., 2014).

B7-H2 (ICOS-L) is a new member of the B7-family receptors that have the co-stimulatory function on T cell activity upon binding to inducible costimulator (ICOS). Recently, the B7-H2/ICOS interaction in Th17 cell development, maintenance and function has been identified. The virulence factor CagA also shows a key role in the modulation of Th17 cell response indirectly through restricting expression of B7-H2 on gastric epithelial cells. Th17 suppression leads to the persistence of *H. pylori* infection in stomach (Lina et al., 2013).

#### 4.2.2. Deviation in T cell response

Unusual activation of Tregs by microbial antigens may provide a mechanism of *H. pylori* evasion from immune response. The gamma-glutamyl transpeptidase (GGT) and VacA from *H. pylori* molecules indirectly affect the activity of T lymphocytes and promote the differentiation of effector $CD4^+$ T cells to Tregs (Oertli et al., 2013). The gastric mucosal inflammatory response to H. pylori could be modulated by Tregs, which is characterized with the expression of transcription factor FOXP3, CD25, and production of IL-10. Tregs can suppress cytokine proliferation and production of other T cells (Algood and Cover, 2006). The interaction between the naïve $CD4^+$ T cell and tolerogenic dendritic cells exposed to *H. pylori* is crucial for Tregs differentiation. In addition, gastric epithelial cells exposed to *H. pylori* induced Tregs. This interaction mostly happens in the gastric mucosa or the mesenteric lymph nodes (Lina et al., 2014; Salama et al., 2013). Dendritic cells that are exposed to *H. pylori in vivo* and *in vitro* cannot induce Th1 and Th17 responses, while they induce Tregs expression. It seems that the induction of Tregs is dependent on the age when the host gets the infection. Hence, the level of Tregs in children with *H. pylori* infection has increased, and gastric pathology has reduced in comparison with adults (Oertli and Muller, 2012)

A study showed that outer inflammatory protein A (OipA) of *H. pylori* is a DC maturation suppression factor. In fact, *H. pylori* OipA helps the establishment of chronic infection through decreasing IL-10 levels and suppressing DC maturation. Hence, tolerogenic programming in DCs by *H. pylori* leads to persistent gastric colonization (Teymournejad et al., 2014). Furthermore, H. pylori-induced tolerogenic DCs are not able to induce effector functions in naive T cells, and these cells became very efficient in inducing Tregs (Lina et al., 2014). Therefore in this context with dominant Treg-induced responses, there was a high tendency for the *H. pylori* control in chronic infection conditions (Bagheri et al., 2016). In *H. pylori* infected human especially in children and asymptomatic carriers, Tregs are accumulated in the gastric mucosa and effectively inhibits the response of specific T cell memory against *H. pylori* (Lundgren et al., 2003). On the other hand, the experiments on vaccinated mice showed that the depletion of Tregs can facilitate the removal of *H. pylori* in infected animals and increases vaccine protection (Anderl and Gerhard, 2014). Tregs facilitating *H. pylori* persistence required T-cell expressing IL-10. In fact, deficient IL-10 animals are capable controlling experimental infections spontaneously, while control or even clearance of *H. pylori* in various animals has led to significant changes in stomach immunopathology such as atrophy and metaplasia.(Liu et al., 2016) In addition to the presence of Tregs, their potential for inducing the tolerance of *H. pylori*-specific dendritic cells is critical. In a study, it was shown that in spite of the abundant presence of Tregs, the high colonization of *H. pylori* occurred in carriers and developed gastritis (Raghavan and Quiding-Jarbrink, 2012). It seems that the activity of both VacA and GGT is required for T cell immune response deviation, but their exact mechanisms for inducing the tolerance of *H. pylori*-specific dendritic cells is unclear. It has recently been noted that the function of both factors is critical for Tregs induction (Oertli et al., 2013).

## 5. Development of *H. pylori* vaccine; hopes and failures

In early 1990, infection with *H. pylori* was introduced as the main cause of peptic ulcer and a serious risk factor for gastric cancer development. Gastric carcinoma is now the third leading cause of the death due to malignancy and the majority of these cancers develop due to *H. pylori* infection (Sutton and Boag, 2018). Hence, a vaccine against the *H. pylori* would be a powerful tool to prevent gastric carcinoma. Efforts for *H. pylori* vaccine development has begun for a quarter of century now, and countless efforts were made to produce an effective vaccine. (Talebi Bezmin Abadi, 2016). However, the development of vaccine against *H. pylori* was found to be extremely challenging as vaccines in clinical trials were found to be less effective.

In this context, the best preclinical result was obtained from vaccines that often induced T cell-mediated immune response rather than humoral immunity. Th1 and Th17 responses in the stomach are more protective (Sun et al., 2018). The common immunogenic antigens of *H. pylori* that were able to produce immunity in mice models are urease enzymes, CagA, VacA, neutrophil activating proteins (NAPs), and heat shock proteins (HSP). These antigens can enter the stomach via various mucosal routes such as intranasal, sublingual and rectal. Additionally, systemic immunization through intraperitoneal and subcutaneous routes can be more effective for *H. pylori* vaccination. Vaccination involving these wide range of antigens, adjuvants, and delivery systems yielded only a partial reduction of bacterial colonization in mice, and thus are less effective. *H. pylori* persistence mechanisms and utilization of a wide range of mechanisms to overcome adaptive immunity are recognized as important barriers to vaccination (Robinson et al., 2017).

The partial success achieved in animal models has not translated to protection in clinical trials, although with few exceptions. A clinical phase III trial conducted in China with a prophylactic vaccine containing a fusion protein of urease with *E. coli* heat-labile toxin B subunit has shown promising reduction in H. pylori natural infections in children. The vaccine given to children aged 6–15 is found to be effective in prevention of natural acquisition of H. pylori infections in 71.8% participants after one year and 55% participants after two years. However, the vaccine may unlikely be feasible for the global distribution in the current formulation since vaccine recipients need to be given bicarbonate solution 2 h prior to oral vaccination to reduce stomach acids which can degrade the vaccine. Also, the vaccine efficacy can wane after one year needing frequent vaccinations. Nonetheless, this study might be the first demonstration that an effective vaccine can be developed against *H. pylori* infection (Zeng et al., 2015). A phase I clinical trial showed that intramuscular immunization with the three CagA, VacA, and NAPs recombinant antigens combined with alum adjuvant is found to be immunogenic to some or all of the antigens. The T cell response to CagA and VacA antigens was detectable up to 24 months after the first vaccination and provided a protective response (Malfertheiner et al., 2008). However, this vaccine developed by Novartis has not been pursued for further trials. Another phase I clinical trial involving oral therapeutic vaccination of *H. pylori* urease with *E. coli* heat-labile enterotoxin has shown potential efficacy, with small reductions in colonization of *H. pylori* (Michetti et al., 1999). Evidence also suggests that oral vaccination with *Salmonella enterica* serovar *typhi* TY21a expressing *H. pylori* urease can stimulate cell mediated immune response and reduces infection (Londono-Arcila et al., 2002). The most important efforts that have been made in the past for the *H. pylori* vaccine as well as the prospects for the future are summarized in Table 1. Therefore, it seems that the efforts for *H. pylori* vaccine development are in primary steps of a long road and will require more diligence and attention in the future.

## 6. Conclusion

Efforts to develop specific treatments of *H. pylori* were initiated concurrently with the identification of bacteria as the main cause of gastric ulcer and a risk factor for gastric cancer (Lina et al., 2014). H. pylori virulence factors such as CagA, VacA, and HP-NAP cause major damages in the gastric epithelium which results in gastrointestinal disorders including peptic ulcer or gastric cancer. Beside these,

**Table 1**
Approaches was applied in *H. pylori* vaccine in past and may be examined in future.

| Past experimental approaches to *H. pylori* vaccine | | | |
|---|---|---|---|
| Vaccine (Antigen + Adjuvant) | Route | Result | Ref |
| Urease + LT | Oral | Decrease of bacterial load in vaccinated groups | Michetti et al. (1999) |
| Whole cell + dmLT | Oral | No bacterial clearance | Kotloff et al. (2001) |
| Urease or HP0231 + Salmonella Ty21a | Oral | Bacterial clearance in both vaccinated and control | Aebischer et al. (2008) |
| Urease + LT | Oral | Efficacy 72% | Zeng et al. (2015) |
| CagA, VacA, NAP + Alum | IM | Clearance equivalent between vaccinated and | Malfertheiner et al. (2018) |
| **Newer experimental approaches to *H. pylori* vaccine** | | | |
| Multi-epitope DNA-prime/peptide (EpiVax) | IN | Some therapeutic protection in mice | Moss et al. (2011) |
| GGT (Imevax/IMX101 X) | IP | Protection against allergic asthma | Oertli et al. (2013) |
| *Lactococcus lactis* expressing CTB and urease (Probiotic vaccine) | Oral | | Li et al. (2014) |
| UreI-UreB + CTB (Urease epitope vaccine) | Oral | Limited protection in BALB/c mice | Yang et al. (2015) |
| Lp220 + CTB | IP | Limited protection in BALB/c mice | Li et al. (2016) |
| A non-pathogenic Vibrio cholerae strain engineered to express HpaA, UreB and FlaA (Helicovaxor®) | Oral | Introduced as oral inactivated vaccine | Tobias et al. (2017) |

CTB, cholera toxin subunit B; dmLT, double mutant LT; GGT, gamma-glutamyl-transpeptidase; IM, intramuscular; IN, intranasal; IP, intraperitoneal; LT, *Escherichia coli* heat-labile enterotoxin; UreI-UreB, *H. pylori* urease I and urease B.

deviation in host immune responses determines the severity of gastrointestinal disorders. Immune evasion mechanisms are recognized as a remarkable challenge for development of specific therapies to overcome gastrointestinal disorders that are associated with *H. Pylori* infection. Although the host immune responses clears most pathogens, but H. pylori evolved a set of mechanisms to evade both innate and adaptive immune responses that guarantees bacterial persistence. In fact, immune response can't clear the bacterium but facilitates the bacterial colonization and survival in stomach. (Abadi, 2017; Lina et al., 2014; Mejias-Luque and Gerhard, 2017). On the other hand, vaccination against *H. pylori* infection as promising strategy is facing with drastic challenges. Therefore, vaccination strategies that lead to protective immune response by generating Th1 and Th17 responses in the stomach was more reliable than Tregs dependent responses in preclinical animal models. Taken together, a better understanding of *H. pylori* and host cells interaction is critical for the development of specific protection and treatment in the future.

## Conflict of interest

The authors have no conflicts of interest.

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