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Immune responses to *Helicobacter pylori* infection

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Abstract

Helicobacter pylori (*H. pylori*) infection is one of the most common infections in human beings worldwide. *H. pylori* express lipopolysaccharides and flagellin that do not activate efficiently Toll-like receptors and express dedicated effectors, such as γ-glutamyl transpeptidase, vacuolating cytotoxin (vacA), arginase, that actively induce tolerogenic signals. In this perspective, *H. pylori* can be considered as a commensal bacteria belonging to the stomach microbiota. However, when present in the stomach, *H. pylori* reduce the overall diversity of the gastric microbiota and promote gastric inflammation by inducing Nod1-dependent pro-inflammatory program and by activating neutrophils through the production of a neutrophil activating protein. The maintenance of a chronic inflammation in the gastric mucosa and the direct action of virulence factors (vacA and cytotoxin-associated gene A) confer pro-carcinogenic activities to *H. pylori*. Hence, *H. pylori* cannot be considered as symbiotic bacteria but rather as part of the pathobiont. The development of a *H. pylori* vaccine will bring health benefits for individuals infected with antibiotic resistant *H. pylori* strains and population of underdeveloped countries.

Key words: *Helicobacter pylori*; Vaccine; Immune response; Peptic ulcer; Gastric cancer

Core tip: *Helicobacter pylori* (*H. pylori*) infection is one of the most common infections in human beings worldwide. *H. pylori* actively induce tolerogenic signals and can be considered as a commensal bacteria belonging to the stomach microbiota. However, *H. pylori* also promote a chronic inflammation in the gastric mucosa and the direct action of virulence factors confers pro-carcinogenic activities to *H. pylori*. Hence, *H. pylori* cannot be considered as symbiotic bacteria but rather as part of the pathobiont. The development of a *H. pylori* vaccine will bring health benefits for individuals infected with antibiotic resistant *H. pylori* strains and population of underdeveloped countries.

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INTRODUCTION

Helicobacter pylori (*H. pylori*) infection is one of the most common infections in human beings worldwide[1]. After entering the stomach, this spiral, Gram-negative, microaerophilic bacterium penetrates the mucus gastric layer[2] but does not traverse the epithelial barrier[3], and therefore it is considered as a non-invasive bacteria. Most of *H. pylori* organisms are free living in the mucus layer, but some organisms attach to the apical surface of gastric epithelial cells[3] and small numbers have been shown to invade epithelial cells[4]. Humans carry an estimated of 10^4 to 10^7 *H. pylori* CFU per gram of gastric mucus[5].

Upon infection, *H. pylori* uses urease and α-carbonic anhydrase to generate ammonia and HCO_3^{2-} which mitigate the effects of low pH[6,7]. Moreover, thanks to its flagella and shape, *H. pylori* penetrate the mucus layer. *H. pylori* null mutant defective in production of flagella are unable to colonize gnotobiotic piglets[8]. Once established in the inner mucus layer, several outer membrane proteins, including BabA, SabA, AlpA, AlpB and HopZ can mediate bacterial adherence to gastric epithelial cells. Once attached, bacterial effector molecules, both secreted [vacuolating cytotoxin (VacA) and cytotoxin-associated gene A (CagA)] or attached [components of the type Ⅳ secretion system (CagL)], modulate gastric epithelial cell behaviour leading to loss of cell polarity, release of nutrients and chemokines [*e.g.*, interleukin (IL)-8], and regulation of acid secretion *via* control of gastrin and H^+/ K^+ ATPase[9,10].

The infections are acquired during childhood; frequent clonal transmission of *H. pylori* between first degree relatives demonstrates intra-familial transmission of *H. pylori* in developed countries. In developing world, members of the same family can be infected with widely diverse strains, and multiple infections were common arguing for horizontal transmission of *H. pylori* infection[11]. After ingestion, there is a period of intense bacterial proliferation and gastric inflammation. Concomitant with the intense gastritis is hypochlorhydria. Fecal shedding of *H. pylori* is maximal during this period, facilitating transmission to new hosts. Ultimately, the inflammatory response is reduced to a low-level stable state, normal gastric pH is restored, and most of the infected person becomes asymptomatic[12]. This outcome persists for years or decades and appears to predominate in the population. Depending on *H. pylori* virulence factors, environmental factors and the host response to bacterial infection, *H. pylori* infection can be associated with several clinical complications such as gastritis, peptic ulcer disease, gastric cancer and mucosa-associated lymphoid tissue (MALT) lymphoma[13-15]. *H. pylori* eradication therapies have revolutionised the natural course of peptic ulcer disease[13]. Antibiotic treatment of *H. pylori* infection is relatively successful, with the organism being eradicated from around 80% of patients[16].

IMMUNE RESPONSE TO *H. PYLORI* INFECTION

Immune responses to *H. pylori* infection have been studied in twenty adult volunteers experimentally infected with *H. pylori*[17]. Gastric biopsies performed 2 wk after infection showed infiltration of lymphocytes and monocytes, along with significantly increased expression of IL-1, IL-8, and IL-6 in the gastric antrum[17]. Anti-*H. pylori* immunoglobulin (Ig)M and IgG responses were detected in the serum of infected individuals. In addition, 4 wk after infection, the numbers of gastric $CD4^+$ and $CD8^+$ T cells were increased compared to preinfection levels[18]. These data provide evidence that gastric and systemic immune responses develops within a short period of time after *H. pylori* infection.

Gastric mucosal biopsies from humans persistently infected with *H. pylori* reveal an increased infiltration of various types of leukocytes compared to biopsies from uninfected humans[19]. Lymphocytes (T and B cells), monocytes, eosinophils, macrophages, neutrophils, mast cells and dendritic cells are usually present[19,20]. B cells and $CD4^+$ T cells together with dendritic cells (DC) sometimes organize into lymphoid follicles[21] reflecting ongoing antigen presentation and chronic immune responses. *H. pylori*-specific $CD4^+$ T cells are detectable in the gastric mucosa and peripheral blood of infected-individuals but not uninfected humans[22]. Levels of cytokines [interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), IL-1, IL-6, IL-7, IL-8, IL-10, and IL-18] are increased in the stomach of *H. pylori*-infected humans compared to uninfected humans[23]. IL-4 has not been detected in the gastric mucosa of most *H. pylori*-infected individuals[24]. Therefore, it has been concluded that *H. pylori* infection leads to a T helper cell (Th)1-polarized response. *H. pylori* infection has also been associated with upregulation of IL-17A expression in the gastric mucosa[25]. IL-17A is the most widely studied member of the IL-17 family of cytokines (IL-17A-F), and is produced by Th17 $CD4^+$ T cells as well as other subsets of immune cells[26]. Extracellular bacterial and fungal infections elicit strong IL-17A responses that stimulate stromal and epithelial cells to release pro-inflammatory cytokines and chemokines, *e.g.*, TNF-α, IL-1β, IL-6, CXCL1, CXCL2, CCL2, CCL7, CCL20, which recruit neutrophils, macrophages and lymphocytes to the site of infection[27]. Furthermore, it has been described that *H. pylori* infection also leads to the generation of regulatory T cells (Treg)[28-30]. Depletion of Treg through injection of anti-CD25 antibodies to mice before *H. pylori* infection promoted gastritis and reduced bacterial load[31]. Very elegant studies originated from the group of PD Smith clearly showed that in children[30,32], *H. pylori* infection is associated with low Th17 and Th1 responses, high Treg response and reduced gastritis as compared with adults, suggesting that *H. pylori* specific Treg play key roles in bacterial persistence.

Associated with cellular responses, a humoral immune response is elicited in nearly all *H. pylori*-infected humans[33]. Serum IgA and IgG antibodies in chronically infected persons are directed toward many different *H. pylori* antigens[33]. A local antibody response directed toward *H. pylori* antigens is also detectable with chronic *H. pylori* infection. These subjects have remarkably higher frequencies of total IgA- and IgM-secreting cells than the noninfected subjects, while the frequencies of IgG-secreting cells were virtually the same in the different groups[34]. Notably, *H. pylori* infection induces autoantibodies reactive with gastric epithelial cells, which could drive gastritis[35]. These autoantibodies could be directly cytolytic to epithelial cells through activation of complement, inducing apoptosis or triggering an antibody-

dependent cellular cytotoxicity reaction leading to the tissue destruction.

GASTRO-INTESTINAL TRACT IMMUNE DEFENCES

H. pylori colonizes the gastro-intestinal tract, thus there is a need to study the immune responses directed toward *H. pylori* in the context of the general functioning of the gastro-intestinal tract immune defences. In the following paragraph, we will briefly summarize our current understanding of the functioning of the mucosal immune responses.

The mucosal defences are multiple and might be physical, chemical and immune-mediated. The mucosal epithelium blocks invasion by pathogenic and commensal bacteria by forming multiple layers of physical (tight junctions), chemical nitric oxide and immune protection (local secretion of defensins, anti- and/or pro-inflammatory chemokines/cytokines and IgA/IgG/IgM transport). In addition, numerous bone marrow-derived cells belonging to the innate or adaptive immune systems colonized the intestinal mucosa to fight the invaders, but at steady state the same cells have to tolerate commensals.

IgA response

A major defensive mechanism that excludes commensals and pathogens from the mucosal surface involves IgA[36]. Mucosal IgA comprises antibodies that recognize antigens with high- and low-affinity binding modes. In general, high-affinity IgA neutralizes microbial toxins and invasive pathogens, whereas low-affinity IgA confines commensals in the intestinal lumen. High-affinity IgA is thought to emerge in Peyer's Patches (PPs) and mesenteric lymph nodes (MLNs) from follicular B cells stimulated *via* T cell-dependent pathways, whereas low-affinity IgA likely emerges in PPs, MLNs and lamina propria from B cells stimulated *via* T cell-independent pathways[36]. IgA response is powerfully induced by the presence of commensal microbes in the intestine[37,38] and has been shown to promote the maintenance of appropriate bacterial communities in specific intestinal segments[39]. In contrast to the lungs, vagina and most of the gastrointestinal tract, the healthy mammalian stomach produces very low level of polymeric immunoglobulin receptor (pIgR)[40,41], the receptor mediating IgA transport into the gastrointestinal lumen. Studies in *H. pylori*-infected humans have shown that baseline pIgR expression by the gastric epithelium can be up-regulated in response to gastric inflammation[42] due to increased local IFN-γ production[43]. However, despite significantly increased pIgR expression and IgA plasma cell infiltration in response to *H. pylori* infection[44] there is no concomitant increase in IgA secretion into the stomach; and it is non-secretory monomeric IgA which predominates in the stomach of *H. pylori*-infected individuals[45]. Hence, the IgA that is present in the gastric lumen would be unstable, susceptible to degradation by proteases. These observations suggest that, the stomach anti-*H. pylori* IgA responses do not play similar biological roles as compared with anti-commensal or anti-pathogen IgA response taking place in the intestine.

IgG response

In unmanipulated specific pathogen-free animals it has been showed that there was no specific serum IgG response detectable directed against commensal bacteria[46]. In pathogen-free mice, the systemic immune system appeared to remain ignorant of the commensal microbes. However, in human, a certain degree of systemic exposure to gut commensal bacteria and the associated priming of systemic immune response seems to be well tolerated, harmless and common in healthy humans since systemic antibody responses against live gut commensal bacteria and fungi can be detected[47]. Most of the *H. pylori* infected individuals develop systemic anti-*H. pylori* IgG responses[18]. Recently, Ben Suleiman *et al*[48] detected the expression of neonatal Fc receptor in gastric epithelial cells, this receptor was shown to transport IgG into gastric secretion. These results indicate that systemic anti-*H. pylori* IgG response might gain access to the gastric mucosa and exert some anti-bacterial and/or pro-inflammatory activities.

$CD4^+$ T cell responses

Since *H. pylori* is an extra-cellular bacteria, anti-*H. pylori* specific $CD8^+$ T cell responses are inadequate to protect the host against such pathogen. Hence, in this review we will only describe the priming of $CD4^+$ T cell response. As discussed above for IgA response, $CD4^+$ T cell responses are initiated within the PPs and MLNs. DC capture, process and present antigens to naive T cells in PPs and MLNs. In the stomach, DCs are penetrating the mucosa[49] to sample luminal antigens and migrate to the stomach lymph node[50].

At steady state, mucosal $CD4^+$ T cells are tolerant to microbiota-derived antigens[51]. Remarkably, systemic $CD4^+$ T cells are not tolerant to microbiota-derived antigens and conserved a naïve state to these antigens[52]. It has recently been suggested that antigen-specific intestinal IgA play a critical role in inhibiting the systemic $CD4^+$ T-cell responses to commensal antigens by providing immune exclusion[51].

At mucosal surfaces, DCs maintain homeostasis by dampening inflammatory Th1 and Th17 cell responses[53]. Mucosal DCs are particularly skilled in eliciting these anti-inflammatory responses because they receive conditioning signals from intestinal epithelial cells (IECs)[54,55]. One of these signals is provided by thymic stromal lymphopoietin (TSLP), that shifts the Th1/Th2 balance toward Th2 polarization by attenuating DC production of IL-12 but not of IL-10[56]. In addition to TSLP, IECs release transforming growth factor (TGF)-β and retinoic acid, which stimulate the development of $CD103^+$ DCs[53]. These DCs promote the formation of

Treg cells *via* TGF-β and retinoic acid and suppress the development of inflammatory Th1 and Th17 cells[53].

In addition to initiating responses that create an overall tolerant state towards harmless intestinal antigens, mucosal DCs are also implicated in the generation of protective immune responses aimed at the clearance of enteric pathogens. A fundamental difference between the steady state and a state of infection may lie in the greater propensity of pathogens to invade and penetrate beneath the epithelial-cell layer. Invasion of IECs would allow for the activation of cytosolic pattern-recognition receptors, TLRs and both quantitative and qualitative changes in the secretion of pro-inflammatory cytokines and chemokines. Consistent with this, IECs produce CXC-chemokine ligand 8 (CXCL8) when infected with strains of *Salmonella* spp. that are both invasive and flagellated[57]. CXCL8 may serve to attract neutrophils to the site of infection, furthering the inflammatory milieu. As a result, the rate of blood-borne DC precursors migrating into the tissues and becoming DCs will increase. These cells will not have been subjected to IECs conditioning and can be directly activated by a combination of pathogens that have breached the epithelial-cell barrier and the pro-inflammatory cytokine milieu. Experimental data support this scenario; human monocyte-derived DCs conditioned with IEC supernatants are impaired in their ability to secrete IL-12 and drive Th1-cell responses following exposure to pathogenic *Salmonella* spp[56] but can drive Th1-cell responses if they encounter bacteria before conditioning by IEC-derived factors. One other possible route for the generation of protective immunity to pathogens may be the uptake of pathogenic species by DCs that are normally resident in the MLNs. In this respect, $CD103^-$ MLN DCs have been shown to produce higher levels of pro-inflammatory cytokines than their intestinal-derived $CD103^+$ counterparts and drive IFNγ and IL-17 production by $CD4^+$ T cells[53].

Collectively, since *H. pylori* is mostly a non-invasive bacteria living within the stomach mucosa, these observations suggest that, the $CD4^+$ T cells responses directed against *H. pylori*, initiated within PPs, MLNs and stomach draining lymph node, might be naturally more tolerogenic than pro-inflammatory. This assumption is corroborate by the recent demonstration that in children, *H. pylori* infection is associated with low Th17 and Th1 responses and high Treg response[32]. However, the detection of *H. pylori* specific Th17/Th1 in chronically infected individuals[24,25] shows that the initial tolerogenic response is progressively lost, showing that with time the mucosal immune system identified *H. pylori* as a pathogen.

Intra-epithelial lymphocytes, innate immune cells and others

Intra-epithelial cells[58], innate immune cells[59], natural killer cells[60], neutrophils[61], mast cells[62], eosinophils[63], macrophages[64], monocytes[64], suppressive myeloid cells[65] are playing roles in the functioning of the mucosal immune system, however due to space limitation we will not discuss their roles in the context of *H. pylori* infection.

STOMACH MICROBIOTA

It was previously admitted that the stomach was a sterile organ and that pH values < 4, peristalsis and high bile concentration were able to sterilize the stomach, but in the past 30 years with the discovery of *H. pylori* it is now known that the stomach supports a bacterial community with hundreds of phylotypes[66-68] Although, the stomach, along with the esophagus and the duodenum, are the least colonized regions of the gastro-intestinal (GI) tract, in contrast to the high bacterial counts (10^{10} to 10^{12} CFU/g) observed in the colon. While it has been postulated that the indigenous stomach microbiota might be a reflection of transient bacteria from the mouth and esophagus, three separate studies demonstrated that in spite of high inter-subject variability, the gastric microbiota were distinguishable from microbiota found in the mouth, nose, and distal GI tract[69]. The most abundant phyla in *H. pylori* positive subjects are *Proteobacteria*, *Firmicutes* and *Actinobacteria*. In the absence of *H. pylori*, the most abundant phyla are *Firmicutes*, *Bacteroidetes* and *Actinobacteria*[69].

In the gastro-intestinal tract, the microbiota has a major impact on the functioning of the mucosal immune system and vice versa. Germ-free mice have small size of PPs, decrease number of lamina propria IgA secreting-plasmocytes, low levels of serum immunoglobulin and demonstrate no Th17/Th1 in the intestine[70]. The composition of the intestinal flora modulates the functioning of the immune system, for instance, the presence of *Segmented filamentous bacteria* (*SFB*) in the microbiota is associated with the development of Th17 in the intestinal lamina propria[71]. The presence of some *Clostridia* strains within the human intestinal microbiota has been recently associated with the development of intestinal Treg[72]. In addition, some commensal bacteria and microbiota-derived metabolites like short-chain fatty acids have been shown to inhibit inflammatory reactions at intestinal levels and promote pathogen clearance[59,73,74]. Inversely, defects in antibody response lead to a modification of the bacterial composition of the intestinal flora[39]. Collectively, these observations suggest that the colonization of the stomach mucosa by *H. pylori* and/or the associated microbiota might also impact the functioning of the immune system of the host and vice versa.

TOLEROGENIC ACTIVITIES OF *H. PYLORI*

Studies indicate that *H. pylori*-derived factors are capable to inhibit T-cell proliferation. Using normal T cells and Jurkat cells, a human T-cell line, it was demonstrated that VacA interfered with calcium-signaling events inside the cell and prevented activation of the calcium-

dependent phosphatase calcineurin[75,76]. The subsequent dephosphorylation of nuclear factor of activated T cells (NFAT), a transcription factor that regulates immune responses, was suppressed resulting in inhibition of IL-2 expression and proliferation of T cells. Similar anti-proliferative effect on T cells was reported for the γ-glutamyl transpeptidase (γ-GGT), this immunosuppressive factor inhibits T-cell proliferation by induction of a cell cycle arrest in the G(1) phase[77]. In addition to VacA and γ-GGT, *H. pylori* arginase can impair T-cell function during infection. Using Jurkat T cells and human normal lymphocytes, it was found that a wild type *H. pylori* strain, but not an arginase mutant strain, inhibited T-cell proliferation, depleted L-arginine, and reduced the expression of the CD3 chain of the T-cell receptor[78]. Most (80%-90%) *H. pylori* strains display Lewis blood-group antigens on their LPS, and these are similar to the Lewis blood-group antigens that are expressed on the mucosal surface of the human stomach[79]. Lewis positive *H. pylori* variants are able to bind to the C-type lectin DC-SIGN and present on gastric DCs, and demonstrate that this interaction blocks Th1 development[80].

In addition to suppress T cell activation, *H. pylori* has been demonstrated to decrease the functioning of the innate immune system. For instance, efficient phagocytosis and killing of *H. pylori* is prevented by the presence of the *cag* pathogenicity island[81,82] and *H. pylori* induces but survives the extracellular release of oxygen radicals from professional phagocytes using its catalase activity[83]. Importantly, at the opposite to the LPS and flagellins of others gram-negative bacteria, the LPS and flagellins of *H. pylori* do not adequately activate the antigen presenting cells *via* the Toll-like receptors[84,85].

Collectively, *H. pylori* counteract innate and T cell responses and clearly exhibited tolerogenic activities on the immune system. It can be suggested that these tolerogenic activities participate to the *H. pylori* persistence within the stomach mucosa.

VACCINE-INDUCED PROTECTIVE IMMUNE RESPONSES

H. pylori infection is the main cause of gastritis, peptic ulcers, and gastric adenocarcinoma. It is believed that *H. pylori* contributes to gastric cancer development by direct action of its virulence factors and indirectly by initiation and maintenance of a chronic inflammation in the gastric mucosa[86]. Hence, gastroenterologists use a combination of anti-secretory and antimicrobial agents to eradicate *H. pylori*[16]. Similar to other antimicrobial treatments, the therapy may select resistant *H. pylori* strains[16]. Therefore, alternative therapies to eradicate *H. pylori* infection have been evaluated like the development of a vaccine against *H. pylori*.

In the seminal work reported in 1990 by Lee *et al*[87] demonstrated the feasibility to study different aspects of the pathology and the immune response induced by *Helicobacter* species in mice. These investigators using germ-free mice and *H. felis*, a bacteria that naturally infects cats and dogs, achieved successful long-term colonization and associated gastritis in these mice. This model became very popular and a large number of immunization studies were performed in *H. felis* infected mice. This was made possible by the fact that vaccine candidate antigens are shared between *H. felis* and *H. pylori* species (*i.e.*, urease and heat shock proteins). Thereafter, *H. pylori* strains have been adapted to the mouse stomach and this experimental model reproduces several aspects of the human infection[88-90]. Successful colonization with *H. pylori* has been reported in rats, guinea pigs, Mongolian gerbils, Gnotobiotic pigs, cats and Beagle dogs[90]. *H. pylori* naturally infects some species of nonhuman primates, with pathological changes in the stomach resulting from *H. pylori* infection being very similar to those observed in humans[91].

Numerous studies in animals suggested that T cells, mast cells and neutrophils are of prime importance for protection, while B cells (antibodies) are dispensable for protection[61,62,92,93]. However some studies suggested that antibodies can also participate to the vaccine-induced *H. pylori* clearance in some circumstances[94-98]. Indeed, vaccination-induced protection against *H. pylori* in mice requires major histocompatibility complex class II-restricted $CD4^+$ T cells[90,92], Th-1, Th-2 and/or Th-17 $CD4^+$ T cell responses and the α4β7 integrin-mediated homing process[99] have been implicated in protection[100-103]. Recently, the production of IL-17, by Th17 cells, has been clearly identified as a key player in the vaccine-induced *H. pylori* clearance. IL-17 has also been linked to neutrophil recruitment and activation through the induction of granulocyte-stimulating factor and IL-8[104] and to resistance against extracellular microbial infections[105], leading to the conclusion that IL-17 production by *H. pylori* specific Th17 cells can mediate the vaccine-induced *H. pylori* clearance (Figure 1).

Collectively, it was clearly demonstrated that *H. pylori* infections could be substantially prevented, reduced or even eliminated by prophylactic and therapeutic mucosal and systemic vaccinations[106-110]. This result is of great interest not only for the development of *H. pylori* vaccine but also for vaccine strategy aimed at clearing commensal bacteria with genotoxic and mutagenic activities[111].

CONCLUSION

H. pylori can be considered as a commensal bacteria belonging to stomach microbiota. Indeed, *H. pylori* promote the generation of *H. pylori* specific Treg. The tolerogenic environment created by *H. pylori* might explain that *H. pylori* seropositivity was inversely related to recent wheezing, allergic rhinitis, dermatitis, eczema, asthma or rash[112]. Very elegant pre-clinical studies conducted by the group of A Müller recently gave support to this assumption by showing that *H. pylori* infection during the neonatal period promote the development of Treg responses that protect adult mice from asthma[113]. Hence,

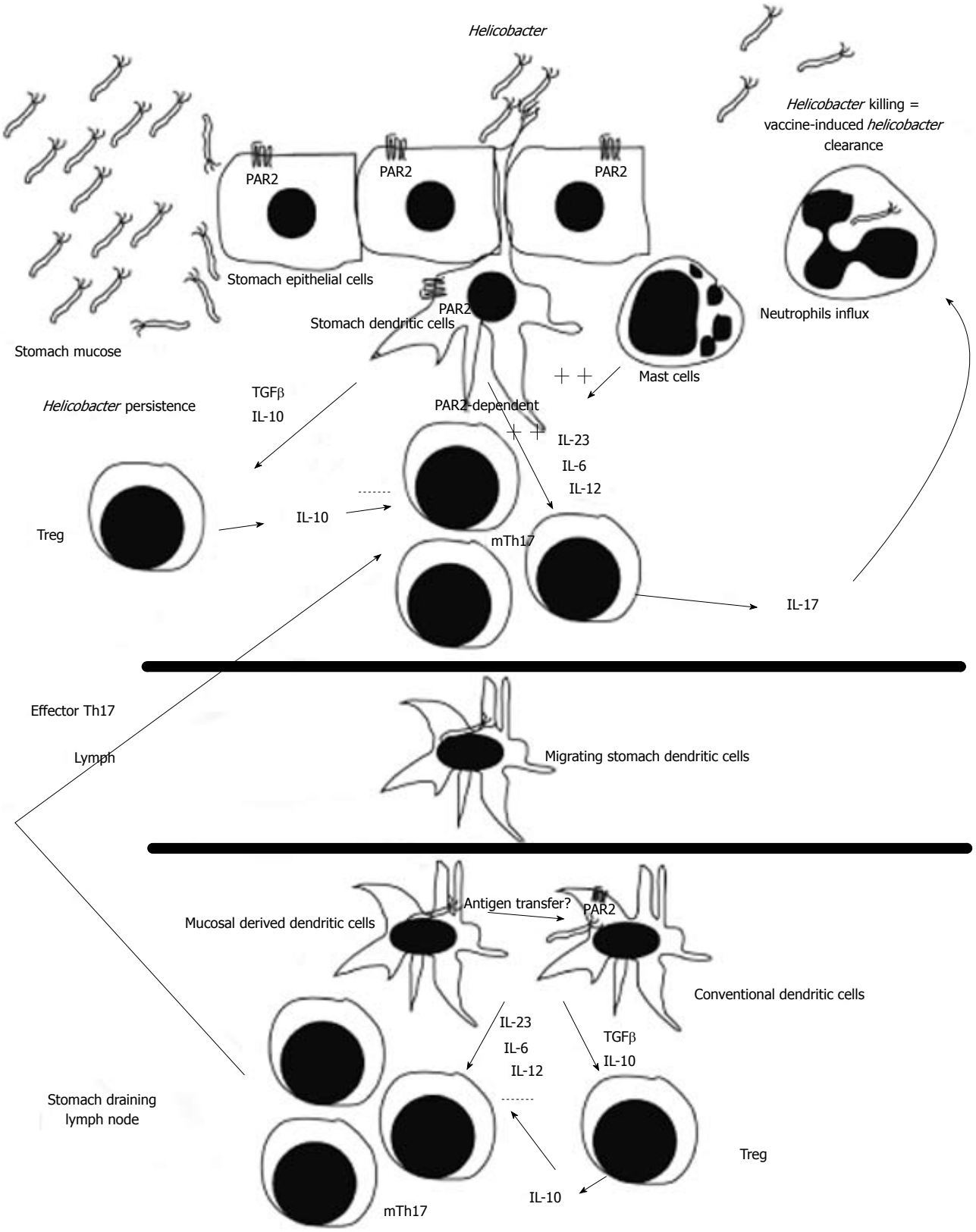

Figure 1 Schematic representation of the vaccine-induced *Helicobacter pylori* clearance. During *Helicobacter* infection of vaccinated hosts, memory T helper (Th)17 cells (mTh17) are primed by protease-activated receptor (PAR)2-dependent dendritic cell (DC)[126] directly in the stomach and/or in the stomach draining lymph nodes (conventional DCs). Effector memory Th17 cells originated from the stomach and/or from the stomach draining lymph nodes will produce high levels of interleukin (IL)-17 leading to recruitment of neutrophils and to *Helicobacter* clearance. In naïve hosts, DCs mainly prime regulatory T cells (Treg), leading to *Helicobacter* persistence.

H. pylori, like other commensal bacteria such as *SFB*[71], *Calibacterium prausnitzii*[74], *Lactobacillus reuteri*[59], *Lactobacillus Acidophilus*[59], and *Clostridia*[72] profoundly impact the functioning of the immune system of the colonized host.

Although *H. pylori* infection can be beneficial for the host, when present in the stomach, *H. pylori* reduce the overall diversity of the gastric microbiota[114] and promote gastritis. The modification of the stomach microbiota might, independently or not of the presence of *H. pylori*, modulate the susceptibility of the host to immune-mediated diseases. The *H. pylori*-induced gastritis is most probably cause by the type Ⅳ secretion apparatus-dependent introduction of muropeptides into epithelial cells, that promote Nod1-dependent induction of a proinflammatory program[115]. In addition *H. pylori* promote gastric inflammation through the production of a neutrophil activating protein[116]. In spite of the natural tolerogenic environment provided by the stomach mucosa and the tolerogenic activities of *H. pylori*, these pro-inflammatory signals initiating systemic and local pro-inflammatory Th1/Th17 responses[22-24].

Since *H. pylori* possess pro-carcinogenic activities *via* maintenance of a chronic inflammation in the gastric mucosa and by direct action of its virulence factors (vacA and cagA), *H. pylori* cannot be considered as symbiotic bacteria but rather as part of the pathobiont[117]. Hence, *H. pylori* has to be eliminated when individuals are prone to develop duodenal and stomach ulcers[118,119] to prevent further major diseases development like MALT lymphoma and stomach adenocarcinoma. Although, the design of a vaccine directed *H. pylori* is challenging since it has to overcome the natural tolerogenic environment provided by the stomach mucosa and the tolerogenic activities of *H. pylori*, its development will bring health benefits for individuals infected with antibiotic resistant *H. pylori* strains and population of underdeveloped countries[120-125].

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